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Vitamin D on COVID-19 Patients During the Pandemic, 2022. A Systematic Review and Meta-Analysis

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Abstract

Numerous connections between the level of vitamin D (Vit-D) and the novel coronavirus disease -19 (COVID-19) have surfaced during the pandemic. So, we conducted this systematic review and meta-analysis to explore the effect of Vit-D deficiency and its supplementation on the clinical outcomes of COVID-19 patients. We looked for relevant articles in Cochrane Library, Scopus, Web Science, PubMed, and EBSCO up until the end of 2022. The Open Meta Analyst software was used to analyze the extracted data. We classified them into two main categories based on their objectives. First, the studies that evaluated the effects of Vit-D deficiency in patients, and lastly, the studies that evaluated Vit-D as a supplement, both on mortality rate, hospitalization duration, ICU admission rate, and mechanical ventilation rate. A total of 8001 COVID-19 patients from 42 studies were included. A high serum Vit-D concentration compared to those with lower levels was associated with a significantly lower mortality rate (RR = 1.5, 95% CI = 1.11: 2.02, p = 0.01). According to the estimated effect of 18 studies, those who took Vit-D supplements had a significantly lower mortality rate, hospitalization duration, ICU admission rate, and mechanical ventilation rate than those who did not. The group receiving Vit-D doses

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between 50 000 to 100 000 IU had a significantly better clinical outcome compared to lower and higher doses. COVID-19 patients with normal Vit-D levels had significantly lower death rates than those with hypovitaminosis. Vit-D supplements in COVID-19 significantly improved clinical outcomes. Vit-D supplementation between 50 000 to 100 000 IU, in patients with COVID-19 significantly outperformed other doses in terms of mortality.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is a serious global threat resulting from the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. SARS-CoV-2 had affected nearly 306 million cases and resulted in more than 5.4 million deaths as of early January 2022.[1] The severity of the SARS-CoV-2 infection depends on the development of acute respiratory distress syndrome (ARDS), pneumonia, thrombosis, and vital organ failure.These complications arise from initiating a cytokine storm that involves an aggressive inflammatory response causing multi-system damage.[2] Individuals with risk factors, including advanced age, hypertension, diabetes mellitus, cardiovascular diseases, and obesity, frequently experience more severe illness following COVID-19 infection.[3–6] A lack of Vitamin D (Vit-D) has also been considered a possible risk factor for bad outcomes.[7,8]

Vitamin D is a fat-soluble vitamin obtained through diet, sunlight, and dietary supplements.[9] Calcitriol (1,25-dihydroxy vitamin D3) is the active form of Vit-D that exhibits a potent immunomodulatory effect by enhancing innate and acquired immune responses. Vit-D improves innate immunity by activating antimicrobial peptides, including defensins and cathelicidin. Calcitriol also inhibits the expression of pro-inflammatory mediators and increases anti-inflammatory mediator production from macrophages.[10,11] Regarding acquired immunity, calcitriol suppresses T helper lymphocyte type 1, which produces inflammatory cytokines.[10] These anti-inflammatory effects of Vit-D contribute to alleviating the COVID-19 cytokine storm. Vit-D also increases the levels of T-regulatory lymphocytes, which protect against inflammation and sviral infections.[12]

In addition to the role of Vit-D in immunity, it exhibits anti-thrombotic actions that can interfere with the microvascular thrombosis caused by SARS-CoV-2.[12,13] Moreover, Vit-D increases the genetic expression of enzymes related to antioxidant production, mainly glutathione.[12,14] This antioxidant effect protects the cells from the oxidative stress caused by the infection and lowers patients' viral loads. All these beneficial actions promise that Vit-D supplementation should improve the outcomes of COVID-19 patients.

During the pandemic, numerous observational studies assessed the association between Vit-D insufficiency and patients' prognosis. Other interventional studies aim to determine the effect of Vit-D supplementation on disease severity. For this reason, we hypothesize that Vit-D deficiency may be a risk factor in patients with COVID 19 and its supplementation would improve their clinical outcomes. Therefore, we conducted this systematic review and meta-analysis to explore the effect of vitamin D deficiency and its supplementation on the clinical outcomes of COVID-19 patients.

Methods

We conducted this meta-analysis and reported it following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement guidelines and followed the criteria used in the Cochrane Handbook of Systematic Reviews and Meta-analyses.[16]

Eligibility Criteria

We came up with a PICOs strategy, which stands for population, intervention, comparison, outcome, and study design. We defined the PICOs as follows: P = COVID-19 patients, I = Vitamin D deficiency or supplementation, C = comparator or control group; O = mortality rate as the primary outcome and ICU admission or hospitalization duration as secondary outcomes, S: randomized controlled trials, cross-sectional, prospective, and retrospective cohort studies.

Eligibility Requirements: 1) Both observational (prospective or retrospective, cohort or case-control design) and randomized controlled trials (parallel or cross-over), blinded (single-blind, double-blind, or open-label) studies. 2) Studies including COVID-19 individuals. 3) At least one of the clinical outcomes of COVID-19 patients (mortality, ICU admission, ventilation, or hospitalization duration). 4) The clinical outcomes should be presented as the number of "events" in patients with COVID-19 who received Vit-D treatment compared to those who did not get Vit-D.

Exclusion Criteria for clinical case series, review papers, book chapters, study procedures, critiques, editorials, comments, letters to the editor, studies without peer review, and finally, incompleteness in data.

Search Strategy

We conducted a basic search independently through a systematic literature search across five different databases: PubMed, Cochrane Library, Scopus, Web of Science, and EBSCO, for relevant studies from 2019 up to the end of 2022. There were no limitations related to language or specific durations. The following keywords are interposed with "COVID-19" or "SARS-CoV-2" and “Vitamin D” (deficiency or supplementation). Searching relevant review references and retrieved documents for potentially qualifying articles. The corresponding authors of potentially eligible papers were contacted whenever possible for missing data.

Selection Process

The study selection process consisted of two steps. First, two review authors (R.A.F. and E.E.) independently screened the titles and abstracts (TAs) of the retrieved records based on the PICOS strategy to exclude duplicate studies and those that did not meet the qualifying criteria. Secondly, the same reviewers assessed the full text of the selected ones. Any disagreement between the reviewers was resolved by discussion or with the senior author (M.M.A.).

The extracted Data

Two authors (A.A.N. and A.A.) independently extracted required data from the included studies using a well-organized Excel sheet. The extracted data included: 1) baseline characteristics data, including age, gender, sample size, and health status. 2) The study characteristics, including setting and study design, 3) The reported serum vitamin D levels were classified into three groups based on a normal range (10-30 ng/mL): Group A (< 10 ng/mL, severe deficiency), Group B (< 20 ng/mL) and Group C (> 30 ng/mL, normal), 4) Vit-D supplementation-related data, including the dose and follow up duration, the formulation and method of Vit-D administration, the number of patients who received Vit-D, the number of COVID-19 patients who received Vit-D, and 5) The reported clinical outcome compared to those who did not receive Vit-D (ICU admission rate, mechanical ventilation, length of hospitalization, mortality rate).

