



Systematic Review and Meta-Analysis

Zinc Deficiency as Predictor of COVID-19 Severity: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Despite the fact that zinc deficiency is asymptomatic, its incidence is rising worldwide, with no visible clinical manifestation. Mineral and vitamin supplementation to prevent the inflammatory response is a major concern during the COVID-19 pandemic. Zinc may play a role in the development of a stronger immunological response. Nonetheless, there is insufficient information to investigate the benefits of zinc on its own regarding COVID-19. Sufficient zinc serum alone should decrease the severity of COVID-19 to some extent. This systematic study discussed the impact of zinc deficiency on the severity of COVID-19 infection.

Material and Methods: We used the search phrases "COVID-19" or "SARS-CoV-2" and "Zinc Deficiency" to look for publications published between 2020 and April 2021 in Google Scholar, PubMed, SCOPUS, and ProQuest. All of the information was examined qualitatively.

Results: There are three papers that discuss the benefits of zinc and indicate that zinc deficiency has a key influence on the severity of COVID-19. According to one study, there is no link between zinc deficiency and COVID-19 severity.

Conclusions: COVID-19 infection is linked to low zinc levels in the blood. It may become a risk factor for COVID-19 severity or a contributing factor that goes unnoticed in regular practice. Zinc supplementation or zinc baseline serum may play a role in determining potential daily supplementation and treatment for patients at risk of zinc insufficiency in the COVID-19 group in RCT and better design studies.

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INTRODUCTION

Zinc's contribution to human health is confined to a few areas, such as diarrhea and immunological function. A pro-inflammatory condition and a disruption of reduction-oxidation metabolism are linked to zinc deficiency. While the SARS-CoV-2 pandemic, also known as COVID-19, continues to spread, research into the best treatment options is limited, and some studies suggest that zinc deficiency may be linked to severe COVID-19 infection [1].

Many versions of the disease remain asymptomatic over the world (40 percent of cases), while 15% of cases

are severe and have a high fatality rate [2]. Patients with comorbidities such as diabetes, hypertension, immunological weakness, metabolic disease, kidney or cardiac disease, and even pregnancy, according to many reports, are vulnerable to severe forms of COVID-19. These comorbidities are likely due to immune system weakness [3,4].

Zinc aids the immune system by balancing the neutrophil-lymphocyte ratio, improving T cell function and balancing the Th17/Treg ratio, and regulating interferon release, among other things. Zinc is also required for DNA synthesis, protein stability, the apoptosis process, and signalling in body cells [5]. When

zinc shortage arises, the risk of bacterial pneumonia rises, owing to a reduction in macrophage alveolar activity and the adaptive immune response. In COVID-19 infection, such a mechanism is unknown [6].

Zinc is one of the minerals recommended by the Ministry of Health as a supportive treatment for COVID-19 infection, however, its effectiveness is debatable [7]. As a result, we undertake a systematic review to assess the impact of zinc deficiency on COVID-19 infection.

MATERIAL AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline was used in this systematic review. We systematically searched databases using the search keywords "COVID-19" or "SARS-CoV-2" and "Zinc Deficiency" that were published between 2020 and 2022 using google scholar, PubMed, SCOPUS, and ProQuest. Similar results were quickly ruled out. All investigators extensively screened the whole text and abstracts before compiling a list. Severity of COVID-19 in this study was defined as moderate, severe or critically ill patients. Non-symptomatic and mild were defined as non-severe, which were not included in the Forest plot analysis. The studies should mention the severity explicitly.

Article Eligibility

The retrieved articles' titles and abstracts were scanned for potential relevance and reviewed inclusion eligibility. All titles and abstracts will be screened according to strict criteria as listed in Table 1.

The physician (AR) re-examined the mismatched findings to see if they fit the inclusion eligibility requirements. Full versions or pre-proofed journals may be used for data analysis among the papers that met the selection criteria, and a secondary search of the specified citations was undertaken to guarantee that all relevant

publications were included. This systematic review covered articles written in both English and Indonesian. The searches were placed between January 2020 and April 2022.

Data Appraisal and Extraction

Data extracted from the identified publication included: study design and outcome, number of patients, follow-up during the intervention, intervention information, efficacy, and comments. We used a table where each piece of information was written descriptively (Table 2).

