



## RESEARCH ARTICLE

# Assessment of the role of zinc in the prevention of COVID-19 infections and mortality: A retrospective study in the Asian and European population

Nurshad Ali<sup>1</sup>  | Khandaker A. Fariha<sup>1</sup> | Farjana Islam<sup>1</sup> | Nayan C. Mohanto<sup>1</sup>  |  
Iftekhar Ahmad<sup>2</sup> | Mohammad J. Hosen<sup>3</sup> | Shamim Ahmed<sup>1</sup>

<sup>1</sup>Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet, Bangladesh

<sup>2</sup>Department of Food Engineering and Tea Technology, Shahjalal University of Science and Technology, Sylhet, Bangladesh

<sup>3</sup>Department of Genetic Engineering and Biotechnology, Shahjalal University of Science and Technology, Sylhet, Bangladesh

## Correspondence

Nurshad Ali PhD, Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet-3114, Bangladesh.

Email: [nur\\_rubd@yahoo.com](mailto:nur_rubd@yahoo.com) and [nali-bmb@sust.edu](mailto:nali-bmb@sust.edu)

## Abstract

Several studies have demonstrated an association between individual zinc status and viral respiratory infections; however, evidence regarding COVID-19 is still missing or insufficient. This study aimed to evaluate the correlation between the prevalence of zinc deficiency and COVID-19 cases and deaths per million population in the Asian and European countries. The COVID-19 data from two different time points, that is, May 30 and June 30, 2020 for the Asian population and May 15 and June 15, 2020 for the European population, were analyzed to determine the correlation with the estimated zinc deficiency for these two continents. The prevalence of zinc deficiency was about two times higher in the Asian population (mean 17.5%) than in the European population (mean 8.9%). A significant positive correlation ( $p < .05$ ) was observed between the prevalence of zinc deficiency and COVID-19 cases at both time periods for the Asian population. However, the correlation between zinc deficiency prevalence and COVID-19 deaths was not significant in the Asian population. In contrast, a significant but negative correlation ( $p < .05$  for all cases) was observed for zinc deficiency with both COVID-19 cases and deaths per million population at both time periods in the European countries. Considering the direct antiviral properties of zinc, it can be suggested that zinc supplementation may be beneficial for most of the population, especially older people and those who are at risk of COVID-19 infections. In conclusion, there is not enough evidence on the association between individual zinc status and COVID-19 infections and mortality. Therefore, cohort studies and randomized controlled trials are required to test this hypothesis.

## KEYWORDS

COVID-19, infections, deaths, population, zinc

## 1 | INTRODUCTION

COVID-19 pandemic is one of the greatest health burdens in the world. Physicians and health workers are struggling in reducing the severity and mortality of COVID-19.<sup>1</sup> Across the globe, extensive

research efforts are underway to identify specific treatment strategies. However, a reasonable time is required to develop a specific vaccine with its effective application against COVID-19. Therefore, a cost-effective, easily available, and safe option with little to no side effects and simple applications of therapeutic options are

desperately needed. Zinc is an important trace element being involved in numerous biological processes due to its role as a cofactor, signaling molecule, and structural component.<sup>2</sup> Moreover, zinc exhibits potent immunoregulatory and antiviral properties. Several studies have demonstrated its importance in the development and functions of the immune system of all kinds of species.<sup>3,4</sup>

Zinc deficiency is associated with altered numbers and impaired functions of all immune cells, and individuals with a suboptimal zinc status have an increased risk for infectious and autoimmune diseases.<sup>4,5</sup> Mild zinc deficiency is largely considered as subclinical and often unnoticed in a majority of people. However, according to the assumption of the World Health Organization (WHO), about one-third of the global population is affected by zinc deficiency.<sup>6</sup> The fact that zinc deficiency is related to about 16% of all respiratory diseases worldwide<sup>6</sup> provides a hint of a possible link between zinc deficiency and the risk of infections and progression of the severity of COVID-19 and suggests beneficial effects of zinc supplementation.<sup>7</sup>