A senior author (M.M.A.) reviewed the extraction sheet, and any disagreement was solved by discussion amongst the aforementioned investigators by debate, consensus, or arbitration. The included studies were divided into two main groups, those that evaluated Vit-D deficiency on clinical outcomes in people with COVID-19, and those that evaluated the effect of Vit-D supplementation on clinical outcomes.

Quality Assessment

M.A.A. and I.M.E., two independent authors, assessed the risk of bias in the included studies using two validated tools. First, the tool for bias assessment, the Cochrane risk assessment for randomized controlled trials (RCTs), is in chapter 8.5 of the Cochrane Handbook of Systematic Reviews of Interventions, 5.1.0. This tool consists of six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and any other bias). Bias is assessed as a judgment. Each domain's risk of bias was graded as "low," "unclear," or "high." Thus, a study with appropriate processes in all domains was classified as having a low risk of bias, whereas a study with deficient procedures in at least one category was rated as having a high risk of bias. In all other instances, studies were classified as having an uncertain risk of bias.[17]

Secondly, the Methodological Index for Non-Randomized Studies Scale (MINORS), which is a valid instrument to assess 12 items, the first eight of which are specifically for non-comparative and single-arm studies, a third reviewer settled any disagreements.

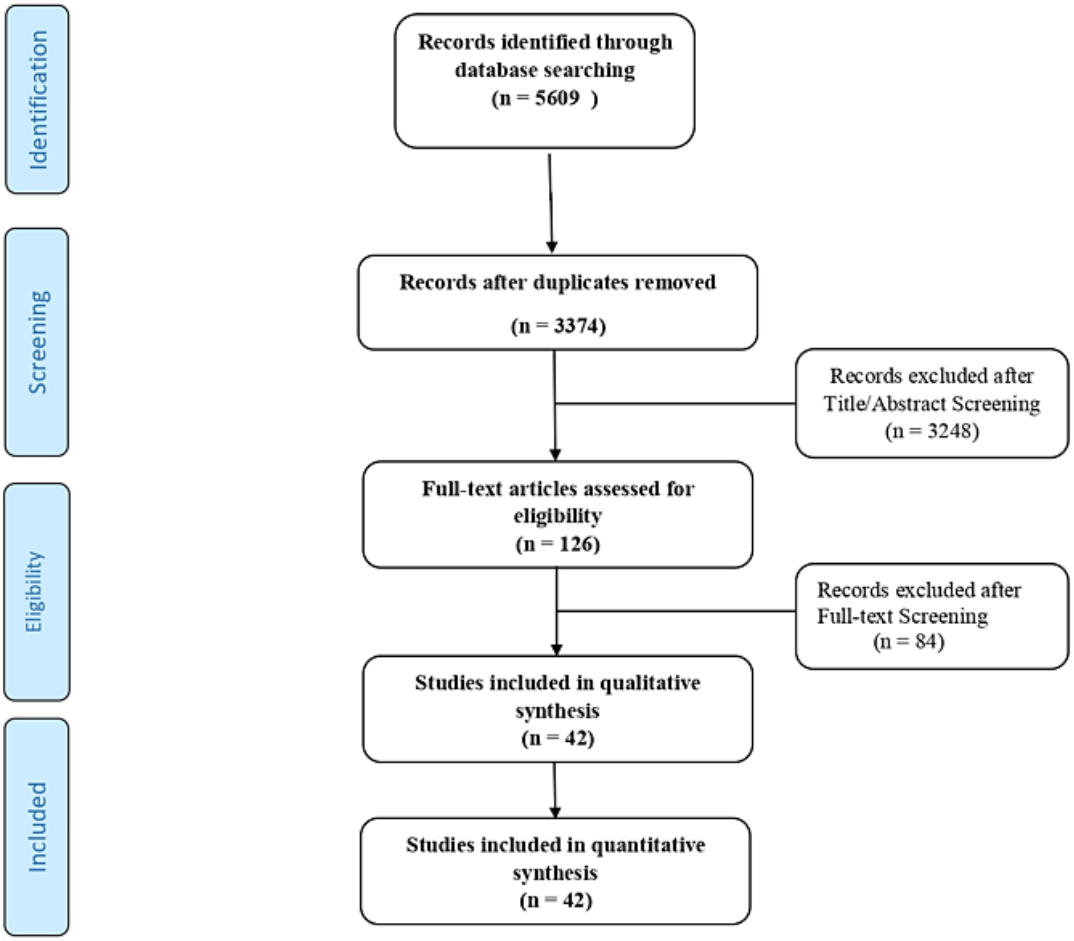

Fig. 2: Forest plots of mortality (a) and ICU admission (b) on COVID-19 patients with vitamin D deficiency

Data Synthesis

At a level of significance *p-value* was < 0.05. We pooled continuous data as the mean difference (MD) with a 95% Confidence Interval (C.I) and dichotomous data as the risk ratio (RR) with a 95% C.I. All data were analyzed using Open Meta Analyst software for Windows; an open-source, cross-platform software for advanced meta-analysis. Statistical heterogeneity between studies was assessed by the Chi-squared (x^2) and I-squared tests. Heterogeneity was evaluated as low, moderate, or high, with upper limits for I^2 of 25%, 50%, and 75%, respectively. When the I^2 value was 50% and the *p-value*= 0.05, heterogeneity was considered significant in the current meta-analysis. Using the random-effects model, considerable heterogeneity was reanalyzed and reported for the outcomes. Subgroup analysis was performed based on Vit-D levels (< 50 000, 50 000 – 10 000, > 100 000 International Unit (IU), etc.) and Vit-D supplementation (doses, the timing of administration, etc.), to clarify how efficacy differed and to reduce heterogeneity among the included studies.

Ethical Considerations

The data collection took place in accordance with the Bahrain Personal Data Protection Law (PDPL) and the European Data Protection Regulation. As it's a systematic review and meta-analysis, we used secondary data from ethically approved studies, and the results were collected anonymously.

Table 1: A summary of the baseline characteristics of included studies that assess the effect of serum Vitamin D levels on several clinical outcomes in Covid-19 patients.

