

Zinc deficiency is a potential risk factor for COVID-19 progression to pneumonia requiring oxygen therapy

Koji Fujita^{a,b}, Kazuki Ocho^b, Tomoka Kadowaki^c, Takashi Yorifuji^c, Hideharu Hagiya^d,
Fumio Otsuka^{a*}

^aDepartment of General Medicine, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

^bDepartment of General Internal Medicine and Infectious Diseases, Tsuyama Chuo
Hospital, Tsuyama, Japan

^cDepartment of Epidemiology, Okayama University Graduate School of Medicine,
Dentistry and Pharmaceutical Sciences, Okayama, Japan

^dDepartment of Infectious Diseases, Okayama University Hospital, Okayama, Japan

Corresponding author:

Fumio Otsuka, MD, PhD

Department of General Medicine

Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical

Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama, 700-8558, Japan

TEL: +81-86-235-7342; FAX: +81-86-235-7345

E-mail: fumiotsu@md.okayama-u.ac.jp

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ABSTRACT

Introduction: Various risk factors for developing severe coronavirus disease 2019 (COVID-19) have been reported. However, studies on the nutritional-related risk factors are limited. In this study, we investigated the effects of serum zinc deficiency on the severity of COVID-19.

Methods: The study included a total of 60 COVID-19 patients who were admitted to Tsuyama Chuo Hospital between March 2020 and April 2021. We divided the patients into two categories based on serum levels of zinc (normal and latent zinc deficiency vs. zinc deficiency [$<60 \mu\text{g/dL}$]) at the time of diagnosis. Severity of COVID-19 was defined as the most exaggerated disease status during admission. The associations between serum zinc deficiency and the severity of COVID-19 were examined using a logistic regression model adjusted for potential confounders.

Results: Patients who required oxygen therapy had a higher prevalence of comorbidities and poorer nutritional status, including zinc deficiency, than those who did not require oxygen therapy. Zinc deficiency was associated with an increased risk of COVID-19 severity, with an adjusted odds ratio of 7.29 (95% confidence interval: 1.70–31.18). This result remained significant in the sensitivity analyses conducted after adjusting for patient background factors.

Conclusions: Zinc deficiency at the time of COVID-19 diagnosis is an independent risk factor for severe disease. Our findings need to be validated in external studies.

Key word: COVID-19; zinc; severity; nutritional risk factor

1. Introduction

The coronavirus disease 2019 (COVID-19) which is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has tremendously impacted human health [1]. After infection with SARS-CoV-2, most patients typically experience mild symptoms or are asymptomatic [2]. The prognosis of the disease varies greatly and is influenced by several factors such as the virus strain, underlying diseases, and other clinical variables [3,4]. When patient health deteriorates and the infection becomes severe, a prompt transfer to a specialized, acute-care facility is necessary. However, in the chaos of the pandemic, managing both hospital bed availability and inter-facility transfers was challenging. Therefore, it is important to predict patient outcome from a bed management perspective.

Currently, various risk factors for severe COVID-19 have been described [5,6]. However, there is a paucity of reports examining the nutritional-related factors affecting the severity of COVID-19. Of all the nutritional factors, the role of zinc has recently garnered significant attention because of its function in maintaining host immunity [7]. Notably, zinc is an important mineral that has anti-inflammatory and

antioxidant properties [8]. Even before the COVID-19 pandemic, several studies have described the importance of zinc in preventing severe cases of pneumonia [9]. After the COVID-19 pandemic, some clinical studies supported the role of zinc in mitigating the pathogenesis of COVID-19 [10,11]. But these findings are yet to be fully corroborated.

In the present study, we aimed to examine the association between serum zinc deficiency and COVID-19 severity in patients admitted to a Japanese acute-care hospital.

2. Patients and Methods

2.1 Study participants

This retrospective, observational study included a total of 60 COVID-19 patients admitted to the Tsuyama Chuo Hospital between March 31, 2020 and April 30, 2021.

The hospital is a core healthcare facility in the northern part of Okayama, Japan, covering a population of approximately 300,000 people. The facility is designated as a Class II Designated Medical Institutions by the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases.

