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REVIEW

Effect of vitamin D supplementation on clinical outcomes in adult patients with COVID-19: A GRADE-assessed systematic review and meta-analysis of randomized controlled trials

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Abstract

The COVID-19 pandemic has emerged as a major global health crisis. Vitamin D, a crucial fat-soluble vitamin, has been recommended for COVID-19 patients, though evidence of its effectiveness is inconsistent. This systematic literature review and meta-analysis aimed to evaluate the impact of vitamin D supplementation on COVID-19-related outcomes. A comprehensive search was conducted across PubMed, Scopus, Web of Science, Embase, and Cochrane databases. Primary outcomes included mortality and hospital length of stay, while secondary outcomes encompassed C-reactive protein (CRP), ferritin, D-dimer, hemoglobin (Hb) concentrations, and lymphocyte, neutrophil, and platelet counts. Data analysis was performed using Stata™ Version 14. A total of 16 trials were analyzed. The meta-analysis revealed that vitamin D supplementation significantly reduced hospital length of stay (mean difference = −1.16; 95% confidence interval [CI]: −2.23, −0.09; $p = .033$) with significant heterogeneity ($I^2 = 69.2\%$, $p = .002$). Subgroup analysis showed a more pronounced reduction in studies with vitamin D dosages ≤10 000 international units (IU) (mean difference = −1.27; 95% CI: −1.96, −0.57; $p < .001$) and in patients over 60 years old (mean difference = −1.84; 95% CI: −2.53, −1.14; $p < .001$). Additionally, vitamin D significantly reduced CRP concentrations in older adults (>60 years) (mean difference = −1.13; 95% CI: −2.07, −0.18; $p = .019$). No significant changes were found in ferritin, D-dimer, Hb concentrations, or in lymphocyte, neutrophil, and platelet counts ($p > .05$). In conclusion, while vitamin D supplementation did not significantly affect most COVID-19-related biomarkers, however, it reduces the length of hospital stay.

KEYWORDS
COVID-19, meta-analysis, systematic review, vitamin D

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ARDS, acute respiratory distress syndrome; CIs, confidence intervals; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; Hb, hemoglobin; ICU, intensive care unit; IU, international units; PICOS, population, intervention/exposure, comparator, outcome, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SD, standard deviation; WHO, World Health Organization.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) epidemic, which began in China in late 2019, quickly spread worldwide, infecting millions and causing numerous deaths.[1–3] According to the latest statistics from the World Health Organization (WHO) as of June 2023, over 767 million COVID-19 cases have been confirmed, with approximately 7 million fatalities.[4] Since the outbreak began, extensive investigations have explored the effects of pharmacological interventions, herbal remedies, traditional medicine, and other factors in managing COVID-19.[5–8]

Nutritional factors are recognized as important in the prevention and treatment of COVID-19.[9,10] Various researchers have focused on nutritional factors that can strengthen the immune system against COVID-19 or support the treatment process, leading to numerous studies in this area.[11,12] Most of these studies have focused on antioxidant compounds or diets designed to increase the intake of antioxidants and immune system-enhancing nutrients.[13]

Vitamin D, a key modulator of the immune system, plays a crucial role in both innate and adaptive immunity.[14,15] Since the outbreak of COVID-19, vitamin D has been extensively studied and is considered one of the most crucial nutrients.[16] Vitamin D insufficiency has been associated with worse outcomes, greater severity, and a higher incidence of comorbidities in respiratory infections.[17] Serum concentrations of 25-hydroxyvitamin D [25(OH)D] <20 ng/mL have been shown to increase the risk of pneumonia by over 60%.[18] There is an inverse correlation between 25(OH)D concentrations and both the severity of the disease and specific clinical biomarkers in COVID-19 patients.[19–21] Vitamin D may also mitigate the negative effects of COVID-19 by regulating the renin-angiotensin system and the production of angiotensin-converting enzyme 2, which helps reduce lung leakage in acute respiratory distress syndrome (ARDS) animal models.[22]

Several clinical trials have evaluated the effects of different doses of vitamin D on COVID-19 outcomes, but the results have been contradictory.[23,24] To our knowledge, two recent meta-analyses have examined the effects of vitamin D supplementation in COVID-19 patients.[25,26] However, these studies faced issues such as incomplete inclusion of primary articles, inclusion of retracted articles, and methodological limitations. Additionally, the factors investigated differed from those examined in the current study. Therefore, this systematic review and meta-analysis aimed to assess the effects of vitamin D supplementation on clinical outcomes in adult COVID-19 patients. Our primary objective was to evaluate the impact of vitamin D supplementation on mortality and hospital length of stay. Secondary objectives included investigating changes in C-reactive protein (CRP), ferritin, D-dimer, hemoglobin (Hb) concentrations, and lymphocyte, neutrophil, and platelet counts following vitamin D supplementation.

2 | METHODS

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[27] The study was registered in the Systematic Review Registration: PROSPERO (registration ID: CRD42023441017).

2.1 | Search study

To find relevant articles, a systematic search was performed in PubMed, Scopus, Web of Science, Embase, and Cochrane databases. The search strategy involved two concept keywords: COVID-19 and vitamin D supplementation. The details of the search strategy used in this search are shown in Table S1. We also conducted a manual search of references listed in relevant review articles, including backward and forward searches and queries using Google Scholar, to ensure that no relevant research was missed. The search was conducted without any language restrictions. In our systematic review, while our primary focus was on peer-reviewed papers to ensure reliability and quality, we conducted a targeted search for gray literature. This involved exploring sources such as conference proceedings, dissertations, theses, government reports, and other relevant documents. Additionally, we did not include preprint studies in our analysis. After conducting a systematic search, the obtained records were transferred to the EndNote software to perform the screening process. After removing duplicate records, two researchers independently reviewed the titles and abstracts to exclude articles with unrelated titles from the review process. Any discrepancies between the findings of the two researchers were resolved through consultation with a third person.