Study ID	Country/ Year Centers	Health status	Total Sample size	Age (yr)	Sex M/F	Design of the study	Main findings
Demir 2021	Turkey 2021	Adult positive COVID-19 patients	227	45.2 ± 17.6	98/129	A Retrospective cohort	The risk of getting COVID-19 increased in vit-D deficient people. COVID-19 cases with sufficient vit-D levels significantly showed shorter hospitalization duration.
Lau 2020	USA 2020	COVID-19 patients	20	65.2 ± 16	44/15	A Retrospective observational cohort	Vitamin D insufficiency was associated with COVID-19 severity and ICU admission rates.
Bianconi 2021	Italy 2021	Mild, moderate, and severe COVID-19 patients	250	74 ± 15	110/90	A prospective cohort study	No association between serum vit-D level and COVID-19 patients prognosis.
Bennouar 2021	Algeria 2020	severe to critical cases of this infection.	120	62.3 ± 17.6	83/37	A prospective cohort study	Severe COVID-19 cases showed low serum calcium and vit-D levels.
Reis 2021	Brazil 2020	Moderate to severe COVID-19	220	55.1 ± 14.6	117/103	A prospective cohort study	Patients with reduced 25OHD levels (<10 ng/mL) showed longer hospitalization duration than those with higher levels.
Baktash 2020	UK 2020	COVID-19 patients	70	81 ± 9.25	42/28	A prospective cohort study	Worse COVID-19 prognosis was associated with hypo-vitaminosis D and older ages.
Ricci 2021	Italy 2021	COVID-19 patients	52	68.4 ± 16.2	25/27	retrospective	COVID-19 cases with hypovitaminosis D exhibited attenuated inflammatory response

								and increased respiratory involvement.
Campi 2021	Italy	2020	Mild and severe COVID-19 patients	361	66.1 ± 14.1	101/54	A prospective cohort study	An inverse correlation was found between reduced 25OHD and elevated IL-6 concentrations, both levels independently predicted the severity and mortality of COVID-19.
Orchard 2021	UK	2020	critically ill COVID-19	50*	9.4 ± 12	28/22	A cohort study	This small sized study didn't detected any difference in the prognosis of critical COVID-19 cases.
Herrera-Quintana 2021	Granada (Spain)	2021	Severe ICU COVID-19 patients	37	60.0 ± 10.2	26/11	A prospective analytical study	High prevalence of vit-D deficiency in all critical patients at ICU admission, that increased after only three days of ICU stay.
Sulli 2021	Italy	2021	severe respiratory failure and all patients needed hospital-ization	130	76 ± 13	60/70	A prospective cohort study	Vitamin D deficiency was significantly associated with higher risk of respiratory complications and death in elderly COVID-19 cases.
ÖZGER 2021	Turkey	2021	Uncomplicated, mild and severe COVID-19 infections.	196	44.2 ± 21.2	87/109	A cohort study	Vitamin D deficiency was associated with higher risk of COVID-19 positivity and wasn't associated with the severity of the condition or the prognosis.
Maghbooli 2020	Iran	2020	Severe COVID-19 infection	235	58.7 ± 15.2	144/91	A cohort study	Improving vitamin D status in the general population and in particular hospitalized

								patients has a potential benefit in reducing the severity of morbidities and mortality associated with acquiring COVID-19.
Jevalikar 2021	India	2021	Hospitalized patients with COVID-19 infection	409	52.4 ± 16.8	282/127	A prospective, single-center, cross-sectional, observational study	No correlation between serum 25-OHD levels with COVID-19 prognosis or risk of death
Angelidi 2021	USA	2021	Patients with COVID-19 infection	144	65 ± 14.2	64/80	A retrospective, observational, 2-center cohort study	An inverse correlation existed between 25OHD concentration and the rates of death and mechanical ventilation.
De Smet 2021	Belgium	2021	Hospitalized patients with COVID-19 infection	186	67 ± 21	109/77	A retrospective observational study	Reduced serum 25OHD concentration was associated with higher risk of death.
Charoenngam 2021	USA	2021	Hospitalized patients with COVID-19	287	61.9 ± 15.8	124/163	A retrospective chart review cross-sectional study	Sufficient serum 25-OHD levels independently decrease the death risk in older hospitalized COVID-19 cases.
AlSafar 2021	UAE	2021	Patients with COVID-19 infection	464	46.6 ± 14.9	372/92	A multicenter observational study	Low serum 25OHD levels were associated with the severity of COVID-19 and related mortality.
Carpagnano 2021	Italy	2020	Hospitalized adult inpatients with COVID-19	42	65 ± 13	30/12	A retrospective, observational study	Severe hypovitaminosis D was significantly associated with a higher risk of death.
Radujkovic 2020	Germany	2020	Consecutive symptomatic COVID-19-positive patients	185	59.6 ± 15.7	95/90	A prospective non-intervent-ional register	This study demonstrated an association between Vit-D deficiency and mortality.
Vassiliou 2021	Greece	2021	Consecutive COVID-19	39	61.2 ± 13	31/8	An observ-ational,single-	Patients with vit-D deficiency had a higher death risk.

Vassiliou 2020	Greece	2020	patients Consecutive, critically ill COVID-19 patients	30	65 ± 11	24/8	center study A prospective, observational study	Patients who died in the ICU within 28 days showed lower 25OHD levels on ICU admission compared to survivors.

Table 2: A summary of the baseline characteristics of included studies that assess the effect of Vitamin D supply on several clinical outcomes on Covid-19 patients.

Study ID	Country/ Centers	Year	Health status Sample size	Total	Age (yr)	Sex	Vit-D dose	Follow up Duration	Design of the study	Main findings
Elamir 2021	USA	2021	Hospitalized adult patients with COVID-19.	50	66.5 ± 17	25/25	0.5 mcg daily	14 days or discharge	An Open-label RCT	Covid-19 patients calcitriol who received showed better improvement of oxygenation than the control, as the change from baseline in the SaO2/FIO2 ratio for this arm is greater. The control group showed a longer hospital stay, and more ICU admissions, deaths and readmission than the calcitriol arm.
Tan 2020	Singapore	2020	Hospitalized COVID-19 patients.	43	61.8 ± 7.9	26/17	1000 IU daily. for ≤14 d	30 d from symptoms onset / discharge	A prosp -ective cohort	Patients who received vit-D significantly showed a lower need for oxygen therapy during hospita-lization than their controls.

Murai 2021	Brazil	2021	Hospitalized moderate and severe COVID-19 cases	237	56.2 ± 14.4	133/104	Single dose of 200 000 IU of vitamin D3	Till discharge	Double-blinded RCT	No significant effects were caused by the single high dose of vit-D3 on patients' outcomes, including their hospital stay duration, mortality, ICU need, or mechanical ventilation rates, when compared to the placebo.
Castillo 2020	Spain	2020	Hospitalized patients with COVID-19	76	53 ± 10	45/31	Patients received 0.532 mg of oral calciferol on the day of admission, 0.266 mg on days 3 and 7, and then every week until their discharge or ICU admission.	Till discharge, ICU admission, or death	Parallel pilot open label RCT	High dose of calcifediol significantly lowered COVID-19 severity and ICU admission need.
Annweiler 2020 (a)	France	2020	Elderly hospitalized COVID-19 patients	77	88 ± 5	39/38	Group 1: Bolus 50 000 IU vitamin D3 monthly, or 80 000 IU or 100 000 IU vit-D3 every 2−3 months. Group 2: oral 80 000 IU	1 year	A quasi-experimental study	Regular bolus vit-D3 significantly showed more improvement and longer survival duration

