ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine
www.aaem.pl

The effect of zinc supplementation on the course of COVID-19 – A systematic review and meta-analysis

Monika Olczak-Pruc[1,E-F], Lukasz Szarpak[2,3,A-D,F] ✉, Alla Navolokina[4,E-F], Jaroslaw Chmielewski[5,E-F], Lech Panasiuk[6,E-F], Raúl Juárez-Vela[7,E-F], Michal Pruc[8,B,D,F], Damian Swieczkowski[9,E-F], Ryszard Majer[10,E-F], Zubaid Rafique[2,E-F], Frank William Peacock[2,D-F]

[1] *ViaMed Polyclinic, Warsaw, Poland*
[2] *Baylor College of Medicine, Houston (TX), USA*
[3] *Maria Sklodowska-Curie Medical Academy, Warsaw, Poland*
[4] *International European University, Kyiv, Ukraine*
[5] *Institute of Environmental Protection – National Research Institute, Warsaw, Poland*
[6] *Institute of Rural Health, Lublin, Poland*
[7] *University of La Rioja, Spain*
[8] *Polish Society of Disaster Medicine, Warsaw, Poland*
[9] *Medical University, Gdańsk, Poland*
[10] *Jan Dlugosz University, Częstochowa, Poland*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Olczak-Pruc M, Szarpak L, Navolokina A, Chmielewski J, Panasiuk L, Juárez-Vela R, Pruc M, Swieczkowski D, Majer R, Rafique Z, Peacock FW. The effect of zinc supplementation on the course of COVID-19 – A systematic review and meta-analysis. Ann Agric Environ Med.

Abstract

Introduction and Objective. Zinc is a trace element that plays a role in stimulating innate and acquired immunity. The aim of the study was to determine the antiviral effect of the administration of zinc in COVID-19 patients.

Materials and Method. A literature search was performed in P Web of Science, PubMed, Scopus and Cochrane databases from 1 January 2020 – 22 August 2022. In addition, reference lists of the included articles and their related citations in PubMed were also reviewed for additional pertinent studies.

Results. A total of 9 eligible studies were identified. In-hospital mortality in zinc supplementation patients, and patients treated without zinc, varied and amounted to 21.6% vs. 23.04% difference (OR=0.71; 95%CI: 0.62–0.81; p<0.001). 28-day to 30-day mortality in patients treated with zinc was 7.7%, compared to 11.9% for patients treated without zinc (OR=0.61; 95%CI: 0.35–1.06; p=0.08). In-hospital adverse events among patients treated with and without COVID-19 did not show any statistically significant differences in relation to acute kidney injury occurrence (12.8% vs. 12.4%, respectively; OR=0.63; 95%CI: 0.19–2.12; p=0.45, as well as need for mechanical ventilation (13.2% vs. 14.1%; OR=0.83; 95%CI: 0.52–1.32; p=0.43).

Conclusions. Zinc supplementation is associated with lower COVID-19 in-hospital mortality. Additionally, it is risk-free in COVID-19 patients since there have been no negative side effects, such as acute renal damage or the requirement for mechanical ventilation compared to patients without COVID-19. Due to scientific evidence and the role it represents in the human body, zinc supplementation should be taken into consideration for COVID-19 patients as an adjunct therapy.

Key words

meta-analysis, zinc, supplementation, COVID-19, SARS-CoV-2

INTRODUCTION AND OBJECTIVE

Since the outbreak of the coronavirus disease in 2019 (COVID-19), a pandemic caused by the severe respiratory syndrome coronavirus 2 (SARS-CoV-2), millions of people have died and the medical system has faced significant difficulties [1, 2]. The pandemic is still not fully under control and continues to pose a threat to human life [3], despite the availability of vaccinations, new antiviral medications, and virus mutations that have increased survival rates. Additionally, the enhanced infectiousness of the newer novel SARS-CoV-2 virus varieties means the possibility of disease resurgence persists, with the consequence of subsequent overloading of the healthcare systems [4, 5, 6]. For this reason, it is necessary to continue the search for methods of hospitalization prevent and to mitigate the severity of COVID-19 infection when it occurs [7, 8].

Age, lifestyle, socio-economic status, and nutritional state are some of the numerous variables known to affect how a patient reacts to the virus [9, 10]. There is evidence that some micronutrient supplements may also help the immune system of a COVID-19 patient to maintain integrity. Due to their immunomodulatory effects, essential micronutrient supplements [11, 12, 13, 14, 15], e.g., zinc, have recently received critical examination. Zinc is a micronutrient critical for the growth, development, and maintenance of immune barriers, such as the skin and mucous membranes. For a variety of factors, including both direct and indirect antiviral

✉ Address for correspondence: Lukasz Szarpak, Baylor College of Medicine, Houston (TX), USA
E-mail: lukasz.szarpak@gmail.com

Received: 27.09.2022; accepted: 17.10.2022; first published:

action, zinc may also play a significant role in the clinical course of a patient.

The baseline function of zinc is believed to be the reduction of oxidative stress and inflammation [16]. Zinc is essential for the development of immune cells, especially T lymphocytes (Fig. 1), the lack of which reduces helper T cell activation and CD8 + T cell responses [17]. Zinc deficiencies are thus associated with viral infections, and patients deficient in zinc are at an increased risk of death from pneumonia [18], likely the result of de-creased antiviral antibody production [19].

