Check for updates

*CORRESPONDENCE
Shubin Guo
✉ shubin007@yeah.net
Xue Mei
✉ meixue91@yeah.net

†These authors have contributed equally to this work

The impact of supplementing vitamin D through different methods on the prognosis of COVID-19 patients: a systematic review and meta-analysis

Xiangqun Zhang[1,2], Junyuan Wu[1,2], Hongmeng Dong[1,2], Na Shang[1,2], Yixuan Li[1,2], Ying Zhang[1,2], Shubin Guo[1,2*†] and Xue Mei[1,2*†]

[1]Emergency Medicine Clinical Research Center, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China, [2]Beijing Key Laboratory of Cardiopulmonary Cerebral Resuscitation, Clinical Center for Medicine in Acute Infection, Capital Medical University, Beijing, China

Objective: To analyze the impact of different methods of Vitamin D administration on the prognosis of COVID-19 patients.

Methods: A comprehensive literature search was conducted across four databases: PubMed, Embase, Web of Science, and Cochrane, up to January 5, 2024. Eligible studies included randomized controlled trials and cohort studies that compared Vitamin D supplementation with control groups in COVID-19 patients. Outcomes of interest were mortality rate, ICU (Intensive Care Unit) admission rate, length of hospital stay, and endotracheal intubation rate. Subgroup analyses were performed based on the dosing regimen (single-dose vs. continuous-dose), total Vitamin D intake within 14 days ($\geq$100,000 IU vs. <100,000 IU), and baseline serum Vitamin D levels (deficient group: 25OHD < 30 ng/mL vs. non-restricted group). A random-effects model was employed for meta-analysis to account for heterogeneity among studies.

Results: A total of 21 studies involving 4,553 participants were included. In terms of mortality, Vitamin D supplementation significantly reduced the mortality rate (RR = 0.72, 95% CI: 0.54−0.94, I^2 = 54%, p = 0.02), with continuous dosing being more effective (RR = 0.53, 95% CI: 0.34−0.83, I^2 = 55%, p = 0.006) compared to single-dose (RR = 0.88, 95% CI: 0.69−1.12, I^2 = 21%, p = 0.3), and lower total doses (<100,000 IU) showing greater benefit (RR = 0.30, 95% CI: 0.21−0.44, I^2 = 0%, p < 0.0001). Mortality was significantly reduced in the Vitamin D-deficient group (25OHD < 30 ng/mL) (RR = 0.73, 95% CI: 0.59−0.89, I^2 = 0%, p = 0.002) but not in the non-restricted group. Regarding ICU admission, supplementation reduced ICU admission rates (RR = 0.58, 95% CI: 0.38−0.88, I^2 = 74%, p = 0.01), with continuous dosing (RR = 0.44, 95% CI: 0.22−0.90, I^2 = 74%, p = 0.02) being more effective than single-dose (RR = 0.79, 95% CI: 0.61−1.03, I^2 = 22%, p = 0.08), and lower doses (<100,000 IU) providing more significant reduction (RR = 0.31, 95% CI: 0.21−0.47, I^2 = 0%, p = 0.001). ICU admission rates were significantly reduced in the Vitamin D-deficient group (RR = 0.63, 95% CI: 0.42−0.93, I^2 = 0%, p = 0.02) but not in the non-restricted group (RR = 0.59, 95% CI: 0.32−1.11, I^2 = 86%, p = 0.1). For length of hospital stay, no significant differences were observed between Vitamin D and control groups (MD = −1, 95% CI: −2.16 to 0.16, p = 0.13), and subgroup analyses by dosing regimen, total dose, and baseline Vitamin D levels also showed no significant differences. Similarly, for

endotracheal intubation, there was no significant difference in intubation rates between groups (RR = 0.78, 95% CI: 0.56−1.08, p = 0.13), and subgroup analyses confirmed no significant effect of different dosing strategies or baseline Vitamin D status on intubation rates.

Conclusion: Vitamin D supplementation improves clinical outcomes in COVID-19 patients by reducing mortality and ICU admission rates, particularly when administered continuously with a total dose of less than 100,000 IU over 14 days, and among those with baseline Vitamin D deficiency (25OHD < 30 ng/mL). However, there were no significant effects on the length of hospital stay or endotracheal intubation rates, regardless of the dosing regimen or baseline Vitamin D levels. These findings emphasize the importance of considering both the total dose over 14 days and baseline Vitamin D status to optimize therapeutic benefits.

