REVIEW ARTICLE

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Zinc deficiency effect on clinical features of Coronavirus Disease 2019 patients: A scoping review

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ABSTRACT

COVID-19 was declared a pandemic in March 2020. Various therapeutic guidelines have been established for treating COVID-19, such as anti-inflammatory, antiviral therapies, and zinc supplementation. Zinc deficiency is thought to worsen the condition of patients with COVID-19 infection. However, the effect of zinc deficiency on COVID-19 patients has not been widely reported. In this scoping review, we aim to explore the impact of zinc deficiency on the clinical features of COVID-19 patients. A comprehensive search was conducted across the databases, including PubMed, ScienceDirect, Springer Link, ProQuest, and Google Scholar, using the keywords "Zinc" AND "(COVID-19 or SARS-CoV-2)". A total of 2,458 articles published between 2019 and 2020 were screened following the PRISMA guidelines and subjected to critical appraisal. Three articles were included, focusing on the effect of zinc deficiency on the clinical features of COVID-19 patients. As of 2022, two articles reported worsening symptoms, one described an increased hospitalization duration, and one reported worsening treatment outcomes in the zinc deficiency group. This review concludes that zinc deficiency worsens symptoms, increases the duration of hospitalization, and leads to worse outcomes in COVID-19 patients.

Keywords: adjunct therapy, COVID-19, SARS-CoV-2, zinc, zinc deficiency

Introduction

The World Health Organization (WHO) declared a Coronavirus Disease 2019 (COVID-19) pandemic on March 11, 2020 [1]. COVID-19 is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. According to the WHO report, global confirmed COVID-19 cases have surpassed 250 million, resulting in over 5 million reported fatalities. The transmission of COVID-19 primarily occurs through droplets of saliva or nasal secretions containing the SARS-CoV-2 virus [3]. The average incubation period for COVID-19 ranges from 5 to 14 days after infection before symptoms manifest [4]. Most COVID-19 patients experience mild to moderate respiratory distress and recover without requiring special treatment [5]. However, elderly patients or those with underlying chronic conditions such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer face a higher risk of severe symptoms [6]. Efforts to improve the recovery rate for COVID-19 patients have led to exploring various therapies, including anti-inflammatory agents, antiviral drugs, cellular therapy, immunotherapy, and administering micronutrients with potential efficacy [2,7].

One such micronutrient recommended by the National Institute of Health (NIH) as adjuvant therapy is zinc. Zinc has been shown in previous studies to reduce pneumonia incidence in developing countries and positively impact viral infections by acting as an antioxidant and immune system regulator. Furthermore, *in vitro* experiments have demonstrated zinc's ability to inhibit the replication

cycle of coronaviruses, suggesting a possible role in treating COVID-19 patients [8].

Despite these findings, the research on the benefits and potential side effects of zinc adjunct therapy for COVID-19 patients remains limited [9]. Additionally, there are variations in therapeutic guidelines regarding zinc usage across different countries. For instance, while Malaysia's therapy manual and the guidelines issued by the Infectious Diseases Association of America do not include additional zinc therapy for COVID-19 patients, Indonesia's COVID-19 guidelines recommend considering additional zinc therapy based on the symptom severity and patient age. Despite the lack of extensive research and differences in zinc therapy recommendations, zinc deficiency is considered to influence the clinical presentation and treatment outcomes of COVID-19 patients [9]. This study aims to explore the effect of zinc deficiency on the clinical cases of COVID-19 patients.

Methods

Literature search was carried out to identify articles from international journals that focused on the impact of zinc deficiency on the clinical features of hospitalized COVID-19 patients. The search was performed across databases including PubMed, ScienceDirect, SpringerLink, ProQuest, and Google Scholar. Inclusion criteria encompassed articles published between 2019 and 2021, articles written in English, and studies employing either a randomized control trial (RCT) or a cohort study design. Exclusion criteria comprised review articles, theses, dissertations, web-based publications, research reports, and duplicate articles. Studies that did not align with the PICOS criteria, those featuring a different study population or exposure, those lacking a comparison sample, and studies focusing on outcomes other than the clinical features of COVID-19 patients (such as symptom severity, hospitalization duration, and treatment results) were also excluded.

The eligibility of the chosen articles was critically evaluated using the article eligibility criteria checklist designed for cohort studies by the Joanna Briggs Institute [16]. This research protocol adhered to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Scoping Review) method, as illustrated in Figure 1 [10].

Results

The initial research identified a total of 2,458 articles, and following the application of inclusion and exclusion criteria, five articles were subjected to eligibility screening. Ultimately, three articles met the criteria and were included in the review. All three articles, originating from different countries—including India, Spain, and Japan—were published in 2020. These articles constituted cohort and observational studies, which were confirmed through critical review.