Furthermore, zinc is important in macrophage function. When macrophages are stimulated, zinc plays a role in the synthesis of IFN-, IL-2, and IL-12. IL-12 causes the T cytotoxic cells and NK cells to become activated. These cells play significant roles in lowering susceptibility to infectious illnesses brought on by both viral and bacterial pathogens. Zinc deficiency also causes IL-10 production to be dysregulated, which also has an impact on the Th1 response and macrophage activities [20]. Finally, zinc supplementation has been demonstrated to decrease the production of TNF- and IL-1 in healthy individuals [21].

Specific to SARS-CoV-02 infection, zinc may also inhibit its *in vitro* reproduction and proliferation by preventing the synthesis of RNA [22, 23]. Additionally, by modulating cytokine mRNA levels, and inhibiting the expression of essential proteins and enzymes required for mRNA maturation and stability [24, 25, 26], zinc may play a role in preventing the progression of COVID-19 and its resultant cytokine storm [27]. The current state of knowledge provides an insight into whether zinc is helpful in reducing the risk of COVID-19 infection [28].

Considering its potential antiviral and protective potential when used in the setting of a SARS-CoV-2 infection, the aim of the study was to perform a meta-analysis comparing outcomes in hospitalized COVID-19 patients receiving zinc supplementation vs. those receiving conventional treatment, in order to determine the antiviral effect of the administration of zinc in COVID-19 patients.

MATERIALS AND METHOD

A systematic review and meta-analysis was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [29]. The protocol of the systematic review and meta-analysis was registered on the PROSPERO database (Reg. No.: CRD42022349549). Due to the character of the study (meta-analysis), ethical approval or patient consent were not applicable.

Search strategy. Two reviewers (M.P. and M.O.P.) independently searched four major electronic databases (Web of Science, PubMed, Scopus and Cochrane Central Register of Controlled Trials) from 1 January 2020 – 22 August 2022, to identify studies examining the effect of zinc supplementation on the course of COVID-19. Electronic database evaluation was supplemented by searching Google

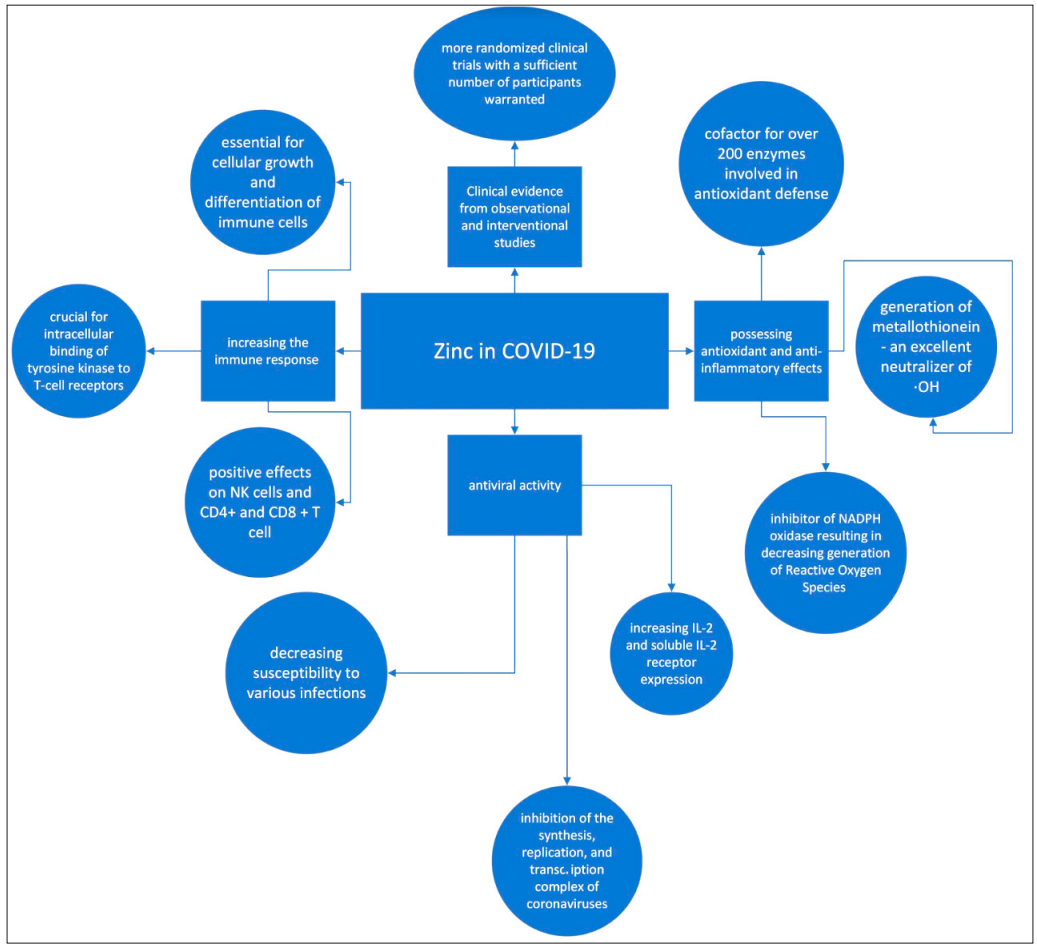

Figure 1. The effect of zinc on the body

Scholar. A specific and appropriate search strategy was used for each database, utilizing the following searching terms: 'zinc', 'SARS-CoV-2' and 'COVID-19'. Search results were managed using EndNote software (version X7; Thomson Reuters); in addition, reference lists of the included articles and their related citations in PubMed were also reviewed for additional pertinent studies.

Study selection. All original English language studies comparing COVID-19 patient's treatment with and without zinc supplementation were included. Exclusion criteria were as follows: (1) studies involving data from paediatric patients; (2) case reports, editorial, conference papers, reviews; (3) studies lacking research indicators required for meta-analysis.

