



RESEARCH ARTICLE

The effect of vitamin D supplementation on mortality and intensive care unit admission of COVID-19 patients. A systematic review, meta-analysis and meta-regression

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Abstract

Aims: The aim of this systematic review and meta-analysis was to investigate the effect of vitamin D supplementation on mortality and admission to intensive care unit (ICU) of COVID-19 patients.

Methods: A systematic search of PubMed, Google Scholar, Embase, Web of Science and medRxiv with terms relative to vitamin D supplementation and COVID-19 was conducted on 26 March 2021. Comprehensive Meta-Analysis software was used for the quantitative assessment of data and random-effects model was applied. To investigate the association between the dose of vitamin D and the outcomes of interest, meta-regression analysis was performed.

Results: Two thousand and seventy-eight patients from nine studies with data on mortality were included (583 received vitamin D supplementation, while 1495 did not). Sixty-one (10.46%) individuals in the treated group died, compared to 386 (25.81%) in the non-treated group (odds ratio [OR]: 0.597; 95% CI: 0.318–1.121; $p = 0.109$). Eight hundred and sixty patients from six studies with data on ICU admission were included (369 received vitamin D supplementation, while 491 did not). Forty-five (12.19%) individuals in the treated group were admitted to ICU, compared to 129 (26.27%) in the non-treated group (OR: 0.326; 95% CI: 0.149–0.712; $p = 0.005$). No significant linear relationship between vitamin D dose and log OR of mortality or log OR of ICU admission was observed.

Conclusion: This meta-analysis indicates a beneficial role of vitamin D supplementation on ICU admission, but not on mortality, of COVID-19 patients. Further research is urgently needed to understand the benefit of vitamin D in COVID-19.

KEYWORDS

calcifediol, cholecalciferol, COVID-19, intensive care unit, mortality, vitamin D

1 | INTRODUCTION

In late December 2019, the first cases of coronavirus disease 2019 (COVID-19), a disease caused by a novel beta-coronavirus named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), were reported in Wuhan, China. By March 2020, the disease had already spread globally, leading to the declaration of a pandemic by the World Health Organization.¹ Since then, the global impact of COVID-19 has undoubtedly been tremendous, and until 29 May 2021, there have been approximately 173 million cases and 3.72 million deaths from COVID-19.²

The clinical manifestations of COVID-19 range from asymptomatic or mild cases with fever, dry cough and fatigue, to severe and even critical cases with dyspnoea, need for intensive care unit (ICU) admission, acute respiratory distress syndrome (ARDS), and multi-organ failure and death.¹ Some of the risk factors that have been associated with COVID-19 severity are older age, black ethnicity, institutionalisation, immunodeficiency, chronic kidney disease, chronic metabolic diseases (including diabetes) and obesity.^{3,4} Interestingly, several of these factors have also been associated with increased risk of vitamin D deficiency (VDD).^{5,6}

The link between VDD and COVID-19 positivity rates and severity has been investigated in several observational studies,⁷⁻¹⁷ as well as in systematic reviews and meta-analyses.¹⁸⁻²² Despite the inconsistency of the results and the need for their critical appraisal due to several reasons (including different designs of the studies and distinct population characteristics, presence of confounding factors and inability to establish causation), the growing amount of evidence points towards a link between serum 25-hydroxyvitamin D (25[OH]D) levels and the risk of infection and disease severity from SARS-CoV-2.⁴

All these observations led to the research question of whether vitamin D supplementation could improve the clinical outcomes of COVID-19 patients and reduce the risk of severe disease and mortality. Some studies have been published to address this question; however, the results are inconsistent. The aim of this systematic review and meta-analysis was to accumulate the existing evidence and investigate the effect of vitamin D supplementation on mortality and need for ICU admission of COVID-19 patients. In addition, using meta-regression analysis, we examined whether the dose of vitamin D after diagnosis of COVID-19 was associated with either mortality or need for ICU admission.

2 | METHODS

This systematic review and meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).²³ The Population, Intervention, Comparison, Outcome, Study design approach was used for the development of the research questions (Table S1).

2.1 | Eligibility

The population of interest was adult patients with COVID-19 receiving any form of vitamin D supplementation.

2.2 | Information sources and search strategy

A comprehensive search of PubMed, Google Scholar, Embase, Web of Science and medRxiv with terms relative to vitamin D supplementation and COVID-19 patients was conducted on 26 March 2021, without limitations in publication dates. The search strategy for PubMed was: ('Vitamin D' [Mesh] OR 'Vitamin D' OR '25[OH]D' OR '25-hydroxyvitamin D' OR 'cholecalciferol*' OR 'ergocalciferol*' OR 'calcifediol*') AND ('COVID-19' [Mesh] OR 'COVID-19' OR 'SARS-CoV-2' OR 'Coronavirus disease').

