

Literature Review**The role of zinc in the management of covid-19 patients: literature review****Annisa Khotimatul Husna[✉], Nurhayani**

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Submitted: December 19, 2023

Revised: April 3, 2023

Accepted: July 18, 2023

Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a new type of coronavirus, SARS-CoV-2. Zinc deficiency appears as a potential risk factor in COVID-19 patients. It is known that zinc acts as a facilitator of the body's immune competence. Zinc is also involved in host cell cytokine storms as an immune response to attack pathogens and as a marker of severity in COVID-19. This study aimed to see the effect of giving zinc as antiviral immunity in managing COVID-19 patients. This research method uses a literature review design based on search results for scientific articles in the PubMed, Science Direct, and Proquest databases. Twenty-five articles from Science Direct and 37 from Proquest were analyzed, and eight met the inclusion criteria. It can be concluded that zinc supplementation can be given as adjuvant therapy and works synergistically with the administration of Hydroxychloroquine to reduce disease severity and reduce mortality in COVID-19 patients, especially in hospitalized patients, and is clinically feasible and safe in treatment and prevention. Twenty-five articles from Science Direct, 37 from Proquest, and eight that met the inclusion criteria were analyzed. It can be concluded that zinc supplementation can be given as adjuvant therapy and works synergistically with the administration of Hydroxychloroquine to reduce disease severity and reduce mortality in COVID-19 patients, especially in hospitalized patients, and is clinically feasible and safe in treatment and prevention.

Keywords: COVID-19; therapy; zinc**1. Introduction**

The COVID-19 pandemic in early 2020 shocked the world because this disease is easily transmitted and spreads quickly. As of November 2021, there were close to 4,250,000 confirmed cases of COVID-19 in Indonesia and ranked 14th in the cumulative total of COVID-19 cases worldwide (Ministry of Health of the Republic of Indonesia, 2021). The disease is caused by a new type of coronavirus not previously identified in humans. This virus can be transmitted through droplets, which are water particles that have very small sizes and usually come out when someone who has been infected sneezes or coughs (Ministry of Health, 2020).

Early in the disease, common manifestations are fever, fatigue or myalgia, malaise, and dry cough. As well as some of the organ systems involved, such as the respiratory system (chest pain, coughing, shortness of breath, sore throat, coughing up blood or hemoptysis), digestive system (nausea, vomiting, diarrhea), nervous system (decreased level of consciousness and headaches). However, the most frequently found signs and symptoms were increased body temperature (83-98%), cough (76-82%), and shortness of breath or dyspnea (31-55%) (Levani et al., 2021). Risk factors predisposing to an adverse outcome from COVID-19 have focused on age, obesity, diabetes, hypertension, ethnicity, and other factors (Bilezikian et al., 2020). Recently, zinc deficiency has emerged as another potential risk factor. It is known that zinc has a role as a facilitator of the body in immunocompetent immunity. Zinc is also known to be involved in cytokine storms from host cells as

an immune response to attack pathogens which is also a marker of severity in COVID-19, so further studies are needed to discuss the effect of zinc supplementation in COVID-19 patients. (Jothimani et al., 2020).

Zinc is an essential micronutrient that plays an important role in the physiology of the immune system by acting as a signaling molecule. Zinc acts as an anti-inflammatory agent and functions as a membrane-stabilizing antioxidant. It is known that zinc levels decrease significantly during infection, and a person's need for zinc can increase along with the severity of the infection. Elderly individuals, infants, and chronic alcoholics are more susceptible to zinc deficiency, increasing their chances of getting viral infections with high mortality (Pal et al., 2021).

This study aims to see the effect of zinc supplementation as antiviral immunity in managing COVID-19 patients.

2. Research Methods

This study used a literature review design. A literature review is a summary, review, and criticism of a particular problem topic from several kinds of literature. It can be used as a theoretical framework or basis for conducting research. The literature review description uses a narrative approach to identify and interpret previously published articles (Don et al., 2016).

Data collection was carried out by taking literature related to the formulation of the problem, namely the effect of giving zinc as antiviral immunity in the management process of COVID-19 patients. Data collection in this study was sourced from several e-databases/search engines, namely PubMed, Proquest, and Science Direct. The keywords that researchers use in the e-database / search engine are ("Coronavirus Disease 2019" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "COVID-19" OR "SARS-CoV-2") AND Zinc.