Two reviewers (L.S. and M.P.), independently screened the titles and abstracts of the studies retrieved by the databases against the search criteria. Afterwards. the full texts of all potentially relevant articles were retrieved and independently assessed by the same reviewers. If any disagreement arose regarding the selection of literature papers, disagreement was resolved through discussion with another reviewer (M.O.P.).

Data extraction. Two investigators (M.O.P. and M.P.) independently performed the study selection for studies that met the above inclusion criteria. Potential disagreement during data extraction was resolved through discussion with another reviewer (L.S.). Data were collected using a predefined form. Data extracted included details regarding the publication data (i.e. first author name, year of publication, study design), population data (i.e. number of participants, age, male gender), mortality outcomes (in-hospital mortality and 28-d/30-d mortality), as well as adverse events.

Quality and risk of bias assessment. Two reviewers (M.P. and R.M.) independently assessed the individual studies for risk of bias. Any discrepancies were resolved by an independent third reviewer (L.S.). The RoB 2 tool (revised tool for risk of bias in randomised trials) was used to assess the quality of randomised studies [30]. For non-randomized trials, the ROBINS-I tool (to determine the risk of bias in non-randomized studies of interventions) was used [31]. For the RoB-2 tool, the following biases were assessed: (1) arising from the randomization process, (2) due to deviations from intended intervention, (3) due to missing outcome data, (4) in measurement of the outcome, and (5) bias in selection of the reported result. In contrast, in the case of the ROBINS-I tool, the following domains were assessed: (1) bias due to confounding, (2) bias due to selection of participants, (3) bias in classification of intervention, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. The risk of bias assessments for randomized trials was visualized using the Robvis application [32].

Statistical analysis. The meta-analysis was conducted in accordance with the Cochrane handbook. Data was analyze using the STATA software (version 14, StataCorp LLC, College Station, TX, USA) and RevMan software (version 5.4, The Nordic Cochrane Center, The Cochrane Collaboration, 2014). The results are presented as forest plots using odds ratios (ORs) for dichotomous data, and the mean difference (MD) for continuous data with 95% confidence intervals (CIs). When data were reported as median with interquartile range, estimated means and standard deviations with the formula described by Hozo were used [33]. Heterogeneity was quantitatively assessed using Cochran's Q statistics and Higgins's Index (I^2), with 25%, 50% and 75% considered moderate, substantial and considerable heterogeneity, respectively [34]. The random-effects model was used for $I^2 > 50\%$; otherwise, the fixed effects model was employed. Egger's test and funnel plots were used to assess potential bias and perform funnel plot tests for asymmetry to investigate potential publication bias if there were more than 10 trials in a single meta-analysis, with $p < 0.05$ considered to present statistical significance.

RESULTS

Results of the Search and Study Characteristics. In total, 2174 studies were identified from various databases during the literature search. After eliminating 1,233 duplicated articles, 941 articles were screened according to the titles and abstracts. Thereafter, 918 irrelevant studies were removed. After reading the full text for the second selection step, 14 articles were excluded. Finally, a total of 9 studies were identified for this meta-analysis [35–43]. Figure 2 presents the flow diagram of study identification and selection. Results of the quality assessment of all included studies are shown in Supplementary Figures 1–4. All the case series were judged to be of adequate quality. The characteristics of each included study are shown Table 1.

Among all the included studies, 5 were designed as randomized controlled trials, among 9 studies, 6 were published in the USA, and one in each of the following countries: Egypt, Saudi Arabia, and Australia.

Zinc supplementation outcomes. Five trials reported in-hospital mortality among patients with and without zinc