2.3 | Outcomes

The outcomes of interest were mortality and ICU admissions.

2.4 | Study selection and data extraction process

Randomized trials and certain observational studies (case-control, cross-sectional and observational cohort) involving vitamin D supplementation and reporting on the selected outcomes were included in this systematic review. Articles with distinct features (e.g., clinical case series, case reports, animal or laboratory studies, reviews and non-English articles) and studies not involving vitamin D supplementation were excluded. Two independent researchers (GS and IE) screened the results by titles and abstracts and assessed the selected full-text articles for eligibility. Any disagreements were resolved with re-evaluation and consensus. After the final assessment, 10 records were selected for qualitative and quantitative synthesis, and data from the selected studies were extracted. Of the 10 studies selected, 2 of them were randomized studies^{24,25} and 8 were non-randomized studies.²⁶⁻³³ In case of missing information from certain studies, corresponding authors were contacted. The detailed PRISMA chart is available in Figure S1 and the characteristics of the included studies in Table 1 and Table S2.

In addition, we calculated the dose of vitamin D, cholecalciferol or calcifediol supplementation post-diagnosis of COVID-19, and the dose was averaged and expressed as dose per month.

2.5 | Risk of bias and quality of the evidence assessment

The risk of bias assessment was performed by two independent reviewers (GS and IE) and any discrepancy was settled through

TABLE 1 Baseline characteristics of the included studies

Authors (year)	Methods	Population	Serum 25 (OH)D (ng/ml)		End of study	Outcomes
			Baseline	Intervention		
Murai et al. (2021)	Multicentre double-blinded, placebo-controlled trial (Brazil)	237 hospitalised patients from 2 hospitals in Brazil with moderate to severe COVID-19. Intervention group N:119 Mean (SD) age: 56.5(13.8) Control group N: 118 Mean (SD) age: 56 (15)	Intervention Mean (SD):21.2 (10.1) Control Mean (SD):20.6 (8.1)	Intervention Mean (SD): 44.4 (15) Control Mean (SD): 19.8 (10.5)	Intervention Single oral dose of 200,000 IU of D3 after the diagnosis of COVID in hospitalised patients with moderate or severe disease Control Placebo	Primary: Length of hospital stay Secondary: 1. Mortality during hospitalisation. 2. N requiring ICU admission. 3. N requiring and duration of mechanical ventilation. 4. Serum levels of 25(OH)D, total calcium, creatinine, CRP.
Entrenas Castillo et al. (2020)	Pilot randomized open label, double masked clinical study (Spain)	76 Hospitalised COVID 19 patients Intervention group: N: 50 Mean (SD) age: 53.1 (10.8) Control group: Mean (SD) age: 52.8 (9.4)	NR	NR	Intervention: Oral calcifediol 0,532 mg on day of admission, 0,266 on day 3 and 7 and then weekly until discharge or ICU admission	1. ICU admission. 2. Mortality.
Anweiler et al. (2020)	Quasi-experimental study with retrospective collection of data from patients records (France)	77 patients hospitalised in a geriatric acute care unit mean (SD) age: 88 (5) years, range 78–100 years 45 patients receiving vit D sup (group 1: 29, group 2: 16) 32 patients with no vit D sup	NR	NR	Group 1: Oral boluses of vit D sup over the preceding year (50,000 IU D3 per month, or 80,000 IU or 100,000 IU vitamin D3 every 2–3 months) Group 2: Oral 80,000 IU D3 within hours of the diagnosis of COVID-19.	Primary: 14-day mortality Secondary: Highest (worst) score on the ordinal scale for clinical improvement (OSCI) measured during COVID-19 acute phase
Cereda et al. (2020)	Prospective observational study (Italy)	170 participants with data about in-hospital and vit D sup from 3 groups (group 1: Patients with PD, group 2: Caregivers of patients with PD, group 3: COVID-19 patients admitted to a referral hospital). 18 received vit D sup in the previous 3 months, 152 did not receive vit D sup.	Mean (SD) levels of 25(OH)D of hospital in-patients (group 3): 13.2 (11.1) Values not available for 25(OH)D supplemented versus non-supplemented		Oral intake of at least 25,000 IU/month (~800 IU/d) in the previous 3 months	1. In hospital mortality. 2. Hospitalisation.
Hernandez et al. (2020)	Retrospective case-control study (Spain)	216 patients with COVID-19 admitted to a university hospital.	Group on vit D sup: 21.1 ± 5.9 Group not receiving vit D sup: 13.8 ± 7.2	NA	11 patients were taking cholecalciferol, 25,000 IU/monthly in 10 cases, and 5600 IU/weekly in 1, and 8	1. ICU admission. 2. Mechanical ventilation. 3. Radiological worsening. 4. Secondary infection. (Continues)

