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
Funded by the Department of Health

EVIDENCE SUMMARY

Should zinc be used as adjunctive treatment for COVID-19 infection?

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Initial review by: Frangelo Conrad P. Tampus, MD; Rowena F. Genuino, MD, MSc; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS

RECOMMENDATION

There is insufficient evidence to recommend zinc as adjunctive treatment for COVID-19 infection. *(Low certainty of evidence)*

Consensus Issues

Despite the risk of adverse events (i.e., infusion site irritation and gastrointestinal side effects), the panelists agreed that the evidence of benefit and harm of zinc as an adjunct therapy for COVID-19 still poses uncertainty. From their experience with the use of oral zinc for prevention of other illnesses, there had been no significant events reported to identify oral zinc as a cause for concern. Its potential for benefit was still given high consideration, particularly pending the results of ongoing studies. One voted against its use due to the signal for harm (i.e., hospitalization) among ambulatory patients and the risk of adverse events in the zinc group.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of zinc as adjunct treatment for patients with COVID-19 infection both in the outpatient and in-patient setting. *(Very low quality of evidence)*

Consensus Issues

There were no issues raised during the consensus panel meeting.

What's new in this version?

This updated review now includes six RCTs, with the addition of four new RCTs that were made available or published after the initial review.

Key Findings

This updated review showed inconclusive results on the efficacy of zinc as adjunctive treatment for COVID-19 for the outcomes of in-hospital mortality and hospitalization of outpatients. There was a significantly higher number of adverse events in the group that received zinc compared to control.

Introduction

Zinc has been shown to inhibit viral reproduction of SARSCOV-2 in-vitro. It also plays a role in the immunological response, associated with the negative feedback that decreases the activity of nuclear factor kappa B, thereby diminishing excessive inflammation and risk for cytokine storm. It was also found to play a role in protecting the respiratory epithelium against oxyradicals and to enhance intestinal wound healing.[1-3]

Zinc supplementation has been used widely in the treatment of diarrhea and taste disorders, which are common among patients with COVID-19.[1] In addition, COVID-19 patients with zinc deficiency were found to have higher complication rates, prolonged hospital stay, and increased rates of mortality.[4]

Review Methods

We comprehensively searched different electronic databases that included MEDLINE via PubMed, Cochrane Library, ClinicalTrials.gov, PubMed Clinical Queries, medRxIV, bioRxIV, and *epistemonikos.com* until November 19, 2021. Free search on Google was also performed. The following keywords were used: “zinc”, “zinc gluconate”, and “zinc sulfate” in free text as well as MeSH terms for “Zinc” and COVID-19 (see Appendix 2). 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. We included studies according to the following eligibility criteria: P – patients diagnosed with COVID-19; I – zinc plus standard of care; C – placebo or no treatment plus standard of care; O – mortality, length of hospital stay, length of ICU stay, adverse effects; M – randomized control trials.

Results

We found a total of six RCTs [5-10] for this updated review on zinc as adjunctive treatment for COVID-19 (see Appendix 3). Two clearly stated that they enrolled ambulatory patients/outpatients [6,7], and the remaining four RCTs stated that either 1) hospitalized patients were enrolled, or 2) their population consisted of patients with COVID-19 across all severities. Among the six RCTs, there were four that used zinc as the sole adjunct, and two that used zinc along with other adjunctive agents.[7,9]

This review includes the mid-2020 RCT of Abd Elsalam et al. [5], which enrolled RT PCR-confirmed patients with COVID-19 (N=191) from three tertiary care centers in Egypt to investigate the effect of zinc added to hydroxychloroquine (HCQ) versus HCQ alone (currently is no longer recommended for treatment of COVID because of safety issues). Thomas et al. [6] enrolled outpatients and investigated the effect of zinc gluconate and ascorbic acid given independently and together, compared to receiving standard of care. The RCT by Kaplan et al. [7] was a Phase I/II study to confirm the safety and efficacy of maximally-tolerated doses of the combination of zinc and resveratrol, compared to placebo, for the treatment of outpatients with mild to moderate COVID-19. The RCT by Patel et al. [8] on high-dose intravenous zinc among hospitalized COVID patients initially planned to enroll 60 hospitalized non-ventilated patients, and 100 ventilated patients (N=160). The study did not reach its target enrolment and has been terminated, but an available publication allowed its inclusion in this review. The RCT by Darban et al. [9] investigated the efficacy of high-dose vitamin C, melatonin, and zinc in patients with severe COVID infection. Finally, the RCT by Abdelmaksoud et al. [10] assessed serum zinc levels among 134 patients with COVID-19, 105 of whom reported anosmia or hyposmia.