.							vit-D3 few hours after COVID-19 diagnosis Group 3: No vitamin D supplements.			
Annweiler 2020 (b)	France	2020	Elderly with COVID-19	66	87.7 ± 9	15/51	Oral bolus of 80 000 IU vit-D3 either during a month before the infection or a week after the suspicion or diagnosis of COVID-19.	2.5 months	A quasi-experimental study	Bolus vit-D3 administration significantly reduced COVID-19 severity and increased patients' survival.
Rastogi 2020	India	2020	Asymptomatic or mild COVID-19 cases with vit-D deficiency	40	45.47 ± 9.65	20/20	Daily 60 000 IU of chole-calciferol (5 ml oral solution in Nano-droplet form)	21 days	RCT	More COVID-19 positive cases became SARS-Cov-2 negative after cholecal-ciferol administ -ration, compared to the placebo group, also fibrinogen evels were significantly reduced
Cereda 2020	Italy	2020	COVID-19 Parkinson disease patients	324	25.36 ± 4.41	157/167	At least 25 000 IU monthly in previous 3 months (800 IU daily)	3 months	A pros-pective cohort	No association appeared between vit-D administration and hospitalization, but supplementation

										increased the risk of in-hospital mortality in this study.
Güven 2021	Turkey	2021	Critical COVID-19 patients	175	72.33 ± 15.7	105/70	Intramuscular single dose of 300,000 IU vit-D3	8.5 months	An observa -tional cohort study	High-dosevit-D3 administration to vit-D deficient COVID-19 patients on ICU admission didn't affect patients' intubation need, hospitalization duration, or mortality
Soliman 2021	Egypt	2020	Adult diabetic patients with SARS-CoV-2	56	71.26 ± 4.24	NA	single dose of 200 000 IU vit-D	6 weeks	A placebo -controlled randomized prospective trial	The severity of COVID-19 and mortality weren't affected by vit-D administration.
Nogues 2021	Spain	2021	SARS-CoV 2 positive patients with chronic diseases and/or severe COVID-19	838	62.09 ± 16.3	495/343	2 capsules (266µg/ capsule) at baseline, and 1 capsule on day 3, 7, 15, and 30.	3 months	An obser-vational cohort study	Vitamin D therapy significantly reduced ICU admission and mortality among hospitalized patients.
Annweiler 2021	France	2020	Adult patients with COVID-19	95	88 ± 5.5	49/46	50 000 IU monthly, or (80 000 IU or 100 000 IU or 200 000 IU every 2–3 months),or 800 IU daily.	3 months	A quasi experimental COVID study	Vitamin D therapy was associated with improved 3-month survival in elderly COVID-19 cases.
Lakki reddy 2021	India	2020	Adult patients with	87	45 ± 13	65/22	60 000 IU daily for 8-10 days	3 months	A randomized open label clinical trial	Vitamin D therapy in this high dose significantly reduced

			COVID-19							all inflammatory markers, inhibited the cytokine storm, and improved COVID-19 without any adverse events or toxicity.
Yildiz 2021	Turkey	2020	Adult patients with COVID-19.	207	63.7 ± 14.14	126/81	A single 300 000 IU dose	NA	An obser-vational cohort study	The single vit-D dose significantly reduced the mortality rates representing a useful and safe adjunctive treatment.
Annweiler 2022	France	2022	Adult patients with COVID-19	254	87.3 ± 7.4	106/148	High-dose group : two bolus 200 000 IU vials Standard-dose group: one 50 000 IU vial of vit-D3	28 days	Multicenter, open-label, parallel RCT	The high dose group showed a significant reduction in mortality rates at day 14, compared to the standard dose group, this effect wasn't sustained to day 28. No significant adverse events occurred with the high dose.
Cannata Andía 2022	Argentina, Spain, Guatemala, and Chile	2022	Hospitalized patients with COVID-19	543	57.8 ± 16.07	353/190	A single bolus of 100,000 IU of vit-D3, orally.	(1-48)	A multicenter RCT	Vitamin D administration wasn't associated with COVID-19 outcomes improvement.

Mariani 2022	Argentina	2022	Adult COVID-19 patients	218	59.1 ± 10.6	115/103	A single dose of 500 000 IU of vit-D3, orally	30 days	A multicenter, double-blind, sequential, RCT	This trial revealed no significant difference in the clinical outcomes of high-dose vit-D group compared to placebo.
Torres 2022	Spain	2022	Adult COVID-19 patients	85	64 ± 15.8	60/25	A moderate dose of 2000 IU/ day of Vit-D3 or a higher dose of 10 000 IU/daily for 14 days	14 days	A multicenter, singleblind, prospective, RCT	High doses of vit-D3 improved patients' inflammatory profile and immune response against the infection.
Alcala-Diaz 2021	Spain	2021	Adult COVID-19 patients	537	67.2 ± 15.8	317/ 220	Oral 0.532 mg of Vit-D3 on entry, hen oral 0.266 mg on day 3 and 7, and then every week until discharge	30 days	A retrospective, multicenter cohort study.	Lower in-hospital mortality was significantly observed in patients treated with vit-D3, compared to no treatment during the first 30 days.
De Niet 2022	Belgium	2020	Adult hospita -lized COVID-19 patients	43	66.04 ± 12.9	23/20	A dose of 25,000 (IU) vitamin D for 4 days followed by a dose of 25,000 IU weekly.	36 days	A prospective, randomized, parallel, controlled trial	Vitamin D supple -mentation provided better improvement in the clinical outcomes in hospitalized patients.

Results

Study Selection

We found 5609 references in five different databases: Cochrane, Web of Science, PubMed, Scopus, and EBSCO. Only 126 references underwent a full-text screening phase. In the end, our analysis included 8001 COVID patients from 12 randomized control trials, 3 quasi-experimental trials, and 27 non-randomized control trials. [Fig. 1] illustrates the selection process through a PRISMA flowchart.