TABLE 1 (Continued)

Authors (year)	Methods	Serum 25 (OH)D (ng/ml)		
		Population	Baseline	End of study
Jevalikar et al. (2021)	Prospective, single-centre, cross-sectional, observational study (India)	19 patients were on oral vit D sup at admission, 197 patients were not on oral vit D sup	NR	NR
		A total of 410 patients hospitalised for COVID-19. (127 females, 9 paediatric, 17 asymptomatic) with a median age of 54 years (range 6–92 years) were included 197 had VDD defined as 25(OH)D < 20 ng/ml and 128 of them were treated with cholecalciferol. (the outcomes of those treated with cholecalciferol were compared with the ones with no-treated VDD)	For most patients the treatment was administered as cholecalciferol granules (60,000 units per gram), depending on the decision of the treating physician, median administered dose 60,000 IU	Primary outcome: Proportion of severe cases in VDD group versus non-VDD Other outcomes: 1. Admission to ICU. 2. Administration of oxygen. 3. Inotropic support. 4. Renal replacement therapy. 5. Deaths. 6. Difference in the mean levels of inflammatory markers.
Ling et al. (2020)	Retrospective multi-centre cross-sectional observational study (United Kingdom)	968 patients hospitalised with COVID-19 from 3 hospital trusts were included (a primary cohort of 444 and a validation cohort of 541 patients from 2 hospitals [RPH and UHL], of whom 151 received cholecalciferol booster therapy	Primary cohort: Median 25(OH)D level: 12.5 (IQR 7.6, 22), in 230 participants with available values Validation cohort: Median 25 (OH)D: 12.5 (7.6,22) at RPH and 17.2 (10.8,24) at UHL	NA
		157 residents of a nursing home (mean age: 89.8 [6.53]), 98 of them were COVID-19 positive (20 were on vit D sup, while 78 were not)	High-dose cholecalciferol booster therapy (approximately ≥280,000 IU in a time period of up to 7 weeks) in various regimens	COVID-19 mortality
Cangiano et al. (2020)	Observational cohort study (Italy)	43 patients with COVID-19 hospitalised in a tertiary hospital 17 of them received vit D sup (mean age [SD]: 58.4 [7]) 26 of them did not receive vit D sup and were used as control group (mean age[SD]: 64.1 [7.9])	Cholecalciferol 25,000 IU 2 times a month	1. Mortality. 2. Positivity for SARS-CoV-2.
Tan et al. (2020)	Cohort observational study (Singapore)	43 patients with COVID-19 hospitalised in a tertiary hospital 17 of them received vit D sup (mean age [SD]: 58.4 [7]) 26 of them did not receive vit D sup and were used as control group (mean age[SD]: 64.1 [7.9])	A single daily oral 1000 IU dose of vit D3, 150 mg of magnesium oxide, and 500 mg vitamin B12 (methylcobalamine) for ≤14 days	1. Requirement of oxygen therapy. 2. ICU admission. 3. Mortality.

TABLE 1 (Continued)

Authors (year)	Methods	Population	Serum 25 (OH)D (ng/ml)		End of study	Outcomes
			Baseline	Vitamin D administration		
Giannini et al. (2021)	Retrospective study (Italy)	91 patients with COVID-19 admitted in a general medicine ward of a university hospital. 36 received vit D sup (mean age [SD]: 73[13]) while 55 did not receive vit D sup (mean age [SD]: 74 [13])	Group with vit D sup Median 25(OH)D (IQR): 9.9 (4.8,16.9) Group with no vitD sup: Median 25(OH)D (IQR): 14.4 (7.6,30.8)	400,000 IU vit D sup as bolus oral cholecalciferol 200,000 daily for two consecutive days (the second and third day of the in-hospital stay)	NA	Composite outcome of transfer to ICU and/or death from any cause

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CRP, C-reactive protein; D3, cholecalciferol; D sup, vitamin D supplementation; ICU, intensive care unit; IQR, interquartile range; N, number of participants; NA, non-applicable; NR, not reported; PD, Parkinson's disease; RPH, Royal Preston Hospital; SD, standard deviation; UHL, University Hospitals of Leicester; VDD, vitamin D deficiency.