2.2 Data collection

Demographic and clinical data of patients was collected from the electronic chart of the hospital, including age, sex, body mass index, underlying diseases, activities of daily living (ADL), laboratory data on admission, and the most exacerbated status (i.e., severity) of COVID-19 during the hospitalization period. The Sequential Organ Failure Assessment (SOFA) score was used to assess the septic status of the patients at the time of COVID-19 diagnosis. The difference between the baseline SOFA score (i.e., calculated based on the previous data before contracting COVID-19) and the SOFA score at the time of diagnosis (Δ SOFA score) was measured to evaluate sepsis. The baseline SOFA scores were available for all the patients because they all had either regular outpatient visits or had been admitted to the hospital for other reasons.

Performance status (PS) was used to assess ADLs. The PS ranged from 0 to 4, with 0 was defined as fully active, no performance restrictions, 1 was defined as strenuous physical activity restricted, fully ambulatory and able to carry out light work, 2 was defined as capable of all self-care but unable to carry out any work activities, up and about >50% of waking hours, 3 was defined as capable of only limited self-care,

confined to bed or chair >50% of waking hours, and 4 was defined as being completely disabled, cannot carry out any self-care, totally confined to bed or chair. Prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR) were calculated as follows:

$$\text{PNI} = \text{albumin (g/L)} + 5 \times \text{total lymphocyte counts (10}^9\text{/L)}; \text{ and}$$

$$\text{NLR} = \text{total neutrophil counts} / \text{total lymphocyte counts}.$$

2.3 Zinc deficiency

Drawing from our clinical observations, febrile patients often exhibit zinc deficiency, necessitating nutritional intervention. Thus, we have routinely measured serum zinc levels of such cases, while ensuring alignment with insurance provisions. Serum zinc levels were measured using an atomic absorption spectrophotometry at the time of COVID-19 diagnosis. We collected blood samples early in the morning when the patients were awake, fasted, and resting. Based on previous studies [12], zinc status for each patient was defined as zinc deficiency <60 µg/dL; latent zinc deficiency between

60 to 79 $\mu\text{g/dL}$; and normal $\geq 80 \mu\text{g/dL}$. For the analysis, we divided the patients into two groups i.e., normal or latent zinc deficiency vs. zinc deficiency.

2.4 Severity of COVID-19

According to the Japanese guidelines [13], COVID-19 severity was categorized as mild, indicating cases without pneumonia ($\text{SpO}_2 \geq 96\%$); moderate I, indicating pneumonia cases not requiring oxygen therapy ($93\% < \text{SpO}_2 < 96\%$); moderate II, indicating pneumonia cases necessitating oxygen therapy ($\text{SpO}_2 \leq 93\%$); and severe, representing pneumonia cases requiring ventilator or intensive care management. Based on patients COVID-19 severity level during admission we categorized the patients into two groups for the analysis: the oxygen-therapy requiring group (moderate II and severe disease patients) and non-oxygen requiring group (mild and moderate I disease patients).

2.5 Statistical analyses

Baseline characteristics of the patients in the two groups categorized by the disease severity, demographic data, laboratory data, presence or absence of sepsis, COVID-19

severity both on admission and during hospitalization were compared. Continuous variables were summarized as the median and interquartile range (IQR). Data was analyzed using the Fisher's exact test or the Mann-Whitney U test as appropriate.

For the primary analysis, we explored the association between serum zinc deficiency at the initial testing and the severity of COVID-19 using logistic regression, with the normal or subclinical zinc deficiency group as the reference. We estimated crude odds ratios (ORs) and 95% confidence intervals (CIs) for severity, and then performed analysis adjusted for age (continuous), sex (dichotomy), PNI (>40 or ≤ 40 ; dichotomy), and NLR (≥ 5 or < 5 ; dichotomy) to estimate adjusted ORs and 95% CIs. We selected these potential confounders based on our clinical experience and previous research findings [14].

For the secondary analysis, we sub-categorized patients with Δ SOFA score < 2 to exclude those who exhibited severe conditions at admission. Further, we divided the patients into two age groups of < 75 years or ≥ 75 years and repeated the analysis. We used 75 years as the cutoff age because the fatality rate is reportedly high for patients who are into the category of late-elderly patients aged ≥ 75 years [15].

In the sensitivity analysis, we further adjusted for several potential confounders including chronic kidney disease (CKD), congestive heart failure (CHF), and chronic obstructive pulmonary disease (COPD), and serum albumin level, to assess the robustness of the findings. Additionally, we excluded patients who were administered oxygen on admission or at the time of diagnosis and repeated the analysis.

All statistical analyses were conducted using Stata statistical software (Stata SE version 17; Stata Corp LP, College Station, TX, USA). *P*-values less than 0.05 were considered statistically significant.

