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Systematic Review and Meta-Analysis: Effect of Zinc Levels in COVID-19 Patients on Their Clinical Severity

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ABSTRACT

Zinc has anti-inflammatory, antiviral, and antioxidant effects given as an adjuvant therapy for the treatment of COVID-19. Prolonged zinc deficiency is a risk factor for severe COVID-19. This systematic review and meta-analysis study used 4 databases namely ScienceDirect, Cochrane Library, ProQuest, and PubMed. The keywords used are "Zinc" OR "Severity COVID-19" AND "Zinc Deficiency" OR "Mortality COVID-19" AND "Zinc" OR "Clinical Severity COVID-19" AND "Zinc Deficiency" OR "Clinical Severity COVID- 19". The articles identified are articles that are relevant to the title of research, published internationally, accessed free of charge, published between 2019-2021, and published in accredited journals. Out of 8,330 article titles, 944 were excluded due to double counting in each database. A total of 7,371 articles were excluded and a total of 15 articles were included in the qualitative synthesis. Five studies were included in the meta-analysis. Three studies were analyzed with the results that the average zinc level of COVID-19 patients was not much different from that of healthy patients with a mean difference of 1.73 (95% CI -39.14-42.60). Two studies were analyzed with low zinc levels in patients with severe COVID-19 associated with the need to enter the intensive care unit with an OR of 3.62 The SARS-CoV-2 virus spreads through droplets that are expelled while coughing or sneezing. The conclusion is the average zinc level of COVID-19 patients is not different from that of healthy patients, but low zinc levels in patients with severe COVID-19 are associated with the need to enter the intensive care unit

INTRODUCTION

A novel coronavirus known as COVID-19 has the potential to cause ARDS (acute respiratory distress syndrome). The human respiratory tract is attacked by this novel virus, which is currently pandemic all over the world. The majority of COVID-19 infection sufferers experience mild to moderate respiratory disease and recover without the need for special care. People with comorbid conditions such as cardiovascular disease, diabetes mellitus, obesity, hypertension, and advanced age have higher mortality rates[1] . Angiotensin Converting Enzyme 2 (ACE2) is a receptor on the surface of host cells that SARS-CoV-2 binds to in order to infect humans. The viral S protein mediates the process. SARS-CoV-2 has a higher affinity for the S protein's receptor (human ACE2) than SARS-CoV. Lung cells, particularly alveolar epithelial cells, as well as cells in the intestine, kidney, stomach, esophagus, liver, bile duct, and oral mucosal epithelial cells, express ACE2 [2] . The SARS-CoV-2 virus is transmitted through droplets that come out when coughing or sneezing [3] . According to statistics from the Indonesian COVID-19 task force, diabetes mellitus up to 9.5%, hypertension up to 9.2%, and heart disease up to 4.8% were the three most common comorbid or comorbid disorders from COVID-19-positive individuals [4] . All COVID-19 patients must follow the COVID-19 therapeutic guidelines. For various patient demographics, different treatments are advised. These suggestions may be based on the COVID-19 clinical severity[5] . Deficiency of vitamins and minerals can affect the incidence of COVID-19 and disease severity [6] .

Zinc has a role as an anti-inflammatory, anti-viral, and antioxidant[7]. Currently, multiple clinical trials are using the administration of zinc, one of the most prevalent minerals in food, to combat COVID-19[8] . When paired with chloroquine and anti-inflammatory drugs, zinc supplementation in COVID-19 can be administered as an immune system booster and can limit the replication of SARS-CoV-2 in infected cells7. Additionally, zinc can be administered as adjuvant therapy since it protects COVID19 patients by lowering lung inflammation, raising mucociliary clearance, preventing lung damage brought on by ventilator use, and immunomodulation 8 . Zinc deficiency accounts for 16% of respiratory tract infections in the world, this can be used as a strong indicator of the relationship between zinc deficiency and the risk of severe COVID-19 infection [9]. Long-term zinc deficiency is linked to neurological problems, decreased body mass, and immune system failure. disorders of the immune system brought on by a zinc shortage, include a decline in antibody synthesis and a decline in natural killer cell function. Viral infections are more prevalent in this scenario[10] and high *zinc* levels have a lower risk of pneumonia and reduced duration of infection [11] .