2.2 | Eligibility criteria

In the second stage, the screening process was carried out based on the population, intervention/exposure, comparator, outcome, and study design (PICOS) criteria. The PICOS framework was used for inclusion and exclusion criteria. The inclusion criteria include: (1) clinical trial studies with a control group conducted on adults over 18 years old; (2) vitamin D supplementation of at least one dose in patients with COVID-19; (3) comparison of at least one of the outcomes considered in this study (mortality, length of hospital stay, CRP, ferritin, D-dimer, Hb concentrations, and lymphocyte, neutrophil, and platelet counts) between the intervention and control groups reported at the beginning and end of the intervention. Studies that had a design other than a clinical trial, or were conducted on animal samples, or on children, were excluded. Additionally, studies that evaluated vitamin D simultaneously with other agents, where it was not possible to assess the independent effect of vitamin D, were excluded from the analysis. Detailed inclusion and exclusion criteria are described in Table S2.

2.3 | Data extraction

Two researchers independently extracted the required data from the articles. This information includes the name of the first author, year

of publication, country, study sample size and gender distribution, mean age of the participants, vitamin D dosage, duration of the intervention, control group, and the mean and standard deviation (SD) of the investigated variables. Any disagreement between the two researchers was resolved through consultation with a third person.

2.4 | Assessment of the risk of bias and certainty of the evidence

The Cochrane risk-of-bias tool (RoB 2), specifically designed for randomized trials, was utilized to assess the risk of bias within this study. This methodology includes criteria for selection bias, detection bias, performance bias, reporting bias, attrition bias, and other potential biases.[28] The overall strength of the evidence was determined using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method.[29,30] According to our evaluation criteria, the estimates of biomarker effects were categorized into four quality tiers: high, moderate, low, and very low. The reviewers separately conducted GRADE assessments, and conflicts between reviewers were settled by a third reviewer.

2.5 | Data analysis

The information obtained from the primary articles was first entered into Excel software and then transferred to Stata 14 software (Stata Corp, College Station, TX, USA) for statistical analysis. Intervention effects were determined as the mean differences and 95% confidence intervals (CIs) obtained for changes in serum concentrations of CRP and D-dimer, as well as length of hospital stay. We used the following formula to compute SD change from SD baseline in both intervention and control groups: $\sqrt{\left[\left(SD^2_{baseline} + SD^2_{final}\right) - \left(2 \times R \times SD_{baseline} \times SD_{final}\right)\right]}$. The I^2 statistic and Cochran's chi-square test (Q) were used for evaluation of studies heterogeneity. If the I^2 was above 50%, we used the random-effect model, and if the I^2 was below 50%, we used the fixed-effect model. Also, sensitivity analysis was used to evaluate the effect of removing each study on the results. Publication bias was assessed by funnel plot and Egger's and Begg's test.[31] Subgroup analyses were conducted based on participants' baseline vitamin D concentrations (≤22 ng/mL and >22 ng/mL), age (≤60 years and >60 years), and vitamin D dosage (≤10 000 international units [IU] and >10 000 IU). A p-value of <.05 was, a priori, considered statistically significant, unless otherwise specified.

3 | RESULTS

3.1 | Literature search and characteristics of included studies

At the end of the systematic search process, 8661 records were identified, and after removing duplicate records, 5703 articles entered the screening phase. After a systematic search and two stages of screening, 16 studies met the necessary criteria to be included in this study.[23,24,32–45] The article selection process is displayed in the flowchart (Figure 1), following the PRISMA method.[27] From the included studies, two studies were conducted in Egypt, two studies in Brazil, three studies in Spain, and one study each in Croatia, Switzerland, India, Argentina, Israel, Russia, Saudi Arabia, Mexico, and France. The sample size in the evaluated studies ranged from 40 to 237 patients. The characteristics of the included studies are summarized in Table 1. The dose of vitamin D used in the studies varied from 2000 to 500 000 IU. In the comparison group, three studies used a low dose of vitamin D,[32,34,41] and in the remaining studies, placebo was used. No prevention trials were included.

3.2 | Risk of bias assessment

The results of the risk-of-bias assessment are shown in Table 2. All the trials used acceptable random sequence generation. In term of allocation concealment, six studies had acceptable conditions,[32,36,37,40,41,43] three studies had a high risk of bias,[39,42,43] and for the remaining studies, the risk of bias is unclear. Also, in terms of blinding, we found a high risk of bias in four studies, 10 trials had a low risk of bias, and in two studies, the risk-of-bias assessment was unclear. Moreover, only four studies received a low risk-of-bias

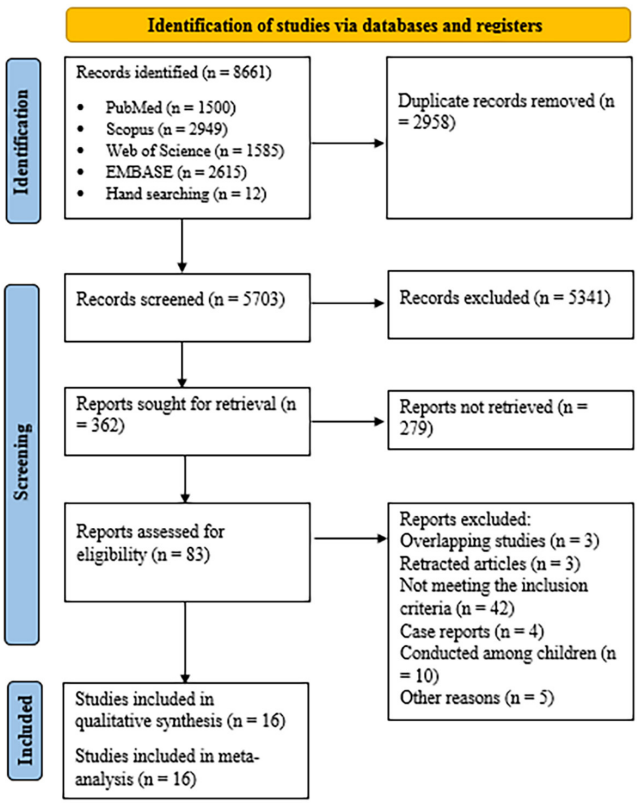

FIGURE 1 Selection process for eligible studies from all identified citations.