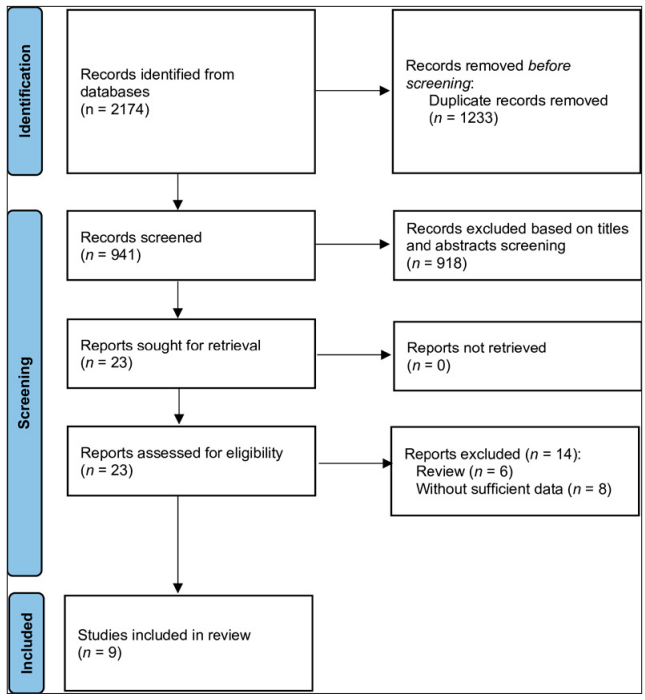

Figure 2. PRISMA flow diagram of the study selection process

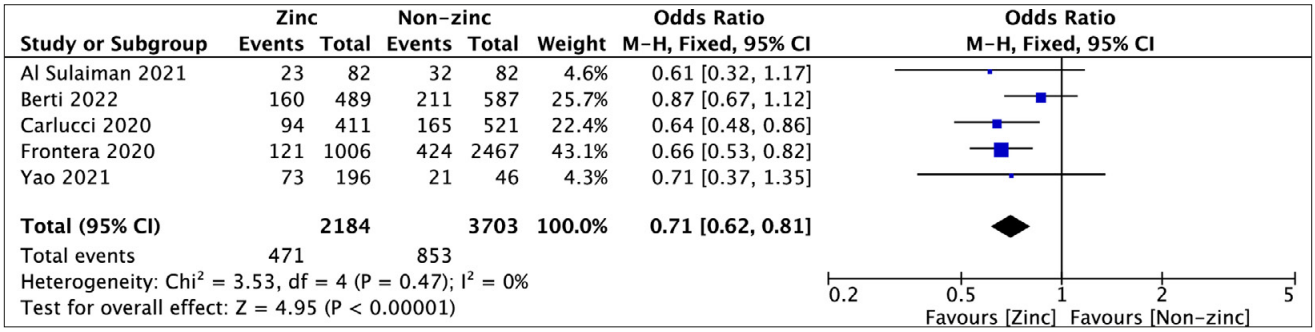

Figure 3. Forest plot of in-hospital mortality among COVID-19 patient with and without zinc supplementation. The centre of each square represents the odds ratios for individual trials; the corresponding horizontal line represents a 95% confidence interval. The diamonds indicate pooled results

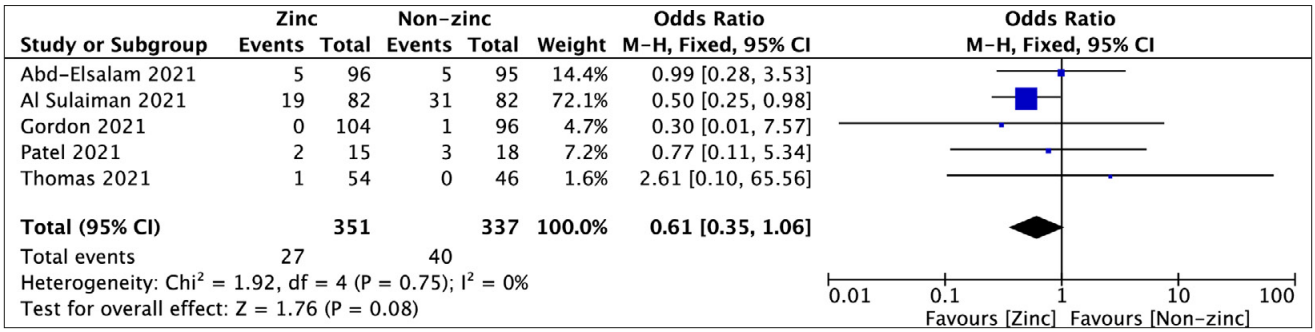

Figure 4. Forest plot of 28-day – 30-day mortality among COVID-19 patient with and without zinc supplementation. The centre of each square represents the odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds indicate pooled results

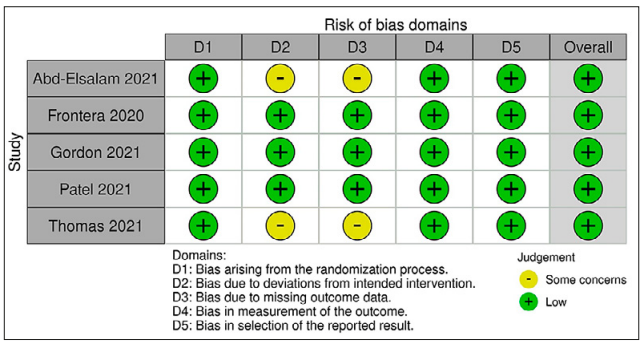

Figure S1. A summary table of review authors' judgements for each risk of bias item for each randomized study

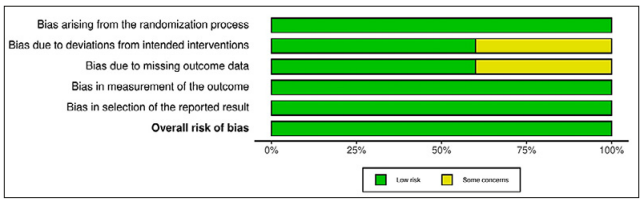

Figure S2. A plot of the distribution of review authors' judgements across randomized studies for each risk of bias item

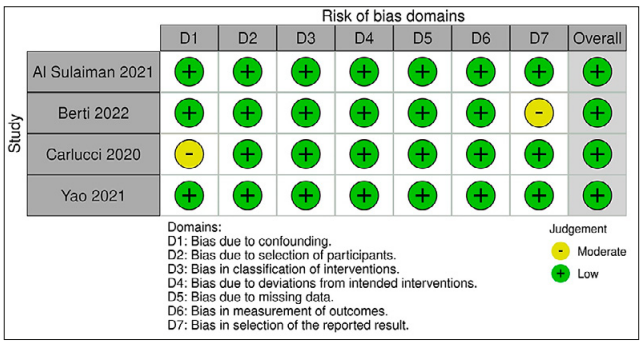

Figure S3. A summary table of review authors' judgements for each risk of bias item for each non-randomized study

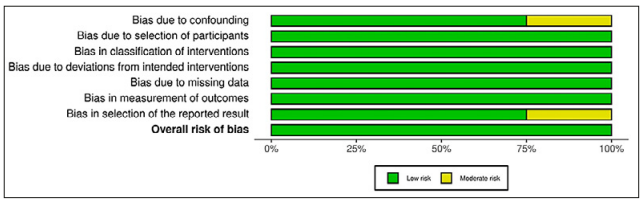

Figure S4. A plot of the distribution of review authors' judgements across non-randomized studies for each risk of bias item

supplementation [36–39, 43]. Pooled analysis showed that in-hospital mortality in zinc supplementation patients, and patients treated without zinc, varied and amounted to 21.6% vs. 23.04% difference (OR = 0.71; 95%CI: 0.62 – 0.81; p<0.001 (Fig. 3). Sub-analysis by group, depending on the type of study, showed that compared to the control group, zinc supplementation was associated with lower in-hospital mortality in randomized trials (12.0% vs. 17.2%; OR = 0.66; 95%CI: 0.53 – 0.82; p<0.001), as well as in retrospective studies (29.7% vs. 34.7%; OR = 0.74; 95%CI: 0.62 – 0.89; p=0.001).

