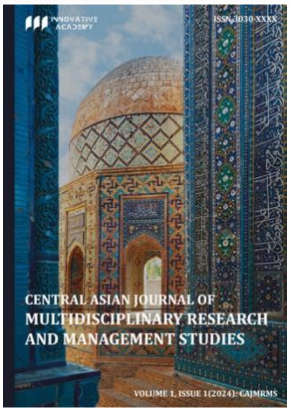


TRACE ELEMENTS AND SARS-COV-2 INFECTION: A SYSTEMATIC REVIEW OF CLINICAL TRIALS

Dr. Deepak Sharma
Department of Physiology
Fergana Medical Institute of Public Health, Fergana, Uzbekistan
Deepak838556@gmail.com
Rakhimova khusnidakhon Abdukarimova
Department of Traditional Medicine and Pharmacology
Fergana Medical Institute of Public Health, Fergana, Uzbekistan
husnidahonrahimovaha@gmail.com
Noor Alam
Department of Traditional Medicine and Pharmacology
Fergana Medical Institute of Public Health, Fergana, Uzbekistan
Noor98alamjh@gmail.com

https://doi.org/10.5281/зенодо.15490304

ARTICLE INFO

Received: 15 th May 2025
Accepted: 19th May 2025
Published: 22nd May 2025

KEYWORDS

SARS-CoV-2; trace elements; Morbidity; Mortality

ABSTRACT

Background: *Trace elements such as copper, zinc, magnesium, etc. are the minerals present in living tissues in small concentrations, which primarily act as catalysts in the enzyme system. Literature has indicated the role and alteration of trace elements in viral infections. However, the role of trace elements in SARS-CoV-2 infection is unclear so far.* ***Aim:*** *The aim of the study was to perform a systematic review to find out the role of trace elements in SARS-CoV-2 infection as well as the effect of SARS-CoV-2 infection on trace elements.* ***Material and Method:*** *The relevant studies were searched in PubMed and clinical trial websites, and screened based on inclusion and exclusion criteria. The quality of studies was assessed using NIH quality assessment tools.* ***Results:*** *A total of 19 studies were found relevant after screening 23,570 studies. The level of zinc was found to be decreased, the level of magnesium was found to be altered, and the level of copper was found to be increased after SARS-CoV-2 infection.* ***Conclusion:*** *Thus, supplementation of a particular trace element can be useful as an add-on therapy for COVID-19 infection. Further, more studies are required to find out the exact role of these elements in COVID-19 infection.*

1. Introduction

The novel coronavirus (2019-nCoV) infection results in unprecedented havoc all over the globe and was declared a pandemic by the World Health Organization (WHO) [1]. As of 19th May 2025, more than 704,753,890 COVID-19 cases have been reported across the globe, resulting in approximately 7,095,349 deaths [2]. The infection of 2019-nCoV involved almost all body systems, including the respiratory system [3]. Literatures have demonstrated the severity of infection in patients with co-morbid conditions such as diabetes, hypertension, etc. [4, 5].

Trace elements act as catalysts in the biological enzymatic system [6]. The well-known trace elements are zinc, copper, magnesium, selenium, etc., which play an important role in various physiological processes. Zinc is a trace element which is known for its anti-oxidant [7], anti-inflammatory [8], immunomodulatory [9], as well as anti-viral activities [10]. Zinc is also effective against the hepatitis C virus, human papillomavirus, viral diarrhoea in children, and HIV infection [11-13]. Copper (Cu) is also an essential trace element required by a variety of cuproenzymes for maintaining redox status and supporting the immune system [14]. The antiviral activity of copper is due to its ability to damage the main components of the virus, such as membranes, envelopes, DNA, RNA, etc. [15]. Magnesium is another important trace element that regulates nerve conduction, controls blood pressure, stabilizes mast cells, and improves lung function [16]. Selenium is also an important trace element that plays an important role in the immunity of the individual [18]. The physiological roles of these trace elements are shown in Figure 1.