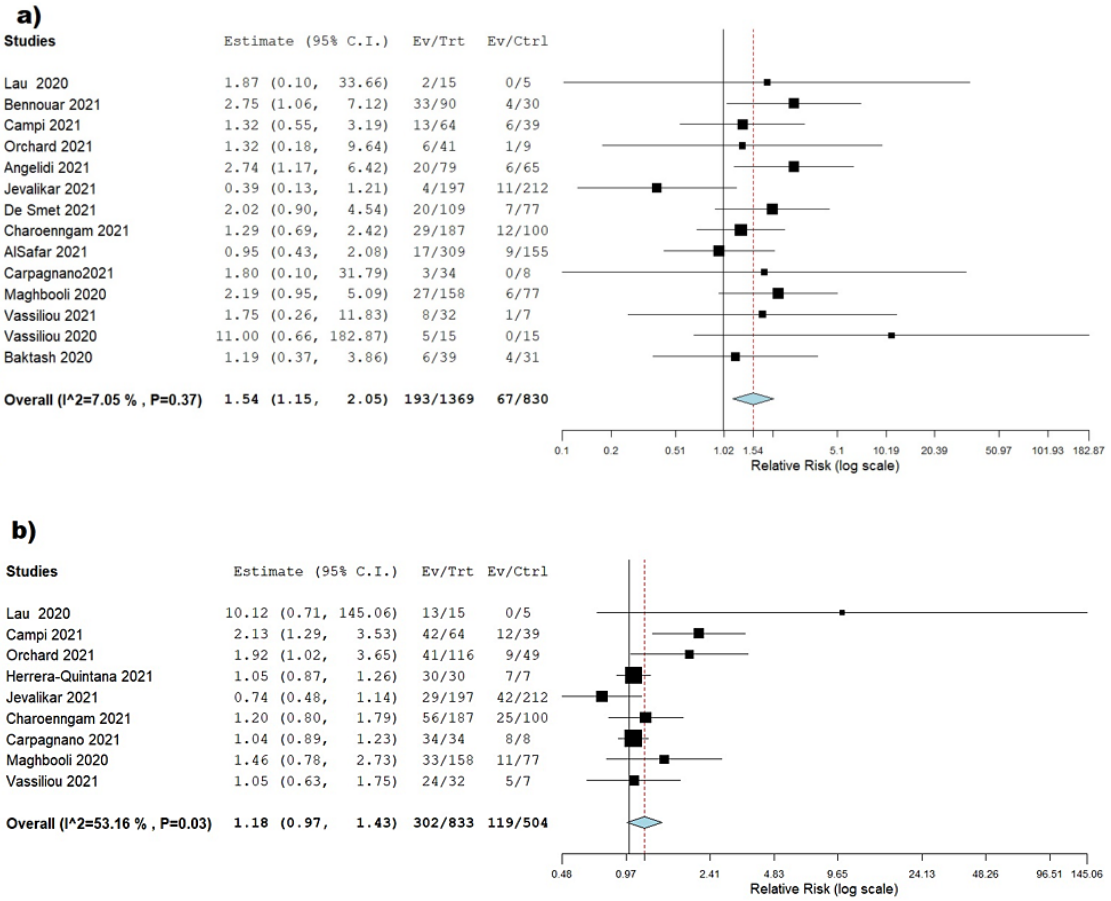

Fig. 2: Forest plots of mortality (a) and ICU admission (b) on COVID-19 patients with vitamin D deficiency.

Fundamental Characteristics

A summary of the baseline characteristics is shown in [Tables 1 and 2]. The included studies were classified into two groups.

1. The vitamin D deficiency group consisted of 22 studies that evaluated the correlation between serum Vit-D levels and various clinical outcomes. This group included 3979 patients with a mean age of 62 years, and the male-to-female ratio was four to three.
2. The vitamin D-supplemented group consisted of 20 studies that looked at how vitamin D supplementation affects different clinical outcomes. These studies included 4022 COVID patients with a mean age of 64 years, and the male-to-female ratio was six to five. The included studies took place in different countries with patients of different ethnicities.

Risk of Bias in Evaluation

Using the Cochrane Risk of Bias Tool for Randomized Control Trials (Rcts)

three studies: Castillo *et al.,*[20] Mariani *et al.*[21] and Murai *et al.*[22] were of good quality, De Niet[23] was of fair quality; and the rest of the studies were of low quality[24–30] [Supplementary Fig. 1].

Based on the MINORS criteria for evaluating the quality of non-randomized studies, comparative studies had a range of 16 to 22 points, with a median of 20 points. Nogues *et al.*[31] had the highest score (22 points), while Yildiz *et al.*[32] had the lowest score (16 points). Non-comparative ones had a range of 6–13 points with a median of 10 points. Jevalikar *et al*.[33] and Reis *et al*.[34] had the highest score (13 points), while Vassiliou *et al.*[35] had the lowest score (6 points). [Sup. Table.1]

Outcomes

Outcomes Pooled Analysis in Vitamin D-deficient COVID-19 Patients

Regarding the mortality rate, the analysis of the pooled studies significantly favored the group with high serum Vit D levels (8.07%) over the group with low Vit D levels (14.09%) (RR = 1.54, 95% CI = 1.15: 2.05, *p* value = 0.01). Pooled results were homogeneous (*p* value = 0.37, I2 = 7.05%). [Fig. 2a]. Concerning the rate of admission to the ICU (RR = 1.18, 95% CI = 0.97: 1.43, *p* value = 0.09; [Fig. 2b]); mechanical ventilation (RR = 1.06, 95% CI = 0.82: 1.37, *p-value* = 0.64; [Fig. 3a]); and length of hospitalization (MD = 0.05, 95% CI = -3.04: 3.14, SE = 1.58, p value = 0.97; [Fig. 3b]), pooled studies were heterogeneous.

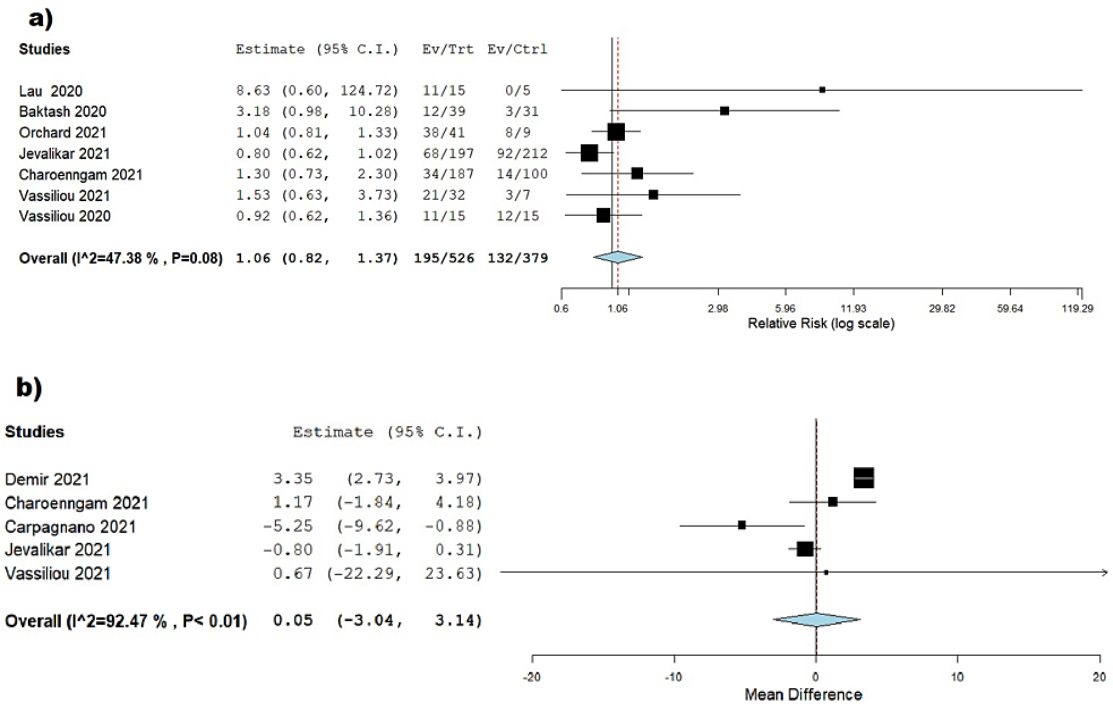

Fig. 3: Forest plots of mortality (a) and ICU admission (b) on COVID-19 patients with vitamin D deficiency.

