

## **Evaluate the Effect of Vitamin D Supplementation on Mortality and Intubation Rate in COVID-19 Patients: A Systematic Review and Meta-Analysis**

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### **Abstract**

**Background and aim:** the purpose of present study was Evaluate the effect of vitamin D supplementation on mortality and intubation rate in COVID-19 patients

**Method:**all articles published in international databases such as PubMed, Scopus, Science Direct, Embase between January 2019 and March 2022 included. 95% confidence interval on risk ratio (RR) were done with fixed effect model and Mantel-Haenszel method. Meta-analysis of data collected from selected studies was performed using STATA.V16 software.

**Result:** full text of 31 articles was reviewed; finally, eight articles entered the analysis. Risk ratio of Effect on mortality and intubation rate between Vitamin D and standard-of-care regarding was -0.09 (RR; 95% CI (-0.28, 0.10), p=0.36) and -0.25 (RR; 95% CI (-0.59, 0.08), p=0.14).

**Conclusion:** According to the meta-analysis, vitamin D administration is not effective on low intubation rate and reduce mortality rate of Covid-19 patients.

**Key words:** COVID-19, Vitamin D Supplementation, Mortality

### **Introduction**

Covid-19 disease is caused by the acute respiratory syndrome 2 virus. The first case of the disease was observed in Wuhan, China in December 2019, and was eventually introduced as a pandemic by the World Health Organization(1). Since appropriate and effective treatment has not yet been introduced for patients with COVID19, identifying individuals at high risk for the disease is of great importance; because by identifying people at high risk of contracting the disease and also those at high risk of contracting this form of the disease, can take preventive measures. On the other hand, due to the high number of patients with COVID19 and the collapse of the health care system in many countries, identifying patients who are at high risk for ICU services may be more or less appropriate(1). Studies have shown an association between vitamin D deficiency and the incidence of upper respiratory tract infections and mortality from new coronavirus(2). Numerous studies have previously examined the relationship between low levels of vitamin D and high rates of other types of respiratory infections(3). Vitamin D affects innate and adaptive immunity in a number of ways, so that vitamin D receptors are continuously on the surface of epithelial cells as well as cells of the immune system of monocytes and monocytes. Therefore, it is possible that vitamin D has a protective role against COVID19(4). One of the roles of vitamin D is to suppress the release of excessive levels of inflammatory cytokines, which may lead to cytokine storms. This complication is one of the major causes of mortality and complications from COVID19(5). Findings of different studies showed a

significant difference in serum levels of vitamin D in patients with COVID-19 compared with healthy individuals(6, 11). One study also showed that a large proportion of COVID-19 patients had vitamin D deficiency or insufficiency (7, 8). The aim of present study was evaluating the effect of vitamin D supplementation on mortality and intubation rate in COVID-19 patients (12-14)

## **Method**

### ***Search strategy***

Present study is based on PRISMA guidelines(9), all articles published in international databases such as PubMed, Scopus, Science Direct, Embase between January 2019 and March 2022 included. Google Scholar search engine was used.Used PICO strategy to answer theresearch questions (Table1).

### ***Inclusion criteria***

The selection criteria were RCT studies, cohort studies, observational studies, full text available, published in English language, with control group. Studies other than these study designs were excluded.

### ***Statistical analysis***

95% confidence interval on risk ratio (RR) and mean differences were done with fixed effect model and Mantel-Haenszel or in-variance method.  $I^2$  index test was used to evaluate the level of heterogeneity ( $I^2 < 50\%$  = low levels,  $50 < I^2 < 75\%$  = moderate and  $I^2 > 75\%$  = high levels). Meta-analysis of data collected from selected studies was performed using STATA.V16 software.

Table1. PICO strategy

<b>PICO strategy</b>	<b>Description</b>
<b>P</b>	Population: COVID-19 patients
<b>I</b>	Intervention: micronutrients supplementation
<b>C</b>	Comparison: vitamin D vs. standard-of-care regarding
<b>O</b>	Outcome: mortality and intubation rate

## **Result**

Using related keywords, the initial search in the database was started and 132 articles were found. These articles were entered into EndNote.X8 software and 12 duplicate articles were removed from them. 120articles entered and examined in second stage. At this stage, while reviewing the titles of articles and their abstracts, 89 unrelated articles excluded. In the third stage, the full text of 31 articles was reviewed. Eventually eight articles that were published between January 2019 and March 2022 and met the inclusion criteria, entered the analysis (Figure 1).