Pooled analysis of 28-day to 30-day mortality in patients treated with zinc was 7.7% compared to 11.9% for patients treated without zinc (OR = 0.61; 95%CI: 0.35 – 1.06; p=0.08 (Fig. 4) [35, 36, 40, 41, 42]. Sub-analysis, depending on the type of study, showed that 28-d/30-d mortality supplementation, compared to the control group, was 3.0% vs. 3.5%, respectively (OR=0.91; 95%CI: 0.36 to 2.32; p=0.84). In contrast, in a retrospective study by Al Sultaman et al., 30-day mortality in the case of using zinc was statistically significantly lower than in the control group (23.2% vs. 37.8%, respectively; OR = 0.50; 95%CI: 0.25 – 0.98; p=0.04).

Table 1. Baseline characteristics of included trials

Study	Country	Study design	With zinc supplementation			Without zinc supplementation		
			No. of patients	Age	Gender male	No. of patients	Age	Gender male
Abd-Elsalam et al. 2021	Egypt	Randomized trial	96	43.48 ± 14.62	52 (54.2%)	95	43.64 ± 13.17	64 (67.4%)
Al Sulaiman et al. 2021	Saudi Arabia	Retrospective study	82	58.2 ± 13.9	65 (79.3%)	82	58.0 ± 16.5	54 (67.2%)
Berti et al. 2022	USA	Retrospective study	489	65.5 ± 9.35	323 (67.9%)	587	67.8 ± 9.7	369 (62.8%)
Carlucci et al. 2020	USA	Retrospective study	411	63.19±15.18	264 (64.2%)	521	61.83±15.97	320 (61.4%)
Frontera et al. 2020	USA	Randomized trial	1006	63.75 ± 3.5	604 (60.0%)	2467	63.25 ± 4.5	1344 (38.8%)
Gordon et al. 2021	USA	Randomized trial	104	74.0 ± 6.74	40 (38.5%)	96	71.1 ± 8.15	37 (38.5%)
Patel et al. 2021	Australia	Randomized trial	15	59.8 ± 16.8	11 (73.3%)	18	63.8 ± 16.9	10 (55.5%)
Thomas et al. 2021	USA	Randomized trial	58	44.1 ± 14.8	21 (36.2%)	50	42.0 ± 14.6	19 (38.0%)
Yao et al. 2021	USA	Retrospective study	196	65 ± 4.0	110 (56.1%)	46	71 ± 6.5	27 (58.9%)

In-hospital adverse events among patients treated with and without COVID-19 did not show any statistically significant differences in relation to acute kidney injury occurrence (12.8% vs. 12.4%, respectively; OR = 0.63; 95%CI: 0.19 – 2.12; p=0.45), as well as the need for mechanical ventilation (13.2% vs. 14.1%; OR = 0.83; 95%CI: 0.52 – 1.32; p=0.43).

DISCUSSION

Data from this systematic review and meta-analysis were compiled from 9 studies which investigated the effects of zinc supplementation on the mortality rate of COVID-19 patient. The main finding was that zinc supplementation improved the outcomes of COVID-19 when measured in terms of in-hospital mortality. The zinc-supplemented group had a significantly lower mortality rate in COVID-19 patients. Administration of zinc to patients with COVID-19 should be considered, especially in patients in whom it is significantly reduced, as this may result in the reduced production of antibodies against the virus and impeded activation of cytotoxic T lymphocytes and NK cells that enable the fight against infection [44, 45, 46].

Recent studies have also shown that a higher zinc level suppresses the expression of ACE2, which may reduce the SARS-CoV-2 virus interaction with its receptor. Conversely, lower zinc levels may increase the interaction of ACE2 with the viral spike protein, which may suggest the mechanism of a preventive role of zinc in COVID-19 [47].

Previously published meta-analyses indicated the high efficacy of zinc on mortality in COVID-19 patients [48]. One such meta-analysis confirmed that the use of zinc was associated with significantly lower mortality; pooled OR [95%CI] was 0.57 [0.43 – 0.77] ($p < 0.001$) [49]. However, that meta-analysis included a much smaller number of study participants compared to the current study. It should be noted that even earlier meta-analyses showed that oral and nasal zinc was effective in reducing the duration of viral infection and the intensity of symptoms [50]. However, the results of analysis of the influence of zinc on the prevention of viral infection are inclusive [51].

