

# The relationship between COVID-19, Zinc and Vitamin D: A Systematic Review

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## ABSTRACT

**Background:** The 2019 coronavirus illness (COVID-19) pandemic emphasizes the value of consuming necessary nutrients, particularly those that strengthen an organism's inbuilt immune system in the case of COVID-19 or other viral diseases. The nutritional condition of COVID-19 individuals should be assessed at the time of admission, according to a few recent studies, to help medical professionals balance and normalize the case's nutritional needs. Zinc and its ionophores are candidates against COVID-19 due to the mineral's immunomodulatory and antiviral properties. In addition to playing a crucial part in cell maintenance, development, and activation during innate and adaptive immune responses, zinc is crucial for the health of the immune system. The function of calcium and vitamin D as immunomodulators has received attention. Vitamin D in its active form has strong immunomodulatory properties. T lymphocytes, macrophages, and dendritic cells are only a few immune system cells that have vitamin D receptors on them.

**Objectives:** The study aims to summarize current evidences regarding the relationship between COVID-19, Zinc and Vitamin D.

**Methodology:** PubMed, Web of Science, Science Direct, EBSCO, and Cochrane library were searched. Study articles were screened by title and abstract using Rayyan QCRI then a full-text assessment was implemented.

**Results:** A total of 286 study articles resulted from the systematic search, and then 88 duplicates were removed. Title and abstract screening were conducted on 198 studies, and 54 studies were excluded. Finally, 146 studies were screened for full-text assessment; 139 were excluded and 9 eligible study articles were included in this systematic review. All of studies reported correlation between severity of infection with both two variables (zinc and vitamin D levels).

**Conclusion:** The likelihood of hospitalization was considerably greater in individuals who had both low serum zinc levels and COVID-19. Serval Studies' findings suggested that severe COVID-19 in adults may be caused by genetic variations related to vitamin D. This could influence preventative plans based on nutrigenetic profiles particular to a group. When compared to patients who were admitted to the ICU or non-ICU and survived, researchers discovered that blood levels of zinc, vitamin B12, and 25(OH)D were lower in patients who died. Results in COVID-19 patients appear to be generally influenced by blood levels of 25(OH)D, vitamin B12, and particularly zinc at the time of admission.

**Keyword:** COVID-19, immune system, Zinc, Vitamin D, T lymphocytes, macrophages, Systematic review.

## Introduction

The 2019 coronavirus illness (COVID-19) pandemic emphasizes the value of consuming necessary nutrients, particularly those that strengthen an organism's inbuilt immune system in the case of COVID-19 or other viral diseases. The coronavirus

Family, so named because of the spikes that resemble a crown on the pathogen's surface, is made up of viruses that attack the human respiratory system. People in the Chinese city of Wuhan were given the diagnosis of pneumonia at the end of 2019 as a result