### ***Characteristics***

Five retrospectives' studies and one randomized controlled trial study and two cross-sectional included in present article. The number of patients in intervention group and control group were 646 and 2089, respectively; a total 2735 with 68.87 years mean of age (Table2).

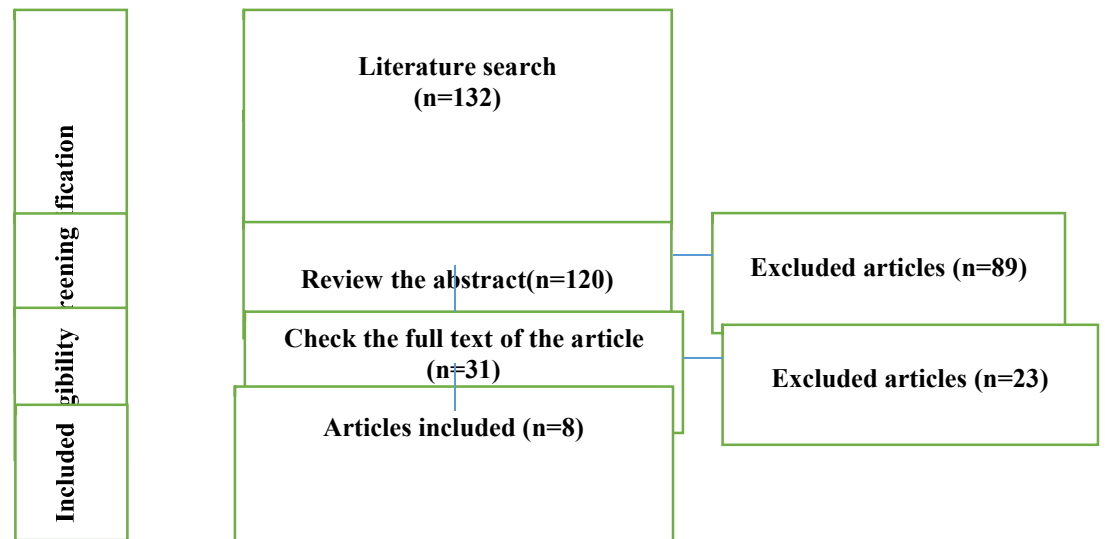


Figure 1. PRISMA flowcharts

Table 2. Studies selected for systematic review and meta-analysis

Study. Years	supplemente d	Study design	Number of Patients		Age (mean) (years)	Mortality		length of hospital stay	Follow- up
			intervention	control		intervention	control		
Arroyo-Diaz et al., 2021	pre-COVID-19	Cross-sectional	189	1078	64	50	167	NA	NA
Cangiano et al., 2021	pre-COVID-19	retrospective	20	78	89	3	39	NA	60 days
Cereda et al., 2021	pre-COVID-19	retrospective	38	286	70	7	40	NA	NA
G. Annweiler et al., 2020	pre-COVID-19	retrospective	29	32	88	2	10	NA	14 days
Alcala-Diaz et al., 2021	post-COVID-19	retrospective	79	458	67	4	90	NA	30
Castillo et al., 2020	post-COVID-19	randomized controlled trial	50	26	53	0	2	NA	NA
Guyen et al., 2021	post-COVID-19	retrospective	113	62	74	43	30	9	14
Jevalikar et al., 2021	post-COVID-19	Cross-sectional	128	69	46	1	3	NA	NA

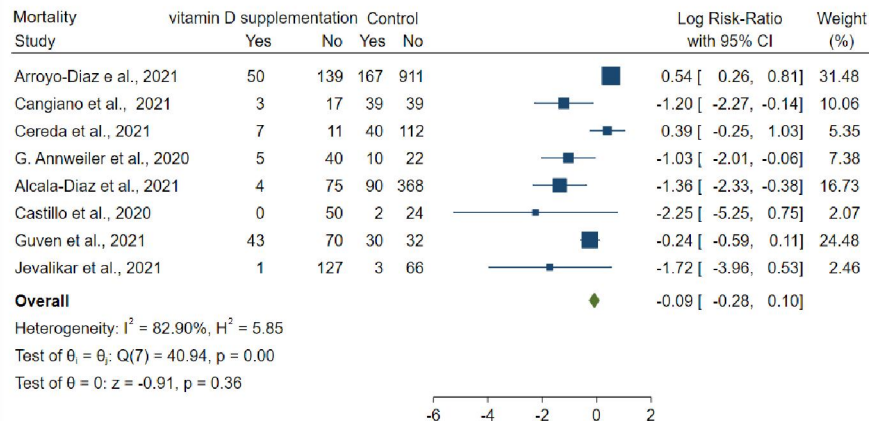
**Effect on mortality**

Risk ratio of Effect on mortality between Vitamin D and standard-of-care regarding was -0.09 (RR; 95% CI (-0.28, 0.10), p=0.36) (I<sup>2</sup>=82.90%; p=0.00, high heterogeneity).