TABLE 1 Characteristics of included studies.

Study (year)	Study design	Country	Total sample size (intervention/control)	Age, mean (SD)	Baseline 25(OH)D concentrations	Vitamin D dosage/duration	Control	Outcomes
Bugarin et al. (2023)[24]	Open-label randomized clinical trial	Croatia	152 (55/57)	64.95 (31.85)	24.4 (16.95–36.8)	10000 IU/14 days	Without vitamin D supplementation	Median number of days spent in the ICU, mean WHO clinical progression scale, CRP, neutrophil/lymphocyte ratio, fibrinogen
Jaun et al. (2023)[23]	Multicenter, randomized, placebo-controlled double-blind trial	Switzerland	78 (39/39)	60.49 (13.84)	31.46 (10.95)	140000 IU single dose plus 800 IU daily/until discharge	Standard treatment	Length of hospital stay
Cervero et al. (2022)[32]	Multicenter, single-blinded, prospective randomized pilot clinical trial	Brazil	85 (44/41)	65 (17.32)	14.8 (6.2)	10000 IU cholecalciferol/14 days	2000 IU cholecalciferol	Length of the hospital stay and ARDS development, LDH, D-dimer, platelet count, ferritin
Rastogi et al. (2022)[33]	Randomized, placebo-controlled, study	India	40 (16/24)	50 (11.11)	8.6 (7.1–13.1)	60000 IU/7 days	Placebo (5 mL distilled water)	D-dimer, fibrinogen, CRP, procalcitonin
Torres et al. (2022)[34]	Multicenter, single blind, prospective, randomized clinical trial	Spain	85 (44/41)	65.0 (53.0–74.0)	22.4 (25.07)	10000 IU/14 days	2000 IU cholecalciferol	Length of hospital stay, changes in the cytokine profile, distribution of CD4+ T cell
Soliman et al. (2022)[35]	Placebo-controlled randomized prospective study	Egypt	56 (40/16)	71.3 (4.16)	14.8 (6.2)	200000 IU single dose	Placebo	6 Weeks mortality, D-dimer, CRP, platelet count, Hb, lymphocytes
Sarhan et al. (2022)[36]	Prospective randomized controlled trial	Egypt	116 (58/58)	65 (15.55)	18.33 (7.5)	200000 IU single dose	Standard COVID-19 management	Ferritin, D-dimer, LDH, CRP
Mariani et al. (2022)[37]	Multicenter, randomized, double-blind, sequential, placebo-controlled trial	Argentina	218 (115/103)	55.8 (10.70)	32.5 (12.59)	500000 IU single dose	Matching placebo	rSOFA, change in SpO_2, length of hospital stay
Elamir et al. (2022)[38]	Randomized pilot study	Israel	50 (25/25)	69 (18)	25.8 (11.26)	2000 IU/14 days	Matching placebo	Length of hospital stay, mortality, endotracheal intubation
Karonova et al. (2022)[39]	Randomized, open-label, single-center study	Russia	110 (56/54)	57 (11.11)	17.8 (10.4)	100000 IU single dose	Placebo	Neutrophil and lymphocyte counts, CRP, frequencies of CD38++ CD27
Murai et al. (2021)[40]	Multicenter, double-blind, randomized, placebo-controlled trial	Brazil	237 (119/118)	56.5 (13.8)	21.2 (10.1)	200000 IU single dose	10 mL of a peanut oil solution	Hospital length of stay, duration of mechanical ventilation, CRP
Sabico et al. (2021)[41]	Randomized clinical trial	Saudi Arabia	69 (36/33)	49.8 (14.3)	53.4 (2.9)	5000 IU/14 days	1000 IU/14 days	IL-6, D-dimer

TABLE 1 (Continued)

Study (year)	Study design	Country	Total sample size (intervention/control)	Age, mean (SD)	Baseline 25(OH)D concentrations	Vitamin D dosage/duration	Control	Outcomes
Sánchez-Zuno et al. (2021)[42]	Open-label randomized clinical trial	Mexico	42 (22/20)	43.0 (20–74)	22.4 (12.1–45.9)	10000 IU/14 days	Standard COVID-19 management	Mortality
Annweiler et al. (2020)[43]	Clinical trial	France	48 (32/16)	88.0 (5.5)	65.2 (34.8)	800 IU/3 months	Standard COVID-19 management	Mortality
Caballero-García et al. (2021)[45]	Double-blind	Spain	30 (15/15)	60.6 (1.7)	27.30 (10.5)	2000 IU/6 weeks	Placebo	CRP, ferritin, Hb, lymphocytes
Castillo et al. (2020)[44]	Pilot randomized clinical study	Spain	76 (50/26)	53 (10)	21.2 (1.4)	Loading dose of 532 μg, followed by 266 μg on days 3, 7, 14, 21, and 28	Standard COVID-19 management	Mortality Need for ICU admission

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; Hb, hemoglobin; ICU, intensive care unit; IL-6, interleukin 6; IU, international units; LDH, lactate dehydrogenase; rSOFA, respiratory sepsis-related organ failure assessment; WHO, World Health Organization.

grade in terms of blinding of outcome assessment.[23,37,41,44] Except for two studies whose status was unclear,[34,36] the rest of the studies were in a good condition in terms of attrition bias. Finally, except for one trial,[44] all other studies provided a low risk of bias in terms of selection bias and other sources of bias.