Previous studies have demonstrated that low zinc status is associated with the prevalence of respiratory tract infections in both children and adults.<sup>2,8</sup> The high prevalence of zinc deficiency with its impact on public health is considered as an important global health issue.<sup>9</sup> Moreover, certain groups of the population, especially children, preterm ones, and the elderly, are at higher risk of zinc deficiency and its adverse outcomes.<sup>10</sup> Although the antiviral properties of zinc have been investigated in different viral infections including hepatitis C virus, human immunodeficiency virus (HIV), and coronavirus,<sup>11</sup> the potential role of zinc in SARS-CoV-2 has not been well investigated yet. A recent study in India has reported zinc deficiency among a significant number of COVID-19 patients.<sup>12</sup> Moreover, patients with zinc deficiency developed more health complications, and this deficiency was associated with extended hospital stay and deaths.<sup>12</sup> However, it remains unclear whether zinc deficiency is directly related to COVID-19 infections and deaths, thereby requiring further investigations. This study aimed to evaluate the correlation between the prevalence of zinc deficiency and COVID-19 incidence (cases) and adverse outcomes (deaths) in the Asian and European population.

## 2 | METHODS

The data for COVID-19 cases and deaths per one million populations were collected for 45 Asian countries at two different time points (May 30, 2020, most countries at peak, and June 30, 2020, most countries after peak) using data from the coronavirus pandemic data portal <https://www.worldometers.info/coronavirus/>. Similarly, COVID-19 cases and deaths per million population were collected for 39 European countries at two different time points (May 15, 2020, most countries at peak, and June 15, 2020, most countries after peak) using data from this pandemic data portal.<sup>13</sup> Zinc deficiency can be defined either as insufficient zinc to meet the needs of the body or as the zinc level in serum below the normal range. In the present study, the zinc deficiency estimate data for different

countries based on the Food and Agriculture Organization's (FAO's) food balance datasheet and the prevalence of stunting in the countries were obtained from the previous estimate reported by Wessells and Brown<sup>14</sup> and data from the global prevalence of zinc deficiency 2005 (<https://ourworldindata.org/grapher/global-prevalence-of-zinc-deficiency?time=2005>). Pearson's correlation coefficient test (two-tailed) was used to determine the correlation of zinc deficiency with COVID-19 cases and deaths per million population in the Asian and European countries.

## 3 | RESULTS

The prevalence of zinc deficiency was about two times higher in the Asian population (mean, 17.5%) than in the European population (mean, 8.9%). The number of COVID-19 cases and deaths per million populations varied from one country to another country at both periods. A significant positive correlation ( $p < .05$ ) between the prevalence of zinc deficiency estimate for the Asian countries and COVID-19 cases per million population was consistently observed at two time points analyzed, covering infection peak time (May 30, 2020) and post-infection peak time (June 30, 2020) (Table 1 and Figure 1). However, the correlation between the prevalence of zinc deficiency and COVID-19 deaths per million populations in the Asian countries was not significant at any time point (Table 1 and Figure 1). However, a significant but negative correlation ( $p < .05$  at least for all cases) was observed between the prevalence of zinc deficiency estimate for the European countries and COVID-19 cases and deaths per million population at both time points analyzed, covering infection peak time (May 15, 2020) and post-infection peak time (June 15, 2020) (Table 2 and Figure 2).

## 4 | DISCUSSION

This study showed a significant positive correlation between zinc deficiency prevalence and COVID-19 cases per million population in Asian countries. However, the correlation between zinc deficiency and COVID-19 deaths was not significant for the Asian population. In contrast, a significant but negative correlation was observed for zinc deficiency prevalence with both COVID-19 cases and deaths in the European population. At present, it is not clear whether the correlation between zinc deficiency and COVID-19 cases and deaths is causal or an epiphenomenon. Moreover, the negative correlation of zinc deficiency prevalence with COVID-19 impact in terms of cases and deaths raises the question whether individual zinc status plays a positive role in preventing COVID-19. Other potential factors could affect the correlation of zinc with COVID-19 infections and mortality.