According to earlier research, people with zinc deficiencies experience more difficulties than those with normal zinc levels 1[2]. Prolonged zinc deficiency is a risk factor for severe COVID-19 [13] . Based on this interpretation, the researchers became curious about the literature regarding the relationship between zinc levels in COVID-19 patients and the clinical severity of their condition. Based on this interpretation, the researchers became curious about the literature regarding the relationship between zinc levels in COVID-19 patients and the clinical severity of their condition

METHODS

The research is an analytical observational study using a quantitative systematic review approach. For article collecting, four databases—ScienceDirect, Cochrane Library, ProQuest, and PubMed—were used. The keywords "Zinc" OR "Severity COVID-19" AND "Zinc Deficiency" OR "Mortality COVID-19" AND "Zinc" OR "Clinical Severity COVID-19" AND "Zinc Deficiency" OR "Clinical Severity of COVID-19" we used to search for articles. Articles that were open to access, published from 2019 to 2021, published internationally, and with accreditation met the inclusion criteria. They were relevant to the research theme. In the henceforth, the exclusion criteria were irrelevant abstracts and a lack of full text. The PRISMA approach was used to pick subsequent papers and determine their eligibility.

RESULTS

STUDY SELECTION

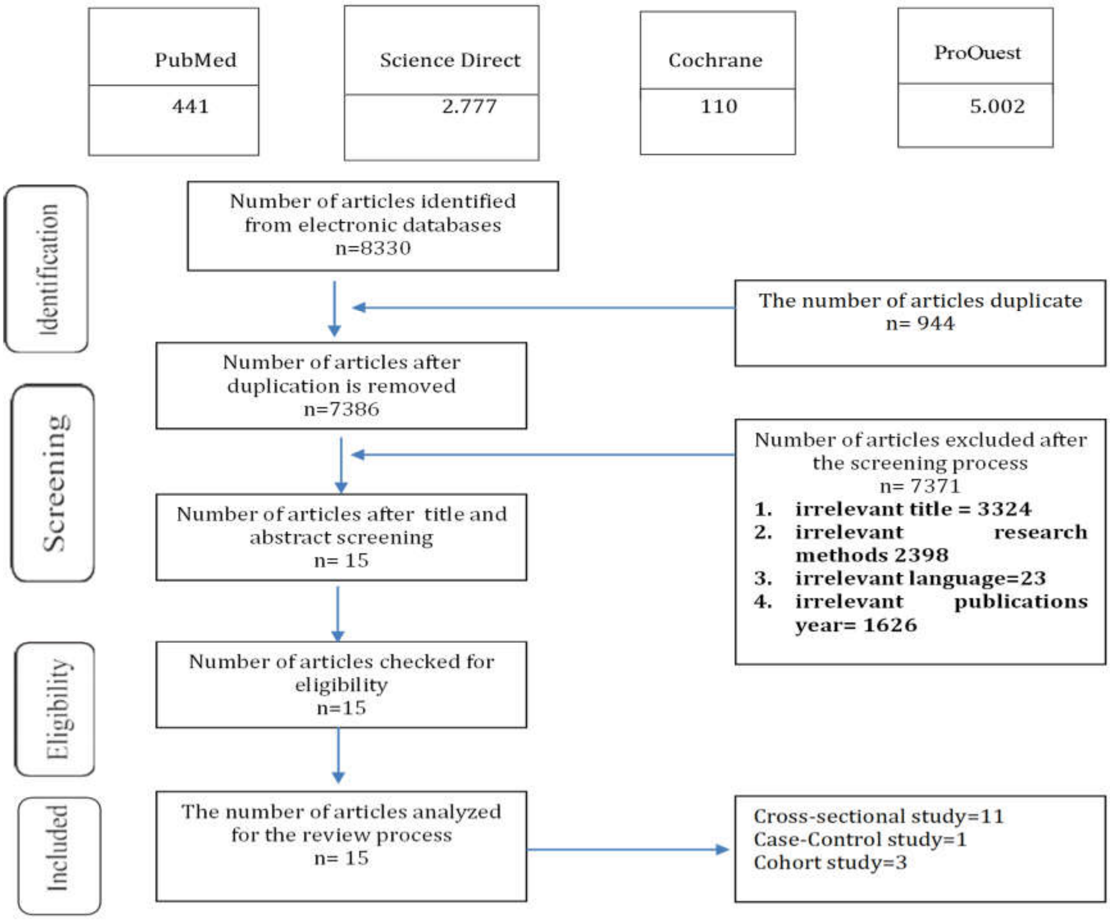

Figure 1. PRISMA flowchart of study selection process

Based on search results in four databases, namely Science Direct, Cochrane library, Pro Quest, PubMed, 8.330 articles were found. The due diligence assessment was carried out on the remaining articles and 15 articles were obtained to be included in the study. There are 11 articles with a cross sectional research design, 3 articles with a cohort design , and 1 article with a case control design . After qualitative synthesis, 15 articles were obtained, 10 articles were excluded on the grounds that the data could not be analyzed and there was no comparison so that 5 articles with a Cross Sectional design were obtained for meta-analysis as shown in Figure 1.

BIAS CHARACTERISTICS

Table 1. Characteristics of Cross-Sectional Study Article Bias

Studies	Question								Total	Score