2.6 Ethics

This study was approved by the Institutional Review Board of Tsuyama Chuo Hospital (No. 521). The ethics committee exempted the requirement for informed consent because this was a retrospective study and complete anonymity was ensured. We conducted the study in compliance with the guidelines for the Declaration of Helsinki.

3. Results

Table 1 shows a descriptive analysis of the patients categorized by COVID-19 severity.

Patients age was significantly higher in the oxygen-therapy requiring group (median, 75 years vs. 71 years). Comparison of comorbidities indicated proportions of ex-smokers (43.9% vs. 10.5%), current-smokers (7.3% vs. 5.3%), medical history of coronary heart disease (24.4% vs. 5.3%), diabetes mellitus (61.0% vs. 21.1%), and hypertension (65.9% vs. 15.8%) were significantly higher in the oxygen-therapy group vs. non-oxygen-therapy group. All the 60 patients had not been vaccinated against COVID-19. PS in the oxygen-therapy group appeared to be higher than the non-oxygen therapy group, but the difference was not statistically significant. Among 41 patients in the oxygen-therapy group, 20 (48.8%) patients were initially diagnosed as mild and 9 (21.9%) patients as moderate I cases at the time of diagnosis.

Regarding the laboratory data, inflammatory parameters such as white blood cell counts (median, 5,300 / μ L vs. 4,100 / μ L) and serum C-reactive protein (median, 4.5 mg/dL vs. 0.4 mg/dL) were significantly higher in the oxygen-therapy group vs. non-oxygen therapy group. The oxygen-therapy group had significantly higher NLR (median, 5.2 vs. 2.1) vs the non-oxygen therapy group. The serum albumin level

(median, 3.2 g/dL vs. 3.7 g/dL) and PNI (median, 35.1 vs. 42.7) in the oxygen-therapy group were significantly lower than the non-oxygen therapy group, indicating a nutritionally deteriorated status of the patients. Based on the serum zinc values, 35 (58.3%) patients had deficiency, 21 (35.0%) had latent deficiency, and 4 (6.7%) had zinc values within the normal range. Serum zinc levels were significantly lower in the oxygen-therapy requiring group (median, 51.0 µg/dL vs. 61.0 µg/dL; $p<0.001$). None of the patients had received prior supplementation with zinc.

Table 2 shows results for the primary analysis that examined the association between zinc deficiency and a deterioration of COVID-19 severity. Of the 25 normal or latent zinc deficiency patients, 10 (40%) patients were included in the oxygen-therapy requiring group. Among the 35 zinc deficiency patients, 31 (88.6%) patients had deteriorated during their clinical course and were categorized as oxygen-therapy requiring group. Crude OR for oxygen requirement in the zinc deficiency category was 11.63 (95% CI: 3.13–43.22). Even after adjustment for the potential confounders, zinc deficiency at the time of COVID-19 diagnosis was associated with the deterioration of COVID-19 condition, with an adjusted OR of 7.29 (95% CI: 1.70–31.18).

Table 3 shows the outcomes of the secondary analysis, which focused on patients with a Δ SOFA score <2 . There were 58 cases that met the criteria for the sub-analysis. The case numbers and proportions of normal or latent zinc deficiency were identical to the primary analysis. For this analysis, the total number in the zinc deficiency group decreased to 33, among which 29 (87.9%) patients required oxygen during hospitalization. Similar to the primary analysis, crude and adjusted ORs for oxygen therapy in the zinc deficiency category were as high as 10.88 (95% CI: 2.92–40.57) and 7.15 (95% CI: 1.67–30.59), respectively. After age-stratification of the data (at 75 years) the results did not change remarkably (**Supplementary Table 1**).

Table 4 shows the results of the sensitivity analysis. The adjusted OR for oxygen requirement in the zinc deficiency category after adjusting for CKD, CHF, and COPD was 7.76 (95% CI: 1.48–40.63). Similarly, the adjusted OR when adjusted for serum albumin level was 8.43 (95% CI: 1.81–39.30). After excluding 12 patients (20%) who had received oxygen before the onset of COVID-19, the adjusted OR was 9.44 (95% CI: 2.04–43.75).