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Of Coronavirus Type 2 coupled with severe acute respiratory syndrome (SARS-CoV-2). Due because of the substantial growth in SARS-CoV-2 cases across all continents, COVID-19 was classified as a pandemic by the World Health Organization (WHO) in March 2020 [1-8]. The nutritional condition of COVID-19 individuals should be assessed at the time of admission, according to a few recent studies, to help medical professionals balance and normalize the case's nutritional needs. Nutritional support should be given to subjects as soon as feasible, with an emphasis on boosting oral amino acid intake. All COVID-19 patients should maintain an appropriate protein intake of 1.5 g/d, even if they do not first report to the hospital with symptoms of malnutrition. The inclusion of certain vitamins and minerals in the diet of COVID-19 patients may be due to their antioxidant and anti-inflammatory capabilities [9-11]. The function of calcium and vitamin D as immunomodulators has received attention. Vitamin D in its active form has strong immunomodulatory properties. T lymphocytes, macrophages, and dendritic cells are only a few immune system cells that have vitamin D receptors on them. There is a lot of evidence that 1-25 dihydroxy vitamin D3 affects the immune system in many ways. As a result, it raises immunity and lowers autoimmunity. The cells that fight illness directly interact with vitamin D. Therefore, scientists have come a lack of vitamin D may increase the risk of viral infections, researchers have concluded. The vitamin D3 1-alpha-25-dihydroxy signaling pathway interferes with other growth hormone factors, resulting in cell proliferation, differentiation, and viability, which is the basis for the molecular functional mechanism [12]. Previous research has linked various vitamin and mineral deficits to weakened immune defenses against respiratory infections as well as longer healing times after illness. For instance, it has been shown that the immune system is strengthened by the vitamins C, D, and E as well as some minerals including omega-3 fatty acids, selenium, and zinc in order to prevent and cure infectious infections. It has been suggested that pairing these medications with azithromycin may increase the likelihood that a patient infected with SARS-CoV-2 may recover quickly. Internal antiviral medications known as interferons (IFNs) may have synergistic effects on the COVID-19 illness when used with such supplements [13]. Zinc and its ionophores are candidates against COVID-19 due to the mineral's immunomodulatory and antiviral properties. In addition to playing a crucial part in cell maintenance, development, and activation during innate and

adaptive immune responses, zinc is crucial for the health of the immune system. It also affects the strength of epithelial barriers, which are necessary for preventing pathogen invasion and defending against it. A cytokine storm, which is characterized by high levels of pro-inflammatory cytokines and chemokines and impairs the systemic immune response, zinc can lower by regulating the growth and activation of T lymphocytes. Multi-organ failure or acute respiratory distress syndrome (ARDS) may arise from this. When zinc levels are low, cytolytic T cells and natural killer (NK) cells are less active [1, 14–25]. The study aims to summarize current evidences regarding the relationship between COVID-19, Zinc and Vitamin D.

### Methods

**Study design:** In order to clarify a coherent a plan for empirical study based on current understanding, a systematic review of the current evidence on the relationship between COVID-19, Zinc, and Vitamin D is thought to be a reliable method of locating and compiling the relevant information from the peer-reviewed papers. Only an interpretation could be made from the qualitative material in this review. Additionally, the evidence at hand attempts to produce conclusions that are meaningful, pertinent, and appropriate for people, to guide future research, and eventually to improve current behaviors about the relationship between obesity and breast cancer. The review combined, integrated, and, where appropriate, interpreted the data from the included studies using qualitative synthesis approaches. The assessment makes an effort to provide additional interpretive insights into the data that go beyond the mere data collecting the link between COVID-19, Zinc, and Vitamin D and to identify areas where additional research can advance the current body of knowledge.

**Search strategy:** A comprehensive literature search was conducted in five major databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane Library, to identify the relevant literature. Our search was limited to English, and each database's specific requirements were taken into account. The right studies were located using the following keywords, which were transformed into Mesh terms in PubMed; "COVID-19, corona virus outbreak, zinc supplement, vitamin D "The appropriate keywords were paired with "OR" and "AND" Boolean operators. The search results comprised English, full-text publications, freely available articles, and human trials.

**Inclusion criteria:** The subjects were chosen for addition founded on their applicability to the research,

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which has the following criteria; studies assessing level of Vitamin D and zinc in COVID-19 patients.

Exclusion criteria: All additional publications, current research, and analyses of completed studies that did not focus on one of these subjects were disregarded.

Data extraction: We used Rayyan (QCRI) to look for duplicate results from the search strategy. The researchers determined the relevance of the titles and abstracts by limiting the combined search results based on a set of inclusion/exclusion criteria. The whole texts of the papers that fulfilled the requirements for inclusion were examined by the reviewers. The authors talked about how to settle disputes. Using a constructed data extraction form, the qualified study was included. The authors extracted data about the study titles, authors, study year, study designs, participant number, mean age, cancer type, duration of exercise programs, type of program, and main outcomes.