	1	2	3	4	5	6	7	8		
[14]	√	√	-	-	-	√	√	√	5/8	62.5%
[15]	√	√	-	-	-	√	√	√	5/8	62.5%
[16]	√	√	-	-	-	√	√	√	5/8	62.5%
[17]	√	√	-	-	√	√	√	√	6/8	75%
[18]	√	√	-	-	-	√	√	√	5/8	62.5%
[19]	√	√	-	-	-	√	√	√	5/8	62.5%
[20]	√	√	-	-	-	√	√	√	5/8	62.5%
[21]	√	√	-	-	-	√	√	√	5/8	62.5%
[22]	√	√	-	-	-	√	√	√	5/8	62.5%
[23]	√	√	-	-	-	√	√	√	5/8	62.5%
[12]	√	√	-	-	-	√	√	√	5/8	62.5%

Based on the results of the due diligence assessment using *the Joanna Briggs Institute* (JBI) *critical appraisal* for the *Cross Sectional research design,* 11 articles were obtained with a score of ≥ 50% so that all articles could be included in the study. The results of the assessment can be seen in table 1.

Table 2. Characteristics of Cohort Study Article Bias

Writer	Question											Total	Score
	1	2	3	4	5	6	7	8	9	10	11		
[24]	√	√	-	-	√	-	√	-	-	√	√	6/11	54.54%
[13]	√	√	-	-	√	-	√	√	-	√	√	7/11	63.63%
[25]	√	√	-	-	√	-	√	√	-	√	√	7/11	63.63%

Based on the results of the due diligence assessment using *the Joanna Briggs Institute* (JBI) *critical appraisal* for the *cohort research design* , 3 articles were obtained with a score of ≥ 50% so that all articles could be included in the study. The results of the assessment can be seen in table 2.

Table 3. Characteristics of Case Control Study Article Bias

Writer	Question										Total	Score
	1	2	3	4	5	6	7	8	9	10		
[26]		√			√		√	√	√	√	6/10	60%

Based on the results of the due diligence assessment using *the Joanna Briggs Institute* (JBI) *critical appraisal* for the *Case Control research design,* 1 article was obtained with a score of ≥ 50% so that all articles could be included in the study. The results of the assessment can be seen in table 3.

META-ANALYSIS

The analysis was carried out using the *Review Manager application* version 5.4.1 with two types of analysis models, namely *the fixed effect model* and *the random effect model.* Based on table 6, the analysis model used is *the random effect model.* This is because the p value of the heterogeneity test results is p <0.00001, the three studies are heterogeneous. The resulting *pooled mean difference* was 1.73, while the results of the analysis obtained showed that the average *zinc level* did not show a significant difference between COVID-19 patients and healthy patients, as evidenced by the p value = 0.93.