3.3 | Effects of vitamin D supplementation on COVID-19-related mortality

Overall, nine trials considered the effects of vitamin D supplementation on mortality rate.[24,34–38,40,43,44] Due to high heterogeneity in the reporting of deaths, meta-analysis was not possible. One study showed a non-significant difference between the vitamin D and control group in terms of all-cause mortality on day 60 (26.2% vs. 40.6% mortality rate).[24] Similar findings were observed in Murai et al. (7.6% vs. 5.1%),[40] and Torres et al. studies (2.44% vs. 2.27%).[34] Soliman et al., in a trial among diabetic elderly patients, did not find any significant differences in mortality rate between the vitamin D and placebo groups (17.5% vs. 18.8%).[35] In line with the results of this study, there were no significant differences between vitamin D and control groups in terms of COVID-19 mortality in other studies, including Sarhan et al. (45% vs. 51%, $p = .49$),[36] Mariani et al. (4.3% vs. 1.9%, $p = .451$),[37] and Elamir et al. (three deaths in the control group and none in the vitamin D group, $p = .23$).[38] However, in one study conducted among older adult patients with COVID-19, it was reported that a single oral high dose of cholecalciferol led to a significant improvement in overall mortality at day 14 (adjusted hazard ratio = 0.39 [95% CI: 0.16, 0.99], $p = .049$).[43]

3.4 | Effects of vitamin D supplementation on hospital length of stay

Eight trials, including 944 patients (471 treated and 473 controls), provided data related to the effects of vitamin D supplementation on hospital length of stay.[23,24,34,35,37,38,40,43] As shown in Figure 2, vitamin D supplementation led to a significant reduction in hospital length of stay (mean difference = −1.16 [95% CI: −2.23, −0.09]; $p = .033$), with a significant heterogeneity ($I^2 = 69.2\%$, $p = .002$). In the subgroup analysis, we found that vitamin D supplementation reduced the length of hospital stay in studies where the vitamin D dosage was ≤10000 IU (mean difference = −1.27 [95% CI: −1.96, −0.57]; $p < .001$) and in older adult patients over 60 years old (mean difference = −1.84 [95% CI: −2.53, −1.14]; $p < .001$). The results of the subgroup analysis are summarized in Table 3. The leave-one-out sensitivity analysis showed that leaving each of the trials resulted in a range from −0.809 [95% CI: −1.79, −0.17] by Torres et al. to −1.40 [95% CI: −2.58, −0.23] by Mariani et al., with no significant effect on the pooled effect size.[34,37] A funnel plot (Figure 3A) indicated no substantial evidence of publication bias (Egger's test $p = .784$; Begg's test $p = .71$).

TABLE 2 Study quality and risk-of-bias assessment of included studies in the meta-analysis.

Study (year)	Sequence generation	Allocation concealment	Blinding	blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bugarin et al., 2023	+	?	+	−	+	+	+
Jaun et al., 2023	+	?	+	+	+	+	+
Cervero et al., 2022	+	+	+	−	+	+	+
Rastogi et al., 2022	+	?	?	−	+	+	+
Torres et al., 2022	+	?	+	−	?	+	+
Soliman et al., 2022	+	?	−	−	+	+	+
Sarhan et al., 2022	+	+	?	?	?	+	+
Mariani et al., 2022	+	+	+	+	+	+	+
Elamir et al., 2022	+	?	−	−	+	+	+
Karonova et al., 2022	+	−	+	?	+	+	+
Murai et al., 2021	+	+	+	?	+	+	+
Sabico et al., 2021	+	+	+	+	+	+	+
Annweiler et al., 2020	+	−	−	−	+	+	+
Caballero-García. 2021	+	?	+	?	+	+	+
Castillo et al., 2020	+	+	+	+	+	+	?
Sánchez-Zuno et al., 2021	+	−	−	−	+	+	+

Note: +: low risk, −: high risk and ?: unclear.

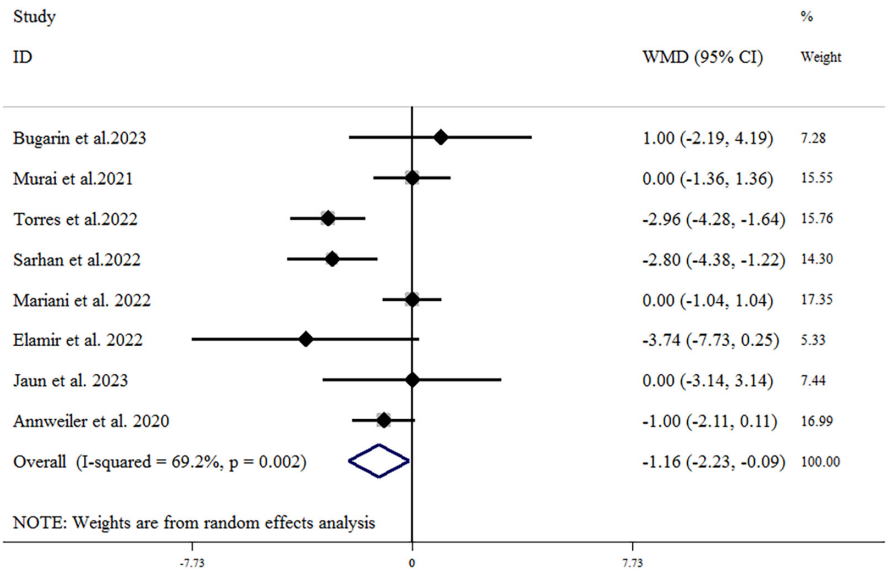

FIGURE 2 Forest plot detailing weighted mean difference and 95% CIs for the impact of vitamin D supplementation on hospital length of stay. CI, confidence interval; WMD, weight mean difference.

TABLE 3 Subgroup analyses for the effect of vitamin D on COVID-19-related outcomes.