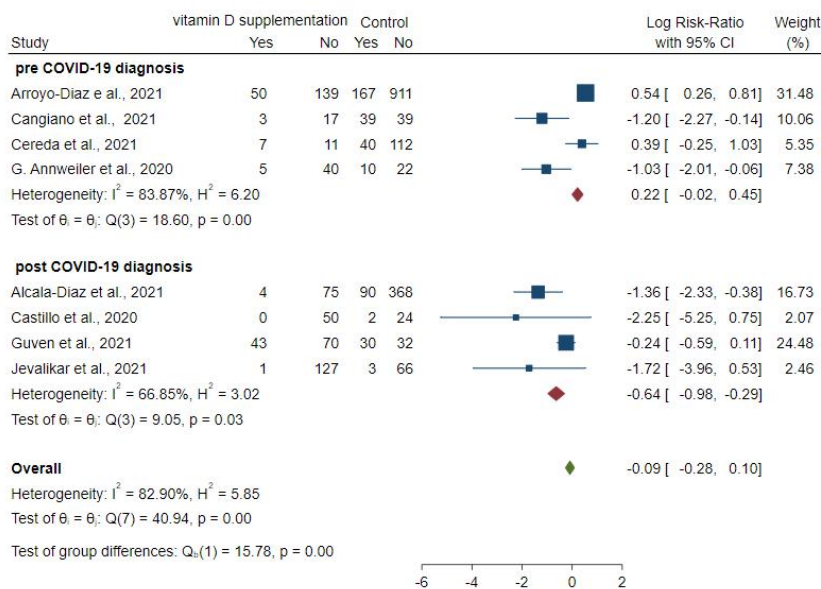
**Effect of intubation rate**

Risk ratio of Effect on intubation rate between Vitamin D and standard-of-care regarding was -0.25 (RR; 95% CI (-0.59, 0.08), p=0.14) (I<sup>2</sup><0%; p=0.58, low heterogeneity).

**Subgroup meta-analysis**



Fixed-effects Mantel-Haenszel model



Fixed-effects Mantel-Haenszel model

**GRAPH 1.** The meta-analysis graphs

**Discussion**

Vitamin D has immunomodulatory properties, such as the down-regulation of inflammatory cytokines; Studies have shown that blocking inflammatory cytokines in the angiotensin 2 and angiotensin-renin signaling pathway reduces acute lipopolysaccharide-induced lung damage in mice (15-17). It has been shown that in both mice with intermediate pneumonia caused by bleomycin and in human cell lines, vitamin D is locally activated in lung tissue and has prophylactic effects on interstitial pneumonia (18-20). However, it is possible that any protective effect of D against covid-19 is related to suppressing the cytokine response and reducing the severity of the risk of ARDS (21-23). Statistical analyzes and scientific studies have also shown evidence that regular vitamin intake provides immunity (24) and protection (25) against acute respiratory infections, especially in people with vitamin D deficiency(10). Therefore, it seems that drug prophylaxis with vitamin D (in appropriate doses) may be helpful in reducing the severity of 2-CoV-SARS-induced disease (26-28), especially in the prevalence of vitamin D deficiency

(15, 16). According to present meta-analysis (29-31) vitamin D administration is not effective in mortality, intubation rate and length of hospital stay of Covid-19 patients (32-35).

### **Conclusion**

Based on the available evidence, vitamin D can have a potential effect on respiratory infections; it is still widely used in the Covid-19 epidemic due to its cheapness and harmlessness. The present meta-analysis is consistent with the findings of studies that vitamin D supplementation did not significantly affect mortality rates and intubation rates. Further studies are needed to confirm the present evidence, and future studies should consider separate micronutrient supplements and their impact on mortality, intubation rate, and length of hospital stay. Micronutrient supplements such as vitamin D have no effect on reducing mortality and low intubation rates in patients with COVID-19. However, physicians and nurses should provide the necessary measures and training for patients to use micronutrient supplements such as vitamin D; further studies are needed on the importance of using micronutrient supplements in patients with COVID-19.

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