1 Introduction

Coronavirus Disease 2019 (COVID-19) is a systemic respiratory disease caused by the novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2:SARS-CoV-2). Since December 2019, COVID-19 has spread globally, affecting millions of people and resulting in hundreds of thousands of deaths. Significant progress has been made in the prevention and treatment of COVID-19 using effective vaccines and antiviral drugs. However, intermittent outbreaks of the novel coronavirus continue worldwide, posing a threat to human health and life. Thus, there is a need to explore effective preventive and therapeutic drugs to aid epidemic control. Previous studies have stated that Vitamin D enhances innate and cellular immunity (1–3) and reduces the survival and replication of respiratory viruses. Besides, numerous studies have established an association between low Vitamin D levels and an increased risk of acute respiratory virus infections (4, 5), which can be reduced through Vitamin D supplementation (6, 7). Moreover, Vitamin D supplementation has also been associated with a reduction in all-cause mortality (8). Since the COVID-19 pandemic began, some studies and meta-analyses have confirmed an association between low blood Vitamin D levels and adverse outcomes in patients with novel coronavirus infection (9–13). Nevertheless, research results regarding using Vitamin D supplementation to improve outcomes in patients with COVID-19 infection are not clear. Previous systematic reviews and meta-analyses of RCTs (randomized controlled trials) have yielded inconsistent results. Some RCT studies have asserted that supplementation with Vitamin D shortens the recovery time for mild to moderate COVID-19 symptoms such as cough and loss of taste (14). Furthermore, there have been reports of reduced severity (length of hospital stay, need for oxygen or respiratory support, etc.) and mortality rates (15–19). However, these findings are inconsistent, since other studies have concluded that supplementation with Vitamin D does not improve mortality rates or any other severity indicators in COVID-19 patients, including the need for endotracheal intubation and length of hospital stay (20–24).

By pooling results from diverse studies, we aim to provide a clearer understanding of the overall impact of Vitamin D supplementation on COVID-19 outcomes. This approach not only enhances the statistical power and generalizability of our findings but also helps to identify patterns and factors that may explain the variability in individual study results. Specifically, this review examines whether immediate Vitamin D supplementation upon hospital admission can improve the prognosis of COVID-19 patients. By comparing the outcomes across various target populations, dosages, and methods of Vitamin D supplementation, we aim to identify the most effective strategies for administering Vitamin D to these patients.

2 Research methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (25) and is registered in PROSPERO website: https://www.crd.york.ac.uk/prospero/ID:CRD42024545945, PROSPERO Registration No: CRD42024545945.

2.1 Search strategy

Searches were conducted in the PubMed, Embase, Web of Science, and Cochrane databases, with search dates ranging from inception to January 5, 2024. The search strategy followed the PICOS principles, primarily focusing on the study population, intervention methods, and research methodology. The search terms and keywords used were: "COVID-19," "2019-nCoV Infection," "infection 2019-nCoV," "SARS-CoV-2 Infection," "SARS CoV 2 Infection," "2019 Novel Coronavirus Disease," "2019 Novel Coronavirus Infection," "COVID-19 Virus Infections," "Infection COVID-19 Virus," "Virus Infection COVID-19," "Coronavirus Disease 2019," "Disease 2019, Coronavirus," "Coronavirus Disease 19," "Severe Acute Respiratory Syndrome Coronavirus 2 Infection," "COVID-19 Virus Disease," "Disease COVID-19 Virus," "Virus Disease, COVID-19," "SARS

Coronavirus 2 Infection," "2019 nCoV Disease," "Disease, 2019-nCoV," "COVID-19 Pandemic," "Pandemic, COVID-19," "Vitamin D," "Calciol," "Vitamin D 3," "Cholecalciferol," "25 HydroxyVitamin D3," "Calcidiol," "25 Hydroxycholecalciferol," "Calcifediol," "Dedrogyl," "Hydropherol," and "Calderol." The specific search strings are provided in Supplementary Table S1. To supplement the research, manual searches were conducted by retrieving bibliographies of relevant reviews and identified articles. If necessary, contact was made with the study authors to obtain additional information.