Based on table 7, the analysis model used is *the fixed effect model.* This is because the p value of the heterogeneity test results is p = 0.85, both studies are homogeneous. The resulting *pooled odds ratio is 3.62.* While the results of the analysis obtained were that there was a relationship between low *zinc levels* in severe COVID-19 patients and the need to enter the intensive care unit as evidenced by a p value <0.05, namely p = 0.006.

DISCUSSION

Zinc Levels of COVID-19 Patients

Based on the results of the study there was no significant difference in the average *zinc levels* of COVID-19 patients compared to healthy patients. Several previous studies have examined the relationship between *zinc levels* and SARS-CoV-2 infection. In a cohort study conducted by Yasui [27]showed that of 29 adult COVID-19 patients, 9 patients (31%) were found to have low serum *zinc levels.* In a *case control study* conducted by Shahvali[26] showed that there were significant differences between the two groups, serum *zinc* was lower in the case group compared to the control group. Differences in research results found with previous studies could be due to differences in sampling time to measure *zinc levels.* As is the case in a study conducted by Shakeri [18] *zinc* levels at admission can affect the clinical outcomes of COVID-19 patients, supported by the studies of Du Laing *et al* [20]and Heller *et al* low *zinc* levels at admission sick but recovered relatively quickly and there was an increase in concentration after hospitalization. Other causes of the results of this study are not significant because the relationship between *zinc deficiency* and the severity of COVID-19 is still in the clinical trial stage[28] . The results of this study did not compare each degree of COVID-19 disease as was the case with the study by Du Laing *et al* [20] zinc levels did not differ between groups of patients with mild, moderate or severe illness.

COVID-19 patients have low zinc levels, this is because *zinc* plays a role as anti-inflammatory, anti-viral, and antioxidant [7] and also a decrease in *zinc* is an immune response from nutritional immunity. The mechanism of nutritional immunity against pathogens is starvation and/or metal toxicity mechanisms for protection against infection [29] . *Zinc* levels are tightly regulated and optimally maintained in tissues, organs, and immune cells to regulate inflammation, clear pathogens, and reduce ROS. In the mechanism of metal starvation can interfere with the process and replication of pathogens that are dependent on *zinc,* whereas the mechanism of toxicity helps the formation of local ROS to immobilize and eliminate pathogens effectively. During infection and fever, as a result of nutritional immunity, cellular and systemic *zinc availability is reduced to inhibit the growth of pathogens. Intracellular zinc* availability is immobilized in an attempt to reduce free *zinc availability* to limit pathogen survival and replication; this mechanism simultaneously signals to surrounding cells that the pathogen is present and triggers a balanced inflammatory response. Infected cells will reduce the flow of *zinc* in cells and prevent pathogens from gaining access to *the zinc* they need because *zinc* is an essential micronutrient for the survival and proliferation of bacteria, including pathogens which are the main cause of morbidity and mortality [30] .

Zinc Levels in Severe COVID-19 Patients and Need for Intensive Care Unit Admission

Based on the results of the study, there is a relationship between low *zinc* levels in severe COVID-19 patients and the need to enter the intensive care unit. COVID-19 is a multi-organ disease that is correlated with increased intensive care and high morbidity rates [31] . WHO has recommended that patients hospitalized with COVID-19 require regular monitoring of vital signs [32] . According to Phua *et al* [33]25% of hospitalized COVID-19 patients admitted to the intensive care unit had severe symptoms. According to research conducted by Yasui *et al* [27] in severe COVID-19 have low zinc levels so that prolonged *zinc deficiency can be a risk factor for severe COVID-19.* There are several significant risk factors for severe COVID-19 infection, including poor nutritional status and pre-existing non-communicable diseases (NCDs) such as diabetes mellitus, chronic lung disease, cardiovascular disease, obesity. These diseases are characterized by systemic inflammation that affects patient outcomes against COVID-19 [34] . Patients with two or more co-morbidities have significantly increased risks of intensive care unit admission, invasive ventilation, and death compared with those with a single co-morbidity, and even more than those with no co-morbidities [35] .