4. Discussion

In this study, we examined the associations between serum zinc deficiency and the COVID-19 severity at an emergency hospital in Japan. The results showed that even after adjusting for potential variables, zinc deficiency in the early stages of the infection was related with an increased risk of COVID-19 severity. Furthermore, the results remained statistically significant in the sensitivity analyses. These findings are consistent with previous basic research studies [10,11], which demonstrated that zinc had anti-inflammatory properties and antioxidant effects and was significant in suppressing respiratory infections. In addition, our results align with previous clinical studies that reported an impact of zinc deficiency on COVID-19 severity and hospitalization duration [16]. Collectively, we provided new evidence on the association between zinc deficiency at the onset of COVID-19 and COVID-19 severity which might help predict the subsequent need for oxygen therapy in those patients.

Zinc is an essential mineral for the human body. Chronic zinc deficiency can cause taste disorders, anorexia, dermatitis, alopecia, dermatitis, and stomatitis [17]. In addition, recent report has shown a relationship between zinc deficiency and various

clinical symptoms that persist for a long time as Long COVID-19, such as fatigue and headache [18]. There are at least three mechanisms that possibly explain the present findings. First, the spike protein of SARS-CoV-2 interacts with human angiotensin-converting enzyme 2 (ACE2) enabling the SARS-CoV-2 to enter the cell. This ACE2 is a zinc-dependent peptidyl dipeptide hydrolase, and high zinc levels are known to suppress ACE2 expression and reduce its interaction with the virus [19,20]. Second, zinc can also exert its antiviral effects by inhibiting viral RNA synthesis, replication, DNA polymerase, reverse transcriptase, and protease [21,22]. Finally, defense mechanisms against viral infections are suppressed by zinc deficiency. Zinc is an antioxidant and can reduce lung damages, minimize secondary infections, improve the clearance function of the airway mucosa, and reduce the risk of hyperinflammation [23,24]. Also, zinc deficiency leads to decrease in lymphoid tissue and innate immunity possibly resulting in lower immune response to SARS-CoV-2 [7].

The clinical question to be solved is whether supplementing zinc in the early phase of COVID-19 can prevent the severity progression of COVID-19. Currently available data do not support the initiation of zinc therapy immediately after the disease

onset to mitigate the clinical course of COVID-19 [24]. However, a meta-analysis suggests that zinc therapy can reduce mortality in patients with COVID-19 [25]. The severity of the infection varies on a case-by-case basis, and it remains to be elucidated whether zinc administration can help inhibit the disease progression in patients with COVID-19. Nevertheless, older individuals who constitute the majority of hospitalized patients during the COVID-19 pandemic had zinc deficiency [26]. The findings of this study indicate that zinc deficiency could be a contributing factor to severe disease, and it may be worthwhile to broadly remedy zinc deficiency in the high-risk elderly population, especially during a pandemic when there is a shortage in availability of hospital beds.

The study has several strengths. First, the effect of zinc deficiency was evaluated in unimmunized patients because the vaccination had yet to be available at that time. Second, we accurately assessed the severity of patients right from the time of disease onset because it was necessary to hospitalize every COVID-19 patient during the study period.

The study also has several limitations that need to be addressed. First, some of the included patients had required oxygen before the disease onset, which could have impacted our assessment of severity of the infection. However, the findings remained significant in the sensitivity analysis. Second, it is difficult to distinguish whether the serum zinc levels evaluated upon admission is reflective of baseline values before the COVID-19 onset or due to an influence of acute phase of the disease. But the statistical significance of the results remained consistent when we excluded the patients with sepsis at admission. Third, because this is a single-center study, generalizability may be limited. Fourth, as it is a retrospective observational study, residual confounding may be present. Furthermore, the small sample size may have limited the ability of logistic regression to adjust for confounders in the multivariable analysis; therefore, the findings need to be externally validated. Fifth, the study included unvaccinated patients admitted between March 31, 2020 and April 30, 2021 when therapeutic agents recommended in current guidelines were unavailable. Given that currently most of the population has received multiple vaccinations and effective treatment modalities are now in place, the influence of zinc deficiency during the initial phases of COVID-19 on the subsequent

clinical course may differ from the findings of this study. Sixth, 10 patients received zinc supplementation during their hospitalization based on test results (see Table 1). Because the zinc assays were outsourced, the turnaround time for results spanned one to two weeks. Thus, at the time of zinc administration, the severity of the patients' conditions had stabilized, categorized either as mild to warrant discharge or as severe to necessitate oxygen therapy. Therefore, the impact of zinc supplementation on the necessity for oxygen therapy—the primary endpoint of this investigation—appears negligible. Finally, this study did not explore whether administering zinc at the onset of COVID-19 could impede disease progression.