2.2 Inclusion and exclusion criteria

The inclusion criteria for this meta-analysis were based on the following Population, Intervention, Comparison, Outcomes, and Study design (PICOS) criteria: (1) Participants: admitted patients aged ≥ 18 years with confirmed COVID-19 diagnosis; (2) Intervention: supplementation with Vitamin D; (3) Comparison: no Vitamin D supplementation or lower-dose supplementation; (4) Outcome: mortality, ICU admission, length of hospital stay, or need for endotracheal intubation; (5) Study design: randomized controlled trials or observational studies. Certain articles including reviews, simulation studies, animal studies, letters, conference papers, and case studies were all excluded from this study.

2.3 Data extraction

Data extraction was performed independently by two researchers (Yixuan LI and Ying Zhang). Any discrepancies were resolved by referring to the third author, Zhang Xiangqun, if necessary. The following information was extracted from all eligible studies: first author's name, publication year, country of study, study design, patient characteristics, intervention methods and dosage, and clinical outcomes (mortality rate, ICU admission rate, length of hospital stay, and rate of endotracheal intubation). Data from included studies were entered into a dedicated spreadsheet using Microsoft Excel (Microsoft Corporation, Redmond, WA, United States). In cases of missing data regarding the primary outcomes, we contacted the corresponding authors of the original studies.

2.4 Statistical analysis

All analyses were conducted using Review Manager software version 5.4 (Nordic Cochrane Center, Cochrane Collaboration). A significance level of $p < 0.05$ (two-tailed) was used for all statistical tests. For binary data, risk ratios (OR) and their 95% confidence intervals (CI) were calculated. For continuous data, mean differences (MD) and their 95% CIs were calculated.

In assessing heterogeneity, we selected the model based on its extent. A fixed-effects model was employed when the variability across studies was minimal, suggesting similar effect sizes. Conversely, a random-effects model was used when substantial variability was present, reflecting diverse effect sizes. This approach not only considers the degree of heterogeneity but also accounts for study characteristics such as design, sample demographics, intervention specifics, outcome measurement methods, and contextual factors. By integrating these

considerations, we aimed to accurately reflect both within-study and between-study variations, ensuring a robust and reliable overall effect estimate.

If the effect size was represented by standardized mean differences (MD) along with 95% CIs, the mean (26) and standard deviation (27) of the quartile data were calculated using the provided formulas. Publication bias for each study was assessed by constructing funnel plots of the effect size against standard error. Sensitivity analysis was conducted by systematically excluding individual studies to assess the robustness of the results. Subgroup treatment effects were compared using Cochran's Q test and Higgins's I^2 statistic, with $p < 0.05$ indicating a statistically significant difference.

2.5 Assessment of study quality

The quality of the included literature was assessed by author Hongmeng Dong and Na Shang according to the quality assessment criteria of the Cochrane Collaboration (28). When including randomized controlled trials, the Cochrane Handbook recommends using a revised version of the Cochrane tool, known as the Risk of Bias tool (RoB 2) (29). The RoB 2 tool provides a framework for assessing the risk of bias for individual outcomes in any type of randomized trial. Evaluation criteria include random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other biases. In this study, the reviewers assessed different studies based on the Cochrane Handbook guidelines. The risk of bias for each domain can be categorized into three levels: "low risk," "some concerns," and "high risk." If all domains are assessed as low risk, the overall risk of bias is low. If one or more domains are judged as "some concerns" but none are assessed as high risk, the overall risk of bias is "some concerns." If at least one domain is evaluated as high risk, the overall risk of bias is considered "high risk" (30).

3 Results

3.1 Study selection

The systematic review, selection, and exclusion criteria are summarized in Figure 1. A total of 1,548 articles were retrieved, and after removing duplicate publications, 1,463 articles were included for analysis. After carefully reviewing the titles and abstracts, 225 articles remained. The full texts were all read thoroughly, and then a final selection of 21 articles (14, 16–21, 23, 24, 31–42) was made. These studies included a total of 4,553 patients, with 2,164 patients in the Vitamin D supplementation groups and 2,389 patients in the control groups.

3.2 Study characteristics

There were a total of 21 studies from Spain ($n = 5$), Turkey ($n = 2$), Brazil ($n = 2$), France ($n = 1$), Argentina ($n = 1$), Croatia ($n = 1$), Egypt ($n = 1$), Saudi Arabia ($n = 1$), Belgium ($n = 1$), Italy ($n = 1$), the United States ($n = 1$), Ireland ($n = 1$), Russia ($n = 1$), Thailand ($n = 1$), and India ($n = 1$). Among them, 16 were randomized controlled trials and five were cohort studies.

