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Research Article

The Role of Vitamin D in COVID-19 Survival and Prevention: A Meta-analysis

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Abstract

Background: COVID-19 is still ongoing with frequently discovered new strains, although vaccines are highly effective for prevention. Literature on vitamin D supplementation in COVID-19 prevention and its effect on survival is scarce. This meta-analysis assessed the role of vitamin D supplementation in COVID-19 prevention and survival.

Methods: Four databases (Web of Science, SCOPUS, PubMed, MEDLINE, and the first 100 articles of Google Scholar) were searched for articles published up to September 2023. The keywords used were COVID-19, mortality, vitamin D supplementation, calcitriol, cholecalciferol, Calcifediol, survival, death, and prevention. Six hundred and seven studies were retrieved, and four hundred and three remained after duplication removal; of them eighty-three full texts were screened, and of them, only sixteen (prospective, randomized controlled trials, and retrospective studies) were included in the final meta-analysis.

Results: Sixteen observational studies including 5905,109 patients and 186,500 events were included. Vitamin D supplementation reduced mortality among patients with COVID-19 patients, odd ratio, 2.31, 95% *CI*, 1.49–3.58; in addition, supplementation was effective in COVID-19 prevention, odd ratio, 1.92, 95% *CI*, 1.01–3.64.

Conclusion: Vitamin D supplementation prevented COVID-19 and increased survival among patients admitted with moderate/severe COVID-19.

Keywords: vitamin D supplementation, COVID-19 prevention, mortality

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1. Introduction

The Covid-19 pandemic has become the most dramatic event of the current century with more than 50 million confirmed cases and 18.2 million deaths during the period January 2020–December 2021 [1]. In the aftermath of COVID-19, a great challenge is still present due to the long-COVID or post-acute COVID-19 syndrome. The persistence of symptoms (fatigue, cognitive decline,cough, sputum, headache, chest pain, insomnia, wheeze, taste and smell disturbances) among those who recovered is called post-COVID-19 syndrome or long COVID-19. The prevalence of post-COVID-19 at 90 days is substantial with a great burden on the patients and the healthcare system [2]. Vitamin D performs both skeletal and extra-skeletal functions, and vitamin D receptors are expressed in various tissues. Vitamin D receptors are expressed in the lung, brain, heart, and immune system. Therefore, vitamin D deficiency is associated with immune and inflammatory conditions, chest infections including COVID-19. In addition, vitamin D deficiency is associated with type 1 diabetes, demyelination, and rheumatoid arthritis [3]. Importantly, enzyme 1 alpha-hydroxylase (CYP27B1) is expressed in many organs and can activate vitamin D to exert autocrine or paracrine effects [4]. Evidence regarding the effects of vitamin D deficiency and vitamin D supplementations on COVID-19 is contradicting; some studies found a reduction in severity and mortality [5], while Hastei and colleagues who published a study with large population size and long follow-up study period showed no association of vitamin D deficiency, disease severity, and mortality [6]. A meta-analysis with a high selection bias and heterogeneity showed no difference among patients who took vitamin D and their counterparts without supplementation regarding COVID-19 outcomes [7]. On the other hand, Naguyen *et al.* found better outcomes among patients with normal vitamin D levels [8]. The controversy is ongoing; Hu *et al.* found no association of vitamin D levels on severity, ventilation need, and mortality [9], and Tomaszewska *et al.* concluded no evidence of vitamin D in treatment of COVID-19 [10]. Moreover, new studies have been published covering this topic – Cannata-Andia *et al.* [11] showed no benefit of single oral dose of vitamin D on outcomes; Fernandes and colleagues [12] found no benefits of single 200,000 IU vitamin D3 on cytokines, growth factors, and chemokines among hospitalized patients with severe COVID-19, and Annweiler *et al.* [13] found the benefit of the early high-dose chemokinese vitamin D supplementation among patients with severe COVID-19. Therefore, a meta-analysis on the effects of vitamin D supplementation on COVID-19 mortality and prevention is justifiable. Thus, this meta-analysis aimed to assess the same among patients with COVID-19.