	Number of effect sizes	WMD (95% CI)	*p* Effect	*p* Within subgroup[a]	I^2 (%)	*p* Between subgroups[b]
Subgroup analyses of vitamin D on hospital length of stay						
25(OH)D concentrations (ng/mL)						.643
≤22	4	−1.19 (−1.93, −0.45)	.002	.035	65.2	
>22	4	−0.94 (−1.71, −0.17)	.016	.003	78.4	
Age (years)						.001
≤60	2	0.00 (−0.83, 0.83)	1	1	0.0	
>60	6	−1.84 (−2.53, −1.14)	.000	.04	57	
Vitamin D dosage (IU)						.390
≤10000	4	−1.27 (−1.96, −0.57)	.000	.01	69.9	
>10000	4	−0.79 (−1.63, 0.05)	.065	.013	77	
Subgroup analyses of vitamin D on CRP concentrations						
25(OH)D concentrations (ng/mL)						<.001
≤22	7	0.07 (−0.45, 0.59)	.788	.025	58.6	
>22	4	−1.74 (−4.86, 1.39)	.276	<.001	95.4	
Age (years)						<.001
≤60	4	0.78 (−0.11, 1.67)	.086	.017	70.6	
>60	7	−1.13 (−2.07, −0.18)	.019	<.001	84.3	
Vitamin D dosage (IU)						.108
≤10000	6	−0.35 (−1.42, 0.71)	.518	<.001	94.8	
>10000	5	−0.74 (−2.14, 0.66)	.299	.013	64.6	
Subgroup analyses of vitamin D on D-dimer concentrations						
25(OH)D concentrations (ng/mL)						<.001
≤22	5	0.02 (−0.27, 0.32)	.871	.004	73.5	
>22	2	1.48 (0.08, 2.88)	.038	<.001	95.1	
Age (years)						.277
≤60	3	0.62 (−1.07, 2.31)	.474	<.001	97.5	
>60	4	0.18 (−0.32, 0.68)	.484	<.001	86.2	
Vitamin D dosage (IU)						<.001
≤10000	4	0.86 (−0.01, 1.73)	.052	<.001	96.4	
>10000	3	−0.43 (−1.25, 0.4)	.309	.019	74.6	
Subgroup analyses of vitamin D on lymphocyte numbers						
25(OH)D concentrations (ng/mL)						-
≤22		50 (−190, 280)	.707	<.001	82.1	
>22		−1600 (−1790, −1410)	<.001	-	-	
Age (years)						<.001
≤60		−630 (−1640, 380)	.221	<.001	98.5	
>60		−2.53 (−9.37, 4.30)	.351	.001	91.5	
Vitamin D dosage (IU)						<.001
≤10000		−600 (−1570, 370)	.228	<.001	99.1	
>10000		−270 (−930, 390)	.467	<.001	89.7	
Subgroup analyses of vitamin D supplementation on ferritin concentrations						
25(OH)D concentrations (ng/mL)						-
≤22		−3.09 (−10.06, 3.89)	.386	.032	62	
>22		4.40 (−0.82, 9.62)	.098	-	-	

(Continues)

TABLE 3 (Continued)

	Number of effect sizes	WMD (95% CI)	*p* Effect	*p* Within subgroup[a]	I^2 (%)	*p* Between subgroups[b]
Age (years)						.156
≤60		−0.87 (−10.20, 8.45)	.854	.115	53.7	
>60		−1.09 (−11.44, 9.27)	.21	.007	80	
Vitamin D dosage (IU)						.350
≤10000		4.35 (0.11, 8.60)	.044	.99	0.0	
>10000		−8.23 (−10.99, −5.48)	<.001	.729	0.0	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; CRP, C-reactive protein; IU, international units; WMD, weighted mean difference.

[a]*p* For heterogeneity, within subgroup.

[b]*p* For heterogeneity, between subgroups.

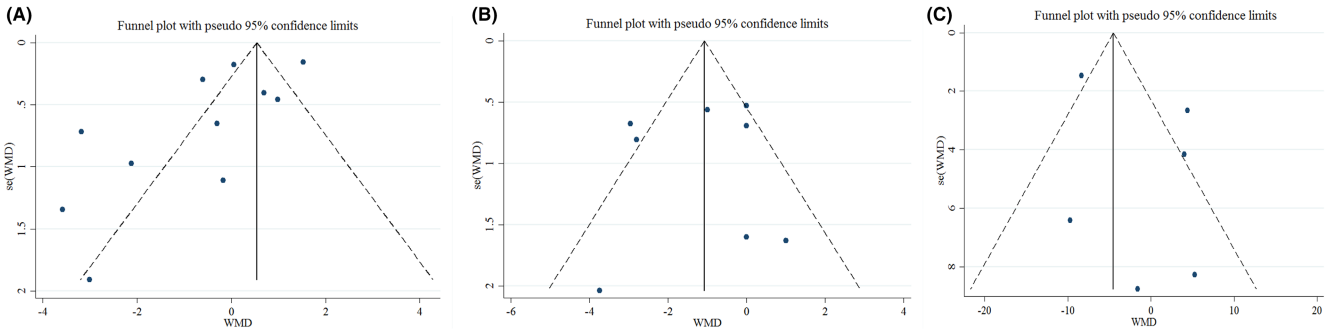

FIGURE 3 Funnel plots detailing publication bias in the studies selected for analysis. (A) Hospital length of stay; (B) CRP; (C) ferritin. Visual inspection of funnel plots indicating that there is no publication bias among studies. CI, confidence interval; CRP, C-reactive protein; WMD, weight mean difference.

3.5 | Effects of vitamin D supplementation on inflammatory markers

The effect of vitamin D supplementation on CRP concentrations in patients with COVID-19 was investigated in 11 studies.[23,24,32–36,39–41,45] The results showed that vitamin D supplementation did not lead to a significant decrease in CRP concentrations compared to placebo (mean difference = −0.48 [95% CI: −1.30, 0.34]; $p = .255$), with a significant heterogeneity ($I^2 = 91.1\%$, $p < .001$) (Figure 4). The subgroup analysis reported that vitamin D supplementation led to a significant reduction in serum concentrations of CRP in older adult patients over 60 years old (mean difference = −1.13 [95% CI: −2.07, −0.18]; $p = .019$). The results of sensitivity analysis showed that removing each of the trials in a range from −0.28 [95% CI: −1.1, 0.53] by Jaun et al. to −0.67 [95% CI: −1.57, 0.22] by Murai et al., did not change the significance of the results.[23,40] There was no substantial evidence of publication bias based on the funnel plot (Figure 3B) and Egger's test (Egger's test $p = .132$; Begg's test $p = .484$).