This study took data from research articles from various countries as observational studies (cross-sectional, case-control, or cohort) and random controlled trial (RCT) experimental studies with a time limit for searching articles published in 2019-2021. The Ethics Commission has approved the writing of this review article with Number. 3927/C.1/KEPK-FKUMS/XI/2021.

Table 1. Inclusion and Inclusion Criteria

Inclusion Criteria	Exclusion Criteria
Articles in English with a time limit from 2019-2021	It does not specifically discuss the effect of zinc on COVID-19 patients
Observational research (cross-sectional, case-control, or cohort) and experimental research (RCT).	
Research discussing the effect of giving zinc as antiviral immunity to COVID-19 patients.	

3. Results and Discussion

3.1. Results

The PRISMA flowchart results that have been listed take online databases from PubMed, Science Direct, and Proquest using keywords ("Coronavirus Disease 2019" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "COVID-19" OR "SARS-CoV-2") and Zinc. Search results using time limitations from 2019-2021 on the Pubmed web obtained as many as 459 pieces of literature. Search results on the Science Direct web totaled 856 literature; on the Proquest web, obtained 3,213 literature. After that, the title exception in each web database was obtained 102 on the PubMed web, 25 on the Science Direct web, and 37 on the Proquest web, so the literature based on the database amounted to 164 literature. After that, duplicates were removed using Ms. Excel, and the same 34 journals were obtained on the three web databases. The results of removing duplicates left

130 journal literature. Then a screening stage was carried out based on abstracts, and 111 literature titles were obtained that did not match the title of this study, so the remaining 19 literature. The last stage is screening by reading the full literature text and obtaining eight that match the inclusion criteria.