Strategy for data synthesis: Summary tables comprising the information acquired from the eligible studies were made in order to provide a qualitative summary of the included study components and outcomes. The optimal way to use the data from the included study articles was decided after data extraction for the systematic review. Studies that met the full-text inclusion criteria but did not provide any data on the effect of exercise programs on lymphoma patients were excluded.

### Results

A total of 286 study articles resulted from the systematic search, and then 88 duplicates were removed. Title and abstract screening were conducted on 198 studies, and 54 studies were excluded. Finally, 146 studies were screened for full-text assessment; 139 were excluded and 9 eligible study articles were included in this systematic review. A summary of the study selection process is presented in (Figure 1). The study included 7 studies assessing correlation between severity of COVID-19 infection with serum zinc and vitamin D levels. All of studies reported correlation between severity of infection with both two variables (zinc and vitamin D levels). RazeghiJahromi, S., et al. a substantial correlation between COVID-19 severity and with Zn and Se levels, per the findings of the linear regression test. However, the significance vanished once confounding variables were taken into account. The blood Zn, Se, and CRP levels significantly correlated negatively, according to Spearman correlation analysis [26]. Additionally, In EkemenKeleş, Y., et al. study with 100 children who had verified COVID-19 and 269 children in the

control group. Hospitalization rates were significantly higher for patients in the low zinc group (5 patients (45.5%) and 10 patients (11.2%), respectively) than those in the group receiving regular zinc ( $p = 0.011$ ). The median blood zinc level in patients with COVID-19 was 88.5 mcg/dL, which was significantly lower than the median level of 98 mcg/dL in the control group. The severity of COVID-19, however, was not correlated with the children's serum zinc levels [27]. In Hosseini, S. J., Study Serum vitamin D levels were, on average, 31.03 plus or minus 15.49, 37.25 plus or minus 18.49, and 39.33 plus or minus 14.83 in severe cases, nonsevere cases, and HVs, respectively ( $P = 0.05$ ). Additionally, the average serum zinc concentrations for HVs, non-HVs, and severe cases, respectively, were 31.03, 37.25, and 39.33 ( $P = 0.01$ ) [29]. Furthermore, Shakeri, H., et al. Study Researchers found that blood levels of zinc, vitamin B12, and 25(OH) D were lower in patients who died when compared to patients who were admitted to the ICU or non-ICU and survived. For vitamin B12 and 25(OH) D, these increases weren't statistically significant, though ( $p > 0.05$ ). The blood levels of zinc, vitamin B12, and 25(OH) D at the time of admission in COVID-19 patients did not affect how long they stayed in the hospital. The blood levels of 25(OH) D, vitamin B12, and particularly zinc at the time of admission appear to have a general influence on clinical outcomes in COVID-19 patients [30]. The rest of results are detailed at a (Table 1).

### Discussion

The desk (1) Individuals with severe COVID-19 had blood Se levels that were significantly lower than those with mild or moderate disease at the time of this examination. Significant evidence on the relationship between COVID-19 cure rates and Se status has been obtained from a recent population-based study carried out in 17 Chinese cities. They asserted that the population's Se hair content increased concurrently with the rate of COVID-19 recovery. According to the findings of a clinical experiment carried out in Germany, the outcomes of COVID-19 in patients who are hospitalized were closely connected with blood levels of selenium, with low serum Se levels reported in 39% of survivors and 65% of the dead [26, 33]. In order to ascertain the relationship between COVID-19 and 25-hydroxyvitamin D, numerous investigations have been carried out. When D'Avolio et al. compared COVID-19 PCR positive vs. negative cases, they found that the PCR-positive patients had considerably lower plasma 25-hydroxyvitamin D levels.