The pooled estimates for the outcomes of in-hospital mortality (two studies: RR 0.92, 95% CI 0.35-2.44, i^2=0%) and hospitalization of ambulatory outpatients (two studies: RR 1.35, 95%CI 0.40-4.67, i^2=0%)) were inconclusive. Adverse events were significantly higher in the zinc group than in the control (two studies: RR 13.62; 95%CI 1.78-104.43, i^2=0%).

In the RCT by Kaplan et al. [9] (adverse events data not included in the pooling), the adverse events reported in the treatment group (diarrhea, nausea and abdominal pain) were deemed to be caused by the resveratrol component.

Overall certainty of the evidence was low, because of issues of imprecision and indirectness.

Evidence to decision

No research evidence was found that analyzed the cost-effectiveness, equity, acceptability and feasibility of the use of zinc among patients with COVID-19. The estimated cost of zinc gluconate is Php 5.00 per tablet (70mg) while zinc sulfate (60mL) is Php 96.00[11,12]. Other nutritional supplements contain both vitamin C and zinc, with prices ranging from Php 8.00 to Php 12.75 per capsule or tablet in local drugstores.[13,14]

Recommendations from Other Groups

The US-NIH COVID-19 Treatment Guidelines Panel found insufficient evidence for or against the use of zinc for the treatment of COVID-19. They recommend against using zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial (BIII) (Last updated in April 2021).[15] Currently, there are no recommendations from CDC, WHO, and the Infectious Diseases Society of America on the use of zinc as an adjunct treatment in COVID-19.

Research Gaps

As of November 2021, there are eight ongoing trials investigating the effectiveness of zinc as adjunctive treatment for COVID-19 (see Appendix 8).

References

[1] Wessels I, Rolles B, Rink L. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. Front Immunol. 2020 Jul 10;11:1712. doi: 10.3389/fimmu.2020.01712. PMID: 32754164; PMCID: PMC7365891.

[2] Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, Apostolopoulos V, Stojanovska L. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas. 2021 Jan;143:1-9. doi: 10.1016/j.maturitas.2020.08.003. Epub 2020 Aug 9. PMID: 33308613; PMCID: PMC7415215.

[3] Nabi-Afjadi M, Karami H, Goudarzi K, et al. The effect of vitamin D, magnesium and zinc supplements on interferon signaling pathways and their relationship to control SARS-CoV-2 infection. Clin Mol Allergy 19, 21 (2021). https://doi.org/10.1186/s12948-021-00161-w

[4] Jothimani D, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P, et al. COVID-19: Poor outcomes in patients with zinc deficiency. Int J Infect Dis. 2020 Nov;100:343-349. doi: 10.1016/j.ijid.2020.09.014. Epub 2020 Sep 10. PMID: 32920234; PMCID: PMC7482607.

[5] Abd-Elsalam S, Soliman S, Esmail ES, et al. Do zinc supplements enhance the clinical efficacy of hydroxychloroquine? A randomized, multicenter trial. Biol Trace Elem Res. 2021; 199: 3642-3646

[6] Thomas S, Patel D, Bittel B, 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 Netw Open. 2021; 4: e210369

[7] Kaplan HG, Wang K, Reeves KM, Scanlan JM, Nunn CC, Kieper DA, et al. Resveratrol and zinc in the treatment of outpatients with covid-19 – the reszinate study - a phase 1/2 randomized clinical trial utilizing home patient-obtained nasal and saliva viral sampling. SSRN. 2021 Oct; [cited 2021 Nov 20]. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3934228.