It is important to mention that the prevalence of zinc deficiency was about twofold higher in Asian countries than in European countries. In the European and North American countries, zinc deficiency prevalence is lower as compared with other parts of the

**TABLE 1** The number of COVID-19 cases and deaths per million population at two different time periods in 45 Asian countries

Countries	Zinc deficiency (%)	May 30, 2020		June 30, 2020	
		Cases/1 M Pop.	Deaths/1 M Pop.	Cases/1 M Pop.	Deaths/1 M Pop.
Afghanistan	20.2	373.3	6.4	809.9	19.2
Armenia	16.3	3012.6	42.9	8619.7	149.5
Azerbaijan	22.4	517.4	6.0	1728.5	21.0
Bahrain	24.8	6828.1	10.0	15,738.4	51.2
Bangladesh	29.7	270.9	3.7	883.5	11.2
Bhutan	31.7	42.8	0.0	99.8	0.0
Brunei	10.6	322.3	2.3	322.3	6.9
Cambodia	16.4	7.5	0.0	8.4	0.0
China	7.5	57.7	3.2	58.0	3.2
Cyprus	6.1	781.1	14.1	826.7	15.7
Georgia	23.6	189.8	3.0	232.6	3.8
India	31.2	131.8	3.8	424.5	12.6
Indonesia	31.2	94.2	5.8	206.2	10.5
Iran	23.2	1773.6	92.1	2710.9	128.8
Iraq	13.1	153.7	4.8	1172.7	48.3
Israel	5.5	1849.6	30.9	2744.6	34.8
Japan	16.4	132.9	7.0	147.0	7.7
Jordan	16.3	71.9	0.9	111.0	0.9
Kazakhstan	4.9	553.0	2.0	1162.2	10.0
Kuwait	15.4	6134.3	48.0	10,819.1	82.9
Kyrgyzstan	6	264.0	2.5	811.9	8.7
Laos	14.8	2.6	0.0	2.6	0.0
Lebanon	14.3	174.5	3.8	260.5	5.0
Malaysia	11.3	239.9	3.6	267.0	3.7
Maldives	14.4	3094.0	9.3	4368.9	16.7
Mongolia	4.1	54.6	0.0	67.1	0.0
Myanmar	19.5	4.1	0.1	5.5	0.1
Nepal	23.7	48.1	0.2	465.7	1.0
Oman	21.2	2042.0	8.2	7850.4	34.5
Pakistan	20.4	300.9	6.3	948.0	19.5
Philippines	9.9	157.2	8.7	342.4	11.6
Qatar	33.4	19,681.6	12.8	34,221.7	40.2
South Korea	13	223.2	5.2	249.7	5.5
Saudi Arabia	19.2	2395.6	13.8	5482.4	47.4
Singapore	15.4	5874.6	3.9	7505.6	4.4
Syria	15.2	7.0	0.2	15.9	0.5
Taiwan	21.7	18.6	0.3	18.8	0.3
Tajikistan	18.9	399.3	4.9	618.8	5.5