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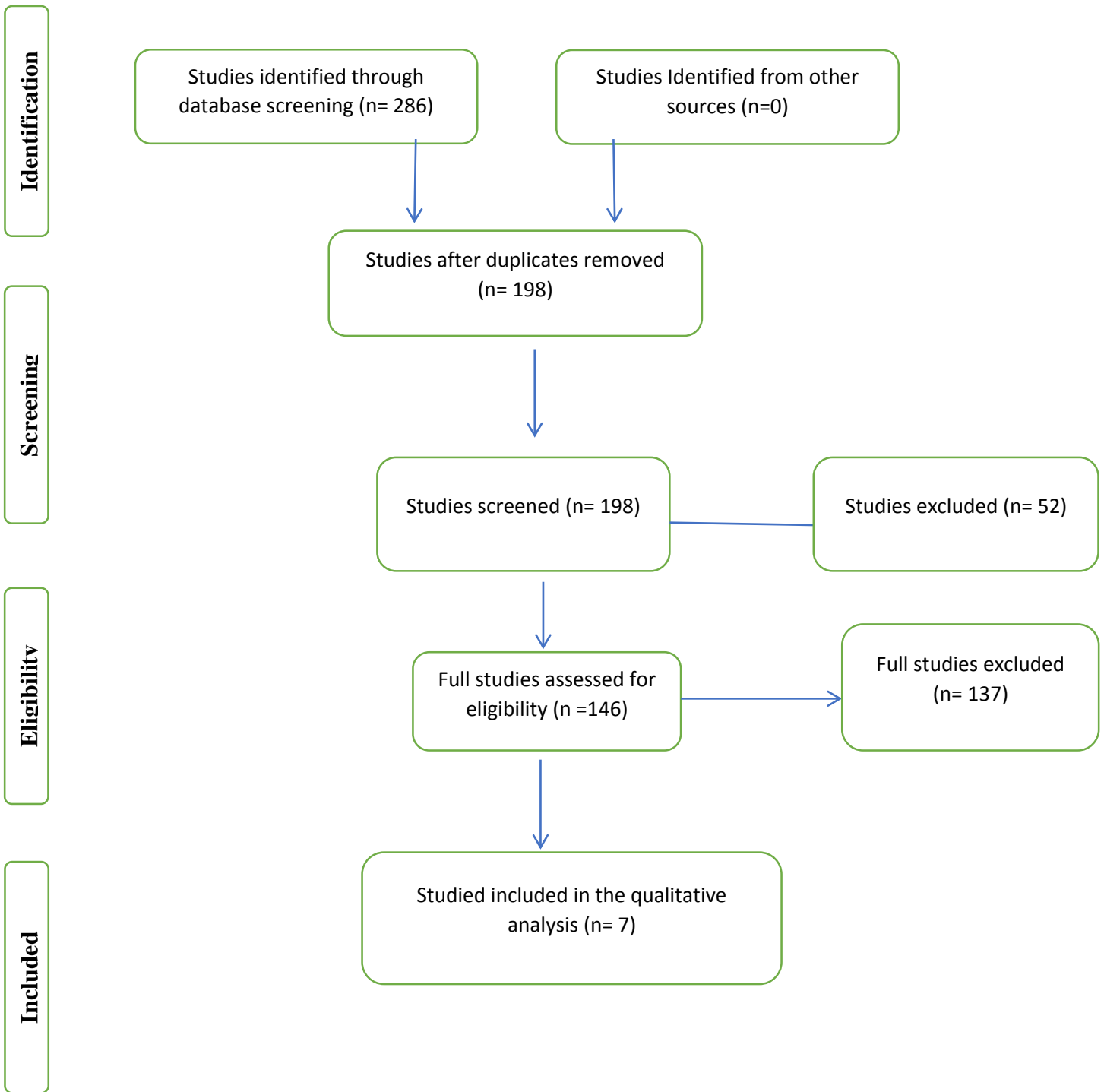


Figure 1: The included studies had different study designs.