[8] Patel O, Chinni V, El-Khoury J, Perera M, Neto AS, McDonald C, et al. A pilot double-blind safety and feasibility randomized controlled trial of high-dose intravenous zinc in hospitalized COVID-19 patients. (Short Communication) J Med Virol. 2021 May;93(5):3261-3267. doi: 10.1002/jmv.26895. Epub 2021 Mar 9. PMID: 33629384; PMCID: PMC8014767.

[9] 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. J Cell Mol Anesth. 2021;6(2):164-7.DOI: https://doi.org/10.22037/jcma.v6i2.32182

[10] Abdelmaksoud AA, Ghweil AA, Hassan MH, et al. Olfactory Disturbances as Presenting Manifestation Among Egyptian Patients with COVID-19: Possible Role of Zinc. Biol Trace Elem Res 199, 4101–4108 (2021). Available from: https://doi.org/10.1007/s12011-020-02546-5

[11] South Star Drug. Zinbee 70 mg [Internet]. Available from: https://southstardrug.com.ph/products/zinbee-70-mg-chewable-tablet

[12] Watsons. Multivitamins and Overall Wellness:Immuzinc [Internet]. Available from: https://www.watsons.com.ph/zinc-sulfate-syrup-60ml/p/BP_10047627

[13] Watsons. Multivitamins and Overall Wellness: Conzace multivatimins + minerals 1 softgel capsule [Internet]. Available from: https://www.watsons.com.ph/conzace-multivitamins-minerals-1-softgel-capsule/p/BP_10065073

[14] Watsons. Multivitamins and Overall Wellness: Immunpro 500 mg/10 mg 1 tablet [Internet]. Available from: https://www.watsons.com.ph/immunpro-500-mg-10-mg-1-tablet/p/BP_10099808

[15] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. 2021; [cited 2021 Nov 19]. Available from: https://www.covid19treatmentguidelines.nih.gov/.

[16] Szarpak L, Pruc M, Gasecka A, et al. Should we supplement zinc in COVID patients? Evidence from a meta-analysis. Pol Arch Intern Med. 2021; 131 (9): 802-807, doi:10.20452/pamw.16048

[17] Carlucci PM, Ahuja T, Petrilli C, et al. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. J Med Microbiol. 2020; 69: 1228-1234

[18] Yao JS, Paguio JA, Dee EC, et al. The minimal effect of zinc on the sur¬ ̈vival of hospitalized patients with COVID 19: an observational study. Chest. 2021; 159: 108-111

[19] Seet R, Quek A, Ooi D, et. al. Positive impact of oral hydroxychloroquine and povidone-iodine throat spray for COVID-19 prophylaxis: An open-label randomized trial. Int J Infect Dis. 2021; 106:314-322. Available from: https://doi.org/10.1016/j.ijid.2021.04.035

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 (1)	Yes (7)					• Zinc has been shown to inhibit viral reproduction of SARS-CoV-2 in-vitro. • It also plays a role in immunological response, associated with the negative feedback decreasing the activity of nuclear factor kappa B, decreasing excessive inflammation and risk for cytokine storm.
Benefits	Large	Moderate	Small (2)	Uncertain (6)			• This updated review showed inconclusive results on the efficacy of zinc as adjunctive treatment for COVID-19, for the outcomes of in-hospital mortality and hospitalization of outpatients.
Harm	Large	Small (2)	Uncertain (6)	Varies			• There were significantly higher adverse events in the group of patients with COV ID-19 that received zinc than in control.
Certainty of Evidence	High	Moderate	Low (4)	Very low (4)			• The overall certainty of evidence is low due to issues of indirectness and imprecision.
Balance of effects	Favors zinc (1)	Does not favor zinc (4)	Uncertain (3)	Varies			• *Consider natural sources of zinc (panel who does not favor zinc)*
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability (1)			
Resources Required	Uncertain (2)	Large cost	Moderate Costs (2)	Negligible costs or savings (3)	Moderate savings (1)	Large savings	Estimated costs: • Zinc gluconate is Php 5 per tablet (70 mg) • Zinc sulfate (60 mL) is Php 96. • Other nutritional supplement contains both vitamin C and zinc and price varies from

FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
							Php 8 to Php 12.75 per capsule or tablet in local drugstores
Certainty of evidence of required resources	No included studies (7)	Very low (1)	Low	Moderate	High		• Currently, no cost-effectiveness study on zinc as adjunctive treatment for COVID-19 infection is available for review.
Cost effectiveness	No included studies (6)	Favors the comparison	Does not favor either the intervention or the comparison (2)	Favors the interventio n			• Currently, no cost-effectiveness study on zinc as adjunctive treatment for COVID-19 infection is available for review
Equity	Uncertain (6)	Reduced	Probably no impact (2)	Increased			• No research evidence found.
Acceptability	Uncertain (7)	No	Yes (1)	Varies			• No research evidence found.
Feasibility	Uncertain (1)	No	Yes (7)	Varies			• No research evidence found.