Outcomes Pooled Analysis in COVID-19 Patients Who Received Vit-D Supplementation vs. COVID-19 patients without Vit-D supplementation

The analysis showed significant differences between the two groups. Regarding the mortality rate, the pooled effect estimate revealed that the Vit-D group had a significantly lower mortality rate (9.7%) than the control group (15.29%), and the results were statistically significant (RR = 0.64, 95% CI = 0.45: 0.92, *p-value* = 0.02). The studies were diverse (*p-value* = 0.01, I2 = 57.575%). [Fig.4a]

Regarding the rate of admission to the ICU and mechanical ventilation, the Vit-D receiving group had significantly (*p-value* = 0.01) fewer admission rates than the control group (RR = 0.48, 95% CI = 0.25: 0.85, *p-value* =0.01) and (RR = 0.70, 95% CI = 0.57: 0.87) [Fig. 4b, Fig. 5a], respectively.

Concerning the length of hospitalization, vitamin D supplementation was significantly (*p-value* = 0.01) associated with shorter hospitalization duration (MD = -1.28, 95% CI). CI = -2.23, -0.34, SE = 0.48). The studies were homogenous (*p-value* = 0.08, I^2 = 44.38%). [Fig. 5b]

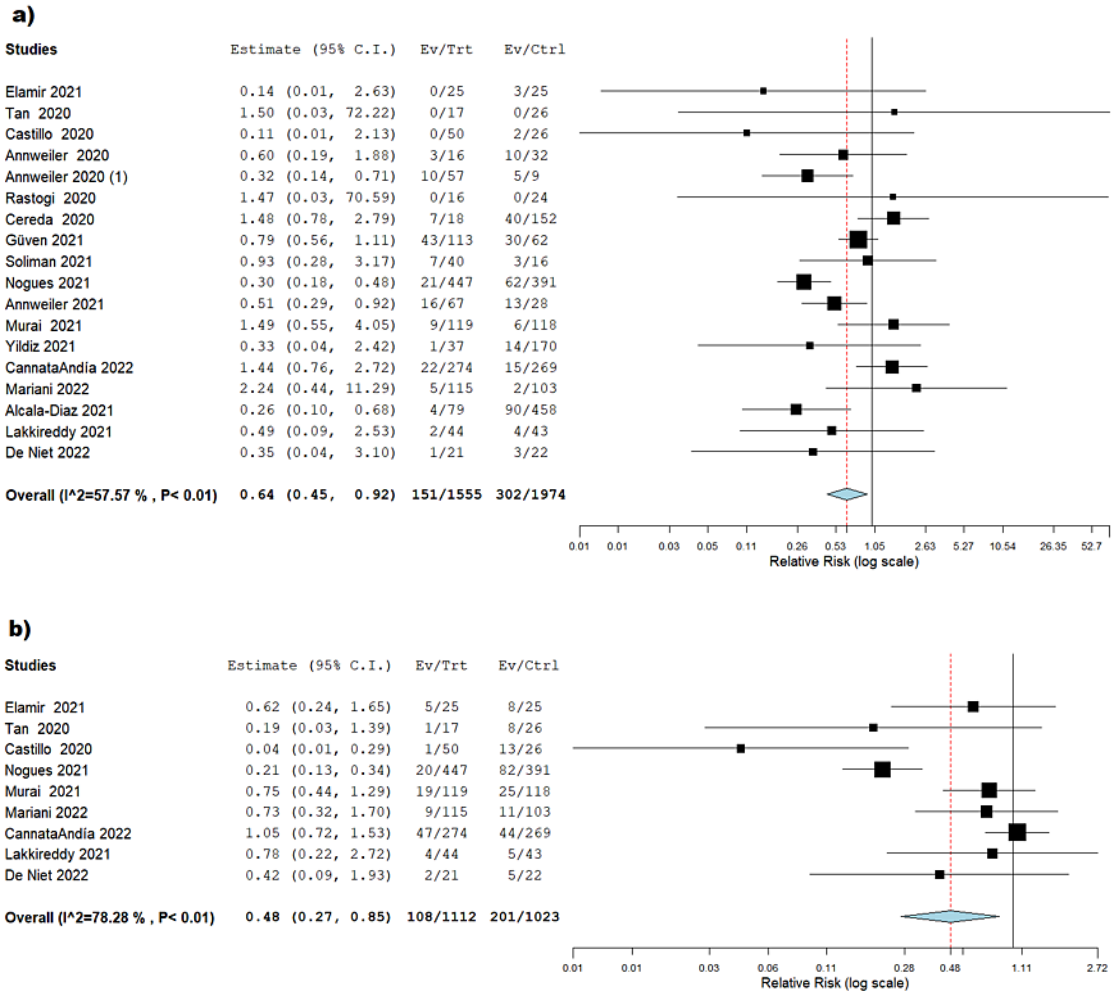

Fig. 4: Forest plots of mechanical ventilation (a) and hospitalization duration (b) on COVID-19 patients with vitamin D supply.

Subgroup and Sensitivity Analysis

The analysis of the subgroup of different Vit-D doses for mortality revealed a significant reduction in mortality in the group that received doses ranging from 50 000 to less than 100 000 IU compared to groups that received doses ranging from 50 000 IU to > 100 000 IU. The pooled data were homogeneous (*p-value*= 0.73, I2 = 0%) (RR = 0.42, 95% CI = 0.23: 0.76, *p-value*=0.005).