re-evaluation and consensus. The version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2 tool) was used for the assessment of risk of bias of randomized trials.³⁴ Each outcome of the included randomized trials was evaluated through the process of signalling questions for the presence of bias in the randomisation process, due to deviations from intended intervention, due to missing outcome data, in measurement of the outcome and in selection of the reported results. Based on the response to each aforementioned domain, an overall judgement regarding the risk of bias of the outcome of interest was made (high, some concerns or low). The robvis tool was used for the production of the final images.³⁵ The ROBINS-I tool was used for the assessment of risk of bias of non-randomized trials.³⁶ According to ROBINS-I methodology, for each non-randomized trial a target (idealised) randomized trial was assumed and assessed for bias in seven domains (confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes and selection of the reported results). Depending on the score of each domain, an overall risk of bias judgement was established. For the overall rating of the quality of the evidence the GRADE approach³⁷ was followed and the GRADEpro Guideline Development Tool³⁸ was used for the creation of the Summary of Findings table.

2.6 | Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis software (CMA, Version 2.0, Biostat, Inc.). The software was used for pooling the data and deriving cumulative effect of the intervention on outcome of interest. The results were specifically assessed for presence of heterogeneity using Q statistics (significant at $p < 0.10$). I^2 —a quantitative measure of heterogeneity—was used to categorise studies into various levels of heterogeneity (high: 75%–100%, medium: 50%–70% and low: 0%–50%). Cumulative results showing mortality and ICU rates with vitamin D supplementation are presented using forest plots. Publication bias was assessed using both quantitative and qualitative methods. The presence or absence of significant bias was concluded from the quantitative results of Egger's and Begg's and Mazumdar rank correlation test, whereas visual inspection of bias was undertaken using Funnel plot. Forest plot was used to display the relative treatment effect (odds ratio [OR]) and its 95% confidence intervals (CI) for each study. To examine if the dose of vitamin D affects the outcomes (mortality, ICU admission), random-effect meta-regression analysis was applied. For this, log OR was used as dependent variable and the dose of vitamin D as moderator variable. Additionally, we performed a separate analysis where we made a distinction between studies with 'high and low' vitamin D administered doses.

The primary outcomes of interest were the impact of vitamin D supplementation on mortality and ICU admission in hospitalised patients with COVID-19. We pre-specified a priori that results for

dichotomous outcomes were to be quantitatively synthesised by individual studies with use of a random-effects model with inverse variance weighting to obtain summary effect estimates represented as OR with associated 95% CI. We consider that the random-effects model approach was more appropriate for this meta-analysis because the studies included did not have the same design, intervention, patient population, dose of vitamin D supplementation and management strategies for COVID-19.

3 | RESULTS

A total of 2078 patients from nine studies hospitalised for COVID-19 were included in this meta-analysis with available data for mortality as outcome; of them, 583 received vitamin D supplementation and 61 (10.46%) died.^{24–31,33} A total of 1495 patients did not receive vitamin D supplementation and 386 (25, 81%) died. The summary estimates indicated that vitamin D supplementation did not reduce mortality in hospitalised patients with COVID-19 (test for overall effect size using the random-effects model OR: 0.597; 95% CI: 0.318–1.121; $p = 0.109$) (Figure 1).

Though three studies favoured the intervention arm, the degree of impact varied among the studies. In addition, significant heterogeneity was found in terms of between-study variance (Q statistic = 21.27, $p = 0.006$, $I^2 = 62.40\%$) and that resulted in deviation from funnel shape (Figure S2). In terms of publication bias, the Egger's and Begg's tests showed the absence of any significant publication bias ($p > 0.05$) (Table 2). The quality of the evidence regarding the effect of vitamin D supplementation on mortality of COVID-19 patients assessed with the GRADE approach was judged as 'very low' (Table 3).

Random-effect meta-regression analysis was applied to estimate functional relationship of log OR of mortality and vitamin D dose; it was found that the regression coefficient of the slope was 0.0000 ($p = 0.72294$), suggesting that there is no significant linear relationship between vitamin D dose and log OR of mortality (Table S3, Figure S3). In addition, in the analysis of variance of random-effect meta-regression analysis of log OR of mortality on dose of vitamin D, Q values of the model (0.12569), the residual (7.31725), and the total (7.44295) were not significant, implying that the relationship between vitamin D dose and mortality were not significant, deviations among log OR values of mortality and regression line were also not significant, and that the amount of total variance is lower than we would expect based on within-study error, respectively (Table S3).

A total of 860 patients from 6 studies hospitalised for COVID-19 were also included in this meta-analysis with available data for the need of ICU as outcome; of them, 369 received vitamin D supplementation and 45 (12.19%) were admitted to ICU.^{24,25,28,29,32,33} A total of 491 patients did not receive vitamin D supplementation and 129 (26.27%) were admitted to ICU. Overall, vitamin D supplementation significantly reduced the need for admission to ICU in hospitalised patients with COVID-19 (test for overall effect size using the random-effects model OR: 0.326; 95% CI: 0.149–0.712; $p = 0.005$) (Figure 2).