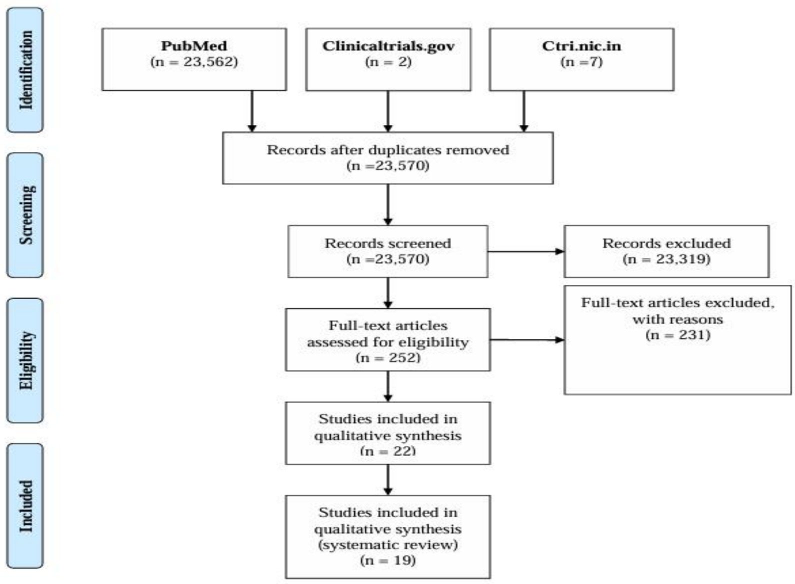
The effect of novel coronavirus (2019-nCoV) on trace elements and their role in this infection is unclear so far. Thus, we have conducted a systematic review of the available literature on trace elements and 2019-nCoV as per the PRISMA guidelines.

2. Methodology

This review was carried out using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [19].

2.1 Data sources and searches

The data related to the trace elements and SARS-CoV-2 infection have been extracted from PubMed, from November 2019 to September 2021 using the following queries: "Covid-19", "Covid-19 infection", "SARS-CoV-2", "2019 novel corona virus infection", and "zinc", "copper", "iron", "magnesium", "selenium". DS, RK, and NA have independently reviewed all abstracts. The clinical trials related to trace elements and COVID-19 were extracted from www.ctri.nic.in and www.clinicaltrial.gov.