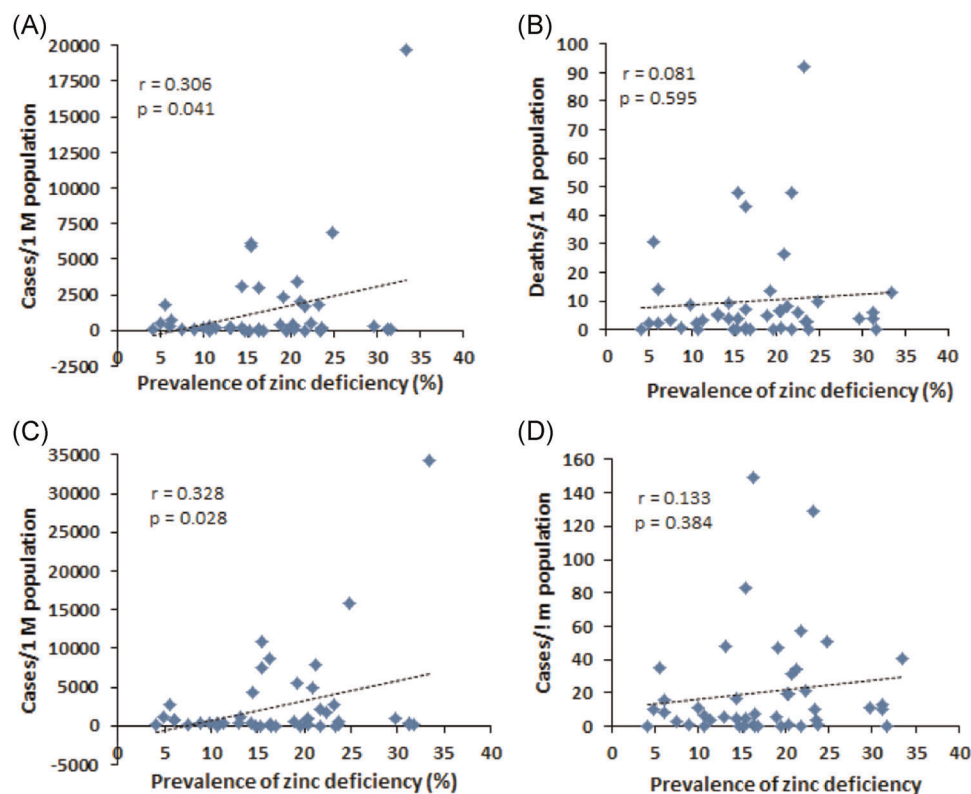
Countries	Zinc deficiency (%)	May 30, 2020		June 30, 2020	
		Cases/1 M Pop.	Deaths/1 M Pop.	Cases/1 M Pop.	Deaths/1 M Pop.
Thailand	20.4	44.1	0.8	45.4	0.8
Timor-Leste	16.9	18.2	0.0	18.2	0.0
Turkey	21.7	1736.7	48.1	2132.5	57.2
UAE	20.8	3427.6	26.5	4921.3	31.9
Uzbekistan	8.8	106.0	0.4	254.1	0.8
Vietnam	10.7	3.4	0.0	3.6	0.0
Yemen	23.4	10.4	2.6	38.8	10.5
Average	17.5 ± 7.5	1413.9 ± 3261.9	10.0 ± 17.4	2661.0 ± 5886.2	20.5 ± 32.0
Correlation (r)		.306	.081	.328	.133
p value		.041	.595	.028	.384

Note: Pearson's correlation coefficient test (two-tailed) was applied to determine the correlation of zinc deficiency with COVID-19 cases and deaths per one million population.

Source: Global prevalence of zinc deficiency 2005 (<https://ourworldindata.org/grapher/global-prevalence-of-zinc-deficiency?time=2005>), and COVID-19 cases and deaths from worldwide COVID-19 pandemic data portal at <https://www.worldometers.info/coronavirus/>.

world.<sup>14,15</sup> Rather, there exist possibilities of adequate zinc intake from diet and supplements.<sup>16,17</sup> Countries with less variation in diet, lower animal protein intake, and high ingestion of phytate (impairs zinc absorption) through diet may tend to have increased zinc

deficiency levels. From our analysis, it seems that the spectrum of zinc deficiency is an important factor that may influence its correlation with COVID-19 infections and deaths. The lower prevalence of zinc deficiency and the high COVID-19 cases and mortality rates in



**FIGURE 1** Correlation between zinc deficiency and the number of COVID-19 cases and deaths/1 M population in 45 Asian countries. Source: Global prevalence of zinc deficiency 2005 (<https://ourworldindata.org/grapher/global-prevalence-of-zinc-deficiency?time=2005>), and COVID-19 cases and mortality as of May 30, 2020 (A and B) and June 30, 2020 (C and D) from worldwide COVID-19 pandemic data portal at <https://www.worldometers.info/coronavirus/>

**TABLE 2** The number of COVID-19 cases and deaths per million population at two different time periods in 39 European countries