Appendix 2. Search Yield and Results

Database	Date of Last Search	Search strategy	Yield	Matching articles
PubMed	October 31, 2021	((("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 ((((((((((zinc [tiab]) OR (zinc gluconate [tiab])) OR (zinc sulfate [tiab])) OR (zinc supplement [tiab])) OR (antioxidant [tiab])) OR (supplement [tiab])) OR (zinc* [tiab])) OR (zinc[MeSH Terms])) OR (zinc gluconate [MeSH Terms])) OR (zinc sulfate [MeSH Terms])) OR (Zinc supplement [MeSH Terms])) OR (antioxidant[MeSH Terms])) OR (supplement[MeSH Terms])	1729	4
Cochrane	Nov 15, 2021	((zinc):ti,ab,kw OR Zinc* OR MeSH descriptor: [Zinc] explode all trees) AND (COVID-19 OR SARS-CoV-2 OR MeSH descriptor: [COVID-19] explode all trees)	111	4
ClinicalTrials.gov	Nov 15, 2021	“zinc” and “COVID”	55	
MedRxiV	Nov 15, 2021	title "zinc" (match all words) and abstract or title "zinc" (match all words) and full text or abstract or title "zinc" (match whole all) and posted between "31 Dec, 2020 and 15 Nov, 2021"	239	0
CovidNMA	October 26, 2021	zinc	3	3
WHO International Clinical Trials Registry Platform	November 19, 2021	“zinc” and “COVID-19”	0	0

*

Appendix 3. Characteristics of Included Studies: Randomized Controlled Trials

Study ID	Setting	Population	Intervention	Control	Outcomes
Abd-Elsalam	Three tertiary care centers in Assiut, Tanta, and Cairo. *Egypt*	N = 191 Confirmed RT-PCR positive in three egyptian tertiary care centers from June 23 to August 23,2020 Divided into mild, moderate, severe and critical based on WHO classification	Zinc sulfate 220mg (elemental zinc 50mg) BID HCQ (400mg BID D1, then 200mg BID x 4 days)	Standard of care (15 days) HCQ (400mg BID D1, then 200mg BID x 5 days)	Recovery within 28 days Death Need for mechanical ventilation Duration of hospital stay (days)
Thomas	Multiple outpatient settings in Ohio and Florida *USA*	N=214 Patients > 18 years old who were newly diagnosed by RT-PCR in an outpatient setting From April 27 to October 14, 2020	Zinc gluconate (50mg OD at bedtime) x 10 days n=58 (20 did not complete follow-up: 11 lost, 9 discontinued intervention) *58 zinc + ascorbic acid x 10 days (11 did not complete: 3 lost, 8 discontinued)	Standard of care only (n=50) *ascorbic acid (8000mg over 2-3x/day) N=48 (14 did not complete, 7 lost, 7 discontinued)	Days required to reach 50% reduction in symptoms Death Hospitalization Serious adverse events
Kaplan et al (Lancet Pre-print; not yet peer reviewed)	Out-patient Phase 1/2 clinical trial *USA*	N= 30 mild-moderate COVID	Zinc methionine/ cysteine (Life Extension) 150 mg daily total (50 mg capsules orally three times daily and resveratrol (Mega Resveratrol) 2000 mg orally twice daily for five days.	Placebo capsules	Primary outcome: Reduction in viral shedding Secondary outcomes: - Reduction of symptoms - Adverse events - Incidence of hospitalization - Length of hospitalization - Days on ventilator support - Time until the 4-symptom score is zero - Composite score at Day 5 - Hospitalization - Deaths
Patel et al (2021)	In-hospital setting *Australia*	N= 33 Hospitalized pts including severeand critical	Zinc chloride IV at a dose of 0.5 mg/kg/d (elemental zinc at 0.24 mkd)	Placebo	Analyzable outcomes from the published report: Deaths Continuing hospitalization