Though two studies favoured the intervention arm, the degree of impact varied among the studies. In addition, significant heterogeneity was found in terms of between-study variance (Q statistic = 12.53, $p = 0.028$, $I^2 = 60.09\%$) and that resulted in deviation from funnel shape (Supplementary Figure 4). In terms of publication bias, the Egger's and Begg's tests showed that there was significant publication bias ($p < 0.05$) (Table 2). The quality of the evidence regarding the effect of vitamin D supplementation on ICU admission of COVID-19 patients assessed with the GRADE approach was judged as 'very low' (Table 3).

Random-effect meta-regression analysis was applied to estimate functional relationship of log OR of ICU admission and vitamin D dose; it was found that the regression coefficient of the slope was 0.0000 ($p = 0.96331$), suggesting that there is no significant linear relationship between vitamin D dose and log OR of ICU admission (Table S4, Figure S5). In addition, in the analysis of variance of random-effect meta-regression analysis of log OR of ICU admission on dose of vitamin D, Q values of the model (0.00212), the residual (5.67562), and the total (5.67773) were not significant, implying that the relationship between vitamin D dose and ICU admission were not significant, deviations among log OR values of ICU admission and regression line were also not significant, and that the amount of total variance is lower than we would expect based on within-study error, respectively (Table S4).

To further investigate the impact of the administered dose of vitamin D on the outcomes of interest we performed a separate analysis, where we categorised the included studies as studies with 'high or low doses' of vitamin D supplementation. Significant heterogeneity between studies, as well as within participants in each study, regarding the dose and duration of vitamin D supplementation was observed, so the use of an arbitrary value of administered vitamin D as a threshold for the distinction between 'high and low doses' seemed inappropriate. Therefore, we decided to analyse separately the two studies that administered very high bolus doses of vitamin D, the randomized control study (RCT) by Murai et al.²⁴ and the study by Giannini et al.,³³ where 200,000 and 400,000 IU of vitamin D were administered respectively ('high doses') while the remaining studies were categorised as 'low doses'. 'High doses' of vitamin D supplementation did not significantly reduce mortality (OR: 1.444; 95% CI: 0.705–2.959, $p = 0.316$) nor ICU admission (OR: 0.603; 95% CI: 0.348–1.045, $p = 0.072$) in patients with COVID-19 (Figures S6 and S7). However, "low doses" of vitamin D supplementation significantly reduced both mortality (OR: 0.437; 95% CI: 0.220–0.867, $p = 0.018$) and ICU admission (OR: 0.157; 95% CI: 0.033–0.743, $p = 0.02$) in COVID-19 patients (Figures S8 and S9).

4 | DISCUSSION

In this systematic review and meta-analysis we examined the effect of vitamin D supplementation on mortality and ICU admission rates of patients with COVID-19. We found that vitamin D supplementation was associated with a significant reduction of the risk for ICU