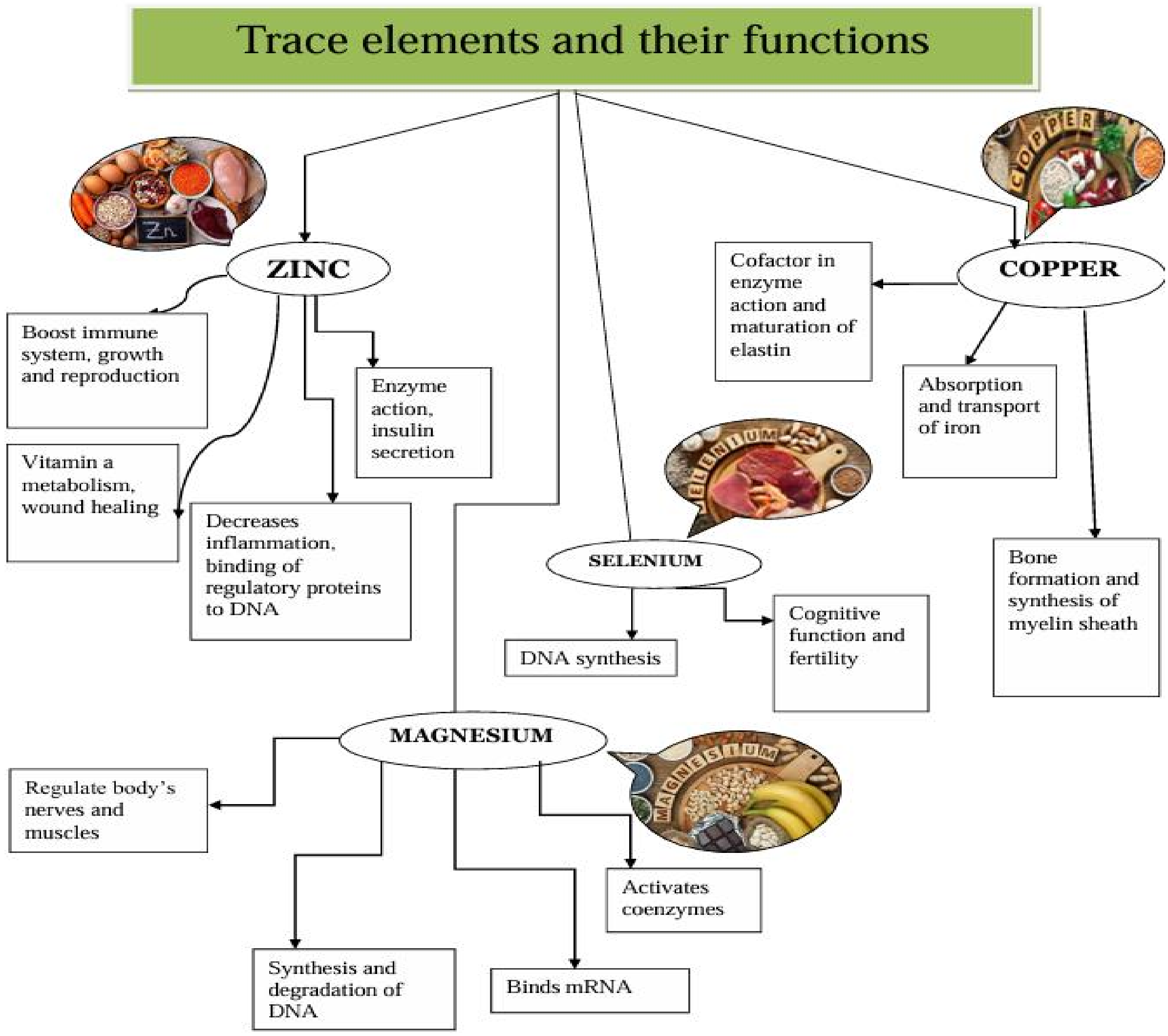


Figure 1: Physiological roles of trace elements in the human body

2.2 Data sources and searches

The data related to the trace elements and SARS-CoV-2 infection have been extracted from PubMed, from November 2019 to September 2021 using the following queries: "Covid-19", "Covid-19 infection", "SARS-CoV-2", "2019 novel corona virus infection", and "zinc", "copper", "iron", "magnesium", "selenium". DS, RK, and NA have independently reviewed all abstracts. The clinical trials related to trace elements and COVID-19 were extracted from www.ctri.nic.in and www.clinicaltrial.gov.

Figure 2: Screening of studies

2.3 Study selection

Studies have been screened according to the inclusion and exclusion criteria described below. The articles published in English were only considered. To remove duplicates and multiple studies of the same set of data, we only considered the most recent or complete study.

2.2.1 Inclusion and exclusion criteria

The inclusion criteria were as follows: articles published from November 2019 to September 2021, studies related to trace elements, i.e., magnesium, zinc, copper, and selenium, and COVID-19. The exclusion criteria are as follows: review articles; meta-analysis was excluded.

Three authors (DS, RK, and NA) separately screened all the titles and abstracts for eligibility criteria as well as performed the screening of full-text articles.

Analysis

The quality assessment was done using the National Institute of Health (NIH) Quality Assessment Tools. The assessment was done by two reviewers (NA and RK) separately. The studies were categorized into three categories, i.e., good, fair, and poor quality. The data were extracted from studies by three authors (DS, RK, and NA) as shown in Tables 1 and 2. The information, such as names of authors with publication year, type, location, total sample size, intervention, dose, route of administration, and outcome, was extracted from full-text articles.

3. Results

We have found 23,570 studies regarding COVID-19 and trace elements (magnesium, zinc, copper, and selenium). Out of 23,570 studies, 23,562 studies were found in PubMed, whereas the remaining 08 studies were found in clinical trials websites. Finally, 19 studies were found relevant and included. The selection of studies was done as per the PRISMA guideline and presented in Figure 2. The quality assessment results have reported 08 of good quality, 04 of fair, and 07 of poor quality studies. The poor-quality studies were clinical trials which are not been completed yet. Among 19 studies, 5 were related to magnesium, 10 were related to zinc, 3 were related to copper, and the remaining 1 was related to selenium.