Overall, six studies provided sufficient data on the effect of vitamin D on ferritin concentrations.[32,33,36,39,41,45] According to the meta-analysis, there were no significant effects of vitamin D on ferritin concentrations (mean difference = −1.24 [95% CI: −8.27, 5.80]; $p = .730$; $I^2 = 79.5\%$, $p < .002$) (Figure 5). Subgroup analysis could not identify the source of heterogeneity. Also, the results of the sensitivity analysis showed that removing any of the studies had no effect on the results. Moreover, based on the publication bias test, there was no substantial evidence of publication bias between studies (Egger's test $p = .322$; Begg's test $p = .851$) (Figure 3C).

Seven studies compared the effects of vitamin D supplementation on D-dimer concentrations.[24,32,33,35,36,40,41] The results of the pooled analysis showed that vitamin D did not significantly change the D-dimer concentrations (mean difference = 0.37 [95% CI: −0.15, 0.9]; $p = .166$), with significant heterogeneity ($I^2 = 94.2\%$, $p < .001$) (Figure 6). Subgroup analysis reported that vitamin D had a significant effect on D-dimer concentrations among patients with baseline 25(OH)D concentrations greater than 22 ng/mL (mean difference = 1.48 [95% CI: 0.08, 2.88]; $p = .038$). Sensitivity analysis suggested no difference in the results following the exclusion of any of the trials. Additionally, no significant evidence of publication bias was found (Egger's test $p = .538$; Begg's test $p = .652$).

3.6 | Effects of vitamin D supplementation on hematological parameters

Four trials with 447 participants investigated the effect of vitamin D supplementation on platelet count.[32,35,40,41] There were no significant

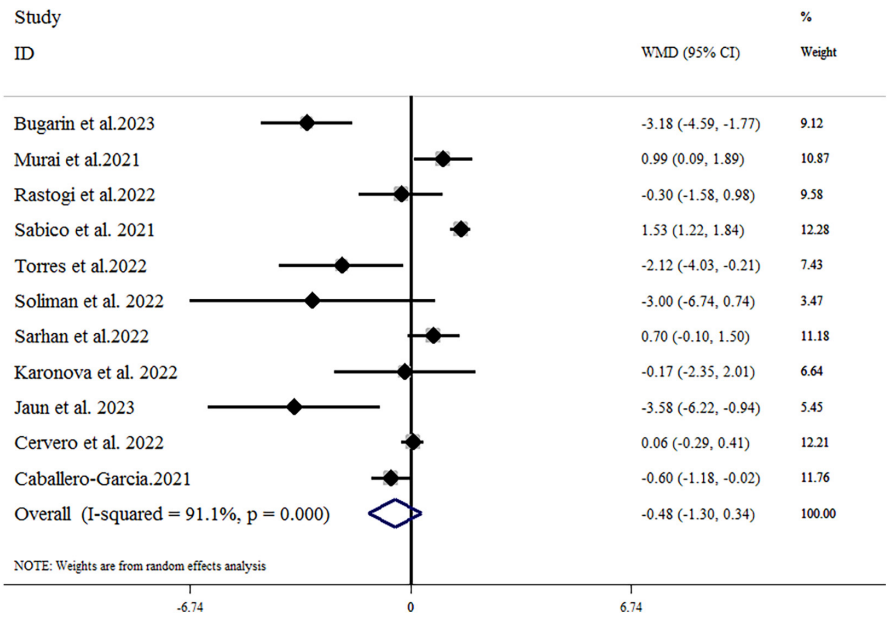

FIGURE 4 Forest plot detailing weighted mean difference and 95% CIs for the impact of vitamin D supplementation on CRP concentrations. CI, confidence interval; CRP, C-reactive protein; WMD, weight mean difference.

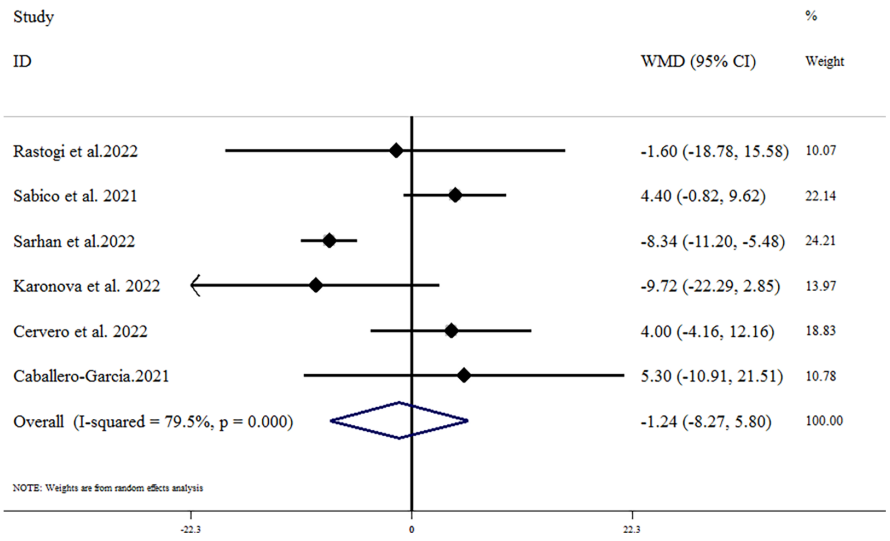

FIGURE 5 Forest plot detailing weighted mean difference and 95% CIs for the impact of vitamin D supplementation on Ferritin concentrations. CI, confidence interval; WMD, weight mean difference.

differences between the vitamin D and control groups in terms of platelets counts (mean difference = −1.82 [95% CI: −61.62, 57.96]; $p = .952$), with a considerable heterogeneity ($I^2 = 98.1\%$, $p < .001$). No new findings were observed in the sensitivity analysis and publication bias test.