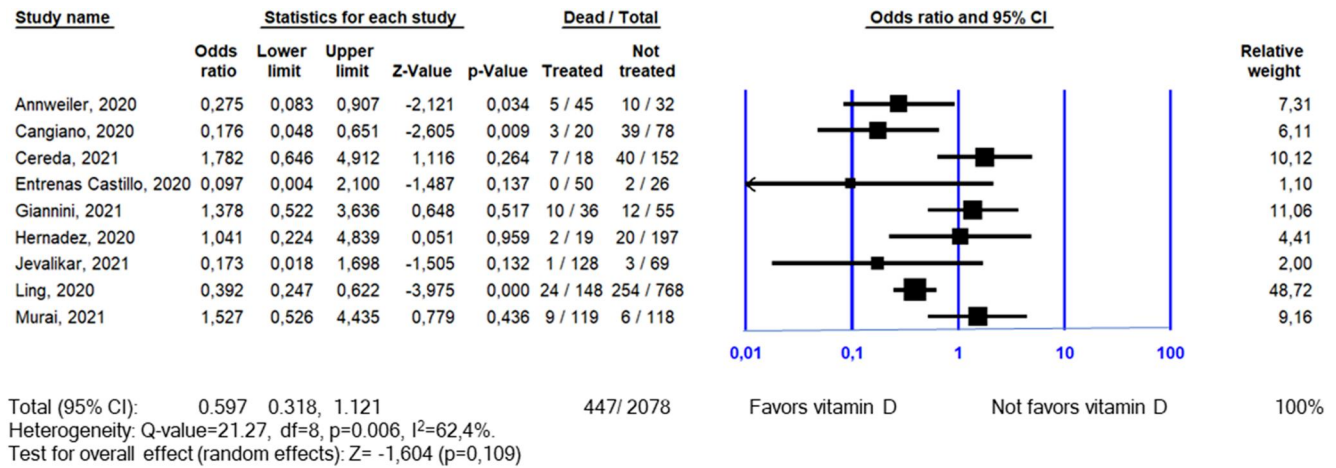


FIGURE 1 Forest plot for vitamin D supplementation and mortality

TABLE 2 Publication bias

Mortality and vitamin D supplementation	
Egger's test	
Intercept	0.09719
95% CI	-2.74118 to 2.93557
Significance level	$p = 0.67666$
Begg's test	
Kendall's tau	-0.11111
Significance level	$p = 0.41712$
ICU admission and vitamin D supplementation	
Egger's test	
Intercept	-3.00006
95% CI	-4.96067 to -1.03945
Significance level	$p = 0.011317$
Begg's test	
Kendall's tau	-0.86667
Significance level	-0.86667

admission, while as far as mortality is concerned, no significant benefit was observed. Moreover, no significant relationship was found between the administered dose of vitamin D and either mortality or ICU admission. The quality of the evidence based on the GRADE approach is characterised as "very low" for both outcomes of interest (Table 3).

The potential protective actions of vitamin D against COVID-19 can be explained by the biological functions of its biologically active form, 1,25-dihydroxyvitamin-D (1,25(OH)₂D), also known as calcitriol. Firstly, calcitriol regulates the innate immune response through the induction of autophagy and the production of cathelicidin, also known as LL-37, by macrophages and epithelial cells of the respiratory system. LL-37 exerts antiviral activities through the disruption of the viral envelope and through binding to SARS-CoV-2 S (spike) protein, interfering with the mechanism of viral

entry into the host cells.^{4,39,40} A second mechanism is the regulation of the adaptive immunity and specifically the shift of the immune response from Th1 and Th17 to Th2 and Treg profile, thereby reducing the production of pro-inflammatory cytokines and the risk of cytokine storm.⁴ Additionally, calcitriol interacts with the renin-angiotensin-aldosterone system (RAAS), mainly through the suppression of renin and angiotensin converting enzyme (ACE) and the induction of ACE 2, which leads to a reduction in the levels of angiotensin II and an increase of angiotensin 1-7. These actions of calcitriol counteract the imbalance of ACE:ACE2 that is caused by the downregulation of ACE2 in lung cells, due to the binding of SARS-CoV-2, and, subsequently, reduce the risk for vasoconstriction, ARDS and cardiac injury.^{4,41} Finally, calcitriol has been found to protect against endothelial dysfunction and to exert antithrombotic actions.⁴

The administered dose of vitamin D may also influence the impact of supplementation on the outcomes of COVID-19. The included studies in this meta-analysis present variability as far as the administered dose of vitamin D is concerned, ranging from low daily doses like 1000 IU of cholecalciferol³² to high-dose boluses like 400,000 IU of cholecalciferol.^{24,33} Recently, it has been advocated that the daily doses of vitamin D rather than the intermittent high-dose boluses are effective for the prevention or treatment of certain diseases, like acute respiratory infections, rickets and tuberculosis.⁴² A plausible explanation for this is that high-dose boluses of vitamin D increase the activity of the inactivating enzyme 24-hydroxylase CYP24A1, as well as the levels of fibroblast growth factor 23. 24-hydroxylase CYP24A1 is an important regulator of vitamin D metabolism, as it converts 25(OH)D and 1,25(OH)₂D to the largely inactive forms of 24,25(OH)₂D and 1,24,25(OH)₃D. This is a mechanism through which vitamin D regulates its own metabolism. Fibroblast growth factor 23 negatively regulates vitamin D metabolism, via the increased expression of 24-hydroxylase CYP24A1 and, at the same time, via the reduction of the mRNA levels of 1- α hydroxylase, the enzyme responsible for 1- α hydroxylation of 25(OH)D.⁴³ Consequently, the activation of these mechanisms after the administration of a high