3.1. Magnesium and COVID-19 infection

Few reports are available regarding magnesium and 2019-nCoV, which indicate a protective role of magnesium in combination with vitamin D and vitamin B12, whereas some studies have indicated the alteration of magnesium levels in COVID-19 infection. A prospective cohort study by Tan et al. [20] was conducted to examine the influence of vitamin D, magnesium, and vitamin B12 (DMB) on the progression of COVID-19 infection into a serious outcome. The authors concluded that patients who received DMB required significantly less oxygen therapy as compared to patients who have not received DMB. This might be due to the anti-inflammatory activity of DMB through down-regulation of various proinflammatory cytokines associated with severe COVID-19 patients.

The level of magnesium was also altered in COVID-19 infection, as indicated by a few studies. Quilliot et al. [21] reported dysmagnesemia in COVID-19 patients in France. The researchers found that hypomagnesemia prevalence (<0.75 mmol/L) in the moderate and severe patients, while hypermagnesemia prevalence (>0.95mmol/L) in critically ill patients. Additionally, this analysis also suggests that dysmagnesemia might be a good predictor for the severity of infection in COVID patients. An observational cohort study was conducted by Stevens et al. [22] and found an association between hypermagnesemic COVID-19 patients and increased mortality. However, the exact mechanism of the relationship is unclear. The prevalence of hypermagnesemia increased with increasing age, male gender, acute kidney injury (AKI), receiving renal replacement therapy (RRT), hyperkalemia, and elevated creatinine phosphokinase (CPK). The studies related to COVID-19 and magnesium are compiled in Table 4.

3.2. Zinc and COVID-19 infection

Serum zinc alteration was seen due to COVID infection, which was explained by a few reports. In a cross-sectional study conducted by Heller et al. [23] at two separate sites in Germany reported the decreased level of zinc and serum selenoprotein P (SELENOP) in COVID-19 patients. Based on their findings, authors have hypothesized that the zinc and serum selenoprotein P (SELENOP) concentrations might be a potential marker to determine the prognosis of COVID-19 patients. Recently, a prospective observational study was conducted by Bagher pour et al. [24] in Iran, and also reported the decreased level of zinc in COVID-19 patients. However, there was no effect on the level of other trace elements (Cu, Se, and Mn). A case-control study was also conducted by Elham et al. [25] in Iran, which reported low levels of serum zinc, calcium, and vitamin D at the initial stage of COVID-19. Overall, based on the findings of these studies, it can be concluded that the level of zinc is decreased in SARS-CoV-2 infection. Thus, zinc supplementation might play an important role in SARS-CoV-2 infection. To the best of our knowledge, three studies have been conducted so far to check the effect of zinc supplementation on SARS-CoV-2 infection. In a non-randomized phase 1 clinical trial conducted by Elalfy et al. [26] at Mansoura University hospital in which a combination of ivermectin, ribavirin, and nitazoxanide, with an add on zinc supplement has found effective against COVID infection in a shorter time than the symptomatic therapy i.e., paracetamol tablets, azithromycin and zinc supplement with proper diet and hydration. A retrospective case series was also reported by Derwand et al. [27], which includes data of COVID-19 outpatients in New York, USA, and found a reduction in deaths of COVID-19 patients who were treated with zinc, a low dose of hydroxychloroquine, and azithromycin (triple therapy). In a Phase IIa pilot-double blind, randomized controlled trial conducted by Patel et al. [28] in Australia reported that high-dose intravenous zinc (HDIVZn) results in improvement of serum zinc level in zinc-deficient COVID-19 patients when compared with placebo. However, another prospective randomized clinical open label trial was conducted by Thomas et al. [29] at different sites of Ohio and Florida in which patients were randomized in 4 groups receiving either zinc gluconate, ascorbic acid, or both and standard treatment with a primary outcome of decreased number of days in symptoms reduction and secondary outcome includes days for symptoms severity to reach 0, deaths, hospitalization etc. The study has reported no significant difference between treatment groups. The data from these studies are compiled in Table 5.