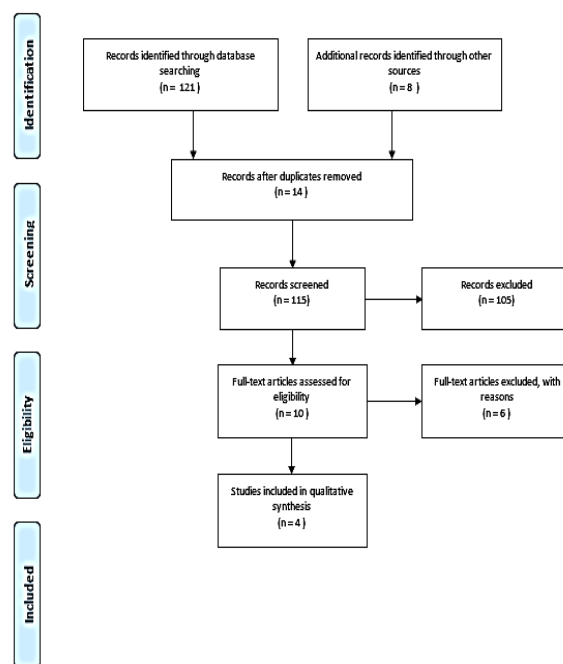


Fig. 1. Summary of database finding

Table 1. Article Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
Types of studies	Retrospective, prospective, or cross-sectional studies, randomized controlled trials evaluate the effect of low zinc levels regardless of clinical status in COVID-19 infection. All evidence levels, including safety data were acceptable for safety analysis inclusion.	No serum zinc mentioned
Types of Participants	Patients (irrespective of age, sex or race) with COVID-19 infection who had zinc serum checked in hospital or out hospital.	a. Non clinical studies or high bias studies b. Editorial letter or expert opinions Patients without COVID-19 infection confirmed or based only on rapid test without RT PCR confirmation.
Types of intervention	Zinc serum baseline	
Types of comparators	COVID-19 patients	
Types of Efficacy Outcome Measures Safety Outcome Measures	Could include (but not limited to): a. Zinc serum and outcome of COVID-19 prognosis Could include (but not limited to): a. Mortality b. Serious adverse events c. Specific adverse events which may be occurred	

Table 2. Characteristics of the included studies

Study Design	Country	Quality Study (NOS Score)	Characteristic of participant	Age (mean / median)	N (A vs B)	Low zinc (A vs B)	Follow up	Comment
Prospective cohort	India	7	Hospitalized COVID-19 patients	34,0 vs 32,0	47 vs 45	27 vs 5	One time sample added	COVID-19 infection is associated with low zinc serum
Prospective observational	Turkey	7	Hospitalized COVID-19 patients	13,3 years	100 patients	11 vs 89	During hospitalization	In low zinc serum population, there is high risk of hospitalization due to COVID-19 infection
Observational Cohort	Spain	6	Hospitalized COVID-19 patients	65 years old	249 patients	58 vs 191	During hospitalization	Lower serum zinc correlates with worsening clinical presentation, mortality, and stabilization
Cross sectional	Iran	6	Non Hospitalized COVID-19 patients	41 ± 13 years old	53 vs 53	14 vs 39	Not mentioned	Zinc deficiency is not related with poor COVID-19 outcome

A, zinc-deficient group; B, non zinc-deficient group; COVID-19, coronavirus disease 2019; NOS: New Castle Ottawa Scale; N/A, not available