A major challenge during a pandemic is to ensure that healthcare facilities can accommodate patients. Reducing the number of hospital admissions is important from both clinical and health economics perspectives. Previous studies have reported an association between zinc deficiency and the severity of other viral respiratory diseases such as influenza and respiratory syncytial virus (RSV) infection [27,28]. Although the clinical impact of zinc deficiency as a factor contributing to COVID-19 severity may have changed owing to high vaccine coverage and the availability of new therapies, the

association between zinc deficiency and COVID-19 severity demonstrated in this study indicates that a similar hypothesis could be applicable to other respiratory viral infections. Given that zinc supplementation is economical and straightforward to administer, it is a potential therapeutic candidate in the early phase of novel viral pandemics when no effective treatment or vaccine is available.

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Conflicts of interest

None

References

1. Das K, Pingali MS, Paital B, Panda F, Pati SG, Singh A, et al. A detailed review of the outbreak of COVID-19. *Front Biosci (Landmark Ed)*. 2021 May 30;26(6):149–70. <https://doi.org/10.52586/4931>
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol*. 2021 Mar;19(3):141–54. <https://www.doi.org/10.1038/s41579-020-00459-7>.
3. Zhang JJ, Dong X, Liu GH, Gao YD. Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality. *Clin Rev Allergy Immunol*. 2023 Feb;64(1):90–107. <https://www.doi.org/10.1007/s12016-022-08921-5>
4. Horita N, Fukumoto T. Global case fatality rate from COVID-19 has decreased by 96.8% during 2.5 years of the pandemic. *J Med Virol*. 2023 Jan;95(1):e28231. <https://www.doi.org/10.1002/jmv.28231>
5. Centers for Disease Control and Prevention. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals, [Internet]. [cited 2023 Dec 3]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html>
6. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med*. 2021 Jun;26(3):107–8. <https://www.doi.org/10.1136/bmjebm-2020-111536>

7. Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *Am J Clin Nutr.* 1998 Aug;68(2 Suppl):447S-463S. <https://www.doi.org/10.1093/ajcn/68.2.447S>
8. Jarosz M, Olbert M, Wyszogrodzka G, Młyniec K, Librowski T. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF- κ B signaling. *Inflammopharmacology.* 2017 Feb;25(1):11–24. <https://www.doi.org/10.1007/s10787-017-0309-4>
9. Wang L, Song Y. Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: A meta-analysis of randomized, double-blind and placebo-controlled trials. *Clin Respir J.* 2018 Mar;12(3):857–64. <https://www.doi.org/10.1111/crj.12646>
10. Skalny A V, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, et al. Zinc and respiratory tract infections: Perspectives for COVID-19 (Review). *Int J Mol Med.* 2020 Jul;46(1):17–26. <https://www.doi.org/10.3892/ijmm.2020.4575>
11. Iddir M, Brito A, Dingeo G, Fernandez Del Campo SS, Samouda H, La Frano MR, et al. Strengthening the Immune System and Reducing Inflammation and Oxidative Stress through Diet and Nutrition: Considerations during the COVID-19 Crisis. *Nutrients.* 2020 May 27;12(6). <https://www.doi.org/10.3390/nu12061562>
12. Kodama H, Tanaka M, Naito Y, Katayama K, Moriyama M. Japan's Practical Guidelines for Zinc Deficiency with a Particular Focus on Taste Disorders, Inflammatory Bowel Disease, and Liver Cirrhosis. *Int J Mol Sci.* 2020 Apr 22;21(8). <https://www.doi.org/10.3390/ijms21082941>