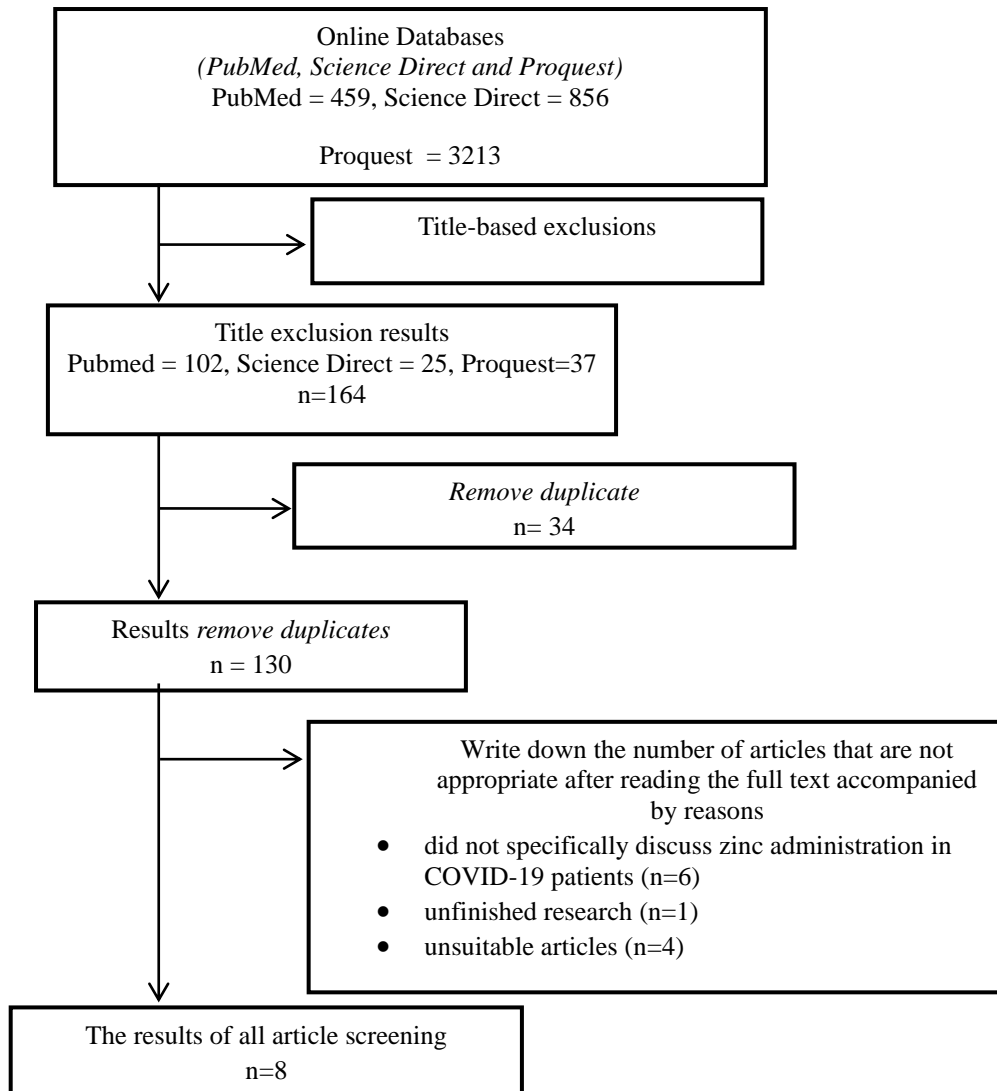


Figure 1. Flowchart Prisma

Table 2. Article Characteristics

No	Author (year)	Title	Types of Articles	Journal Name
1.	(Derwand et al., 2020)	COVID-19 Outpatients: Early Risk-Stratified Treatment With Zinc Plus Low-Dose Hydroxychloroquine And Azithromycin: A Retrospective Case Series Study.	Retrospective Case Series Study	International Journal of Antimicrobial Agents
2.	(Abd-Elsalam et al., 2021)	Do Zinc Supplements Enhance The Clinical Efficacy Of Hydroxychloroquine: A Randomized, Multicenter Trial.	RCT	Biological Trace Element Research

No	Author (year)	Title	Types of Articles	Journal Name
3.	(Frontera et al., 2020)	Treatment With Zinc Is Associated With Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study.	A Multicenter Cohort Study	Research Square
4.	(Carlucci et al., 2020)	Zinc Sulfate In Combination With A Zinc Ionophore May Improve Outcomes In Hospitalized COVID-19 Patients.	Retrospective Observational Study	Journal of Medical Microbiology
5.	(Thomas et al., 2021)	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.	RCT	JAMA Network Open
6.	(Al Sulaiman et al., 2021)	Evaluation Of Zinc Sulfate As An Adjunctive Therapy In COVID-19 Critically Ill Patients: A Two Center Propensity-Score Matched Study.	Retrospective Study	BMC
7.	(Yao et al., 2021)	The Minimal Effect Of Zinc on The Survival Of Hospitalized Patients With COVID-19: An Observational Study.	Observational Study	Chest Infections Research Letter
8.	(Perera et al., 2020)	A Pilot Double-Blind Safety and Feasibility Randomized Controlled Trial Of High-Dose Intravenous Zinc In Hospitalized COVID-19 Patients.	RCT	Journal of Medical Virology

Table 3. Article Interventions and Results

No	Authors (Year)	Intervention	Outcomes	Results
1.	(Derwand et al., 2020)	<i>Zinc Sulfate</i> (220 mg/day, 50 mg elemental zinc); HCQ (200 mg x 2/day); and Azithromycin (500 mg x 1/day)	Decreased hospitalization time and mortality	The decrease in length of stay in the treated patient group was 84% smaller (P<0.001). Probability of death from all causes in the patient group treated was 80% less (P = 0.12)
2.	(Abd-El salam et al., 2021)	HCQ 400 mg twice daily (I), 200 mg twice daily for five days; <i>Zinc Sulfate</i> 220 mg 2 times/day (50 mg elemental Zinc)	Zinc supplementation does not add value or enhance the clinical efficacy of the HCQ.	The mean duration of hospital stay was 13.51±5.34 days in the zinc group and 14.01±6.26 days in the zinc group. free of zinc (p = 0.553). Complete recovery after 28 days (p = 0.969). Patients requiring mechanical ventilation (p= 0.537). Overall mortality (p= 0.986).
3.	(Frontera et al., 2021)	<i>Zinc Sulfate</i> 220 mg x 1-2/day; HCQ 400	Decreased hospitalization time	24% reduced risk of in-hospital death (12% Zn+ionophore vs. 17% no