The analysis focused on the impact of zinc deficiency on clinical features in COVID-19 patients, utilizing the three selected articles (Table 1). All three studies used a cohort study design involving 403 adult research subjects. Zinc deficiency was determined through examinations of serum zinc levels, with values below 50 µg/dl, below 70 µg/dl, and below 80 µg/dl. The measurements were conducted using fully automated analyzers, such as the Indiko Plus analyzer (Thermo Scientific, USA), Accuras Auto Zn (Shino-test Corporation, Tokyo), and Automatic Analyzer AU5800 (Beckman Coulter, Inc., Tokyo, Japan). Through statistical analysis, these studies also controlled and excluded covariate factors, including age, the patient's initial conditions, other laboratory values, and additional variables [11–13]. The analysis of the impact of zinc deficiency on COVID-19 patients' clinical features yielded the following results:

The severity of COVID-19 in patients with zinc deficiency

Vogel-González et al. found that patients with zinc deficiency had a significantly higher severity based on MEWS scores than normal patients (p=0.005). Yasui et al. reported that COVID-19 patients with zinc deficiency experienced more severe cases of COVID-19 compared to normal COVID-19 patients, with a ratio of 3 (14%) vs. 6 (86%), respectively
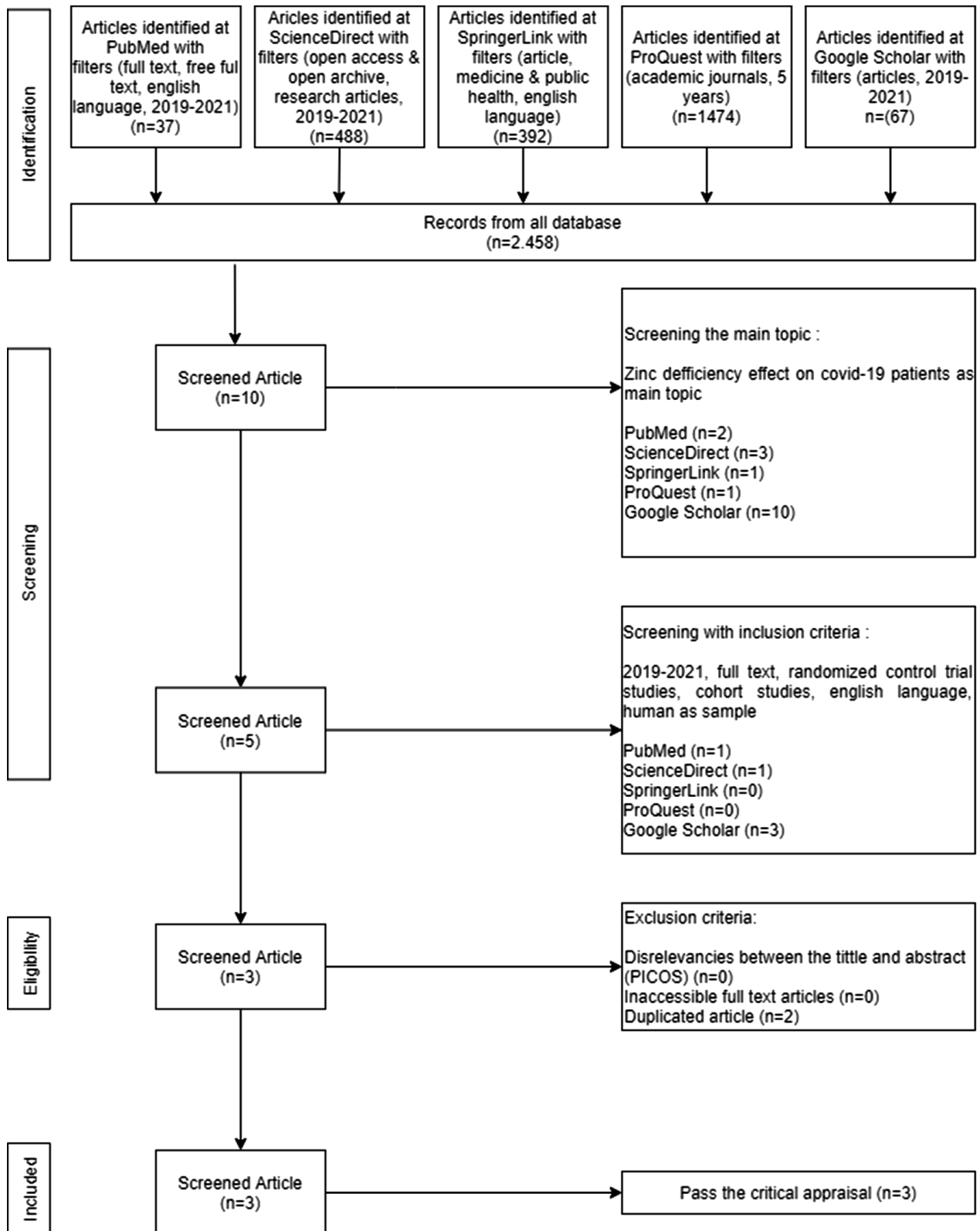
Figure 1. PRISMA-ScR Diagram