3.3. Copper and COVID-19 Infection

To the best of our knowledge, only one study was conducted regarding the effect of SARS-CoV-2 infection on the level of copper. Hackler et al. [30] conducted a cross-sectional study in Germany, which reported the increased level of copper in the serum of survivors as compared to control and non-survivor patients (Table 6). Thus, further studies are required to find the exact role of copper in COVID-19 Infection.

4. Conclusion

SARS-CoV-2 infection alters the level of trace elements. Further, literature has indicated the role of trace elements, particularly zinc, in the treatment of COVID-19. This might be due to immunomodulatory, anti-oxidant, and anti-inflammatory activities of these elements. However, data on the alteration of these elements after infection and their role in treatment are very less so far. Thus, further studies are required to confirm an exact understanding of trace elements and SARS-CoV-2 infection.

References:

1. D. Cucinotta, M. Vanelli, WHO Declares COVID-19 a Pandemic, Acta. Biomed. 91(2020) 157-160. https://doi.org10.23750/abm.v91i1.9397
2. World Health Organization, WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ (Accessed 8 September 2021)
3. Centers for Disease Control and Prevention, Coronavirus Disease 2019 (COVID-19) – Symptoms. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html> (Accessed 5 September 2021).
4. B. de Almeida-Pititto, P.M. Dualib, L. Zajdenverg et al., Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis, Diabetol. Metab. Syndr. 12, 75 (2020). https://doi.org/10.1186/s13098-020-00586-4
5. A. Sanyaolu, C. Okorie, A. Marinkovic et al., Comorbidity and its Impact on Patients with COVID-19, SN. Compr. Clin. Med. (2020)1-8. https://doi.org/10.1007/s42399-020-00363-4

6. National Research Council (US) Committee on Diet and Health, Diet and Health: Implications for Reducing Chronic Disease Risk, Washington (DC): National Academies Press (US); 1989. 14, Trace Elements. https://www.ncbi.nlm.nih.gov/books/NBK218751/
7. M. Jarosz, M. Olbert, G. Wyszogrodzka, K. Młyniec, and T. Librowski, T., 2017, Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. Inflammopharmacology. 25(1(2017) 11-24.
8. AS. Prasad, Zinc is an Antioxidant and Anti-Inflammatory Agent: Its Role in Human Health, Front. Nutr. (2014)1:14. https://doi.org/10.3389/fnut.2014.00014
9. N.A. Tayyib, P. Ramaiah, F.J. Alsolami, M.S. Alshmemri MS, Immunomodulatory effects of zinc as a supportive strategies for COVID-19, Journal of Pharmaceutical Research International. 1(2020) 14-22.
10. S.A. Read, S. Obeid, C. Ahlenstiel, G. Ahlenstiel, The Role of Zinc in Antiviral Immunity, Advances in Nutrition. 10(2019) 696–710, https://doi.org/10.1093/advances/nmz013
11. K. Yuasa, A Naganuma, K. Sato, M. Ikeda, N. Kato, H Takagi, M. Mori, Zinc is a negative regulator of hepatitis C virus RNA replication, Liver Int. 26(9(2006) 1111-8. https://doi.org/10.1111/j.1478-3231.2006.01352.x
12. M. Lazarczyk, C. Pons, J.A. Mendoza, P. Cassonnet, Y. Jacob, M. Favre, Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses, J. Exp. Med. 21;205(1(2008):35-42. https://doi.org/10.1084/jem.20071311
13. Y. Haraguchi, H. Sakurai, S. Hussain, B.M. Anner, H. Hoshino, Inhibition of HIV-1 infection by zinc group metal compounds, Antiviral Res. 43(2(1999) 123-33. https://doi.org/10.1016/s0166-3542(99)00040-6
14. M. Bost, S. Houdart, M. Oberli, E. Kalonji, JF. Huneau, I. Margaritis, Dietary copper and human health: Current evidence and unresolved issues, J Trace Elem Med Biol. 35(2016)107-115. https://doi.org/10.1016/j.jtemb.2016.02.006
15. A. Andreou, S. Trantza, D.Filippou, N. Sipsas, S. Tsiodras, COVID-19: The Potential Role of Copper and N-acetylcysteine (NAC) in a Combination of Candidate Antiviral Treatments Against SARS-CoV-2, In Vivo. 34(3(2020) 1567-1588. https://doi.org/10.21873/invivo.11946
16. K. Agin, & M. Moinazad Tehrany, Status Trace Elements of Zinc, Magnesium and Calcium Electrolytes in Serum, International Journal of Medical Toxicology and Forensic Medicine. 2(1(winter)), (2021) 6-12. https://doi.org/10.22037/ijmtfm.v2i1(winter).2959
17. H. Tapiero, D. M. Townsend, and K. D. Tew, The antioxidant role of selenium and seleno-compounds, Biomedicine & pharmacotherapy. 57(3-4) (2003) 134-144. https://doi.org/10.1016/S0753-3322(03)00035-0
18. L. Duntas, Selenium and inflammation: underlying anti-inflammatory mechanisms, Hormone and metabolic research. 41(06) (2009) 443-447. https://doi.org/10.1055/s-0029-1220724
19. D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement, PLoS Med 6(7)(2009) e1000097. https://doi.org/10.1371/journal.pmed.1000097
20. C.W. Tan, L.P. Ho, S. Kalimuddin, et al., Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B12 in combination on progression to severe outcomes in older patients with coronavirus (COVID-19), Nutrition. (2020)79-80 111017. https://doi.org/10.1016/j.nut.2020.111017