No	Authors (Year)	Intervention	Outcomes	Results
		mg x 1/day	and mortality	Zn+ionophore; [aHR] 0.76, 95% CI 0.60-0.96, P=0.023). Decreased length of stay (72% Zn+ionophore vs. 67% without Zn+ionophore, P=0.003). Mortality 0.63, 95%CI 0.44-0.9, P=0.015)
4.	(Carlucci et al., 2020)	HCQ 400 mg (I), 200 mg twice daily for five days; Azithromycin 500 mg/day; Zinc Sulfate 220 mg x 2/day (50 mg elemental zinc) for five days	Decreased hospitalization time and mortality	Increased frequency of patients being discharged home (OR 1.53, 95% CI 1.12-2.09) and decreased deaths or unnecessary hospital transfers among patients ICU care (OR 0.449, 95% CI 0.271-0.744)
5.	(Thomas et al., 2021)	8000 mg Ascorbic acid; 50 mg of Zinc Gluconate	Decreased symptoms of COVID-19.	Patients receiving usual care without supplementation achieved a 50% reduction in symptoms at a mean (SD) of 6.7 (4,4); 5.9 (4.9) days for the Zinc Gluconate group, and 5.5 (3.4) days for the group receiving both (overall P = .45)
6.	(Al Sulaiman et al., 2021)	Zinc Sulfate 220 mg x / day (50 mg elemental Zinc)	Decreased time to mortality and decreased incidence of AKI in ICU patients	Lower 30-day mortality time (HR 0.52, CI 0.29, 0.92; p=0.03); Development of AKI during ICU stay (OR 0.46 CI 0.19-1.06; p = 0.07)
7.	(Yao et al., 2021)	Zinc Sulfate 440 mg x / day (100 mg elemental Zinc)	Decreased time to death	Decreased mortality timeframe by an additional 0.84 days(ATET: 95% CI, 1.51 to 3.20; P 0.48
8.	(Perera et al., 2020)	Zinc Chloride IV dose of 0.5 mg/kg/day (elemental Zinc, 0.24 mg/kg/day) for seven days	Increased serum zinc levels and decreased oxygenation requirements	Safety and feasibility of intravenous zinc treatment and the ability of HDIVZn to reverse acute phase zinc deficiency associated with COVID-19.

3.2. Discussion

Zinc supplementation empirically can be given to COVID-19 patients because zinc's inhibitory effect on viral replication and low zinc levels are often found in COVID-19 patients.(Jothimani et al., 2020). Zinc deficiency has been associated with a two-fold increase in complication rates, a 20-fold higher risk of developing untuARDS, a longer hospital stay, and an increased risk of death. Research by Perera et al. There were no significant results between zinc supplementation and decreased oxygenation requirements in patients, but increased zinc content in patient serum (Perera et al., 2020).

Research conducted by Yao JS et al. By administering zinc sulfate, we obtained minimal results in reducing the clinical presentation of 242 confirmed COVID-19 patients with an average age of 65. Only 81% of patients received zinc supplementation according to the dose and short observation time(Yao et al., 2021). Combination therapy between ascorbate acid and zinc gluconate was

performed by Thomas et al. It was discontinued because the results showed no difference in the treatment and control groups. Two hundred fourteen patients were randomized into four groups: standard therapy, ascorbic acid, zinc gluconate, and a combination of ascorbate and zinc gluconate. There were no significant differences between the four groups. There would still be a higher reduction in symptoms in the combination-treated group than in the other groups.(Thomas et al., 2021).

Research by R. Derwand, M. Scholz, and V. Zelenko, who were treated with zinc, low-dose Hydroxychloroquine, and Azithromycin, showed a significant reduction in hospitalization time ($p < 0.001$) compared to a group of patients who were not given this therapy. This study's most frequent clinical manifestations of COVID-19 patients were cough and fever, with a median body temperature within normal limits. Nearly 50% of patients with risk stratification treated for shortness of breath had breaths per minute, and oxygen saturation was within normal limits. The reduction in mortality was found to be 80% lower but did not reach a significant number ($p = 0.12$) in the treated group compared to the group not treated with this agent.

Based on the nature of the HCQ ionophore, it has been hypothesized that zinc may increase the efficacy of HCQ in treating COVID-19 patients. In addition to its role as a general antiviral immune stimulant, zinc is known to inhibit coronavirus RNA-dependent RNA polymerase (RdRp) specifically. In addition, zinc can inhibit serine furin protease. Furin is expressed on endothelial cells, monocytes/macrophages, and smooth muscle cells in the body's atherosclerotic plaques and, therefore, may have an important role in severe cardiovascular complications of COVID-19.(Derwand et al., 2020).