(p=0.0003). Jothimani et al. observed that while severity did not exhibit a significant difference, complications were more prevalent in patients with zinc deficiency (70.4%) compared to normal patients (30.3%) (p=0.009) [11–13].

Length of hospital stay in patients with zinc deficiency

Jothimani et al. indicated that COVID-19 patients with zinc deficiency experienced a significantly longer hospitalization duration than normal patients, with a ratio of 7.9 days vs. 5.7 days, respectively (p=0.048) [13].

Treatment outcomes of patients with zinc deficiency

Vogel-González et al. reported significantly higher mortality rates in COVID-19 patients with zinc deficiency than normal patients, with a mortality ratio of 21% vs. 5%, respectively (p<0.001). Conversely, Jothimani et al. found no significant difference in mortality between COVID-19 patients with or without zinc deficiency [11,13].

These outcomes collectively suggest that zinc deficiency may impact on the severity of COVID-19 cases, length of hospitalization, and treatment outcomes, although variations may exist across the different studies.

Table 1. Zinc deficiency effect on COVID-19 patients clinical features

Title (author)	Time, Location	Research Design	Sample	Exclusion	Exposure	Measurement Method	Results	Statistics and Covariates Tests
Low zinc levels at clinical admission associated with poor outcomes in COVID-19 (Vogel-González et al.) [11]	2020, Barcelona, Spain	Cohort observational retrospective study	Data were taken from the electronic medical records of 249 COVID-19 patients with 58 patients experiencing serum zinc deficiency at the Del Mar hospital from March 9 – To April 1, 2020	Variables have collinearity with MEWS or age	Zinc deficiency (Serum zinc content < 50 µg/dl)	1. **Zinc levels (serum)** (Only mentioned taken from fasting blood) 2. **Degree of severity** Measured with *Modified Early Warning Score* (MEWS)	1. **Serum zinc levels** Median serum zinc at admission 61 µg/dl, 58 (23%) had serum zinc < 50 µg/dl 2. **Degree of severity** Patients with serum zinc <50 µg/dl had worse clinical manifestations vs normal patients with MEWS score (2 (2-3) vs 2 (1-3), (p=0.005). 3. **Median length of time to reach clinical stability** Serum zinc deficiency patients vs normal patients: 25 days (14-36) vs 8 (5-14), (p<0.001) 4. **Death rate** Serum zinc deficiency patients vs normal patients : 21% vs 5% (p<0.001)	**Statistic test**: 1. Mann-Whitney U-test, X^2 test, and Fisher's exact test were used to compare individual differences with serum zinc above and below 50µg/ml 2. Bi-variate comparisons and multiple logistic regression models were used to study the impact of serum zinc levels at hospital admission on mortality adjusted for age, sex, comorbidities, and symptom severity. **Covariate:** It has been controlled by the statistical test