2. Materials and Methods

2.1. Eligibility criteria according to PICOS

We included randomized controlled trials, prospective, and retrospective studies. The studies must assess the effects of vitamin D supplementation on COVID-19 prevention and mortality. Case–control studies, cross-sectional studies, experts' opinions, editorials, case reports, and series were not included.

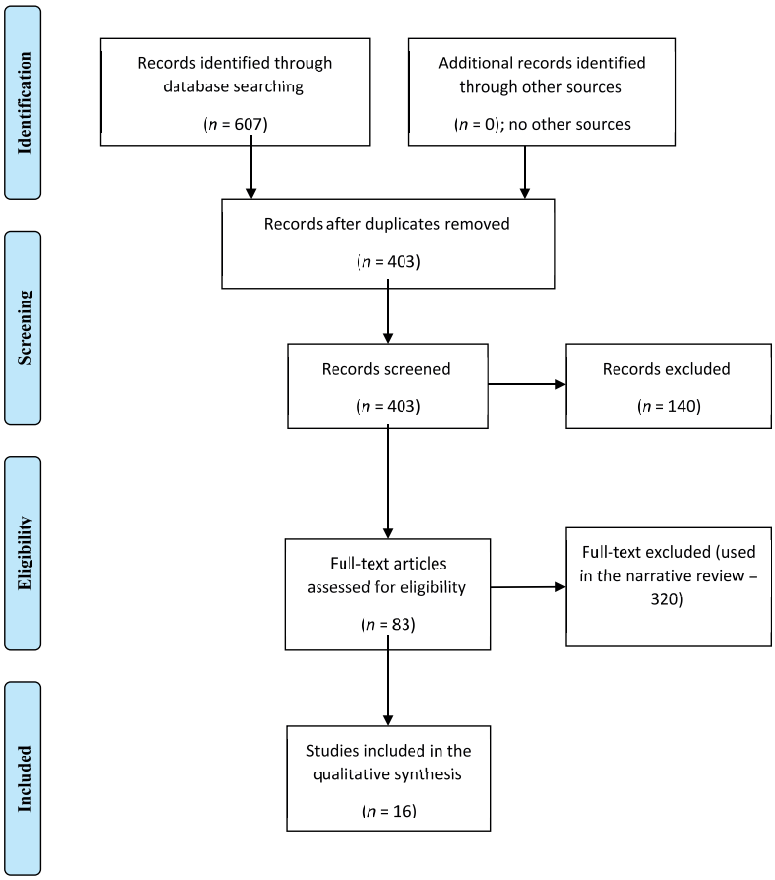

Figure 1: Studies that assessed the effects of vitamin D supplementation on COVID-19 prevention and mortality (the PRISMA Chart).

2.2. Outcome measures

1. **T**he effects of vitamin D supplementations on short-term mortality among patients hospitalized with COVID-19.
2. The effects of vitamin D supplementations on COVID-19 prevention.

The vitamin D status of the patients with COVID-19 was not limited, both vitamin D deficient and those with normal vitamin D levels were included.

2.2.1. Literature search

Two authors independently searched four databases (Web of Science, SCOPUS, PubMed, MEDLINE, and the first 100 articles of Google Scholar). The literature search was set from the first published article to those published till September 2023. The keywords used in the four databases were COVID-19, mortality, vitamin D supplementation, calcitriol, cholecalciferol, calcifediol, survival, death, and prevention. Six hundred and seven studies were retrieved, and four hundred and three remained after duplication removal; of them eighty-three full-texts were screened, and of them, only sixteen (prospective and retrospective studies, and randomized controlled studies) were included in the final meta-analysis. A structured checklist was used to gather the author's name, country, year of publication, number of patients in vitamin D supplementation and control group, age and sex of the participants, the study duration, mortality, and comorbidities.

2.2.2. Risk of bias assessment

The Newcastle Ottawa Scale risk of bias assessment, and a modified Cochrane risk of bias were used [14, 15]. All the included studies were of good quality.