21. D. Quilliot, O. Bonsack, R. Jaussaud, A. Mazur, Dysmagnesemia in Covid-19 cohort patients: prevalence and associated factors, Magnes Res. 33(4(2020) 114-122. https://doi.org/10.1684/mrh.2021.0476
22. S.S. Jacob, A.M. Andrew, L.N. Thomas, A.H. Syed, M. Sumit, Increased Mortality Associated with Hypermagnesemia in Severe COVID-19 Illness, Kidney360. 2 (7(2021) 1087-1094; https://doi.org/10.34067/KID.0002592021
23. R.A. Heller, Q. Sun, J. Hackler et al., Prediction of survival odds in COVID-19 by zinc, age and selenoprotein P as composite biomarker, Redox Biol. 38(2021)101764. https://doi.org/10.1016/j.redox.2020.101764
24. O.B. Pour, Y. Yahyavi, A. Karimi et al., Serum trace elements levels and clinical outcomes among Iranian COVID-19 patients, Int. J. Infect. Dis. S1201-9712(2021). https://doi.org/10.1016/j.ijid.2021.08.053
25. A.S. Elham, K. Azam, J. Azam, L. Mostafa, B. Nasrin, N. Marzieh, Serum vitamin D, calcium, and zinc levels in patients with COVID-19, Clin. Nutr. ESPEN. 43(2021)276-282. https://doi.org/10.1016/j.clnesp.2021.03.040
26. H. Elalfy, T. Besheer, A. El-Mesery et al., Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19, J. Med. Virol. 93(5(2021) 3176-3183. https://doi.org/10.1002/jmv.26880
27. R. Derwand, M. Scholz, V. Zelenko, COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study, Int. J. Antimicrob. Agents. 56(6(2020) 106214. https://doi.org/10.1016/j.ijantimicag.2020.106214
28. O. Patel, V. Chinni, J. El-Khoury et al., A pilot double-blind safety and feasibility randomized controlled trial of high-dose intravenous zinc in hospitalized COVID-19 patients, J. Med. Virol. 93(2021) 3261-3267. https://doi.org/10.1002/jmv.26895
29. S. Thomas, D. Patel, B. Bittel 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. 4(2(2021). https://doi.org/10.1001/jamanetworkopen.2021.0369
30. J. Hackler, R.A. Heller, Q. Sun et al., Relation of Serum Copper Status to Survival in COVID-19, Nutrients. 13(6(2021) 1898. https://doi.org/10.3390/nu13061898

STUDY	TYPE OF STUDY	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality of the study
Tan et al.2020	Cohort observational study	Yes	Yes	No	Yes	No	Yes	Yes	NA	Yes	NA	Yes	NA	NA	Yes	Good
Quilliot et al. 2020	Prospective cohort study	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	NA	Yes	NA	NA	Yes	Good
Jacob et al. 2021	Retrospective cohort study	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	NA	Yes	NA	NA	NA	Fair