In the next study that provided combination therapy with HCQ and zinc, patients confirmed to have COVID-19 by RT-PCR were divided into two randomized groups: the therapy group that was given HCQ and zinc and the control group that was only given HCQ. Patients w/ hypokalemia or hypomagnesemia, porphyria, neutrophilia, myasthenia gravis, maculopathy or visual field changes, heart failure, prolonged QT interval on EKG, cirrhosis of the liver, psoriasis, epilepsy, anemia due to deficiency of pyruvate kinase and G6PD, chronic kidney disease, and women pregnant or breastfeeding were excluded from the study. The results showed no significant difference between the two groups, as seen from the length of stay, the need for mechanical ventilation, and the mortality rate (Abd-Elsalam et al., 2021). In this study, zinc supplementation did not increase the clinical efficacy value of HCQ, which was inversely proportional to research conducted by R. Derwand, M. Scholz, and V. Zelenko.

Subsequent studies assessed the results of laboratory tests of patients treated with zinc sulfate, HCQ, and azithromycin compared to the group that only received HCQ and azithromycin and found results, namely inflammatory markers including white blood cell count, ferritin, D-dimer, creatine phosphokinase, creatinine, and protein. C-reactive is no different. The group of patients treated with zinc sulfate had a higher baseline absolute lymphocyte count, while patients who did not receive zinc had higher baseline troponins.(Carlucci et al., 2020). In the treatment group with zinc sulfate, it was associated with a shorter duration of hospitalization and a significant reduction in mortality, but not significantly in patients with ICU care. Zinc supplementation has also been associated with decreased need for ICU care and the need for invasive assisted ventilation. This is due to the effect of a synergistic mechanism between zinc and HCQ, especially if given at the start of the patient with the clinical presentation of COVID-19.

Research conducted by Frontera et al. with a study group of 1006 patients who received zinc + ionophore (HCQ) therapy were more often male, black, diabetic, had a higher BMI, were more often treated with corticosteroids and azithromycin, and were rarely treated with lopinavir/ritonavir compared with patients who did not receive it. Additionally, we excluded patients receiving IL-6 inhibitors (tocilizumab, sarilumab, clazikuzumab) or remdesivir to avoid observing unintended beneficial effects associated with these agents. The results showed that the in-hospital mortality rate

was significantly lower among patients who received Zn + ionophore than those who did not (12% died versus 17%, $P < 0.001$). Similarly, patient discharge rates from hospitals were significantly higher among patients receiving Zn + ionophore (72% versus 67% of patients not receiving Zn + ionophore, $P < 0.001$) (Frontera et al., 2020).

Furthermore, to see the effect of giving zinc to critical COVID-19 patients in the intensive care unit. After 30 days, the results showed a significant difference between the groups receiving zinc supplementation and those not. In the zinc supplementation group, there was a decrease in mortality ($p=0.03$). In addition, those in the zinc group had a longer median time to stay without a ventilator. Complications also often occur in patients treated in the ICU, including AKI (acute kidney injury). In this study, it was found that the group that received zinc supplementation had fewer AKI events compared to the group that did not receive zinc supplementation ($p=0.02$), so zinc can be associated with a protective effect on the kidneys (Al Sulaiman et al., 2021).

This literature review study found that four articles had a significant effect on giving zinc to COVID-19 patients, and four articles were not significant. In studies that have obtained significant results, some have excluded them to reduce bias in the results and have a large sample size with an observational study design. In addition, there are limitations to the research that has been conducted, such as not measuring zinc in the serum of patients who have been treated with zinc, patients taking other medications that may affect the patient's clinical condition and observations of patients on short therapy and insufficient sample size in insignificant research.

4. Conclusion

Zinc supplementation inhibits viral replication and anti-inflammation, thereby reducing the severity of the disease and the mortality rate of COVID-19 patients, especially hospitalized patients. In addition, zinc also works synergistically with the administration of Hydroxychloroquine, thereby increasing its efficacy. Of the eight studies in the literature review, it shows the potential of zinc in the healing process of COVID-19 with various mechanisms so that zinc supplementation in COVID-19 patients is clinically feasible and safe for treatment and prevention.

The study's limitations are the relatively short period of literature used, the absence of studies measuring zinc levels in COVID-19 patients, and the different types of zinc preparations used in the literature that affect the results of zinc supplementation in COVID-19 patients.

Acknowledgment

The researchers thank those who have helped and participated in this study.