Darban, et al, 2021	In-hospital setting	N = 20 with severe COVID	Oral zinc sulfate (220 mg containing 50 mg elemental zinc, q6hr) for 10 days (5-7) IV vitamin C (2g, q6hr), oral melatonin (6 mg, q6hr) plus standard of care	Standard cares were azithromycin (250 mg/day), lopinavir/ritonavir (100mg/25mg/day), glucocorticoids and necessary oxygen	Primary outcome: changes in severity pf hypoxemia (PaO2/ FiO2 ratio) Other outcomes included inflammatory markers (LDH, ESR, ferritin, CRP at baseline, days 5 and 10 after treatment initiation)
Abdelmaksoud, et al 2021	Quarantine department of hospitals in Egypt	N = 134 patients	Zinc therapy (220 mg zinc sulfate equivocal to 50 mg elemental zinc twice daily [33]) plus the Egyptian protocol of treatment of COVID-19	Egyptian protocol of COVID-19 treatment without zinc therapy	Mean serum zinc levels, median duration of recovery of gustatory/ olfactory function, median duration of complete recovery among those who had anosmia/hyposmia

Appendix 4. Detailed Study Appraisal

Appraising Directness	**Abd-Elsalam, 2020**	**Thomas, 2021**
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	Yes, it had similar population and outcomes, but different interventions (Zinc as add on to HCQ vs HCQ, which is not standard of care currently) P= Patients with COVID (mild, moderate, severity) I=Zinc+HCQ vs HCQ O=Duration of hospital stay, recovery	Yes, similar population and intervention but different outcomes P= Patients diagnosed with COVID I= Zinc, ascorbic acid, ascorbic acid with zinc, standard of care O= Reduction in severity or duration of symptoms
Appraising Validity		
1. Were patients randomly assigned to treatment groups?	Yes, it was a randomized controlled study	Yes, it was a randomized clinical factorial open-label trial
2. Was allocation concealed?	It was not mentioned	No, it was an open-label trial
3. Were baseline characteristics similar at the start of the trial?	Yes, the treatment groups had no significant difference at baseline	Yes, they were similar characteristics at baseline
4. Were patients blinded to treatment assignment?	It was not mentioned	No
5. Were caregivers blinded to treatment assignment?	It was not mentioned	No
6. Were outcome assessors blinded to treatment assignment?	It was not mentioned	No

7. Were all patients analyzed in the groups to which they were originally randomized?	Yes	Yes
8. Was follow-up rate adequate?	Yes	Yes
Appraising Results		
1. How large was the effect of treatment?	The Zinc group had a mean hospital stay of 13.51 ± 5.34 days, while the Zinc + HCQ group had 14.01 ± 6.26 days, with p=0.553 In terms of in hospital mortality, the risk difference in 0.05 (-0.06, 0.06) N	The primary endpoint was time to 50% reduction of symptoms, 5.9 (4.9) days in the Zinc group, 6.7 (4.4) days for SOC (p=0.38)
2. How precise was the estimate of the treatment effect?	Length of hospital stay: Group 1: 13.51, 5.34 days 95% CI: 12.47 to 14.594 Group 2 : 14.01, 6.26 days 95% CI: 12.734 to 15.286 days Mean difference: 0.500 (-1.16, 2.16), p=0.55 In-hospital mortality Zinc: 5/96 (5.21%) HCQ: 5/95 (5.26%) Risk difference: 0.05 (-0.06, 0.06) NS	Zinc group: 95% CI: 0.40 (−1.77 to 2.58) Ascorbic acid only: 95% CI 0.40 (−1.99 to 2.80) Ascorbic acid with zinc: 95% CI: 0.07 (−1.94 to 2.09)
Assessing Applicability		
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)	None	None
2. Are there socio-economic issues affecting applicability of treatment?	None	None
Individualizing the Results		
1. What is the likely effect of the treatment on your individual patient?	No significant difference in length of hospital stay, recovery, need for ventilation, survival between Zinc+HCQ and HCQ.	No reduction in severity nor duration of COVID
2. Would you offer the treatment to your patients?	No	No