Severe COVID-19 patients may be admitted to the intensive care unit due to organ failure manifested by severe ARDS requiring mechanical ventilation. This is in line with research conducted by Gonçalves *et al* [14]showing that critically ill patients with low *zinc levels will show a diagnosis of severe ARDS.* According to Verschelden *et al* [25]the average *zinc level* was lower in mechanically ventilated cases compared to COVID-19 cases who did not use mechanical ventilation. Criteria for admission to the intensive care unit include oxygen requirements equal to or higher than 6-8 L/min to achieve a peripheral oxygen saturation of 90-92%, respiratory failure, shock, acute organ dysfunction, and patients at high risk of clinical deterioration (36) . Patients are admitted to the intensive care unit if clinical deterioration results in hemodynamic instability and mechanical ventilation [12] .

STUDY CHARACTERISTICS

Table 4. Characteristics of *Cross-Sectional* Study Results

Author	Study Design	Inclusion and Exclusion Criteria		Data Collection Period	Number of Samples	Sampling Time	*Zinc* Levels	Results	Information
		inclusion	exclusion						
14	*Cross Sectionals*	- Age ≥ 18 years - Data collected on the first day of admission to the intensive care unit - Diagnosed with ARDS ($PaO_2/FiO_2 \leq 300$ mmHg) - Positive swab results & chest CT scan showing a " *Ground-glass* " picture	- Patients who have used *zinc supplements* for any reason in the last 3 months - Acute or chronic liver failure or patients on chronic kidney dialysis	Hospital: On admission to the intensive care unit between 15 March and 3 May 2020	A total of 152 of 269 critical patients had severe ARDS.	*Zinc* levels were measured once on admission to the intensive care unit.	NR: 70-120 µg/dL	Adjusted for the variables age, sex, BMI, and SAPS III critically ill patients with low *zinc levels* presented with severe ARDS (OR 15.4; 95% CI 6.5–36.3; $p < 0.001$	Not included because there is no comparison.
15	*Cross Sectionals*	- Gender (male & female) - Age - Timeframe for discharge or death		Hospital and Laboratory	A total of 35 patients. Divided into patients who died, discharged, controls. Serum zinc was determined in serum samples (n=171) collected sequentially from COVID-19 survivors (n=29) or non-survivors (n=6). Control sample 136 patients.	Taken sequentially per patient in the Hospital	Deficiency < 64.25 µg/dL	Zinc concentrations in patient samples were low compared to healthy subjects (Mean ± SD ; 71.74 ± 24.62 µg/dL vs 97.57 ± 29.40 µg/dL, $p < 0.0001$)	Included in the analysis
16	*Cross Sectionals*	- Age > 20 years - Gender (male & female) - Diagnosed with COVID-19 - Agree to do research	- Patients who have undergone chemotherapy in the previous 3 months - Immunosuppression (HIV) - Take a vitamin or mineral supplement within the previous 3 months	Hospital: On admission to the intensive care unit between March and June 2020.	60 patients were enrolled and categorized into 2 groups at the time of analysis: APACHE score ≥ 25 (n=20) and APACHE score < 25 (n=40)	Using a blood sample from the antecubital vein on admission.	NR: 70-120 µg/dL	Serum levels of vitamin D and zinc were significantly lower in the APACHE score ≥ 25 group compared to the APACHE score < 25 group ($p < 0.001$)	Data cannot be analyzed.