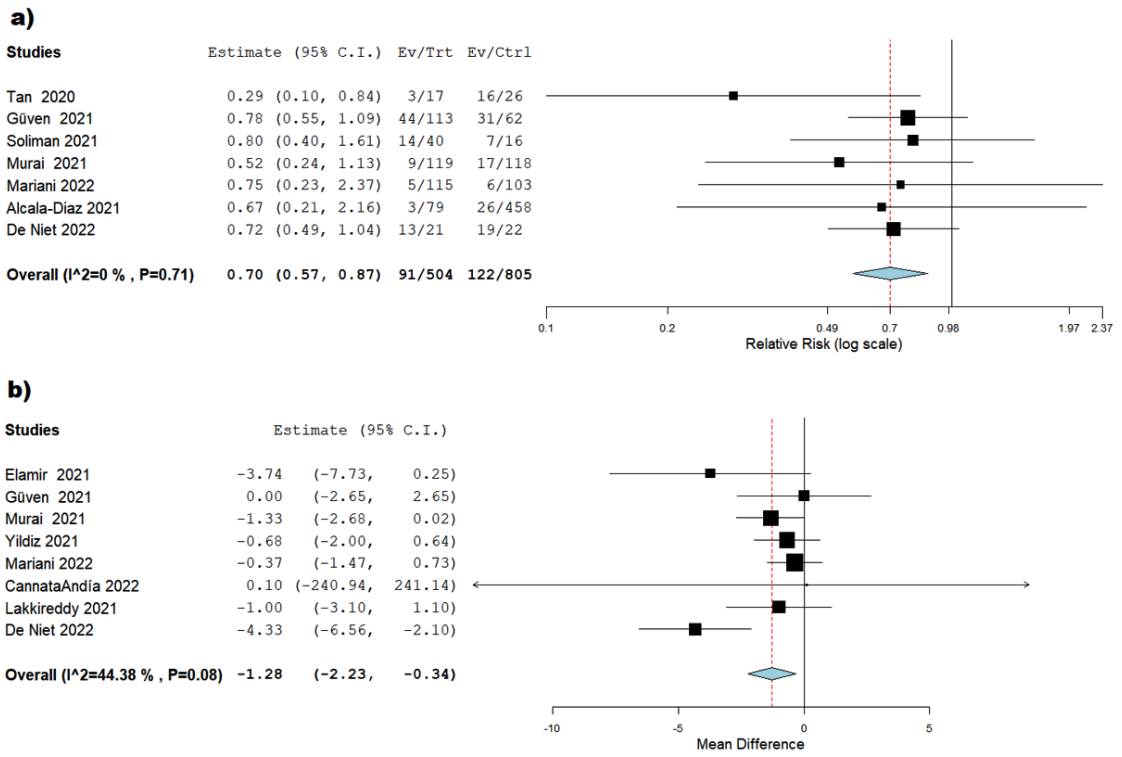

Fig. 5: Forest plots of mechanical ventilation (a) and hospitalization duration (b) on COVID-19 patients with vitamin D supply.

We conducted a subgroup analysis according to Vit-D levels in COVID patients. The results of the analysis didn't show any clear differences in mortality or ICU admission rates among the groups with high and low levels of Vit-D.

We discovered a significant reduction in mortality rates of receiving Vit-D supplementation over placebo after excluding ICU admission rates after excluding Murai *et al.* (RR = 0.23, 95% CI = 0.09: 0.56, *p-value*= 0.01) and Nogues et al (RR = 0.67, 95% CI = 0.46: 0.98, *p-value*= 0.04).[36,22]

We discovered that high Vit-D levels outperformed low Vit-D levels in ICU admission rates after excluding Campi *et al.*[37] and mechanical ventilation rates after excluding Jevalikar *et al.*[33] while low concentration levels outperformed high concentration levels in hospital duration outcomes after excluding Demir *et al.*[38]

Discussion

The analysis included data through the end of 2022 from 42 studies with 8001 COVID patients. We conducted it to explore the effect of Vit-D deficiency and its supplementation on the clinical outcomes of COVID-19 patients. The findings showed that Vit-D deficiency significantly increases the mortality rates of patients with COVID-19. In addition, Vit-D supplementation in COVID-19 patients showed significant decreased mortality rates, ICU admission rates, mechanical ventilation needs, and duration of hospitalization. Therefore, Vit-D supplementation would represent a possible complementary therapy in the management of COVID-19.

Vitamin D Deficiency and the Clinical Outcome Among COVID-19 patients

As regards the clinical outcome, our analysis significantly favored the high serum Vit-D concentration group over the low concentration group as regards hospitalization duration, ICU admission rates, and the need for mechanical ventilation. In agreement with other studies that found evidence of a link between vitamin D deficiency and the severity of COVID-19 and associated deaths.[7,39,40] Moreover, other systematic reviews and

meta-analyses revealed a negative correlation between serum vitamin D levels and the severity of COVID-19 patients[8,41–43]

Concerning SARS-CoV-2 infection rates, numerous observational studies[44–47] investigated the low levels of serum Vit-D as a risk factor for SARS-CoV-2 infection, including a previous retrospective observational study, which included 191,779 COVID-19 patients, that proved that the rates of SARS-CoV-2 positivity were independently associated with lower circulating 25-hydroxyvitamin D levels (25-OHD). Even though the 25-OHD level is important for all races and ethnicities, patients from predominantly black non-Hispanic zip codes had a higher SARS-CoV-2 positivity rate than patients from predominantly white non-Hispanic zip codes with the same 25-OHD level. This suggests that patients' ethnicity may affect their risk of getting COVID-19.

This vitamin D deficiency might be attributed to several hypotheses that had been tested in order to determine the relationship between Vit-D and COVID-19. First, vitamin D activates cathelicidin (LL-37), and defLL-37 acts at various stages of viral infection, regardless of whether the virus is enveloped or not. Increased serum levels of OREL-37 are known to correlate with decreased expression of interleukin (IL-17), which is implicated in COVID-19 pathophysiology, including the development of thrombosis and acute respiratory distress syndrome (ARDS).[48–51] As a result, the association between vitamin D and the severity and acute complications of COVID-19 may be explained by an increase in IL-17. Second, vitamin D modulates cytokine production by upregulating anti-inflammatory cytokines like IL-10 and downregulating pro-inflammatory cytokines like IL-1, IL-6, and tumor necrosis factor-alpha. This transition from pro-inflammatory to anti-inflammatory cytokines can minimize the danger of the cytokine storm induced by the COVID-19 infection. Finally, Vit-D stimulates the renin-angiotensin-aldosterone system and angiotensin-converting enzyme 2 (ACE2), which are important in lung protection against ARDS due to their anti-inflammatory and antioxidant properties. In fact, ACE2 is proven to protect against lethal avian influenza[53–55] and may protect against acute lung injury.[7,39,40,46,47,56]

Vitamin D supplementation and the clinical outcome among COVID-19 patients

As regards the clinical outcomes, this meta-analysis showed that Vit-D supplements significantly improved the clinical outcome (mortality rates, duration of hospitalization, ICU admission rates, and mechanical ventilation) in COVID-19 patients who received Vit-D supplements versus patients who did not receive any supplementation. In agreement with other studies that reported the beneficial effect of Vit-D supplements in improving the clinical outcomes of COVID-19 patients, especially mortality and ICU admission rates, this was confirmed in multiple observational and experimental investigations,[56–60] whether administered before or after a COVID-19 diagnosis.