Countries	Zinc deficiency (%)	May 15, 2020		June 15, 2020	
		Cases/1 M Pop.	Deaths/1 M Pop.	Cases/1 M Pop.	Deaths/1 M Pop.
Albania	5.3	318.3	10.8	552.5	12.5
Austria	7.3	1788.7	69.7	1902.6	75.3
Belarus	9	2934.6	16.5	5786.6	33.0
Belgium	6.8	4715.1	773.0	5185.8	833.6
Bosnia and Herzegovina	16.7	681.5	39.0	926.3	50.0
Bulgaria	15.3	307.7	14.7	480.8	25.3
Croatia	12.4	541.2	23.1	549.0	26.1
Czechia	11	784.4	27.5	939.8	30.8
Denmark	6.2	1863.1	92.7	2109.3	103.2
Estonia	10.5	1331.3	47.5	1488.1	52.0
Finland	4.6	1124.1	52.9	1282.9	58.8
France	3.9	2174.3	421.8	2411.0	451.0
Germany	9	2097.1	95.5	2244.4	106.0
Greece	7.2	269.6	15.4	300.7	17.7
Hungary	8.4	353.7	45.8	421.9	58.3
Iceland	3.1	5281.0	29.3	5304.4	29.3
Ireland	4	4852.2	307.5	5128.6	345.5
Italy	5.8	3702.4	521.8	3924.4	567.5
Latvia	11.6	514.3	10.1	581.6	14.8
Lithuania	7.5	563.5	19.8	651.3	27.9
Malta	8.1	1204.9	13.6	1472.1	20.4
Moldova	20	1424.1	50.1	2944.7	101.9
Montenegro	7.5	515.9	14.3	519.1	14.3
Netherlands	5	2549.3	329.3	2856.7	354.0
North Macedonia	14.1	835.2	46.6	1995.3	92.6
Norway	6.2	1516.2	42.8	1595.1	44.6
Poland	10.3	476.0	24.0	787.1	33.2
Portugal	6.3	2803.1	116.7	3632.1	149.1
Romania	7.5	854.4	55.6	1152.1	74.2
Russia	8.3	1801.1	16.6	3681.2	48.6
Serbia	7	1194.6	25.8	1415.4	29.2
Slovakia	16.3	271.1	4.9	284.3	5.1
Slovenia	9.8	704.7	49.5	719.6	52.4
Spain	5.4	5868.2	581.6	6228.0	605.3
Sweden	6.1	3015.0	385.2	5261.3	507.9
Switzerland	4.9	3526.0	217.0	3597.3	224.1
UK	4.6	3487.0	500.8	4373.1	614.8
Ukraine	11.4	396.3	10.9	727.3	20.6

TABLE 2 (Continued)

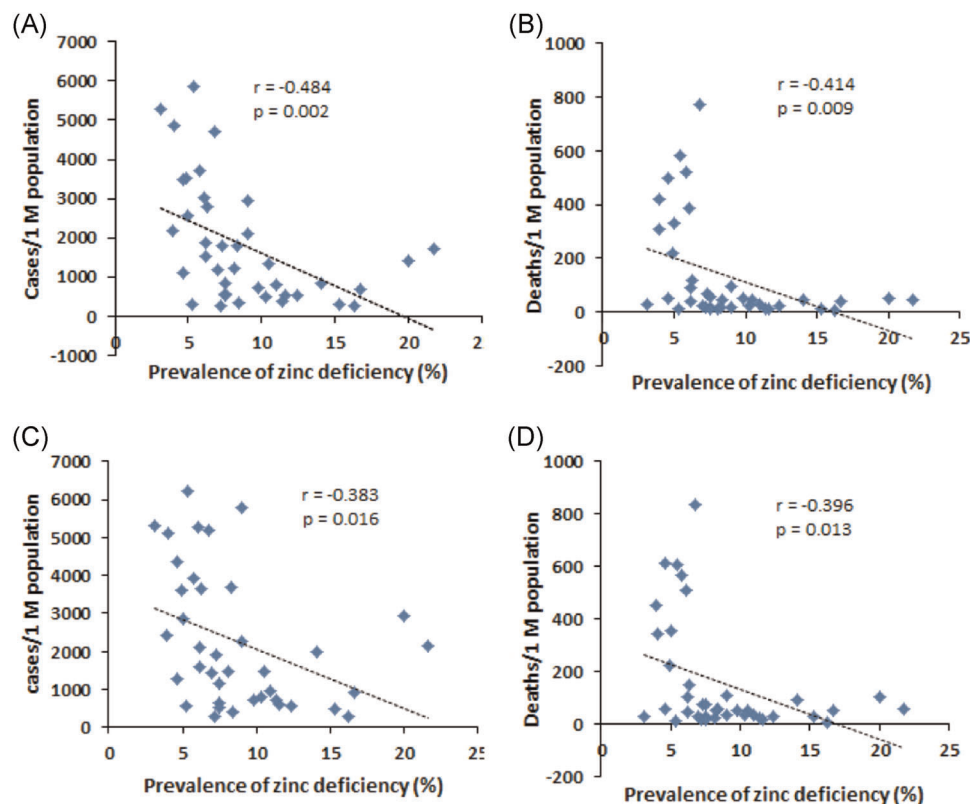
Countries	Zinc deficiency (%)	May 15, 2020		June 15, 2020	
		Cases/1 M Pop.	Deaths/1 M Pop.	Cases/1 M Pop.	Deaths/1 M Pop.
Turkey	21.7	1736.7	48.1	2132.5	57.2
Average	8.9 ± 4.4	1804.6 ± 1528.3	132.5 ± 193.0	2224.8 ± 1782.8	153.0 ± 212.1
Correlation ( <i>r</i> )		-.484	-.414	-.383	-.396
<i>p</i> value		.002	.009	.016	.013