13. Ministry of Health, Labor and Welfare of Japan. A Guide on Clinical Management of Patients with COVID-19 for Front-line Healthcare Workers version 10.0. , <https://www.mhlw.go.jp/content/001136687.pdf> [accessed 21 August 2023].
14. Karimi A, Shobeiri P, Kulasinghe A, Rezaei N. Novel Systemic Inflammation Markers to Predict COVID-19 Prognosis. *Front Immunol.* 2021;12:741061. <https://www.doi.org/10.3389/fimmu.2021.741061>
15. Ministry of Health, Labor and Welfare of Japan. Visualizing the data: information on COVID-19 infections [Internet]. [cited 2023 Dec 3]. Available from: <https://covid19.mhlw.go.jp/en/>
16. Jothimani D, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P, et al. COVID-19: Poor outcomes in patients with zinc deficiency. *Int J Infect Dis.* 2020 Nov;100:343–9. <https://www.doi.org/10.1016/j.ijid.2020.09.014>
17. Ozeki I, Yamaguchi M, Suii H, Tatsumi R, Arakawa T, Nakajima T, et al. The association between serum zinc levels and subjective symptoms in zinc deficiency patients with chronic liver disease. *J Clin Biochem Nutr.* 2020 May;66(3):253–61. <https://www.doi.org/10.3164/jcbn.19-99>
18. Matsuda Y, Tokumasu K, Otsuka Y, Sunada N, Honda H, Sakurada Y, et al. Symptomatic Characteristics of Hypozincemia Detected in Long COVID Patients. *J Clin Med.* 2023 Mar 6;12(5):2062. <https://www.doi.org/10.3390/jcm12052062>
19. Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. *J Microbiol Immunol Infect.* 2020 Jun;53(3):425–35. <https://www.doi.org/10.1016/j.jmii.2020.04.015>

20. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty*. 2020 Apr 28;9(1):45. <https://www.doi.org/10.1186/s40249-020-00662-x>
21. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G. The Role of Zinc in Antiviral Immunity. *Adv Nutr*. 2019 Jul 1;10(4):696–710. <https://www.doi.org/10.1093/advances/nmz013>
22. Ko YL, Morihara D, Shibata K, Yamauchi R, Fukuda H, Kunimoto H, et al. Factors Attenuating Zinc Deficiency Improvement in Direct-Acting Antiviral Agent-Treated Chronic Hepatitis C Virus Infection. *Nutrients*. 2018 Nov 2;10(11). <https://www.doi.org/10.3390/nu10111620>
23. Wessels I, Rolles B, Rink L. The Potential Impact of Zinc Supplementation on COVID-19 Pathogenesis. *Front Immunol*. 2020;11:1712. <https://www.doi.org/10.3389/fimmu.2020.01712>
24. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, 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 Feb 1;4(2):e210369. <https://www.doi.org/10.1001/jamanetworkopen.2021.0369>
25. Tabatabaeizadeh SA. Zinc supplementation and COVID-19 mortality: a meta-analysis. *Eur J Med Res*. 2022 May 23;27(1):70. <https://www.doi.org/10.1186/s40001-022-00694-z>
26. de Faria Coelho-Ravagnani C, Corgosinho FC, Sanches FLFZ, Prado CMM, Laviano A, Mota JF. Dietary recommendations during the COVID-19 pandemic.

Nutr Rev. 2021 Mar 9;79(4):382–93.

<https://www.doi.org/10.1093/nutrit/nuaa067>

27. Gopal R, Tutuncuoglu E, Bakalov V, Wasserloos K, Li H, Lemley D, et al. Zinc deficiency enhances sensitivity to influenza A associated bacterial pneumonia in mice. *Physiol Rep*. 2024;12(1):e15902.
<https://www.doi.org/10.14814/phy2.15902>
28. Sadeghsoltani F, Mohammadzadeh I, Safari MM, Hassanpour P, Izadpanah M, Qujeq D, et al. Zinc and respiratory viral infections: Important trace element in anti-viral response and immune regulation. *Biol Trace Elem Res*. 2022 9;200(6):2556–71. <https://www.doi.org/10.1007/s12011-021-02859-z>

Table 1. Demographic characteristics of the participants at baseline by oxygen supplementation (n=60)

	Oxygen required group (n=41)	Non-oxygen required group (n=19)	<i>p</i> -value
Background			
Sex, male, n (%)	22 (53.7)	9 (47.3)	0.66
Age, years, median (IQR)	75.0 (68.0–82.0)	71.0 (29.5–77.5)	0.002
Body mass index, medial (IQR)	22.7 (20.6–26.4)	23.0 (21.6–23.8)	0.51
Comorbidities			
Smoking status			
Ex-smokers, n (%)	18 (43.9)	2 (10.5)	0.005
Current-smokers, n (%)	3 (7.3)	1 (5.3)	0.76
CHF	10 (24.4)	1 (5.3)	0.03
Emphysema, COPD, or Asthma	12 (29.3)	2 (10.5)	0.11
Diabetes mellitus, n (%)	25 (61.0)	4 (21.1)	0.002
Chronic Kidney Disease, n (%)	5 (12.2)	2 (10.5)	0.85
Malignancy, n (%)	9 (22.0)	2 (10.5)	0.35
Hypertension, n (%)	27 (65.9)	3 (15.8)	<0.001