FIGURE 1
PRISMA flow chart at four levels.
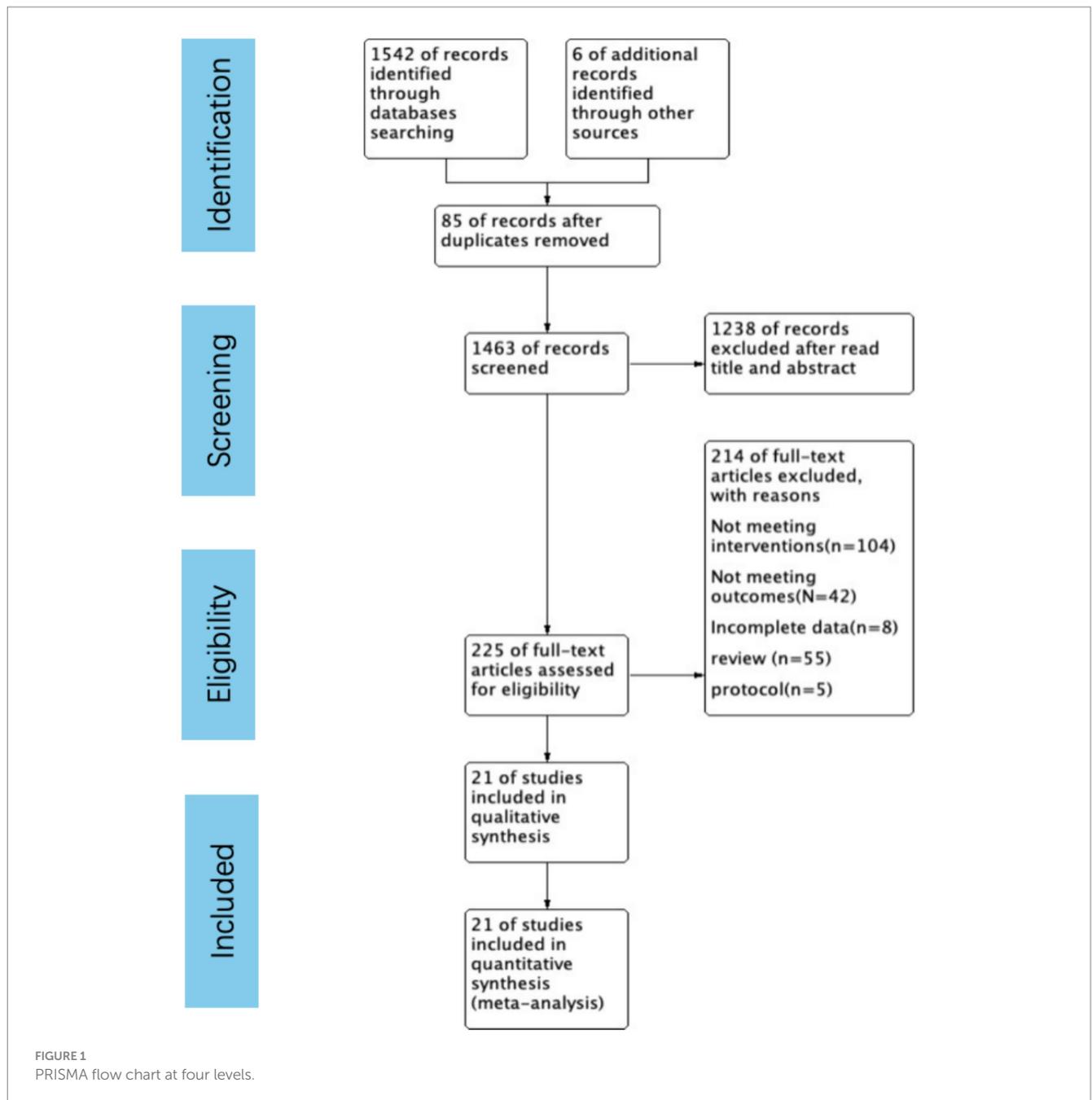
Of the 4,553 participants, 2,164 were in intervention groups and 2,389 were in control groups. The ages of the participants ranged from 31.1 to 93 years. Nineteen studies reported on participant mortality (14, 16–21, 23, 24, 31, 32, 34–36, 38–42), involving 4,115 participants. Thirteen studies reported on ICU admission rates (14, 17, 19, 21, 23, 31, 35, 36, 38–41) and included 2,811 participants. There were 15 studies involving 2,652 participants that assessed the length of hospital stay (14, 17–21, 23, 24, 32–35, 37, 39, 41). Ten studies reported on intubation rates (16, 20, 21, 31–33, 38, 39, 41, 42), with 1,995 participants. Among the 21 clinical trials, the intervention groups received varying daily doses of Vitamin D, ranging from 20 IU to 600,000 IU. In contrast, the control groups in two clinical trials received small doses of Vitamin D orally, relative to the intervention group. The remaining 19 trials used either a placebo or no intervention. In eight clinical trials, the intervention group members were administered Vitamin D as a single dose upon admission, while the remaining 13 trials involved continuous Vitamin D supplementation. The intervention group members of 13 clinical trials received a total Vitamin D dose of greater than or equal to 100,000 IU in the 14 days after hospitalization, while the patients in the remaining eight trials received a total dose of less than 100,000 IU. Table 1 offers further details of the study characteristics.