However, a recently published meta-analysis has led to quite different conclusions. Beran et al. investigated how supplementation with vitamin C, D, and zinc affects mortality in cases of COVID-19 [52]. The intubation rate and length of hospital stay were assumed as secondary endpoints. The meta-analysis showed that neither vitamin C, vitamin D, nor zinc reduced the mortality rate in COVID-19. Only the use of vitamin D influenced the intubation rate and length of hospital stay. The authors concluded that although zinc did not affect mortality, it cannot be ruled out that it affects the intensity of the symptoms of infection and improves the quality of life. It was not without significance that the studies included in the meta-analysis did not identify patients with initial deficiency [52]. The studies published at the beginning of the pandemic, however, emphasized that zinc should be recommended for patients hospitalized due to COVID-19. The authors emphasized a significantly higher benefit-risk ratio in the case of short but intensive supplementation, and the cost-effectiveness of such therapy [53, 54]. Earlier scientific works also indicated an attempt to use zinc in complex therapies, e.g., triple-therapy based on zinc, low-dose hydroxychloroquine, and azithromycin. The development of knowledge has shown, however, that this approach is not an effective therapeutic solution [42]. Moreover, QT prolongation may pose a significant risk, although, the frequency of adverse events remains relatively low [55].

In the context of supplementing micro- and macronutrients in COVID-19, 2 aspects remain invariably important. First, identifying patients with clinically significant deficiencies and replenishing the deficiencies as quickly as possible. Secondly, micronutrient and macronutrient deficiencies may be a predictor of a more severe course of infection and more rapid progression. Both aspects are related to each other and show clinically important implications for routine practice [56, 57].

Currently, it is known that zinc plays a very important role in the human body; therefore, its supplementation should be considered in patients with COVID-19, although more detailed data is needed. Zinc supplementation can result in adverse consequences, including nausea, vomiting, diarrhea, lethargy, and disorders of copper metabolism. Therefore it is necessary to conduct extensive randomized controlled studies to determine the appropriate dose of zinc supplementation in patients with COVID-19 [58, 59]. It should also be borne in mind that long-term zinc supplementation can lead to copper deficiency. Copper deficiency, on the other hand, has serious health consequences, including neurological deficits (cognitive disorders), osteoporosis and hepatosplenomegaly [60].

Limitations of the study. The current study also has limitations since the number of studies currently available do

not provide sufficient data on the impact of various dosages, and the proper length of therapy, on the desired outcome. Additionally, various zinc supplementation durations and dosages were employed in each of the studies cited in the current study. The recommended duration of treatment with zinc, however, remains unknown. To determine the precise impact of the intervention on different variables, evaluation of the impact using a common protocol is needed. This includes the effects of supplementation in individuals with severe baseline zinc insufficiency, and in patients with varying coexisting comorbid illnesses.

Another limitation is the diversity of the therapeutic standard for the treatment of COVID-19. Throughout the epidemic, a different scope and access to the recommended therapies has been observed. It is also difficult to define the standard of care. Additionally, early mortality after admission to hospital, e.g., within 24 hours, should also exclude patients from studies aimed at demonstrating the effectiveness of zinc supplementation. The fact that numerous clinical trials have been conducted during the pandemic should also be carefully considered. The effects of investigated medicinal products and the potential interaction with zinc cannot be completely excluded. To fully comprehend these limitations, more substantial randomized controlled trials with adequate sample sizes are required. Determination of the initial concentration of micro- and macro-elements and identification of clinically significant deficiencies will enable better stratification of the study population. Consequently, it will allow for the creation of evidence-based therapy.

CONCLUSIONS

Zinc supplementation is associated with lower COVID-19 in-hospital mortality. Additionally, it is risk-free in COVID-19 patients since there have been no negative side-effects, such as acute renal damage or the requirement for mechanical ventilation, compared to patients without COVID-19. Due to scientific evidence and the role it represents in the human body, zinc supplementation should be taken into consideration for COVID-19 patients as an adjunct therapy. However, due to the small number of studies included in the presented meta-analysis, more significant randomized studies with large patient populations are required to draw definite conclusions regarding the beneficial effects of zinc supplementation in COVID-19 patients.

Funding
This research received no external funding.

Institutional Review Board Statement
Not applicable.

Informed Consent Statement
Not applicable.

Data Availability Statement
Data supporting the findings of this study are available from the corresponding author [L.S.], upon reasonable request.

Acknowledgments
The study was supported by the ERC Research Net and by the Polish Society of Disaster Medicine.

Conflicts of Interest
The authors declare no conflict of interest.