2.3. Statistical analysis

RevMan, version 5.4 was used to analyze the dichotomous of 16 studies, 8 studies that assessed the effects of vitamin D on mortality, and 8 cohorts that assessed the effects on COVID-19 prevention. The random effect was used (because of the significant heterogeneity). A *P*-value of <0.05 was considered significant.

3. Results

In the present meta-analysis, 5905,109 patients were included from 16 studies, and 186,500 events occurred. Eleven studies were from Europe, two were from the USA, two were published in South America, and one was from Asia. Eight studies assessed vitamin D supplementation on COVID-19 mortality [15–23] and eight cohorts investigated the effects of vitamin D supplementation on COVID-19 prevention [24–31]. Vitamin D supplementation reduced mortality among patients with COVID-19 patients, odd ratio, 2.31, 95% *CI*, 1.49–3.58. The Chi-square was 14.53, and the *P*-value for the overall effect was 0.0002. A significant heterogeneity was found, I^2 for heterogeneity = 52%, *P*-value, 0.04, and the standard difference = 7 (Figure **2**).

Vitamin D supplementation was effective in COVID-19 prevention, odd ratio, 1.92, 95% *CI*, 1.01–3.64. The Chi-square was 204.46, and the *P*-value for the overall effect was 0.05. Significant heterogeneity was found, I^2 for heterogeneity = 97%, *P*-value < 0.001, and the standard difference = 7 (Figure **3**). The source of heterogeneity was the pooling of studies with different methodology. The significant heterogeneity in particular regarding Covid-19 prevention limited the current results. The random effect was used.

4. Discussion

The present meta-analysis pooled 16 cohorts and found that vitamin D supplementation was effective in COVID-19 prevention and all-cause mortality reduction, odd ratio, 1.92, 95% *CI*, 1.01–3.64, and odd ratio, 2.31, 95% *CI*, 1.49–3.58, respectively. A previous meta-analysis with a limited number of studies [32] found no effects of vitamin D supplementation on primary COVID-19 prevention, in contradiction to the present findings, regarding mortality the authors found a positive effect in line with current findings. The current results were in agreement with a previous meta-analysis [33] which found a reduction in all-cause mortality and primary prevention. The authors pointed out that vitamin D supplementation improved outcomes of COVID-19 only when prescribed after COVID-19 diagnosis. The previous study was limited by pooling both randomized and observational studies and included in their results various studies published by the same authors [34, 17]. Shah and colleagues [35] in their meta-analysis found no difference between vitamin D supplementation, placebo, and usual care. A big limitation of Shah *et al.* study is that they included only three underpowered studies with a high baseline heterogeneity. Nikniaz *et al.* [36] included only four studies with a limited number of patients (259) and found lower mortality among the vitamin D supplementation arm. The link between vitamin D

Table 1: Vitamin D supplementation and mortality reduction among patients with COVID-19.

Author name and year of publication	Country of the study	Study type (methodology)	Vitamin D supplementation, mortality/total patients	Control group, mortality/total patients
Alcala *et al.* 2021 [16]	Spain	Retrospective	4/79	90/458
Annweiler *et al.* 2020 m[17]	France	Retrospective	10/57	5/9
Cangiano *et al.* 2020 [18]	Italy	Prospective	3/20	39/78
Cereda *et al.* 2019 [19]	Italy	Prospective	7/18	40/152
Giannini *et al.* 2021 [20]	Italy	Retrospective	14/36	29/55
Hernández *et al.* 2021[21]	Spain	Retrospective	2/19	20/197
Ling *et al.* 2020 [21]	UK	Retrospective	24/148	254/768
Nogués *et al.* 2021 [23]	Spain	Prospective	36/551	57/379

Table 2: Basic characteristics of patients with COVID-19 and vitamin D supplementation.