Four trials reported the results of investigating the effect of vitamin D supplementation on Hb concentrations.[35,40,41,45] The results showed that vitamin D supplementation did not significantly change Hb concentrations in COVID-19 patients (mean difference = −0.11 [95% CI: −0.26, 0.04]; $p = .145$; $I^2 = 0.0\%$). Sensitivity analysis suggests no difference in the results following the exclusion of any of the trials. Additionally, no significant evidence of publication bias was found (Egger's test $p = .988$; Begg's test $p = .734$).

3.7 | Effects of vitamin D supplementation on lymphocytes and neutrophil count

Five studies reported the effect of vitamin D supplementation on lymphocyte numbers.[35,39–41,45] It was found that vitamin D supplementation did not significantly change lymphocyte numbers compared to the control group (mean difference = −270 [95% CI: −930, 390]; $p = .421$), with a significant heterogeneity ($I^2 = 98.4\%$, $p < .001$). The results of the sensitivity analysis showed that removing any of the studies had no significant effect on the results. Additionally, neither Begg's test ($p = .806$) nor Egger's test ($p = .748$), nor a visual inspection of the funnel plot showed any publication bias.

The effect of vitamin D on neutrophil count was evaluated in three studies.[39–41] According to the meta-analysis, vitamin D

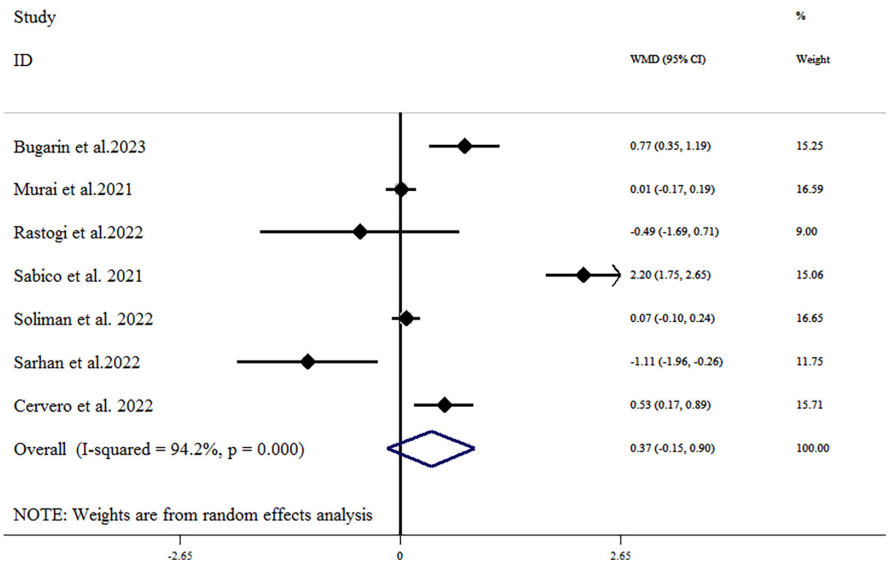

FIGURE 6 Forest plot detailing weighted mean difference and 95% CIs for the impact of vitamin D supplementation on D-dimer concentrations. CI, confidence interval; WMD, weight mean difference.

supplementation did not significantly increase neutrophil count (mean difference = 36.39 [95% CI: −2231.57, 2304.26]; $p = .976$). No new findings were observed in the sensitivity analysis and publication bias test.

3.8 | Grading of evidence

We used the GRADE framework to evaluate the quality of evidence. Based on the GRADE framework, the quality of evidence for hospital length of stay was moderate. The evidence for CRP, ferritin, Hb, and lymphocyte was downgraded to low. Finally, evidence regarding D-dimer, platelet, and neutrophil was identified as very low quality (Table 4).

4 | DISCUSSION

Vitamin D, as a critical fat-soluble vitamin, plays an important role in a large number of metabolic processes within the body. Due to the importance of this vitamin in metabolic processes as well as immune system enhancement, it was one of the main nutritional supplements recommended during the COVID-19 pandemic. However, the evidence regarding the efficacy of this vitamin in managing COVID-19 symptoms remains contradictory.[46,47] The results of the present systematic review and meta-analysis showed that vitamin D supplementation led to a significant reduction in length of hospital stay. Additionally, the results showed that vitamin D supplementation in elderly patients caused a significant decrease in CRP concentrations. However, we did not find any significant effect from vitamin D supplementation in terms of other hematological and immune system biomarkers.

The results of epidemiological studies showed that vitamin D deficiency significantly increases the risk of ARDS.[48,49] Additionally, some studies indicated that an improvement in vitamin D serum concentrations was associated with a reduction in the duration of mechanical ventilation among critically ill patients, particularly those with COVID-19.[50,51] Various reasons can be proposed to explain the mechanisms involved in the shortening of hospital stay after vitamin D supplementation. It has been shown that vitamin D exerts antimicrobial effects by stimulating the production of compounds such as nitric oxide and superoxide.[52,53] Also, some studies have suggested that vitamin D can improve the antimicrobial activity of other proteins, such as cathelicidin.[54] Some studies have shown that vitamin D can strengthen antiviral immunity, which is effective in managing the symptoms of COVID-19 and shortening the length of hospitalization. This includes several concurrent antibacterial processes, such as the activation of cathelicidin and defensins, which can prevent viral entry into cells and decrease viral multiplication.[55] Enhancing autophagy is another characteristic of vitamin D related to both antibacterial and antiviral processes. Autophagy is a crucial biological mechanism that preserves cellular homeostasis by encasing malfunctioning organelles and improperly folded proteins inside the cell membrane.[56]

Unlike the duration of hospitalization, most of the studies reviewed in this article reported that vitamin D supplementation did not have a significant effect on reducing the risk of mortality in COVID-19 patients. In line with our findings, the results of another meta-analysis showed that vitamin D supplementation had no significant effect on reducing the risk of mortality in COVID-19 patients.[26]

In the present study, we could not find significant effects of vitamin D on CRP concentrations, as well as on lymphocyte and neutrophil counts. However, in the subgroup analysis, CRP concentrations in individuals over 60 years old were significantly reduced following vitamin D supplementation. The evaluation of these factors was important because, theoretically, part of the positive effect of vitamin D against COVID-19 is due to its ability to strengthen the host's immune system and suppress inflammatory cytokines in the body.[57,58] However, given that the studied patients differed in terms of their

TABLE 4 GRADE profile of vitamin D supplementation for COVID-19-related outcomes in adults.