3.3 Risk of bias

3.3.1 Methods section

To assess the risk of bias in the included studies, we used the Cochrane Risk of Bias (RoB) assessment tool, which evaluates six domains of bias: selection bias, performance bias, detection bias,

TABLE 1 Study characteristics.

Author/year of publication	Study design	Nationality	Participants	Intervention group	Control group	Age intervention group	Age control group	Intervention group female n (%)	Control group female n (%)	Intervention group: Control group (vitamin D supplement method)	Outcomes	Author/year of publication	Study design
Ajay Singh/2024	RCT/NCT04952857	India	90	45	45	54.54 ± 21.44	46.71 ± 12.52	18 (40)	17 (38)	600,000 IU:0	Mortality/tracheal intubation	Ajay Singh/2024	RCT/NCT04952857
Alan L Fernandes/2022	RCT/NCT04449718	Brazil	144	71	73	55.3 ± 14.2	55.7 ± 14.5	34 (47.9)	33 (45.2)	200,000 IU:0	LOS	Alan L Fernandes/2022	RCT/NCT04449718
Cédric Annweiler/2022	RCT/NCT04344041	France	244	122	122	87 (81–92)	89 (83–93)	66 (52)	82 (65)	400,000I:50,000 IU	Mortality/ICU/LOS	Cédric Annweiler/2022	RCT/NCT04344041
Igor H. Murai/2021	RCT/NCT04449718	Brazil	237	119	118	55.7 ± 16.6	61.3 ± 14.4	7 (43.8)	10 (62.5)	200,000 IU:0	Mortality/ICU/LOS/ tracheal intubation	Igor H. Murai/2021	RCT/NCT04449718
Javier Mariani/2021	RCT/NCT04411446	Argentina	218	115	103	59.8 ± 10.7	58.3 ± 10.6	51 (44.3)	52 (50.5)	500,000 IU:0	Mortality/ICU/LOS/ tracheal intubation	Javier Mariani/2021	RCT/NCT04411446
Jorge B Cannata-Andía/2022	RCT/NCT04552951	Spain	543	274	269	59.0 [49.-70]	57.0 [45–67]	93 (33.9)	97 (36.1)	100,000 IU:0	Mortality/ICU/LOS	Jorge B Cannata-Andía/2022	RCT/NCT04552951
Josipa Domazet Bugarin/2023	RCT/NCT05384574	Croatia	152	75	77	65 (59–71)	65.5 (39–82)	23 (30.7)	19 (25.5)	10,000*14 (at least):0	Mortality/length of LOS	Josipa Domazet Bugarin/2023	RCT/NCT05384574
Juan F. Alcala-Diaz/2021	Cohort study/NA	Spain	537	79	458	69 ± 15	67 ± 16	398 (86.9)	26 (32.9)	D1:21280IU; D3, D7:10640IU;10640IU/W:0	Mortality/tracheal intubation	Juan F. Alcala-Diaz/2021	Cohort study/NA
Marta Entrenas Castillo/2020	RCT/NCT04366908	Spain	76	50	26	53.14 ± 10.77	52.77 ± 9.35	23 (46%)	8 (31%)	D1:21280IU; D3, D7:10640IU;10640IU/W:0	Mortality/ICU	Marta Entrenas Castillo/2020	RCT/NCT04366908
Mehmet Güven/2021	Cohort study/NA	Türkiye	175	113	62	74 (60–81)	75 (62–83)	44 (39%)	26 (42%)	300,000 IU:0	Mortality/length of LOS	Mehmet Güven/2021	Cohort study/NA
Miguel Cervero /2022	RCT (pilot study)/ ID01052020	Spain	85	41	44	64 (44–72)	67 (58–75)	14 (32%)	11 (27%)	10,000 IU/D:2000 U/D	Mortality/ICU/LOS/ tracheal intubation	Miguel Cervero/2022	RCT (pilot study)/ ID01052020
MikhailV. Bychinin/2022	RCT/NCT05092698	Russia	106	52	54	64.5 (57–71)	63.5 (54–81)	30 (54.5)	23 (42.59)	D1:60,000IU, D2–14:5,000单 位/天:0	Mortality/length of LOS/tracheal intubation	MikhailV. Bychinin/2022	RCT/NCT05092698
Mustafa Sait Gönen/2021	Cohort study/NA	Türkiye	314	163	151	55.00 ± 16.45	50.23 ± 12.36	52 (34.4%)	80 (49.4%)	D1:100,000 IU; D2–14 10,000 IU/5,000 IU/2,000 IU:0	Mortality/ICU/LOS	Mustafa Sait Gönen/2021	Cohort study/NA
Neven Sarhan/2022	RCT/NCT04738760	Egypt	116	58	58	66.1 ± 11.2	65.7 ± 12.6	20 (34.5%)	12 (20.7%)	200,000 IU:40 IU/D	Mortality/ICU/LOS/ tracheal intubation	Neven Sarhan/2022	RCT/NCT04738760
Pitchaya Dilokpattanamongkol/2024	RCT/ TCTR20210906005	Thailand	294	147	147	47.90 ± 16.77	53.71 ± 18.80	85 (57.80)	72 (49.00)	80 IU/D*14:0	LOS/tracheal intubation	Pitchaya Dilokpattanamongkol/2024	RCT/ TCTR20210906005
Shaun Sabico/2021	RCT/SCTR20061006	Saudi Arabia	69	36	33	46.3 ± 15.2	53.5 ± 12.3	20 (60.6%)	15 (41.7%)	5,000 IU/D*14:1,000 IU/D*14	Mortality/ICU/LOS	Shaun Sabico/2021	RCT/SCTR20061006
Sophie De Niet/2022	RCT/NCT04636086	Belgium	43	21	22	63.24 ± 14.46	68.73 ± 10.97	8 (38%)	12 (54%)	25,000 IU/D*4, D5–14 25,000/W:0	Mortality/ICU/LOS	Sophie De Niet/2022	RCT/NCT04636086
Vito Fiore/2022	Cohort study/NA	Italy	116	58	58	62.5 ± 14.8	62.9 ± 12.8	25 (22.1)	25 (22.1)	100,000 IU/D*2d:0	Mortality/ICU/ tracheal intubation	Vito Fiore/2022	Cohort study/NA