REFERENCES

1. Dzieciatkowski T, Szarpak L, Filipiak KJ, et al. COVID-19 challenge for modern medicine. Cardiol J. 2020;27(2):175–183. https://doi.org/10.5603/CJ.a2020.0055
2. Szarpak L, Pruc M, Nadolny K, et al. Role of a field hospital in COVID-19 pandemic. Disaster Emerg Med J. 2020;5(4):221–223. https://doi.org/10.5603/DEMJ.a2020.0046
3. Chirico F, Sagan D, Markiwicz A, et al. SARS-CoV-2 virus mutation and loss of treatment and preventive measures as we know it now. Disaster Emerg Med J. 2021;6(4):204–205. https://doi.org/10.5603/DEMJ.a2021.0025
4. Pruc M, Gasecka A, Szarpak L, et al. Adverse reactions of COVID-19 vaccination: where do they come from? Disaster Emerg Med J. 2021;6(1):48–49. https://doi.org/10.5603/DEMJ.a2021.0004
5. Batra K, Effah-Acheampong J, Batra R, et al. Evolution of SARSCoV-2 variants: A rapid literature scan. J Health Soc Sci. 2022;7(2):141–151. https://doi.org/10.19204/2022/VLTN3
6. Gozhenko A, Szarpak L, Jaguszewski MJ, et al. COVID-19 vaccine – third dose, booster dose? What is it and is it necessary? Disaster Emerg Med J. 2021;6(4):208–209. https://doi.org/10.5603/DEMJ.a2021.0027
7. Yaman E, Demirel B, Yimaz A, et al. Retrospective evaluation of laboratory findings of suspected paediatric COVID-19 patients with positive and negative RT-PCR. Disaster Emerg Med J. 2021;6(3):97–103. https://doi.org/10.5603/DEMJ.a2021.0023
8. Katipoğlu B, Öztürk Sönmez L, Vatansev H, et al. Can hematological and biochemical parameters fasten the diagnosis of COVID-19 in emergency departments? Disaster Emerg Med J. 2020;5(4):175–181. https://doi.org/10.5603/DEMJ.a2020.0039
9. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. The Lancet. 2020;395(10229):1014–1015. https://doi.org/10.1016/S0140-6736(20)30633-4
10. Białorudzki M, Izdebski Z. Changes in the body mass of adult residents of rural and urban areas in the initial months of the COVID-19 pandemic vs. their mental, physical and sexual health. Ann Agric Environ Med. 2021;28(4):667–675. https://doi.org/10.26444/aaem/143561
11. Szarpak L, Zaczynski A, Kosior D, et al. Evidence of diagnostic value of ferritin in patients with COVID-19. Cardiol J. 2020;27(6):886–887. https://doi.org/10.5603/CJ.a2020.0171
12. Schmidt W, Jóźwiak B, Czabajska Z, et al. On-admission laboratory predictors for developing critical COVID-19 during hospitalization – a multivariable logistic regression model. Ann Agric Environ Med. 2022;29(2):274–280. https://doi.org/10.26444/aaem/145376
13. Szarpak L, Rafique Z, Gasecka A, et al. A systematic review and meta-analysis of effect of vitamin D levels on the incidence of COVID-19. Cardiol J. 2021;28(5):647–654. https://doi.org/10.5603/CJ.a2021.0072
14. Fialek B, Pruc M, Smereka J, et al. Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis. Cardiol J. 2022 Jun 28. https://doi.org/10.5603/CJ.a2022.0056
15. Mackiewicz B, Lemieszek MK, Dulkiewicz J. COVID 19 – Possible interrelations with respiratory comorbidities caused by occupational exposure to various hazardous bioaerosols. Part II. Clinical course, diagnostics, treatment and prevention. Ann Agric Environ Med. 2021;28(1):27–43. https://doi.org/10.26444/aaem/133896
16. Frangos T, Maret W. Zinc and cadmium in the aetiology and pathogenesis of osteoarthritis and rheumatoid arthritis. Nutrients. 2020;13(1):53. https://doi.org/10.3390/nu13010053
17. Hojyo S, Fukada T. Roles of zinc signaling in the immune system. J Immunol Res. 2016;2016:6762343. https://doi.org/10.1155/2016/6762343
18. Iddir M, Brito A, Dingeo G, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. Nutrients. 2020;12(6):1562. https://doi.org/10.3390/nu12061562
19. Ibs K-H, Rink L. Zinc-Altered Immune function. J Nutr. 2003;133(5Suppl 1):1452S–6S. https://doi.org/10.1093/jn/133.5.1452S
20. Prasad AS. Lessons learned from experimental human model of zinc deficiency. J Immunol Res. 2020;2020:9207279. https://doi.org/10.1155/2020/9207279.
21. Cakman I, Kirchner H, Rink L. Zinc supplementation reconstitutes the production of interferon-α by leukocytes from elderly persons. J Interferon Cytokine Res. 1997;17(8):469–472. https://doi.org/10.1089/jir.1997.17.469