	Quality assessment					Summary of findings			
Outcomes	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Number of intervention/control	WMD (95% CI)	Heterogeneity (I^2)	Quality of evidence
Hospital length of stay	No serious limitations	Serious limitations	No serious limitations	No serious limitations	No serious limitations	471/473	−1.16 (−2.23, −0.09)	69.2	⊗⊗⊗○ Moderate
CRP	No serious limitations	Very serious limitations	No serious limitations	No serious limitations	No serious limitations	522/496	−0.48 (−1.30, 0.34)	91.1	⊗⊗○○ Low
Ferritin	No serious limitations	Very serious limitations	No serious limitations	No serious limitations	No serious limitations	225/225	−1.24 (−8.27, 5.80)	79.5	⊗⊗○○ Low
D-dimer	No serious limitations	Very serious limitations	Serious limitations	No serious limitations	No serious limitations	368/347	0.37 (−0.15, 0.9)	94.2	⊗○○○○ Very Low
Platelet	No serious limitations	Very serious limitations	No serious limitations	Serious limitations	No serious limitations	239/208	−1.82 (−61.62, 57.96)	98.1	⊗○○○○ Very Low
Hb	No serious limitations	No serious limitations	Serious limitations	Serious limitations	No serious limitations	210/205	−11 (−0.26, 0.04)	0.0	⊗⊗○○ Low
Lymphocyte	No serious limitations	Very serious limitations	No serious limitations	No serious limitations	No serious limitations	266/236	−270 (−930380)	98.4	⊗⊗○○ Low
Neutrophil	No serious limitations	No serious limitations	Serious limitations	Very serious limitations	No serious limitations	211/205	36.39 (−2231.57, 2304.26)	0.0	⊗○○○○ Very Low

Abbreviations: CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin; WMD, weighted mean difference.

initial vitamin D concentrations and the severity of the disease, this may impact the accuracy of the results. Also, due to the small number of studies, it was not possible to subgroup the studies based on the severity of the COVID-19 disease.

The results of the meta-analysis showed no significant effect of vitamin D supplementation on Hb, ferritin, and D-dimer concentrations, or on platelet counts. It has been reported that D-dimer concentrations >1 μg/L were an independent predictor of mortality in COVID-19 disease.[59] The current study focused on the relevance of blood inflammatory indicators, such as CRP, homocysteine, and D-dimer concentrations, in the prediction of COVID-19. The results of several studies have shown that ferritin concentrations, as an indicator of immune system response, increase in critically ill COVID-19 patients. Elevated ferritin concentrations could trigger a cytokine storm due to their direct immunosuppressive and pro-inflammatory effects.[60–62]

According to our knowledge, this study was the first meta-analysis that examined the effect of vitamin D supplementation on factors such as length of hospital stay and inflammatory and hematological biomarkers among patients with COVID-19. Previous meta-analyses focused mostly on mortality, intensive care unit length of stay, and risk of infection.[25,26] Also, another strength of this study compared to previous meta-analyses was that the strength of the evidence was also examined based on the GRADE framework.

The present study had several limitations that should be considered when interpreting the results. First, there was significant variation among the participants regarding COVID-19 severity, duration, medications, and baseline vitamin D concentrations, which could influence outcomes and contribute to observed heterogeneity. Second, the types and dosages of vitamin D supplementation varied widely across studies, with some using mega doses and others daily doses, complicating direct comparisons and conclusions about optimal dosing. Third, despite our extensive search and rigorous criteria, the number of studies meeting inclusion criteria was relatively small, limiting our ability to conduct detailed subgroup analyses, especially regarding COVID-19 severity. Fourth, focusing exclusively on peer-reviewed papers might have missed relevant findings from preprints or ongoing studies, affecting the comprehensiveness of our meta-analysis. Fifth, most included studies reported high heterogeneity due to differences in study design, population characteristics, intervention protocols, and outcome measures. Although we used random effects models and conducted sensitivity analyses to address this, variability remains a challenge. Lastly, reliance on published data without access to individual patient data limited our ability to perform detailed analyses and adjust for potential confounders at the patient level.

5 | CONCLUSIONS

Our study focused on the impact of vitamin D supplementation in hospitalized COVID-19 patients, aiming to evaluate its effects on various factors. The results revealed a significant reduction in hospital length of stay among patients who received vitamin D supplementation, particularly in those who received a dosage of ≤10 000 IU and in older adult patients over 60 years old. Additionally, we observed a noteworthy decrease in CRP concentrations in older adults aged over 60 years. Despite these positive outcomes, no significant effects of vitamin D were observed on biomarkers such as ferritin, D-dimer, and Hb concentrations, or on lymphocyte, neutrophil, and platelet counts.

AUTHOR CONTRIBUTIONS

FS, Z-a-sG, and JC participated in the design and coordination of the study. MRZR conceived the study and drafted the manuscript. NA, MN, and MRZR searched for the studies, collected, and analyzed the data. MN participated in the design of this study and edited the manuscript. Z-a-sG, JC, MN, and MRZR did the data management and analyzed the data. All authors read and approved the final manuscript.

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The authors have nothing to report.

FUNDING INFORMATION

No funding was received for this study.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

All data analyzed for this study are included in the manuscript and supplementary tables.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No ethical approval and patient consent are required since this study data is based on published literature. This meta-analysis review was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO/, registration No. CRD42023441017).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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