Nevertheless, contradictory evidence suggests that there is no link between Vit-D administration and clinical outcomes.[22,33,61] The majority of these studies did not give risk estimates for clinical outcomes that were adjusted for potential confounding factors.[22, 33,61] We believe that the present meta-analysis introduces comprehensive pooled data regarding the response of COVID-19 patients to Vit-D supplementation. However, only three trials were included in the meta-analysis. Moreover, the authors published only unadjusted risk estimates, omitting to account for potential confounding variables.[22] In contrast, we combined data from 13 studies and offered both the adjusted and unadjusted risk estimates in order to draw more reliable and generalizable conclusions.

As regards the timing of administering Vit-D, the subgroup analysis revealed that administering Vit-D after a COVID-19 diagnosis is more beneficial than receiving it before the diagnosis, which is consistent with the other two studies that were included in the subgroup analysis and used a cumulatively high dose of cholecalciferol and calcifediol.[57,58] On the other hand, detecting the optimum dose and duration of Vit-D administration as a possible adjuvant treatment for COVID-19 needs further exploration.

Except for Murai *et al.* and Lakki reddy *et al.*[22,27] no study addressed the effect of vitamin D supplementation on increasing serum 25-OHD levels. Despite the inability to determine the precise dose of 25-OHD required to produce its immunomodulatory effect, levels of 25OHD

greater than 30 ng/ml are thought to cause a significant reduction in COVID-19 severity and mortality.[62]

Relating to the number of doses of Vit-D administration, without detecting serum 25-hydroxyvitamin D levels, the most effective treatment plan, whether a single high-dose bolus or a daily modest dose of Vit-D, is still unknown. High-dose bolus vitamin D stimulates the long-term production of 24-hydroxylase and fibroblast growth factor 23 (FGF23). Increased production of 24-hydroxylase results in the conversion of 25-OHD to the inactive metabolite 24,25-dihydroxy Vit-D, and FGF23 results in the inactivation of the enzyme renal 1-hydroxylase, reducing the active metabolite calcitriol. A daily vitamin D intake, on the other hand, has a longer-lasting effect on 25-hydroxy vitamin D levels.[64] In this manner, receiving Vit-D maintenance doses after a single bolus dose is anticipated to maintain adequate vitamin D levels for an extended period.

Despite evidence of high heterogeneity among trials, Vit-D supplementation was safe and lowered the risk of COVID-19 outcomes. Protection was associated with daily 400-1000 IU vitamin D supplementation for up to 12 months. Unknown and requiring examination is the significance of these findings for COVID-19.[68]

Doses of Vitamin D Supplements for Mortality Among COVID-19 Patients

Two previous meta-analyses[65,66] revealed that daily low doses of vitamin D were effective in the prevention of acute respiratory tract infections. The purpose of our study was to examine whether the subgroup of different vitamin D doses was related to the mortality rate, and we found that the group that received doses between 50 000 to 100 000 IU, performed significantly better than the other groups. This may be because physiological doses of Vit-D supplementation manage to achieve commonly accepted levels of 25-OHD when compared to larger doses, as proposed by Binkley and colleagues.[67]

In this light, high doses of vitamin D could produce "drug-like" effects not found with "supplement" dosages. So that we would have the best chance of finding a good effect in patients with life-threatening COVID-19, the dosing schedule for our trial was set up to quickly reach and keep serum levels that were as high as could be done safely.[68] The risk of these adverse events increases when serum concentrations of 25-OHD are greater than 125 nmol/L.

Strength

This systematic review and meta-analysis search was carried out from PubMed, Cochrane Library, Scopus, Web of Science, and EBSCO, for relevant studies for the long period up to May 2022, targeting 8001 COVID-19 patients. We studied the association between four central clinical outcomes, the mortality rates, duration of hospitalization, ICU admission rates, and mechanical ventilation rates, related to vitamin D deficiency and its supplementation in patients affected by COVID-19, searching for the most adequate doses which improved the clinical outcomes in these patients. This systematic review may contribute to confirming the relationship between vitamin D deficiency and COVID-19, and it also provided strong indications on the role of Vit-D supplementation in improving patients and determining the most appropriate doses.

Limitations

Despite our strengths, the meta-analysis showed several flaws. First, some studies did not provide adjusted estimates, so we could not include them in the adjusted pooled analysis. Additionally, the covariates in the included research were inconsistent, and the OR/HR calculated from the studies was corrected for various factors. Second, vitamin D was administered to all patients regardless of their baseline 25-OHD levels in most studies, which limited the ability to detect the difference in the effect of receiving vitamin D on people with and without hypovitaminosis D. All studies rarely told us what the 25-OHD levels were at the start, so we couldn't do a subgroup analysis based on the 25-OHD levels at the start.

Third, the time lag between the development of COVID-19 symptoms and the supplementation of Vit-D was insufficiently described, so conducting a subgroup analysis based on this time lag was not possible. Notably, vitamin D administration occurred 10.3 days (on average) after the onset of symptoms, which may have negated the positive effects of vitamin D if supplemented earlier in the disease

course. Fourth, reporting the data on COVID-19 severity was infrequent and inconsistent across all studies, which limited performing a subgroup analysis depending on the severity of the underlying condition. In addition, conducting another subgroup study displaying the effect of vitamin D administration on men and women would have been beneficial in light of the abundance of evidence showing intersex variations in COVID-19 severity. However, this was not possible due to the absence of such data.

Conclusion

This systematic review and meta-analysis came to the conclusion that compared to COVID-19 cases with hypo vitaminosis D, cases with normal vitamin D levels significantly showed lower mortality rates. Vitamin D supplementation greatly improved death rates, length of hospital stays, ICU admission rates, and the need for mechanical ventilation, especially when this vitamin was given to patients after their diagnosis of COVID-19. Vitamin D supplementation between 50 000 to 100 000 IU, showed among COVID-19 patients significantly outperformed other doses in terms of mortality.

Recommendations

The detection of COVID-19 and the optimization of the dose and duration of Vitamin D administration as a possible adjuvant treatment require further investigation.

Authors Contributions

The manuscript has been read and approved by all the authors, that the requirements for authorship have been met, and that each author has substantial contributions to each of the three components mentioned below:

1. Concept and design of study or acquisition of data or analysis and interpretation of data.
2. Drafting the article or revising it critically for important intellectual content, and
3. Final approval of the version to be published.

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Conflicts of interests

The authors have declared no conflicts of interest.

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Abbreviations

25-hydroxyvitamin D (25-OHD)
Acute respiratory distress syndrome (ARDS)
Angiotensin-converting enzyme 2 (ACE2)
Confidence interval (CI)
Hazard ratio (HR)
International Unit (IU)
Mean difference (MD)
Odds ratio (OR)
Population, Intervention, Comparison, Outcome, and Study Design(PICOs)
Randomized Control Trials (RCTs (
Randomized controlled trial (RCT)
Renin-angiotensin–aldosterone system (RAAS)
Risk ratio (RR)
The Coronavirus disease 2019 (COVID-19)
The Methodological Index for Non-Randomized Studies scale (MINORS)
The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Titles and abstracts (TAs)
Vitamin D (Vit.D)