TABLE 3 Summary of Findings (SoF) table

Vitamin D supplementation compared to no vitamin D supplementation for reducing mortality and ICU admission of COVID-19 patients						
Patient or population: Reducing mortality and ICU admission of COVID-19 patients						
Setting: Hospitalised patients (hospitals, geriatric acute care units, nursing homes)						
Intervention: Vitamin D supplementation						
Comparison: No vitamin D supplementation						
Outcomes	Anticipated absolute effects ^e (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no vitamin D supplementation	Risk with vitamin D supplementation				
Mortality	258 per 1000	172 per 1,000 (100–281)	OR 0.597 (0.318–1.121)	2078 (9 studies)	⊕○○○ Very low ^{a,b,c,d}	Vitamin D supplementation does not reduce mortality in hospitalised patients for COVID-19. The quality of evidence is very low and we have very little confidence in this result
ICU admission	263 per 1000	104 per 1000 (50–202)	OR 0.326 (0.149–0.712)	860 (6 studies)	⊕○○○ very low ^{a,b,c,d}	Vitamin D supplementation reduced the need for ICU admission for hospitalised patients for COVID-19. The quality of evidence is very low and we have very little confidence in this result.

Note: **GRADE Working Group grades of evidence.** **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Abbreviations: CI, confidence interval; OR, odds ratio.

^aSerious overall risk of bias of the included studies. The majority of the included studies are non-randomized (ROBINS-2 tool was used for the assessment of non-randomized studies and RoB2 tool for randomized studies).

^bPresence of significant inconsistency (minimal overlap of CI, large differences in estimation effects, statistical significance for heterogeneity $p < 0.05$ and $I^2 = 62.40$) with no robust explanation available.

^cSerious indirectness (differences in study populations, doses and forms of vitamin D and duration of therapy that affect generalisability).

^dPublication bias strongly suspected (funnel plot asymmetry).

^eThe risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

intermittent dose of vitamin D has a longstanding effect and may result to intracellular VDD, despite the apparently efficient circulating levels. In an attempt to investigate the effect of dose supplementation of the studies included in this meta-analysis on the outcomes of interest, we performed a meta-regression analysis; however, no significant relationship was found. Nevertheless, the sub-analysis of 'high' and 'low' doses showed a significant impact of 'low' administered doses on both outcomes, while 'high' doses were not associated with any significant result. The aforementioned auto-regulatory pathways of vitamin D metabolism could be reflected here and merely justify this lack of association. Additionally, the 'high' doses of vitamin D were administered after the diagnosis of COVID-19 (mean of 10.3 days from symptom onset in the study of Murai et al. and the second and third days of the in-hospital stay in the study of Giannini et al.), a fact that could

reduce the effectiveness of the intervention. However, as previously mentioned, the included studies differ substantially as far as their design, study populations, dose and duration of vitamin D supplementation, rendering the interpretation of these results challenging.

Another issue that has risen is whether the impact of vitamin D supplementation should be considered in the setting of pre-existing deficiency or insufficiency, as supplementation irrespectively of baseline levels is not expected to be beneficial.³⁹ Indeed, levels of 25(OH)D are not measured in all studies included in this meta-analysis. However, even in the cases of measured levels, there is controversy regarding the impact of time of measurement. 25(OH)D is largely bound to vitamin D binding protein and albumin, whose concentrations tend to decrease during acute illness, as a negative acute phase response.⁴⁴ Consequently, the interpretation of these levels in

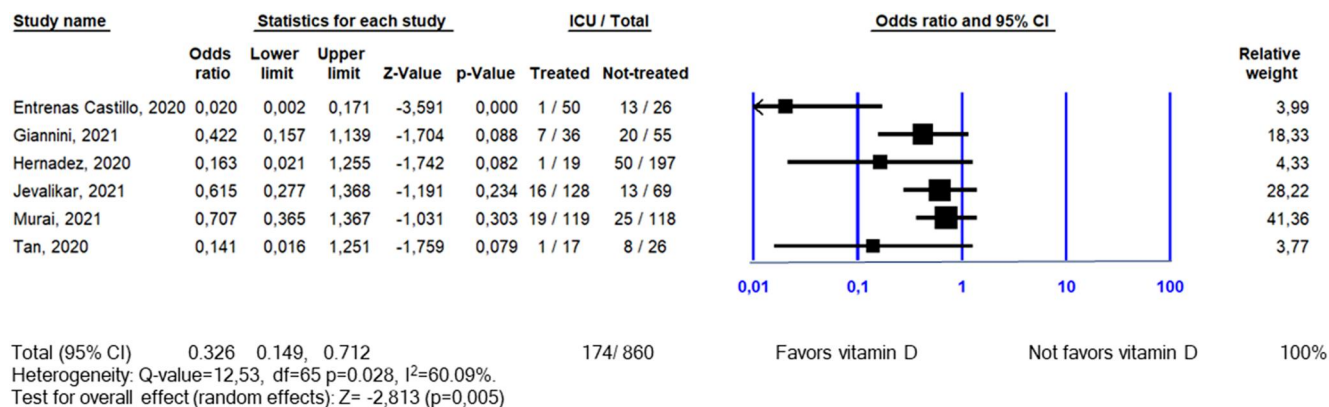


FIGURE 2 Forest plot for vitamin D supplementation and intensive care unit admission

patients with severe COVID-19 remains questionable, as they may reflect reverse causality.