Appraising Directness	**Kaplan, 2021**	**Patel, 2021**
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	The population is similar (COVID patients), but the intervention (Zinc + resveratrol) and primary outcomes are different (reduction in viral shedding)	The population is similar, but the intervention(high-dose IV Zinc) and primary outcome are different (lowest oxygen saturation for non-ventilated and worst PaO2/ FiO2 for ventilated)
Appraising Validity		
1. Were patients randomly assigned to treatment groups?	Yes	Yes

2. Was allocation concealed?	Yes	Yes
3. Were baseline characteristics similar at the start of the trial?	Yes	Yes
4. Were patients blinded to treatment assignment?	Yes	Yes
5. Were caregivers blinded to treatment assignment?	Yes	Yes
6. Were outcome assessors blinded to treatment assignment?	Yes	Yes
7. Were all patients analyzed in the groups to which they were originally randomized?	Yes	Yes
8. Was follow-up rate adequate?	Yes	Yes
Appraising Results		
1. How large was the effect of treatment?	In terms of primary outcome of reduction in viral shedding, there was no statistically significant difference between the 2 groups (p=0.7) In-hospital mortality: Zinc: 0/14 Placebo: 0/16 2 were admitted- one each for the interventions. - Zn: 46-day LOS with 30 days in the ICU Placebo: 11-day LOS with 5 days in the ICU	The study was unable to assess the primary outcomes due to its failure to meet target enrollment In-hospital mortality (28-day outcome): Zinc: 2/ 15 (14.3%) Control: 3/18 (16.7%)
2. How precise was the estimate of the treatment effect?	N/A	N/A
Assessing Applicability		
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)	None	None
2. Are there socio-economic issues affecting applicability of treatment?	None	None
Individualizing the Results		
1. What is the likely effect of the treatment on your individual patient?	No significant difference in reduction in viral shedding or in-hospital mortality	No evidence of benefit in using high-dose IV Zinc among hospitalized COVID patients

2. Would you offer the treatment to your patients?	No	No

Appraising Directness	**Darban, 2021**	**Abdelmaksoud, 2021**
Does the study provide a direct enough answer to your clinical question in terms of patients (P), exposure/intervention (I), and outcome (O)?	Similar population (COVID severe), different intervention (standard of care vs standard of care with oral melatonin, oral zinc, IV vit C), and different outcome (changes in hypoxemia and inflammatory markers)	Similar population (Patients with COVID of various severities), similar intervention (zinc therapy, but different outcome (Mean serum zinc levels, median duration of recovery of gustatory/ olfactory function, median duration of complete recovery)
Appraising Validity		
1. Were patients randomly assigned to treatment groups?	Yes	Yes
2. Was allocation concealed?	No	Not mentioned
3. Were baseline characteristics similar at the start of the trial?	Yes	Yes
4. Were patients blinded to treatment assignment?	No	Not mentioned
5. Were caregivers blinded to treatment assignment?	No	Not mentioned
6. Were outcome assessors blinded to treatment assignment?	No	Not mentioned
7. Were all patients analyzed in the groups to which they were originally randomized?	Yes	Yes
8. Was follow-up rate adequate?	Yes	Yes
Appraising Results		
1. How large was the effect of treatment?	PaO2/FiO2 at day 10 Control: 222.2 ± 65 Treatment: 230.1 ± 59.1, p=0.2 Length of ICU stay: Control: 15 ± 3.3 days Treatment: 14.1 ± 4.2 days p = 0.3	Serum zinc level: Mild: 0.67 ± 0.18 Common: 0.62 ± 0.14 Severe: 0.73 ± 0.18 Extremely severe: 0.72 ± 0.22 p= 0.084 Mean duration of recovery of olfaction: Zinc arm: 7 days (range 5-9 days) Control: 18 days (range 14-22 days) Duration of complete recovery Zinc arm: Median 12 (range 8–17 days) Control: Median 12 (range 8–20 days)
2. How precise was the estimate of the treatment effect?		