Heller et al. 2021	Cross-sectional study	Yes	Yes	Yes	No	No	Yes	NA	Yes	Yes	Yes	Yes	Yes	NA	NA	Fair
Thomas et al. 2021	Prospective randomised open-label trial	Yes	Yes	No	Yes	Yes	Yes	NA	NA	NA	Yes	Yes	Yes	No	Yes	Fair
Derwand et.al.2020	Retrospective case series	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	NA	Good
Elalfy et al.2021	Non-randomized controlled trial	No	NA	NA	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	YES	Yes	Good
Heckler et al. 2021	Cross-sectional studies	Yes	Yes	No	Yes	NA	Yes	Yes	Yes	NA	Yes	Yes	YES	YES	NA	Good
Elham et al.2021	Case-control study	Yes	Yes	No	Yes	Yes	Yes	Yes	NR	NR	Yes	NR	Yes			Fair
Bagher pour et al. 2021	Cohort observational studies	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	NR	Yes	NR	Good
Patel et al. 2021	Pilot double blind randomised controlled trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Good

Table 1: Quality assessment of Published studies using NIH quality assessment tools

STUDY	TYPE OF STUDY	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Quality of the study	Status of trial
Samba shiva	Randomised, parallel group trial	YES	YES	NO	NO	NO	YES	YES	YES	YES	YES	YES	NR	YES	YES	GOOD	Completed
Ramen goel	Randomised, parallel group, active controlled trial	YES	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	POOR	Not completed
dholakia	Randomised factorial trial	YES	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	POOR	Not completed
Sridhar	Randomised, parallel group trial	YES	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	POOR	Not completed
Sridhar	Randomised,	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	POO	Not

	parallel group trial	ES	R**	R**	R**	R**	R**	R**	R**	R**	R**	R**	R**	R**	R**	R	completed
Desouza	Case Control study	YES	YES	NO	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	POOR	Not completed
Mohamed S Ghoweba	Randomized double-blinded, placebo-controlled	YES	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	POOR	Not completed
Indiraneel mittra	Randomised, parallel group, multiple arm trial	YES	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	NR**	POOR	Not completed
NA* not applicable																	
NR** Not reported																	

Table 2: Quality assessment of Clinical trials using NIH quality assessment tools

S.No.	Registration number	Sample size	Name of Intervention	Dose	Route of administration	Type of trial	Type of study	Study design	country	Status of trial	Outcome	References
1	CTRI/2020/12/029	114	CoroQuil-Zinc	750 mg	Oral	Interventional	Ayurveda	Randomised, parallel group trial	India	Completed	useful for mild to moderate COVID patients which reduces patient load in hospital.	Sambashiva

	735											
2	CTRI/2020/07/026340	100	Zinc sulphate	100 mg	Oral	Interventional	Micronutrient	Randomised, parallel group, active controlled trial	India	Not completed	NA	Ramen goel
3	CTRI/2021/04/032593	700	Zinc gluconate	40mg	Oral	Interventional	Micronutrient	Randomised factorial trial	India	Not completed	NA	dholakia
4	CTRI/2020/06/	500	magnesium glycinate, Vitamin D3 and Vitamin K2-7	250 mg /60,000IU /100 mcg per day	Oral	Interventional	Drug	Randomised, parallel group trial	India	Not completed	NA	Sridhar

	026191											
5	CTRI/2020/06/026189	210	Magnesium glycinate and cholecalciferol vitamin D3	250 mg /60,000IU	Oral	Interventional	Drug	Randomised, parallel group trial	India	Not completed	NA	Sridhar
6	CTRI/2020/06/026256	230	NA*	NR**	NR**	Observational	Case Control study	Other	India	Not completed	NA	Desouza
7	NCT048695	100	Selenious Acid	2000 µg on day 1 and 1000 µg from Day 2 to	IV infusion	Interventional	Drug	Randomized double-blinded, placebo-control	US	Not completed	NA	Mohamed S Ghoweba