Note: Pearson's correlation coefficient test (two-tailed) was applied to determine the correlation of zinc deficiency with COVID-19 cases and deaths per one million population.

Source: Global prevalence of zinc deficiency 2005 (<https://ourworldindata.org/grapher/global-prevalence-of-zinc-deficiency?time=2005>), and COVID-19 cases and deaths from worldwide COVID-19 pandemic data portal at <https://www.worldometers.info/coronavirus/>.

most of the European countries might be a reason for the negative correlation in this continent. The underlying differences in the population composition, sex, age distribution, comorbidities, and variation in drugs used in the treatment may be possible confounding factors that could also affect the correlation. It has been demonstrated that pre-existing medical conditions including diabetes, hypertension, chronic liver, and kidney diseases can worsen the COVID-19 disease.<sup>18–22</sup> Therefore, the subject's history of pre-existing diseases should also be considered during such correlations analysis.

A prospective observational study conducted in India between May 17 and May 27, 2020 reported a significant ( $p < .001$ ) low level of zinc in COVID-19 patients (74.5 mg/dl) when compared with healthy controls (105.8 mg/dl).<sup>12</sup> Among COVID-19 patients, 57.4% of the subjects were zinc-deficient. The authors observed that COVID-19 patients with a low zinc status developed more health complications, and zinc deficiency was related to the prolonged hospitalization and increased deaths.<sup>12</sup> However, that study was a single-center analysis with a small number of COVID-19 patients ( $n = 47$ ).<sup>12</sup> Therefore, multicenter studies including both symptomatic



**FIGURE 2** Correlation between zinc deficiency and the number of COVID-19 cases and deaths/1 M population in 39 European countries. Source: Global prevalence of zinc deficiency 2005 (<https://ourworldindata.org/grapher/global-prevalence-of-zinc-deficiency?time=2005>), and COVID-19 cases and mortality as of May 15, 2020 (A and B) and June 15, 2020 (C and D) from worldwide COVID-19 pandemic data portal at <https://www.worldometers.info/coronavirus/>



and asymptomatic COVID-19 patients with no comorbid conditions would be worthwhile in evaluating the role of zinc in preventing COVID-19.