Assessing Applicability		
1. Are there biologic issues that may affect applicability of treatment? (Consider the influence of sex, co-morbidity, race, age and pathology)	No	No
2. Are there socio-economic issues affecting applicability of treatment?	No	No
Individualizing the Results		
1. What is the likely effect of the treatment on your individual patient?	No evidence of benefit in using IV vit C, oral zinc, oral melatonin in PaO2/FiO2, change in inflammatory markers, length of ICU stay among COVID patients	No evidence of benefit in using zinc to decrease duration to recovery of olfaction or full recovery from COVID
2. Would you offer the treatment to your patients?	No	No

Appendix 5: Risk of bias

Figure 1. Risk of Bias Summary with judgements about each risk of bias item for each included study

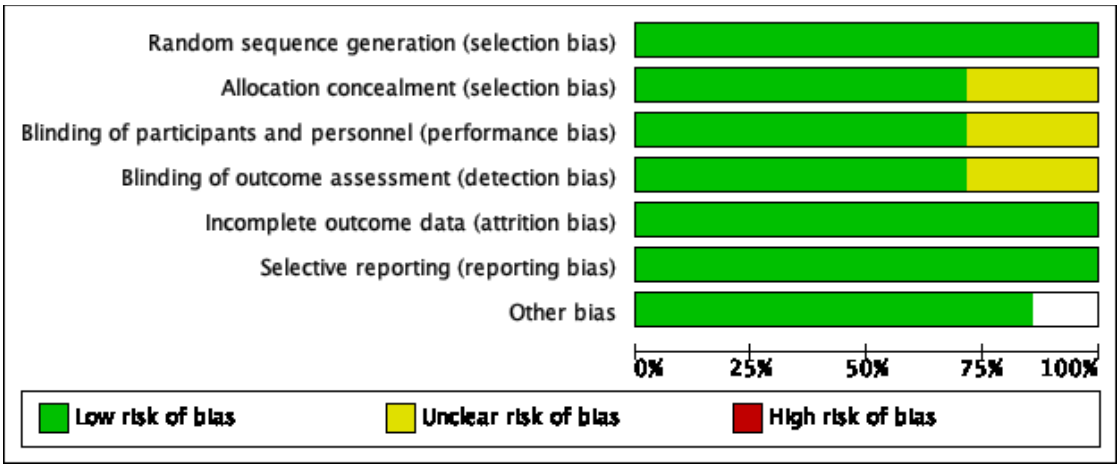

Figure 2. Risk of Bias Graph with authors' judgements about each risk of bias item presented as percentages across all included studies.

Appendix 6: GRADE Evidence Profile

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Question: Zinc with standard of care compared to standard of care alone for adunctive treatment of COVID-19
Setting: In and out-patients
Bibliography:

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Zinc with standard of care	standard of care alone	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
2	randomised trials	not serious	not serious	serious[a]	serious[b]	none	7/111 (6.3%)	8/113 (7.1%)	**RR 0.92** (0.35 to 2.44)	**6 fewer per 1,000** (from 46 fewer to 102 more)	⨁⨁◯◯ Low	CRITICAL
Length of Hospital Stay (assessed with: days of confinement)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	96	95	-	MD **0.5 days lower** (1.16 lower to 2.16 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Hospitalization of Ambulatory Patients												
2	randomised trials	not serious	not serious	serious[a]	serious[b]	none	6/72 (8.3%)	4/66 (6.1%)	**RR 1.37** (0.40 to 4.67)	**22 more per 1,000** (from 36 fewer to 222 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events												
2	randomised trials	not serious	not serious	not serious	not serious	none	13/73 (17.8%)	0/68 (0.0%)	**RR 13.62** (1.78 to 104.43)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁⨁⨁ High	CRITICAL

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

Explanations

a. Experimental arm was zinc, used with other adjuncts
b. Confidence interval crosses the null value