Author name and year of publication	Age of vitamin D supplementation and control groups years	Females% in vitamin D supplementation and control groups	Vitamin D dose in the intervention group	Comorbidities among the study groups
Alcala *et al.* 2021 [16]	69 ± 15 vs 67 ± 16	47% vs 40%	0.266 mg/capsule, 2 capsules on entry and then one capsule on days 3, 7, 14, 21, and 28	More chronic kidney disease in the interventional group
Annweiler *et al.* 2020 m[17]	87.7 ± 9.3 vs 87.4 ± 7.2	78.9% vs 66.7%	80,000 IU vitamin D3 every 2–3 months	Functional abilities and medication use were higher among the intervention group
Cangiano *et al.* 2020 [18]	90.85 vs 89.35	Not reported	Not reported	No differences regarding comorbidities
Cereda *et al.* 2019 [19]	68.8 ± 10.6 vs 70.5 ± 13.1	57.9% vs 50.7%	800 IU/day	No differences regarding comorbidities
Giannini *et al.* 2021 [20]	73 ± 13 vs 74 ± 13	47% vs 43%	200,000 IU administered in two consecutive days	Smoking is common among controls
Hernández *et al.* 2021 [21]	60 vs 61	63.2% vs 37.6%	25,000 IU/monthly or calcifediol, 0.266 mg/monthly	Diabetes is commoner among control, diabetes more in the intervention
Ling *et al.* 2020 [21]	74 years	44.8% females	≥280,000 IU in a period of up to 7 weeks	No differences regarding comorbidities
Nogués *et al.* 2021 [23]	61.81 ± 15.5 vs 62.41 ± 17.2	40.9% vs 40.9%	532 ug on day one plus 266 ug on days 3, 7, 15, and 30	No differences regarding comorbidities

and COVID-19 might be mediated by its effects on inflammation and cytokines release, vitamin D modulates adaptive and innate immunity and might decrease infection [37]. Daily or weekly vitamin D supplementation was shown to reduce respiratory infections, while bolus doses were not effective and daily doses of 400–1000 IU were the most effective [38, 39]. Modulation of the cytokine storm and activation of ACE receptors by the virus are suggested as mediators of vitamin D COVID-19 prevention and outcomes improvement, in addition to pulmonary epithelial barrier maintenance and epithelial repair [40, 41]. The effects of vitamin D status on COVID-19 severity and outcomes

Table 3: Vitamin D supplementation and COVID-19 prevention.

Author name and year of publication	Country of the study	Vitamin D group, mortality/total number of patients	Placebo group, mortality/total number of patients	Results, significance
Brunvoll *et al.* 2022 [24]	Norway	227/17 278	228/17323	Not significant, *P*, 0.41
Jolliffe *et al.* 2022 [25]	UK	100/1515	78/136	Significant, *P* <0.001
Karonova *et al.* 2022 [26]	Russia	10/38	18/40	Not significant
Ma *et al.* 2019 [27]	USA	49/363	1329/7938	Not significant
Murai *et al.* 2021 [28]	Brazil	9/119	6/118	Not significant, *P*, 0.41
Meltzer *et al.* 2020 [29]	USA	17/89	14/80	Not significant
Oristrell *et al.* 2021 [30]	Spain	238/8078	183511/5848778	Chronic kidney disease
Villasis-Keever *et al.* 2022 [31]	Mexico	6/94	24/98	Significant, *P* <0.001

Table 4: Basic characteristics of patients on vitamin D supplementation for COVID-19 prevention.