	79			14				led				
8	CTRI/2020/05/025336	300	Resveratrol-copper		Oral	Interventional	Drug	Randomised, parallel group, multiple arm trial	Inda	Not completed	NA	Indiraneel mittra

NA* not applicable; NR** Not reported

Table 3: Data of Clinical Trials

Name of the authors	Type of study	Location of the study	Total sample size (male/female)	Intervention	Dose and Route of Administration	Effect
Tan et.al. 2020 [20]	Cohort observational study	Singapore	43	DMB	Vit. D 1000 IU, Mg 150mg, Vit B12 500mcg (oral)	Oral administration of DMB reduces the oxygen requirement in covid patients as well as the severity of infection.
Quilliot et.al. 2020 [21]	Prospective cohort study	France	300(183/117)	-	-	Prevalence of hypomagnesemia in moderate and severe conditions, whereas in critical conditions, hypermagnesemia is prevalent.

						Analysis suggests that Dysmagnesemia might predict the severity of infection in Covid patients.
Jacob et al. 2021 [22]	Retrospective cohort study			-	-	An association was found between hypermagnesemic COVID-19 patients and increased mortality. However, the exact mechanism of the relationship is unclear.

Table 4: Studies related to the impact of COVID-19 on magnesium levels

Name of the authors	**Type of study**	**Location of the study**	**Total sample size (male/female)**	**Intervention**	**Dose and Route of administration**	**Effect**
Heller et al. 2021[23]	Cross-sectional study	Germany	35(16/19)	-	-	Serum zinc levels are found to decrease in COVID-19, which can be overcome with the help of zinc and selenium adjuvant therapy.

Bagher Pour et al.2021[24]	Single-centered, prospective, observational study	Iran	226	-	-	Serum zinc level was found to be lower in Iranian COVID-19 patients, while manganese (Mn), copper (Cu), and selenium (Se) levels were within range. So, zinc can be considered a strong indicator for a COVID-19 patient's prognosis.
Elham et al. 2021[25]	Case-control study	Iran	93 (41/52)	-	-	COVID-19 patients show lower concentration of serum zinc, calcium, and vitamin D levels, and therefore can be treated by giving these supplements in the initial stages of COVID-19.
Elalfy et al. 2021 [26]	Non-randomized controlled trial	Mansoura	113(52/61)	Nitazoxanide, ivermectin, ribavirin, and zinc (given to 62 patients)	Zinc (30mg) twice daily (oral)	Zinc as an add-on with ivermectin, nitazoxanide, and ribavirin is a more effective therapy against SARS-CoV-2 (initial stages) than symptomatic treatment.
Thomas wt al. 2021 [27]	Prospective randomized open-label trial	Ohio and Florida	214(82/132)	Zinc gluconate and Ascorbic acid. (given to 164 patients divided in 3 groups)	Zinc gluconate 50mg (oral)	Zinc gluconate, ascorbic acid, or a combination of both doesn't appear to be significantly effective in reducing the duration of symptoms.

Pate Patel et al. 2021 [28]	Pilot double blind, randomised controlled trial	Australia	33	Zinc	High dose intravenous zinc (HDIVZn)	High dose IV zinc is given to zinc-deficient COVID patients which resulting in increased serum zinc levels as compared to the patients administered with a placebo.
Derwand et al. 2020 [29]	Retrospective case series	New York	141	Zinc sulphate, low-dose hydroxychloroquine, and azithromycin	Zinc sulphate 220mg contains 50mg of elemental zinc (oral)	A triple therapy of zinc, low-dose hydroxychloroquine, and azithromycin was given to patients, which resulted in only 1 death compared to a non-treatment group with 13 deaths.

Table 5: Studies related to the impact of COVID-19 on zinc serum levels

Name of the authors	**Type of study**	**Location of the study**	**Total sample size (male/female)**	**Effect**
Hackler et al. 2021[30]	Cross-sectional study	Germany	35(15/20)	It was found that the patients who survived had elevated serum copper levels while the non-survivors and control group had serum copper levels within the reference serum copper range (i.e., 897.8-1906.0 µg/L).

Table 6: Data on copper as a trace element in COVID-19