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**Table 1:** Author, country, year of publication, methodology and outcome:

<b>Author, Publishing Year</b>	<b>Objective &amp; Methodology</b>	<b>Outcomes</b>
<b>Razeghi Jahromi, S., et al. 2021 [26]</b>	Observational research included 84 COVID-19 participants. Using CDC guidelines, the severity of Covid-19 was divided into three groups (mild, moderate, and severe).	The severity of COVID-19 was significantly correlated with Zn and Se levels, per the findings of the linear regression test the blood Zn, Se, and CRP levels significantly correlated negatively, according to Spearman correlation analysis. After controlling for confounding variables, the substantial relationship between Se, Zn, and illness severity was eliminated.
<b>Ekemen Keleş, Y., et al. 2022. [27]</b>	Reverse transcription-polymerase chain reaction was used to confirm COVID-19 in pediatric patients aged 1 month to 18 years for this prospective observational research between August 3 and November 15, 2020.	Patients in the low zinc group had a substantially higher hospitalization rate than those in the normal zinc group. Patients with COVID-19 had a median blood zinc level of 88.5 mcg/dL, which was considerably lower than the control group's median level of 98 mcg/dL.
<b>Ahmet Doğan., et al. 2022 [28]</b>	88 children with COVID-19 disease and 88 healthy children aged 1–18 years were enrolled between 01 July 2021 and 30 October 2021. Serum vitamin D and zinc levels have been measured and NCSS program has been utilized for statistical analysis.	Zinc and vitamin D levels were observed lower in COVID-19 patients than in healthy individuals. Since there is no defined treatment protocol for COVID-19 infection on children yet, zinc and vitamin D supplementation can be used as a supportive treatment in COVID-19 infection.
<b>Hosseini, S. J., 2021. [22]</b>	56 patients (32 severe instances and 24 nonsevere cases) admitted to the COVID-19 ward and 46 HVs residing were the subjects of this single-center, cross-sectional study. Patients who were admitted to the COVID-19 ward and HVs had their blood levels of zinc and vitamin D checked.	Serum vitamin D levels were, on average, 31.03 plus or minus 15.49, 37.25 plus or minus 18.49, and 39.33 plus or minus 14.83 in severe cases, nonsevere cases, and HVs, respectively. Additionally, the average serum zinc concentrations for HVs, non-HVs, and severe cases, respectively, were 31.03, 37.25, and 39.33.

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<p><b>Shakeri, H., et al. 2022. [30]</b></p>	<p>293 COVID-19 patients from electronic medical records, they gathered demographic information, clinical traits, serum biochemical parameter values during the first week of hospitalisation, and clinical outcomes. Within three days of hospitalisation, they also checked the blood levels of zinc, 25(OH)D, and vitamin B12.</p>	<p>In patients with COVID-19, the blood levels of zinc and 25(OH)D at the time of admission had no impact on how long they stayed in the hospital. Clinical results in COVID-19 patients appear to be generally influenced by blood levels of 25(OH)D, vitamin B12, and particularly zinc at the time of admission.</p>
<p><b>Golabi, S., et al. 2022 [31]</b></p>	<p>Zinc and 25-hydroxyvitamin D (25(OH)D) blood concentrations were compared between COVID-19 outpatients and people who may not have been infected. Additionally, the relationship between clinical symptoms and vitamin D and zinc levels was looked at in 53 patients.</p>	<p>A tendency toward a lower blood concentration of 25(OH)D was seen in patients with moderate illness compared to asymptomatic or mild illness patients (19 ng/mL vs. 29 ng/mL). The serum zinc content of infected individuals (108 g/dL) was lower than that of subjects who might not have been infected (114 g/dL).</p>
<p><b>E. Ghanei et al., 2022 [32]</b></p>	<p>A single-center case-control study performed on patients diagnosed with COVID-19 based on a positive nasopharyngeal swab polymerase chain reaction (PCR) test. Controls were selected from patients referred for routine checkups who had a negative COVID-19 PCR test. Age, sex, marital and educational status, comorbidities, and serum 25-hydroxyvitmain D and zinc levels of patients were recorded.</p>	<p>Low serum zinc and 25-hydroxyvitmain D levels appear to be risk factors for COVID-19 affliction; thus, the treatment of individuals with such deficiencies is recommended.</p>