Title (author)	Time, Location	Research Design	Sample	Exclusion	Exposure	Measurement Method	Results	Statistics and Covariates Tests
Analysis of the predictive factors for a critical illness of COVID-19 during treatment — relationship between serum zinc level and critical illness of COVID-19 (Yasui et al.) [12]	2020, Osaka, Jepang	Cohort study	Data were taken from 62 COVID-19 patients with 6 of them having serum zinc deficiency who were treated at Sakai City Medical Center on March 24 – May 24, 2020	Died patient	Zinc deficiency (<70 µg/dL)	1. **Zinc levels (serum)** Accurate Auto Zn (Shino-test Corporation, Tokyo) dan automatic analyzer (Automatic Analyzer AU5800, Beckman Coulter, Inc., Tokyo, Japan) 2. **Degree of severity** Based on the 9 ordinal scale scores described in the synopsis of the COVID-19 therapeutic trial	1. **Zinc levels** There were 9 patients with zinc deficiency 2. **Degree of severity** Mild/moderate vs severe in patients with zinc deficiency: 3 (14%) vs 6 (86%), (p=0.0003)	**Statistic test:** 1. Chi-squared and Student-t-test were used to analyze the categorical data and variables 2. Multivariate logistic analysis to predict severe cases using two factors, lactate dehydrogenase (LDH), and age 3. Multivariate logistic analysis to predict severe cases using two factors, LDH, and age **Covariate:** LDH
COVID-19: Poor outcomes in patients with zinc deficiency (Jothimani et al.) [13]	2020, India	Observational prospective study	Patient data were taken from 47 COVID-19 patients with zinc deficiency and 45 control patients with normal zinc levels on 17 – 27 May 2020	Patients who are not hospitalized and patients who are not willing to participate in the study	Zinc deficiency (< 80 µg/dl)	1. **Zinc levels (serum)** Measured with a fully automated Indiko Plus analyzer (Thermo Scientific, USA) using the colorimetric method. 2. **Degree of severity** (not explained)	1. **Zinc levels** Test patients (IQR 53.4-94.6 µg/dl) vs controls (IQR 95.65-120.90 µg/dl) (p<0.001) 2. **Degree of severity** Test patients vs controls: mild: 21 (77.8%) vs 18 (90%), moderate : 1 (3.7%) vs 2 (10%), severe: 5 (18.5%) vs 0 (p=0.09) 3. **Hospitalization duration** Test patients (≥7 days) (59.2% vs 30.0%, p=0.047); the average length of stay was 7.9 days (test patients) vs 5.7 days (controls) (p=0.048) 4. **Mortality rate** Test patient vs control: 5 (18.5%) vs 0 (0%), p=0.06 5. **Appearance of complication** Test patient vs control : 19 (70.4%) vs 6 (30.0%), p=0.009 6. **ARDS** Test patient vs control : 18.5% vs 0%, p=0.063	**Statistic test:** 1. Fisher's exact test was used to compare proportions and characteristic associations between study samples 2. Mann-Whitney U-test and t-test were used to compare the continuous variables of the study 3. Univariate logistic regression analysis was used to determine the OR and 95% CI **Covariate:** LDH and corticosteroid

Discussion

Based on the findings from articles examining the influence of zinc deficiency on the clinical features of COVID-19 patients, two articles reported an exacerbation of clinical severity, while another article discovered no significant difference in clinical severity. Furthermore, two articles indicated an extension in the length of hospital stay, and two articles reported increased mortality rates among COVID-19 patients with zinc deficiency compared to those exhibiting normal zinc levels [11–13]. These results parallel a previous study by Goncalves et al., which demonstrated a high prevalence of critically ill COVID-19 patients experiencing severe acute respiratory distress syndrome and concurrently low serum zinc levels [14].

The impact of zinc deficiency on the clinical features of COVID-19 patients may be attributed to zinc's role as a trace element that participates in diverse immune responses. Zinc plays a crucial role in the development and activation of innate immune system cells, including neutrophils, natural killer cells, T and B lymphocytes, and macrophages. Moreover, zinc influences the secretion and expression of pro-inflammatory cytokines such as IL-1β, MIP-1α, and NF-κB activation while also stimulating CD4+ cells. Conversely, zinc deficiency is associated with decreased production and expression of anti-inflammatory factors like GATA-3, IL-4, IL-13, and M2 macrophages, indicating an imbalance between pro-inflammatory and anti-inflammatory factors [15,16]. Additionally, zinc's capacity to protect the body from oxidative stress and free radicals holds significance [17,18]. The interplay of an imbalance of immune response, the effects of free radicals, and oxidative stress due to zinc deficiency in COVID-19 patients may exacerbate of severity, prolong hospital stays, inferior treatment outcomes, and even mortality. Notably, plasma zinc levels in elderly individuals tend to be lower than in younger subjects, thereby escalating oxidative stress and pro-inflammatory mediator formation among older individuals [17]. These findings strengthen the association between zinc deficiency and the deterioration of clinical conditions in COVID-19 patients.

However, this study has some limitations. Notably, it should have comprehensively covered other covariates that may influence severity, length of hospitalization, and treatment outcomes. Moreover, the limitation of this study lies in the limited number of available articles on randomized control trials and cohort studies concerning zinc and COVID-19 during the data collection process. Furthermore, the articles under study may have confounding variables that are inherently challenging to eliminate, given sample size constraints.

In conclusion, the discussion above highlights the notable impact of zinc deficiency on the clinical features of COVID-19 patients. These findings align with previous studies and emphasize the importance of considering zinc supplementation as an integral component of the treatment regimen for COVID-19 patients. However, further research is needed to address the limitations and to explore potential confounding factors comprehensively. Figure 2 provides a summary of the discussion.