17	*Cross Sectionals*	- Age > 18 years with symptoms of acute respiratory infection (cough, fever, dyspnea) without other causes - Positive for COVID-19 - Mild and moderate symptoms are included in groups 1 and 2 - Severe and critical symptoms are included in group 3	- Abuse of alcohol or other substances - Pregnancy or breastfeeding - Kidney failure	Hospital: Data collected until 1 September 2020	84 COVID-19 patients in the emergency department.	Only measured at the beginning of the study	deficiency < 70μg/dL	*Zinc* levels differed significantly across severity categories (standardized coefficient = -0.26, p-value = 0.02)	Data cannot be analyzed
18	*Cross Sectionals*	- All patients are positive for COVID-19 - The CT results are related to COVID-19		Hospital: Patients treated between 20 April – 5 August 2020	37 out of 239 patients needed the intensive care unit.	3 days after admission to the hospital.	NR: 70-127 μg/dL	*zinc* levels were significantly lower in those who died compared to those admitted to the intensive care unit and those who survived (94.17 ± 25.95 μg/dL vs. 98.83 ± 30.49 μg/dL and 118.8 ± 34.40 μg/dL, p = 0.002)	The data has no comparison
19	*Cross Sectionals*	**Case group:** - Positive RT-PCR patient for COVID-19 and chest CT scan - Treated in a COVID-19 ward - Age >18 years - Have no thyroid, parathyroid or chronic renal failure disorders or history of dialysis **Group of healthy volunteers:** - Individuals without chronic disease - No symptoms such as fever, headache, sore throat, and myalgia for the last 4 months - age > 18 years	- For the 2 groups, consumption of vitamin D and zinc supplementation during the last 2 weeks - sampling dissatisfaction	Hospital: On the COVID-19 wards between 24 March and 5 May 2020	56 patients (32 severe and 24 non-severe cases) admitted to the COVID-19 ward and 44 healthy patients living in Esfarayen City, North Khorasan Province of Iran.	In patients newly admitted to the COVID-19 ward.	NR: 70-114 μg/dL	Did not show a significant difference between the disease and the control group in terms of *zinc levels* (Mean ± SD : 75.99 ± 20.30 vs 32.10 ± 17.97, p = 0.07)	Included in the analysis
20	*Cross Sectionals*	- Age 18-100 years - Diagnosed positive for COVID-19		Hospital	79 patients admitted to the hospital.	On admission to the hospital	Deficiency < 66.0 μg/dL	*Zinc* concentration in all patients (Mean ± SD: 73.5 vs 16.6 μg/dL)	Data cannot be analyzed

21	*Cross Sectionals*	- The COVID-19 patient was determined by two consecutive positive SARS-CoV-2 RT-PCR tests on nasopharyngeal swabs.		Hospital: Admitted at the COVID-19 screening center from 24 april-23 may 2020	240 COVID-19 patients.	At the time of entry	Deficiency < 65 µg/dL	*Zinc* deficiency associated with hospitalization for respiratory complications within 10 days (OR 10.9, 95% CI 2.3-51.6, p = 0.002)	Not included in the analysis
22	*Cross Sectionals*	- Participants ≥ 11 years of both sexes - participants must have a clear RT-PCR result (positive or negative) - willing to participate in research	- Pregnant and lactating women - participants with uncertain RT-PCr results - patients with sickle cell anemia or thalassemia	Hospital: Outpatients and potentially uninfected participants referred to the center from 6 June 2020-12 August 2020	53 patients were infected and 53 patients were not potentially infected	At the time of entry	Deficiency < 68 µg/dL	Serum *zinc concentrations* were significantly lower in participants than in non-potentially infected participants (Mean ± SD: 101 ± 18 µg/dL vs 114 ± 13 µg/dL)	Included in the analysis
23	*Cross Sectionals*	- Adult patient fulfilling ARDS criteria according to the Berlin definition diagnosed with COVID-19 by PCR positive for COVID-19 on nasopharyngeal swab or in tracheal aspiration culture in an intubated case admitted for severe COVID-19	- Patients younger than 18 years of age or patients being treated for a disease other than severe COVID-19	Hospital: in March and May 2020	A total of 120 patients were included in this study.	On admission to hospital within the first 24 hours, preferably within 48 hours	Deficiency < 70 µg/dL	The variable associated with the need to enter the intensive care unit was low *zinc levels (OR 3.84, 95% CI 1.27-11.65, p = 0.017).*	Included in the analysis
12	*Cross Sectionals*	**Case group:** - COVID-19 positive adult patients who were hospitalized during the study period Control group: - Hospital staff member of outpatient department without underlying comorbidities - Those who are willing to take part in the research and are willing to do a blood test	- Patients who are already taking *zinc supplements* - patients who do not require hospitalization - Do not want to participate in research	Hospital: On May 17-27 2020	A total of 47 patients with cOVID-19 and 45 healthy patients.	After 6 hours of fasting since admission to the hospital	Deficiency < 70 µg/dL	- Low zinc levels associated with the need to enter the intensive care unit (OR 3.15, 95% CI 0.58-17.67, p = 0.266)	Included in the analysis