References

- Abd-El salam, S., Soliman, S., Esmail, E. S., Khalaf, M., Mostafa, E. F., Medhat, M. A., Ahmed, O. A., El Ghafar, M. S. A., Alborai, M., & Hassany, S. M. (2021). Do Zinc Supplements Enhance the Clinical Efficacy of Hydroxychloroquine?: a Randomized, Multicenter Trial. *Biological Trace Element Research*, 199(10), 3642–3646. <https://doi.org/10.1007/s12011-020-02512-1>
- Al Sulaiman, K., Aljuhani, O., Al Shaya, A. I., Kharbosh, A., Kensara, R., Al Guwairy, A., Alharbi, A., Algarni, R., Al Harbi, S., Vishwakarma, R., & Korayem, G. B. (2021). Evaluation of zinc sulfate as an adjunctive therapy in COVID-19 critically ill patients: a two center propensity-score matched study. *Critical Care*, 25(1), 1–8. <https://doi.org/10.1186/s13054-021-03785-1>
- Carlucci, P. M., Ahuja, T., Petrilli, C., Rajagopalan, H., Jones, S., & Rahimian, J. (2020). Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *Journal of Medical Microbiology*, 69(10), 1228–1234. <https://doi.org/10.1099/jmm.0.001250>

- Derwand, R., Scholz, M., & Zelenko, V. (2020). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. January.
- Frontera, J. A., Rahimian, J. O., Yaghi, S., Liu, M., Lewis, A., de Havenon, A., Mainali, S., Huang, J., Scher, E., Wisniewski, T., Troxel, A. B., Meropol, S., Balcer, L. J., & Galetta, S. L. (2020). Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study. *Research Square*, 1–10. <https://doi.org/10.21203/rs.3.rs-94509/v1>
- Jothimani, D., Kailasam, E., Danielraj, S., Nallathambi, B., Ramachandran, H., Sekar, P., Manoharan, S., Ramani, V., Narasimhan, G., Kaliamoorthy, I., & Rela, M. (2020). COVID-19: Poor outcomes in patients with zinc deficiency. *International Journal of Infectious Diseases*, pp. 100, 343–349. <https://doi.org/10.1016/j.ijid.2020.09.014>
- Kemkes RI. Situasi COVID-19. Kementerian Kesehatan RI. 2021. <https://infeksiemerging.kemkes.go.id>
- Levani, Prastya, & Mawaddatunnadila. (2021). Coronavirus Disease 2019 (COVID-19): Patogenesis, Manifestasi Klinis dan Pilihan Terapi. *Jurnal Kedokteran Dan Kesehatan*, 17(1), 44–57. <https://jurnal.umj.ac.id/index.php/JKK/article/view/6340>
- Pal, A., Squitti, R., Picozza, M., Pawar, A., Rongioletti, M., Dutta, A. K., Sahoo, S., Goswami, K., Sharma, P., & Prasad, R. (2021). Zinc and COVID-19: Basis of Current Clinical Trials. *Biological Trace Element Research*, 199(8), 2882–2892. <https://doi.org/10.1007/s12011-020-02437-9>
- Perera, M., El Khoury, J., Chinni, V., Bolton, D., Qu, L., Johnson, P., Trubiano, J., McDonald, C. F., Jones, D., Bellomo, R., Patel, O., & Ischia, J. (2020). Randomised controlled trial for high-dose intravenous zinc as adjunctive therapy in SARS-CoV-2 (COVID-19) positive critically ill patients: Trial protocol. *BMJ Open*, 10(12), 1–9. <https://doi.org/10.1136/bmjopen-2020-040580>
- Thomas, S., Patel, D., Bittel, B., Wolski, K., Wang, Q., Kumar, A., Il'Giovine, Z. J., Mehra, R., McWilliams, C., Nissen, S. E., & Desai, M. Y. (2021). Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction among Ambulatory Patients with SARS-CoV-2 Infection: The COVID A to Z Randomized Clinical Trial. *JAMA Network Open*, 4(2), 1–10. <https://doi.org/10.1001/jamanetworkopen.2021.0369>
- Yao, J. S., Paguio, J. A., Dee, E. C., Tan, H. C., Moulick, A., Milazzo, C., Jurado, J., Della Penna, N., & Celi, L. A. (2021). The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19: An Observational Study. *Chest*, 159(1), 108–111. <https://doi.org/10.1016/j.chest.2020.06.082>