Conclusion

This review establishes a link between zinc deficiency and the exacerbation of COVID-19 symptoms, prolonged hospital stays, and poorer treatment outcomes. These findings highlight the importance of addressing zinc requirements and suggest the potential benefits of implementing supplementary zinc therapy for hospitalized COVID-19 patients. However, further research, particularly randomized control studies with rigorous controls, is necessary to reinforce these conclusions and gain a more comprehensive understanding of zinc's role in shaping the clinical manifestation of COVID-19.

Author contributions

MIJ conducted data collection, formal analysis, methodology, writing – original draft, LAG and MP contributed to conceptualization, writing – review and editing. MP finalized the manuscript.
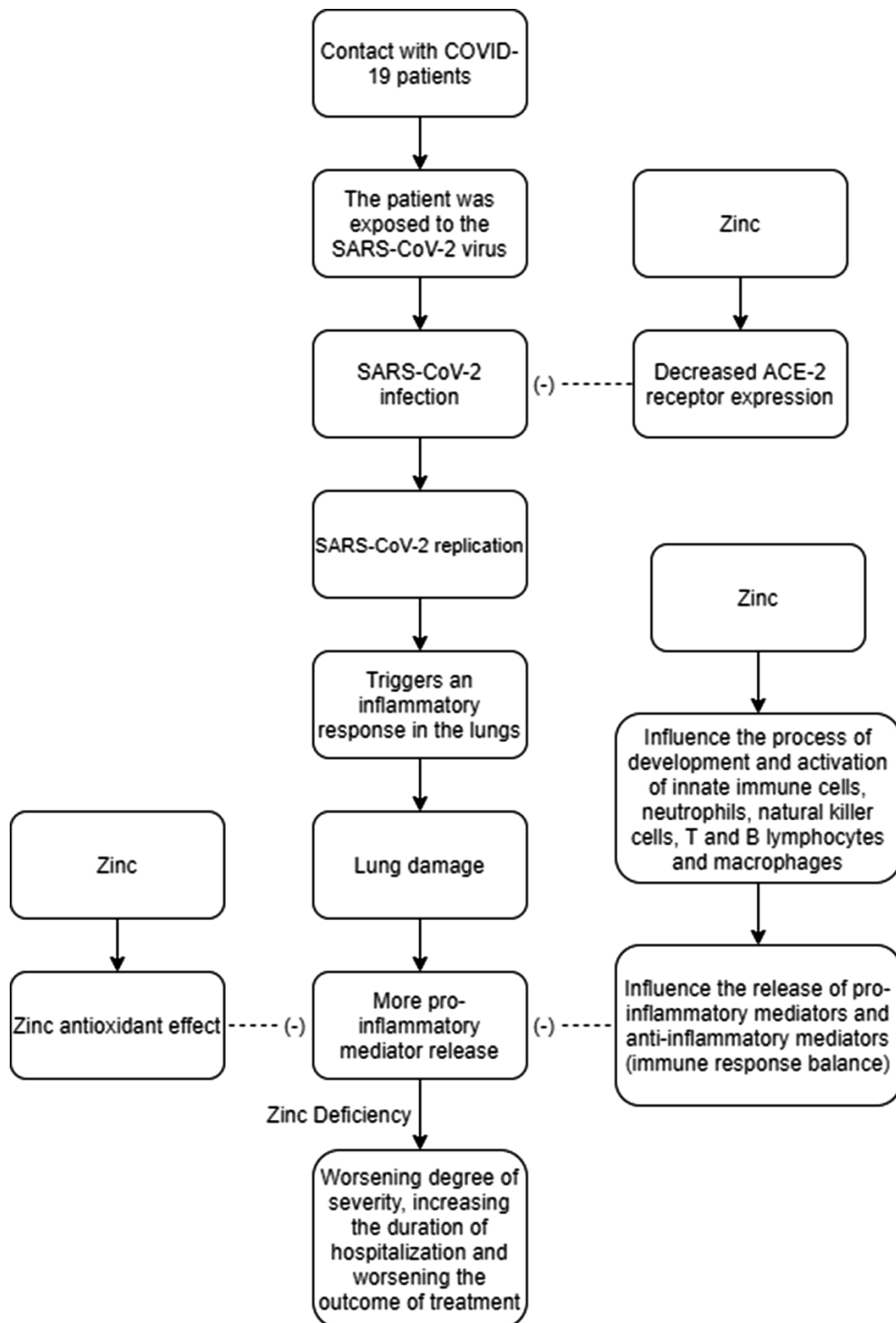
Figure 2. The possibility of zinc's role mechanism

Declaration of interest

The author indicates that there is no conflict of interest in this article.

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