Table 5. Characteristics of Cohort and Case Control Study Results

Author	Study Design	Data collection period	Number of Samples	Sampling Time	*zinc* levels	Results	Information
24	*cohort*	Hospital: October 10-December 10 2020.	226 COVID-19 patients (patients were divided into two groups, namely severe and non-severe based on the intensive care unit and non-intensive care unit)	At the time of admission to the hospital.	NR: 72.6-127 µg/dL for males and 77-140 µg/dL for females	Serum zinc concentration in intensive care unit and non-intensive care unit patients (Mean ± SD: 67.3 ± 1.79 vs 68.42 ± 1.35, p = 0.619)	Not included in the analysis
27	*cohort*	Sakai City Medical Center: on 24 march-24 may 2020	The 62 COVID-19 patients then subgrouped into 29 patients who underwent *zinc assays*	Measured several times during blood sampling on the first day of hospitalization and 2-3 days thereafter.	Deficiency < 70 µg/dL	Zinc level as a predictor of severe cases (intubation) (OR 0.898, 95% CI 0.823-0.983, p = 0.020)	Not included in the analysis
25	*cohort*	Hospital: in May-November 2020	139 hospitalized COVID-19 patients	72 hours after admission to hospital	Deficiency < 70 µg/dL	Relationship between serum levels and use of mechanical ventilation (OR 0.98, 95% CI 0.95-1.00, p = 0.058)	Not included in the analysis
26	*Case Control*	Hospital: On May 13-30 2021	93 COVID-19 patients and 186 healthy patients who had no symptoms of COVID-19	At the time of admission to the hospital.	NR: 70-127 µg/dL	Serum calcium and *zinc levels* differed significantly between the two groups (p<0.001)	There's no comparison

Table 6. Meta-Analysis of Zinc Levels in COVID-19 Patients

Studies	***COVID-19 patient***			***Healthy Patient***			***Weight***	***Mean Difference IV, Random, 95% CI***
	Means	**SD**	**Total**	**Means**	**SD**	**Total**		
[15]	71,74	24,62	35	97.57	29,4	136	33.1%	-25.83 (-35.37, -16.29)
[19]	75.99	20.3	56	32,1	17.97	44	33.4%	43.89 (36.38, 51.40)
[22]	101	18	53	114	13	53	33.5%	-13.00 (-18.98, -7.02)
Total (95% CI)		**144**			**233**		**100.0%**	**1.73 (-39.14, 42.60)**
Heterogeneity				**p<0.00001**				
Mark				**p=0.93**				

Table 7Meta-Analysis of Low Zinc Levels in Severe COVID-19 Patients and Intensive Care Units

Studies	***Logs (Odds Ratio)***	***SE***	***Weight***	***Odds Ratio IV, Fixed, 95% CI***	***Year***
[12]	1.1474	0.8633	30.0%	3.15 (0.58, 17.11)	2020
[23]	1.3455	0.5645	70.0%	3.84 (1.27, 11.61)	2021
Total (95% CI)	100.0%			3.62 (1.43, 9.14)	
heterogeneity	p=0.85				
Mark	p=0.006				

CONCLUSION

There is no difference in the average zinc level of COVID-19 patients and healthy patients with a *mean difference of* 1.73 (95% CI -39.14 – 42.60). zinc levels in patients with severe COVID-19 are associated with the need to enter the intensive care unit with an odds ratio *of* 3.62 (95% CI 1.43-9.14). There is no conclusion regarding the effect of zinc levels on the clinical severity of mild-moderate COVID-19 patients. Our suggestion for the next research that it is hoped that the study year can be expanded so that it can include more articles for analysis and measure *zinc* level sampling time. In future studies it is expected to expand the minimum limit of *zinc deficiency and* to add more databases and keywords to search for published articles.

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