Author name and year of publication	Age of vitamin D supplementation and control groups years	Females% in vitamin D supplementation and control groups	Vitamin D dose in the intervention group	Comorbidities among the study groups
Brunvoll *et al.* 2022 [24]	45.0 ± 13.5 vs 44.9 ± 13.4	64.6% vs 64.6%	10 µg of vitamin D for 6 months	No differences regarding comorbidities
Jolliffe *et al.* 2022 [25]	55 vs 60.8	67.6% vs 64.4%	800–3200 IU for 6 months	Comorbidities more among intervention
Karonova *et al.* 2022 [26]	35 ± 2 vs 35 ± 2	82% vs 87%	Two doses of 50000 IU/week followed by 5000 IU/day	No differences regarding comorbidities
Ma *et al.* 2019 [27]	59.1 ± 8.1 vs 57.4 ± 8.6	61.2% vs 50%	Yes or no answer	Vitamin D patient were less obese, had more cancer and COPD
Murai *et al.* 2021 [28]	56.5 ± 13.8 vs 56 ± 15.0	41.2% vs 46.6%	A single oral dose of 200,000 IU	Diabetes is commoner in the intervention
Meltzer *et al.* 2020 [29]	51.0 ±18.6 vs 45.9 ±17.6	77% vs 74%	1000–3000 IU daily for 14 days	No differences regarding comorbidities
Oristrell *et al.* 2021 [30]	70.2 ±15.6 vs 70.7 ±14.7	57.5% vs 57.5%	Questionnaire-based	Heart failure commoner among controls
Villasis-Keever *et al.* 2022 [31]	Median 36 vs 39	71% vs 68%	4000 IU daily for 30 days	Type 2 diabetes commoner among control

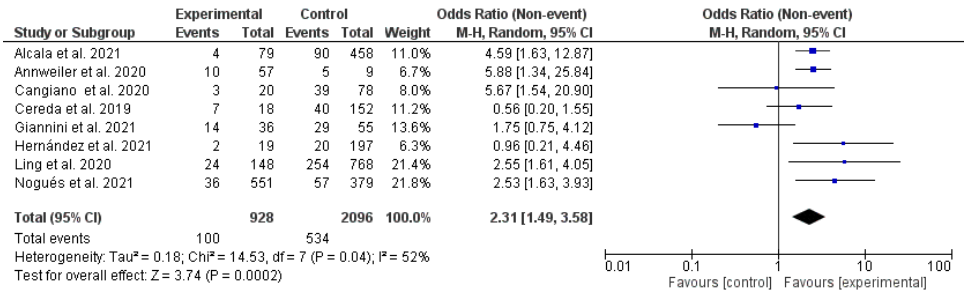

Figure 2: The effects of vitamin D supplementation on mortality among patients with moderate/severe COVID-19.

are limited because vitamin D levels are usually low in acute infection; furthermore, most studies

Table 5: Newcastle Ottawa risk of bias of observational studies.

Author	Selection bias score	Compatibility score	Outcome bias score	Overall bias score
Alcala *et al.* 2021 [16]	4	2	3	9
Annweiler *et al.* 2020 [17]	4	2	2	8
Cangiano *et al.* 2020 [18]	4	2	1	7
Cereda *et al.* 2019 [19]	4	2	2	8
Giannini *et al.* 2021 [20]	4	2	2	8
Hernández *et al.* 2021 [21]	4	2	2	8
Ling *et al.* 2020 [21]	4	2	2	8
Nogués *et al.* 2021 [23]	4	2	2	8
Ma *et al.* 2019 [27]	4	1	2	7
Meltzer *et al.* 2020 [29]	4	1	2	7
Oristrell *et al.* 2021 [30]	4	1	2	7

Table 6: Risk of bias assessment of the included studies according to Cochrane risk of bias of randomized controlled trials.

Author	Selection bias[1]	Selection bias[2]	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
Brunvoll *et al.* 2022 [24]	Low	Low	Low	Low	Low	Low	Low
Jolliffe *et al.* 2022 [25]	Low	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Karonova *et al.* 2022 [26]	Low	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns
Villasis-Keever *et al.* 2022 [31]	Low	Low	Low	Low	Low	Low	Low
Murai *et al.* 2021	Low	Low	Low	Low	Low	Low	Low