Appendix 7. Forest plots

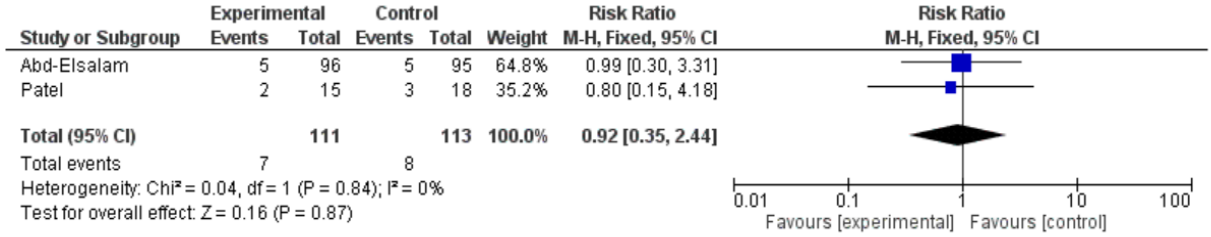

Fig. 1. In-hospital mortality

Fig. 2. Hospitalization among ambulatory patients

Fig. 3. Adverse Events

Appendix 8. Ongoing Trials

Study ID	Setting	Title	Intervention	Control	Outcomes	Status
NCT04641195	India	A Randomized Trial to Determine the Effect of Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India	Dietary Supplement: Zinc (zinc gluconate) 40mg of zinc gluconate taken once per day from enrollment to 8 weeks Dietary Supplement: Vitamin D3 (cholecalciferol) 180,000 international units (IU) of vitamin D3 at enrollment, followed by 2000 IU once per day from enrollment to 8 weeks Dietary Supplement: Zinc (zinc gluconate) & Vitamin D (cholecalciferol) 180,000 IU of vitamin D3 at enrollment, followed by 2000 IU of vitamin D3 and 40mg of zinc gluconate once per day from enrollment to 8 weeks	Placebo	Time to recovery, all-cause mortality, necessity for assisted ventilation, individual symptoms duration, Vitamin D, Zinc, Interleukin 6 (IL-6)	Ongoing
NCT04370782	US	A Randomized Study Evaluating the Safety and Efficacy of Hydroxychloroquine and Zinc in Combination With Either Azithromycin or Doxycycline for the Treatment of COVID-19 in the Outpatient Setting	Hydroxychloroquine Azithromycin Zinc sulfate	Hydroxychloroquine Doxycycline Zinc sulfate	Time to Resolution of Symptoms relative to baseline (Days 5, 14, 21), Number of participants hospitalized and/or requiring repeat ER visits, ICU length of stay, number of days on ventilator	Completed, but no results posted yet
NCT04542993	Sweden	Can SARS-CoV-2 Viral Load and COVID-19 Disease Severity be Reduced by Resveratrol-assisted Zinc Therapy	Resveratrol and Zinc	Placebo	Reduction in SARS-CoV-2 Viral load, Reduction in Severity of COVID-19 Disease	Active, not recruiting
NCT04351490	France	Impact of Zinc and Vitamin D3 Supplementation on the Survival of Aged Patients Infected With COVID-19	Zinc gluconate and 25-OH cholecalciferol	Group usual treatment	Survival rate in asymptomatic subjects at inclusion	Withdrawn
NCT04828538	Mexico	Vitamin D, Omega-3, and Combination Vitamins B, C and Zinc Supplementation for the Treatment and Prevention of COVID-19	Vitamin D, Omega DHA / EPA, Vitamin C, Vitamin B complex and Zinc Acetate	Placebo	Covid infection rate, incidence of severe outcome	Active, not recruiting
NCT04621461	US	Placebo Controlled Trial to Evaluate **Zinc** for the Treatment of **COVID-19** in the Outpatient Setting	**Zinc** Sulfate	Placebo	Number of participants hospitalized and/or requiring repeat emergency room visits, number of participants admitted to ICU, Number of participants on a ventilator, all-cause mortality	Completed, but with only 3 actual enrollment
NCT04342728	US	Coronavirus 2019 (**COVID-19**)- Using Ascorbic Acid and **Zinc** Supplementation	Ascorbic acid, Zinc, Ascorbic acid+Zinc	Standard of care	Symptom reduction	Completed recruitment
NCT04335084	US	A Study of Hydroxychloroquine, Vitamin C, Vitamin D, and **Zinc** for the Prevention of **COVID-19** Infection	HCQ + Vit C + Vit D + Zinc	Placebo	Prevention of COVID-19 symptoms, safety	Ongoing recruitment