However, as one of the earliest studies carried out in this era, theirs had several limitations related to timing and lacked some crucial information regarding potential 25-hydroxyvitamin D supplementation [34]. A previous study by Hurst et al. supported these findings by demonstrating a greater prevalence of 25-hydroxyvitamin D insufficiency/deficiency in COVID-19 hospitalised patients [35]. Through the generation of antimicrobial peptides and binding to the host cell surface receptors, 25-hydroxyvitamin D may diminish the replication and survival of SARS-CoV-2, as well as the cytokine storm by enhancing the body's capacity to inhibit the synthesis of inflammatory cytokines [36]. Zinc induces immunological responses from the innate and acquired immune systems, which have a number of antiviral effects. Zinc has been demonstrated to have antiviral characteristics by decreasing RNA synthesis, viral replication, DNA polymerase, reverse transcriptase, and viral proteases, even if the antiviral regulation of zinc in humans is not fully understood. According to a meta-analysis, zinc supplementation significantly reduced the incidence of acute lower respiratory tract infections in children under the age of five. The authors of the study demonstrated through a randomized experiment that giving zinc supplements to kids with acute lower respiratory tract infections allowed them to avoid the hospital for shorter lengths of time. The zinc level of kids with pneumonia was measured; evaluated in a study by Acevedo-Murillo and coworkers. When compared to the placebo oxygen saturation, respiratory rate, and clinical state of the group were all improved by zinc supplementation [27]. Since the start of the pandemic, a lot of study has been done on the function of vitamin D in the pathophysiology of COVID-19. The primary site of SARS-CoV2 cell entrance is ACE2, and calcitriol (1, 25-dihydroxyvitamin D3) increases the expression of ACE2 to regulate the renin-angiotensin system. Additionally, Vitamin D modulates the immune system and prevents the overproduction of pro-inflammatory cytokines and chemokines by macrophages. A recent study found a negative correlation between higher levels of consumption of important micronutrients like vitamin D and an increased incidence and/or death of COVID-19 [28, 34]. Over the past few decades, our understanding of how Human health as it relates to vitamin D3 has considerably improved. It has been shown that several different cell types, including those of the immune system and the pancreas, prostate, and gut, which are not involved in the metabolism of bones and minerals,

express the 1-hydroxylase vitamin D3 activating enzyme and the vitamin D3 receptor (VDR). This finding demonstrates that vitamin D3 has a larger and more important impact on the health of people than previously thought. More than 2500 genes and many of our most severe medical illnesses, including cancer, diabetes mellitus, acute respiratory infections, chronic inflammatory diseases, and autoimmune disorders like multiple sclerosis, are influenced by the potent epigenetic regulator known as vitamin D [37 - 40]. The poor clinical prognosis in COVID-19 patients with low serum zinc levels may be related to this micronutrient's ability to reduce SARS-CoV2 reproduction by limiting RNA polymerase activity, modulating inflammatory responses, improving the cytotoxic activity of NK cells, and other mechanisms. As well as from its capacity to increase the phagocytic activity of macrophages [30].

### **Conclusion**

The probability of being hospitalized was significantly increased in those with low serum zinc levels and COVID-19. Findings from Serval Studies revealed that genetic differences related to vitamin D may be the cause of severe COVID-19 in adults. This might have an impact on preventative strategies based on nutrigenetic profiles unique to a group. Researchers discovered that when compared to patients who were admitted to the ICU or non-ICU and survived, blood levels of zinc, vitamin B12, and 25(OH) D were lower in patients who passed away. Blood levels of 25(OH) D, vitamin B12, and particularly zinc appear to have a general influence on outcomes in COVID-19 patients at the time of admission.

### **Conflict of Interest**

None

### **Funding**

None

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