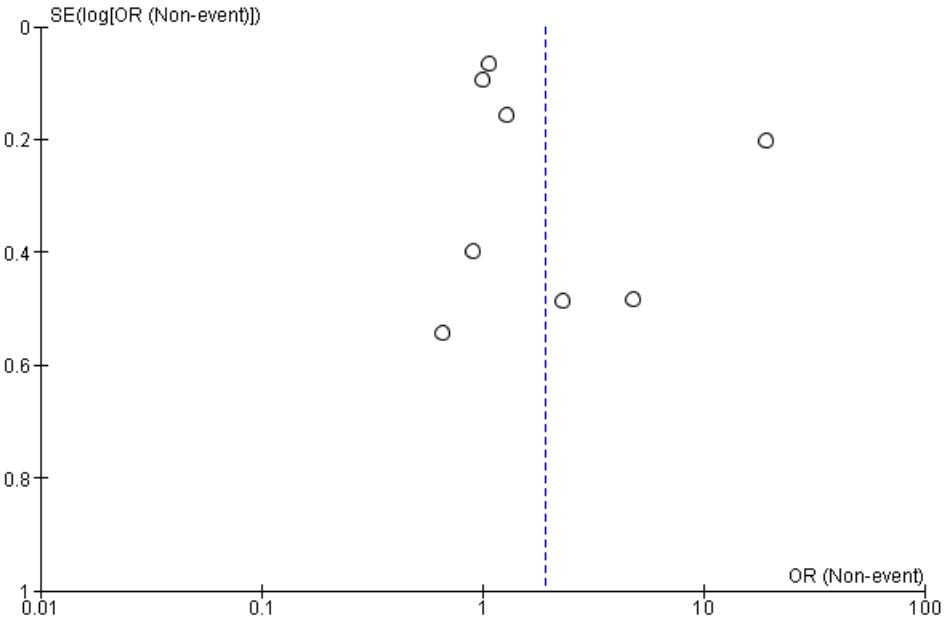

Figure 3: The effects of vitamin D supplementation on COVID-19 prevention.

did not use accurate liquid chromatography-mass spectroscopy [42, 43]. Also, cells from severe

COVID-19 were shown to dysregulate vitamin D response. However, there is a piece of evidence of normal immune response toward COVID-19 among patients with a non-functional vitamin D receptor [44]. Biological and genetic factors play a crucial role in vitamin D deficiency. Although, >60 polymorphisms have been identified, few loci were strictly related to vitamin D deficiency (genome-wide association studies) [45]. Twenty percent of vitamin D deficiency can be explained by genetic variants including single nucleotide polymorphisms [46]. The implications of genetic and biological factors is that certain pathways might be targeted as therapeutic measure for COVID-19 therapy and prevention [47]. Vitamin D was shown to ameliorate the cytokine storm (the release of interleukin (IL)-6, IL-1β, IL-17, and tumor necrosis factor-alpha) and reduce the activation of signal transducer and activator of transcription 3. The above mechanism are central to COVID-19 pathological and clinical features [48]. Regarding vitamin D in COVID-19 prevention, Hosseini *et al.* [32], who included only five studies, and Bassatne *et al.* [37], who included only three, found no benefits, and contradicting the current findings, a Mendelian randomization study failed to support the use of vitamin D for COVID-outcomes [49]. Plausible explanation might be the difference in vitamin D dose, high intermittent doses of vitamin D paradoxically deplete intracellular vitamin D as a rebound in particular in immune cells [50]. For now, doses of 4000 IU daily are recommended [37]. The strength of this meta-analysis is that it is the first to assess the role of vitamin D in COVID-19 secondary prevention and included a large randomized controlled trials. However, the significant heterogeneity observed substantially limited our findings. Further randomized trials with large sample size focusing on the timing of vitamin D supplementations (before against hospital), the dose (continuous or intermittent, high versus low), comorbidities, and vaccination status are recommended.

5. Conclusion

Vitamin D supplementation prevented COVID-19 and increased survival among patients admitted with moderate/severe COVID-19. Further randomized control trials assessing the time, duration, and doses of vitamin D are recommended.

Limitation

The study was limited by the inclusion of observational studies, and significant heterogeneity (due to the pooling of studies with different methodologies) was observed in the mortality arm.

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Ethical Considerations

The authors did not include any manuscript published by them.

Competing Interests

None

Availability of Data and Material

Data are available within the article.

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