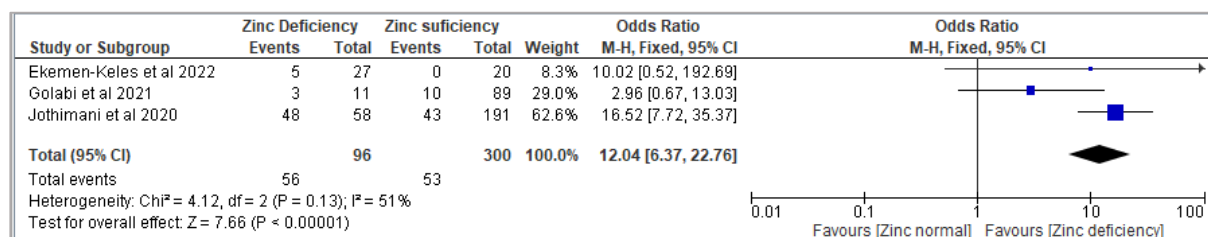


Fig. 2. Forest plot of zinc deficiency related severe COVID-19

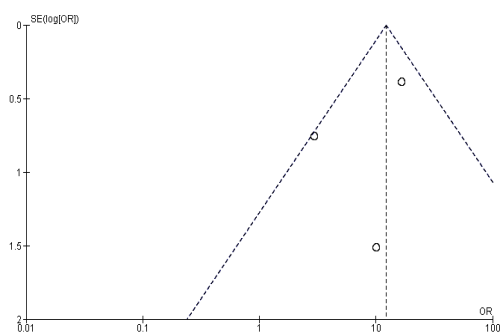


Fig. 3. Funnel plot analysis

RESULTS

Characteristics of Included Studies

There are 129 findings, of which 14 articles were excluded due to duplication. After a thorough screening, 101 papers were discarded. Another ten papers were excluded after a full review, which resulted in 4 studies included in this systematic review (Fig. 1).

Zinc Deficiency Related Severe COVID-19

To test the impact of zinc deficiency on the COVID-19, we included 3 studies [8-10] with 381 participants. We cannot compute the data from Golabi et al [8] because of non-dichotomous data. The data. These data showed that zinc deficiency is not associated with COVID-19 severity (OR 12,04 [6.37 - 22.76], p = 0.13; I²: 51%, p < 0.00001) (Fig. 3).

Publication Bias

The funnel plot of this study based on mortality outcome is shown in Fig. 3. There was no potential publication bias in mortality with some studies falling outside the 95% CI of the funnel plot.

DISCUSSION

The pathogenesis of COVID-19 is linked to immune system imbalance. IL-6, C-reactive protein (CRP), and tumor necrosis factor (TNF)-related hyperinflammatory reactions are linked to the recruitment of a large number of highly activated immune cells, tissue damage, fibrotic

lung, and even mortality. Meanwhile, the anti-inflammatory response is insufficient [9]. Many patients experience severe respiratory distress, which leads to pulmonary edema and limited oxygen perfusion [10].

This study shows no significant effect on zinc-deficiency related severity of COVID-19. Two studies show non-inferiority studies, while only one shows a significant effect of zinc deficiency related to COVID-19 severity. This result may interfere with other known factors such as comorbidity, vitamin D status, and age. We cannot exclude other effects because of the low sample size.

Zinc is an immunomodulator and plays a crucial function in immunological development at many stages. Decreased lymphoid cell linkage and natural killer (NK) cell function are linked to zinc deficiency. The ADAM enzyme (A-disintegrin and metalloproteinase) is an adamalysin protein family inc-dependent cell surface protein that plays a key function in inflammation. By blocking the enzyme and both of these processes, targeting ADAM17 at the zinc cofactor location causes inflammation to be reduced [11]. Zinc serum appears to be low in individuals with COVID-19 compared to healthy subjects, according to a Jothimani study [12], in COVID-19 patients, low baseline zinc serum is linked to increased problems, longer hospital stays, and higher mortality rates [12].

In line with other research, serum zinc levels below 50 g/dL at the time of diagnosis were associated with a poor prognosis, poor stability, and even increased mortality [11,13]. According to the authors, COVID-19 patients with low serum zinc concentrations had a worsened immune response, particularly the innate immune response. Zinc deficiency is linked to the release of pro-inflammatory cytokines to compensate for the innate response, as well as increased reactive oxygen species generation. As a result, both innate and adaptive immunity become unbalanced [14].

The results of Golabi *et al.* are quite different. The main reason is that the study included vitamin D as a covariate in the analysis, which skews the results. Although vitamin D deficiency has been linked to a poorer outcome, zinc deficiency has not been linked to a negative effect. The study's comparator is likely non-infected people who could introduce bias into the results [8]. We searched through all hospitalized patients to measure the zinc serum along with COVID-19 infection progress. In Golabi study, there is a high risk of bias because when the serum zinc was taken, there was no telling whether patient was worsening or not. The study has a high-rate loss to follow-up. We cannot perform ethnic differentiation subgroup due to limited data in our inclusion criteria.

CONCLUSION

Low zinc serum may be associated with poor outcomes of COVID-19 infection and become a risk factor or the contributing factor to COVID-19 severity, which is not noticed in daily practice. This study shows no significant statistic of low zinc serum related to COVID-19. RCT and stronger design studies on zinc supplementation or zinc baseline serum may play a role in determining potential daily supplementation and treatment for people at risk of zinc deficiency in the COVID-19 population

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CONFLICT OF INTEREST

The writer claims to be free of any conflicts of interest.

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