Vitamin D deficiency 'pandemic' has constituted a long-standing issue of debate between experts and medical organisations, concerning the definition of the desirable levels of serum 25(OH)D and the recommended doses of supplementation.⁵ In the setting of the overwhelming impact of COVID-19 pandemic and the urgent need for effective treatments against SARS-CoV-2, a link between these two pandemics has been proposed and vitamin D supplementation has been advocated as a possible adjunctive intervention for the management of COVID-19 patients. Indeed, this possibility seems intriguing, as vitamin D supplementation is a low-cost and safe intervention. Our findings from this meta-analysis, suggest a beneficial role of vitamin D supplementation in the rates of ICU admissions of COVID-19, irrespectively of the administered dose; however, significant reduction of mortality was not observed.

Four other systematic-reviews and meta-analyses on the effect of vitamin D supplementation on mortality and ICU admissions of COVID-19 patients were retrieved from database searching.^{45,46} The first one,⁴⁵ that included 532 COVID-19 patients from three studies, concluded that vitamin D supplementation was associated with significant lower rates of ICU admission ($p < 0.0001$), while no significant benefit for mortality was observed; these findings are similar to the results of our study. However, compared to that study, our meta-analysis includes a larger number of patients because at the time we performed our search more studies had been published. Moreover, as previously explained, we decided a priori to use the random-effects model, which we believe to be more appropriate for this meta-analysis due to different designs of the included studies, while in the aforementioned study the significant result was obtained with the application of fixed effect model. The second meta-analysis, which was obtained from a preprint server,⁴⁶ included only clinical trials, quasi experimental and pilot studies. Only one of the included studies reported on ICU admissions, while 3 studies that included a total of 190 patients reported on mortality. The authors conducted a meta-analysis of these studies and concluded that vitamin D supplementation is associated with a significant reduction

in the odds of mortality ($p = 0.008$). However, they did not describe the model applied for their analysis, and also, no publication bias was reported. An interesting, recently published analysis of 2933 COVID-19 patients from 13 studies (3 RCTs and 10 observational) concluded that vitamin D supplementation significantly reduced the incidence of the composite outcome of ICU admission/mortality; the association remained significant when adjusted risk estimates were analysed.⁴⁷ On the contrary, another recent analysis of 467 patients with COVID-19 that aimed to investigate the effect of vitamin D supplementation on clinical outcomes, including ICU admission and mortality, did not find any significant association.⁴⁸ However, this meta-analysis included only randomized and quasi-experimental trials; consequently, the number of the included patients was small. Another distinction of this meta-analysis from ours and the previously mentioned is that vitamin D was administration was prospective after the diagnosis of COVID-19; as previously mentioned the possible influence of the time of vitamin D administration remains to be elucidated. Additionally, an important asset of our study is the meta-regression analysis regarding the relationship between the administered dose of vitamin D and the outcomes of interest, an approach that had not been applied in the abovementioned studies.

This meta-analysis has several limitations. Firstly, due to the scarcity of RCTs at the moment of data collection, non-randomized studies have been included. The included studies differ as far as their design and sample size is concerned, and most of them present a high risk of bias (Figures S10 and S11, Table S2). Finally, there is heterogeneity between the studies in terms of the form and dose of vitamin D supplementation, the timing of administration in respect of the diagnosis of COVID-19 infection, the baseline levels of 25(OH)D, as well as the characteristics of the studied populations and the presence of comorbidities. Despite these limitations, we believe that our study provides insight of the possible contribution of vitamin D supplementation in the management of COVID-19 patients. Nevertheless, before suggesting the use of vitamin D as a possible adjunct treatment in COVID-19 pandemic, robust evidence from high-quality RCTs is needed.

5 | CONCLUSION

The findings of the present meta-analysis support a beneficial role of vitamin D supplementation in the rates of ICU admission in COVID-19 patients. However, validation of these findings from high-quality RCTs is necessary.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

ETHICS STATEMENT

This study did not involve human participants or animal research. This work was based on already produced and published data.

AUTHOR CONTRIBUTIONS

Georgia Samakidou and Ioanna Eleftheriadou determined the search strategy, screened the selected studies and extracted the data. Nikolaos Tentolouris and Anastasios Tentolouris performed the statistical analysis. All authors participated in the writing and revision of this paper. All authors have read and approved this final manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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PEER REVIEW

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