In vitro studies reveal that the spike protein of SARS-CoV-2 directly interacts with the host cell surface ACE2 (angiotensin-converting enzyme 2) and the cellular protease TMPRSS2 (transmembrane protease serine 2), permitting its entry and replication.<sup>23</sup> Recent studies suggested that a lower zinc level favors the interaction of ACE2 with the viral spike protein, whereas a high level of zinc inhibits the expression of ACE2, resulting in a decreased viral interaction with its receptor.<sup>24,25</sup>

Zinc has been shown to exhibit antiviral effects by inhibition of RNA synthesis, DNA polymerase, viral application, and reverse transcriptase.<sup>26–28</sup> Several studies have demonstrated the direct antiviral effects of zinc against viruses such as herpes simplex virus, papillomavirus, picornavirus, respiratory syncytial virus, hepatitis C virus, and HIV reviewed by Wessels et al.<sup>7</sup> It has been suggested that zinc can prevent fusion with the host cell membrane, reduce the viral polymerase activity, impair the protein translation process, block releasing viral particles, and destabilize the viral envelope.<sup>27,29</sup> However, the evidence is limited regarding the effects of zinc on SARS-CoV-2. More research on the zinc effect on SARS-CoV-2 is highly required.

Zinc plays an important role in immune system development and serves as an immunomodulator.<sup>7</sup> Zinc deficiency is associated with underdevelopment of lymphoid tissue and decreased NK cell (natural killer cell) function, which causes poor innate immune responses.<sup>30</sup> Zinc deficiency is also associated with decreased cytokine production and macrophage activation. Zinc plays a significant role in B- and T-cell function.<sup>30</sup> Moreover, zinc deficiency is associated with increased levels of proinflammatory molecules, higher levels of reactive oxygen species (ROS), and predisposing for rapid progression of some inflammatory diseases, especially those impairing lung functions, and can be reversible with zinc supplementation.<sup>7</sup> Several studies suggested that prophylactic zinc supplementation can be an effective approach than therapeutic proceedings.<sup>31,32</sup> It has been shown that zinc administration can reduce symptom severity and duration of the common cold.<sup>33–35</sup> A recent review highlighted the potential benefits of zinc supplementation for COVID-19 severity.<sup>7</sup> The authors indicated that zinc supplementation can help to preserve antiviral immunity and support antioxidative effects, thus reducing lung injury and minimizing secondary infections.<sup>7</sup> Older people and those who are at risk of COVID-19 infections would be benefited most from zinc supplementation. It has also been hypothesized that zinc supplementation might be beneficial for prophylaxis and treatment of COVID-19.<sup>36</sup>

There are some limitations to the present study. First, the retrospective design of the study used the global prevalence of zinc deficiency data as reported in 2005. At present, the zinc status at the population level in both continents may be improved or changed that could affect such correlation level. Second, the extracted data are heterogeneous, that is, the sample has not been drawn from a single population but rather from a mixture. Third, the potential

confounding variables like, age, sex, ethnicity, and pre-existing diseases were not included in the analysis, which could affect the correlation between zinc and the risk of COVID-19 infections. Therefore, these confounding variables should be considered during the evaluation of the role of zinc in respiratory diseases including COVID-19. Overall, it remains unclear whether the observed relationship is coincidental or causal, which can be revealed by further research only. Extensive research is needed before using zinc as a therapeutic option for COVID-19.

## 5 | CONCLUSION

This retrospective study shows a positive correlation between the high prevalence of zinc deficiency and the COVID-19 cases per million population in Asian countries. Although zinc supplementation has been suggested as beneficial against respiratory tract infections, it is not clear yet whether its supplementation after hospital admission can reduce the severity of COVID-19. To date, little information exists on the relationship between zinc levels and COVID-19 infections and mortality. Therefore, multicenter cohort studies and randomized clinical trials are needed to test this hypothesis.

## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

*Conceptualization:* Nurshad Ali. *Data acquisition and analysis:* Khandaker A. Fariha, Farjana Islam, Nayan C. Mohanto, Iftekhar Ahmad. *Drafting of the manuscript:* Nurshad Ali. *Critical review of the manuscript:* Nurshad Ali, Mohammad J. Hosen, Shamim Ahmed. *Statistical analysis:* Nurshad Ali, Farjana Islam, Nayan C. Mohanto. *Supervision:* Nurshad Ali.

## PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/jmv.26932>

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## ORCID

Nurshad Ali  <https://orcid.org/0000-0003-1649-0887>

Nayan C. Mohanto  <https://orcid.org/0000-0002-5803-1534>

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