22. Te Velthuis AJ, van den Worm SH, Sims AC, et al. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010;6(11):e1001176. https://doi.org/10.1371/journal.ppat.1001176
23. Xue J, Moyer A, Peng B, et al. Chloroquine is a zinc ionophore. PLoS One. 2014;9(10):e109180. https://doi.org/10.1371/journal.pone.0109180
24. Wang J, Mei J, Ren G. Plant microRNAs: biogenesis, homeostasis, and degradation. Front Plant Sci. 2019;10:360. https://doi.org/10.3389/fpls.2019.00360
25. Boretti A, Banik BK. Zinc role in Covid-19 disease and prevention. Vacunas. 2022;23(2):147–150. https://doi.org/10.1016/j.vacun.2021.08.003
26. Zheng J, Zhangm XX, Yum H, et al. Zinc at cytotoxic concentrations affects post-transcriptional events of gene expression in cancer cells. Cell Physiol Biochem. 2012;29(1–2):181–188. https://doi.org/10.1159/000337599
27. Szarpak Ł, Nowak B, Kosior D, et al. Cytokines as predictors of COVID-19 severity: evidence from a meta-analysis. Pol Arch Intern Med. 2021;131(1):98–99. https://doi.org/10.20452/pamw.15685
28. Szarpak L, Pruc M, Gasecka A, et al. Should we supplement zinc in COVID-19 patients? Evidence from a meta-analysis. Pol Arch Intern Med. 2021;131(9):802–807.
29. https://doi.org/10.20452/pamw.16048.
30. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
31. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
32. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
33. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments Res Synth Methods. 2021;12(1):55–61. https://doi.org/10.1002/jrsm.1411
34. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. https://doi.org/10.1186/1471-2288-5-13
35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
36. Abd-Elsalam S, Soliman S, Esmail ES, et al. Do Zinc Supplements Enhance the Clinical Efficacy of Hy-droxychloroquine?: a Randomized, Multicenter Trial. Biol Trace Elem Res. 2021;199(10):3642–3646. https://doi.org/10.1007/s12011-020-02512-1
37. Al Sulaiman K, Aljuhani O, Al Shaya D, et al. Evaluation of zinc sulfate as an adjunctive therapy in COVID-19 critically ill patients: a two center propensity-score matched study. Crit Care. 2021;25(1):363. https://doi.org/10.1186/s13054-021-03785-1
38. Berti AD, Kale-Pradhan PB, Giuliano CA, et al. Clinical Outcomes of Zinc Supplementation Among COVID-19 Patients. Curr Drug Saf. 2022;17(4):366–369. https://doi.org/10.2174/1574886317666220317115023
39. 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(10):1228–1234. https://doi.org/10.1099/jmm.0.001250
40. Frontera JA, Rahimian JO, Yaghi S, et al. Treatment with Zinc is Associated with Reduced In-Hospital Mortality Among COVID-19 Patients: A Multi-Center Cohort Study. Res Sq. 2020; rs.3.rs-94509. https://doi.org/10.21203/rs.3.rs-94509/v1
41. Gordon AM, Hardigan PC. A Case-Control Study for the Effectiveness of Oral Zinc in the Prevention and Mitigation of COVID-19. Front Med (Lausanne). 2021;8:756707. https://doi.org/10.3389/fmed.2021.756707
42. Patel O, Chinni V, El-Khoury J, 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. 2021;93(5):3261–3267. https://doi.org/10.1002/jmv.26895
43. 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(2):e210369. https://doi.org/10.1001/jamanetworkopen.2021.0369
44. Yao JS, Paguio JA, Dee EC, et al. The Minimal Effect of Zinc on the Survival of Hospitalized Patients With COVID-19: An Observational Study. Chest. 2021;159(1):108–111. https://doi.org/10.1016/j.chest.2020.06.082
45. Jothimani D, Kailasam E, Danielraj S, et al. COVID-19: Poor outcomes in patients with zinc deficiency. Int J Infect Dis. 2020;100:343–349. https://doi.org/10.1016/j.ijid.2020.09.014
46. Ghanei E, Baghani M, Moravvej H, et al. Low serum levels of zinc and 25-hydroxyvitmain D as potential risk factors for COVID-19 susceptibility: a pilot case-control study. Eur J Clin Nutr. 2022;76(9):1297–1302. https://doi.org/10.1038/s41430-022-01095-5
47. Ali N, Fariha KA, Islam F, et al. Assessment of the role of zinc in the prevention of COVID-19 infections and mortality: A retrospective study in the Asian and European population. J Med Virol. 2021; 93(7):4326–4333. https://doi.org/10.1002/jmv.26932
48. Devaux CA, Rolain J-M, Raoult D. ACE2 receptor polymorphism: susceptibility to SARS-CoV-2, hyper-tension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect. 2020;53(3):425–435. https://doi.org/10.1016/j.jmii.2020.04.015
49. Szarpak L, Pruc M, Gasecka A, et al. Should we supplement zinc in COVID-19 patients? Evidence from a me-ta-analysis. Pol Arch Intern Med. 2021;131(9):802–807. https://doi.org/10.20452/pamw.16048
50. Tabatabaeizadeh SA. Zinc supplementation and COVID-19 mortality: a meta-analysis. Eur J Med Res. 2022;27(1):70. https://doi.org/10.1186/s40001-022-00694-z
51. Hunter J, Arentz S, Goldenberg J, et al. Zinc for the prevention or treatment of acute viral respiratory tract infections in adults: a rapid systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2021;11(11):e047474. https://doi.org/10.1136/bmjopen-2020-047474
52. Vlieg-Boerstra B, de Jong N, Meyer R, et al. Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: A systematic review and meta-analysis. Allergy. 2022;77(5):1373–1388. https://doi.org/10.1111/all.15136
53. Beran A, Mhanna M, Srour O, et al. Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: A comprehensive systematic review and meta-analysis. Clin Nutr ESPEN. 2022;48:167–177. https://doi.org/10.1016/j.clnesp.2021.12.033
54. Alexander J, Tinkov A, Strand TA, et al. Early Nutritional Interventions with Zinc, Selenium and Vitamin D for Raising Anti-Viral Resistance Against Progressive COVID-19. Nutrients. 2020;12(8):2358. https://doi.org/10.3390/nu12082358
55. Pal A, Squitti R, Picozza M, et al. Zinc and COVID-19: Basis of Current Clinical Trials. Biol Trace Elem Res. 2021;199(8):2882–2892. https://doi.org/10.1007/s12011-020-02437-9
56. Eftekhar SP, Kazemi S, Barary M, et al. Effect of Hydroxychloroquine and Azithromycin on QT Interval Prolongation and Other Cardiac Arrhythmias in COVID-19 Confirmed Patients. Cardiovasc Ther. 2021; 2021:6683098. https://doi.org/10.1155/2021/6683098
57. Pecora F, Persico F, Argentiero A, Neglia C, Esposito S. The Role of Micronutrients in Support of the Immune Response against Viral Infections. Nutrients. 2020;12(10):3198. https://doi.org/10.3390/nu12103198
58. Im JH, Je YS, Baek J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. Int J Infect Dis. 2020 Nov;100:390–393. doi: 10.1016/j.ijid.2020.08.018
59. Fosmire GJ. Zinc toxicity. Am J Clin Nutr. 1990;51(2):225–227. https://doi.org/10.1093/ajcn/51.2.225
60. Meng-Yuan Li, Lin Li, Zhang Yeu, Xiao-Sheng Wang. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020;9(1):45. https://doi.org/10.1186/s40249-020-00662-x
61. Duncan A, Yacoubian C, Watson N, Morrison I. The risk of copper deficiency in patients prescribed zinc supplements. J Clin Pathol. 2015;68(9):723–725. https://doi.org/10.1136/jclinpath-2014-202837