	Oxygen required group (n=41)	Non-oxygen required group (n=19)	<i>p</i> -value
Other conditions on admission			
Number of vaccination	0	0	-
Performance status, median (IQR)	0.0 (0.0–4.0)	0.0 (0.0–1.0)	0.12
delta SOFA Score compared with baseline SOFA, median (IQR)	1.0 (0.0–1.0)	0.0 (0.0–0.0)	<0.001
COVID-19 severity at the time of diagnosis			
mild (%)	20 (48.8)	12 (63.2)	
moderate I (%)	9 (21.9)	7 (36.8)	
moderate II (%)	12 (29.3)	0 (0)	
severe (%)	0 (0)	0 (0)	
Laboratory data			
WBC, /μL, median (IQR)	5300 (4000–8200)	4100 (3200–4950)	0.004
NLR, median (IQR)	5.2 (2.8–11.6)	2.1 (1.4–4.1)	<0.001
PNI, median (IQR)	35.1 (31.4–39.8)	42.7 (38.9–45.8)	<0.001

	Oxygen required group (n=41)	Non-oxygen required group (n=19)	<i>p</i> -value
Platelet, 10 ⁴ /μL, median (IQR)	19.0 (14.3–22.6)	18.1 (14.4–23.7)	0.73
Alb, g/dL, median (IQR)	3.2 (2.9–3.5)	3.7 (3.4–4.1)	<0.001
Cr, mg/dL, median (IQR)	0.75 (0.6–0.9)	0.75 (0.5–0.9)	0.18
CRP, mg/dL, median (IQR)	4.5 (2.8–9.5)	0.4 (0.3–2.0)	<0.001
HbA1c, %, median (IQR)	6.4 (5.6–6.9)	5.6 (5.4–5.9)	0.27
Zn, μg/dL, median (IQR)	51.0 (47.0–56.0)	61.0 (60.0–67.0)	<0.001
Zinc supplementation in patients with zinc deficiency	9 (21.9)	1 (5.3)	-

Abbreviations: IQR, Interquartile range; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; WBC, white blood cell; SOFA, sequential organ failure assessment; NLR, Neutrophile/Lymphocyte ratio; PNI, prognostic nutritional index; CRP, C-reactive protein.

The severity of each case was assessed based on the maximum level of severity observed during the hospital stay.

Table 2. Primary analysis of the association between zinc deficiency and COVID-19 severity.

	Case numbers in the oxygen required group / total number (%)	OR (95% CI)	
		Model 1: Crude (n=60)	Model 2* (n=60)
Zinc status			
Normal or latent deficiency	10/25 (40.0)	reference	reference
Deficiency (<60 µg/dL)	31/35 (88.6)	11.63 (3.13–43.22)	7.29 (1.70–31.18)

CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.

* Adjusted for age, sex, prognostic nutritional index (PNI), and neutrophil-to-lymphocyte ratio (NLR).

Table 3. Secondary analysis of the association between zinc deficiency and COVID-19 severity among patients with Δ SOFA <2 .

	Case numbers in the oxygen required group / total number (%)	OR (95% CI)	
		Model 1: Crude (n=58)	Model 2* (n=58)
Zinc status			
Normal or latent deficiency	10/25 (40.0)	reference	reference
Deficiency (<60 $\mu\text{g/dL}$)	29/33 (87.9)	10.88 (2.92–40.57)	7.15 (1.67–30.59)

CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

* Adjusted for age, sex, prognostic nutritional index (PNI), and neutrophil-to-lymphocyte ratio (NLR).

Table 4. Results of the sensitivity analysis

Zinc status	OR (95% CI)		
	Model 2* plus CKD, CHF, and COPD† (n=60)	Model 2* plus Albumin† (n=60)	Model 2* but excluding participants who already required oxygen at admission (n=48)
Normal or latent deficiency	reference	reference	reference
Deficiency (<60 µg/dL)	7.76 (1.48–40.63)	8.43 (1.81–39.30)	9.44 (2.04–43.75)

CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; OR, odds ratio.

* Adjusted for age, sex, prognostic nutritional index (PNI), and neutrophil-to-lymphocyte ratio (NLR).

† Further adjusted for potential confounders in the Model 2.