(Continued)

TABLE 1 (Continued)

Author/year of publication	Study design	Nationality	Participants	Intervention group	Control group	Age intervention group	Age control group	Intervention group female n (%)	Control group female n (%)	Intervention group: Control group (vitamin D supplement method)	Outcomes
Xavier Nogues/2021	Cohort study/NA	Spain	838	447	391	61.81 ± 15.5	62.41 ± 17.2	183 (40.9%)	160 (40.9%)	D1:21280IU:D3, D7:106:40IU; 106:40IU/W:0	Mortality/ICU
Yasmine M. Elamir/2022	RCT (pilot study)/ NA	The United States	50	25	25	69 ± 18	64 ± 16	13 (52%)	12 (48%)	20IU/D*14.0	Mortality/ICU/LOS
Zhila Maghbooli/2021	RCT/NCT04386850	Ireland	106	53	53	50 ± 15	49 ± 13	41% (22) 38% (20)	41% (22)	1,000IU/D*14.0	Mortality/ICU/LOS/ tracheal intubation

LOS, Length of Hospital Stay; ICU, Intensive Care Unit.

attrition bias, reporting bias, and other biases. Disagreements during the assessment process were resolved through discussion, and if consensus could not be reached, arbitration was conducted by a third reviewer. We also performed sensitivity analyses to evaluate the robustness of the study results, including the exclusion of studies with high risk of bias and studies with extreme effect sizes or outliers. Meta-analyses were conducted using RevMan 5.3 software, generating an overall risk of bias graph.

3.3.2 Results section

Among the 21 clinical trials included, random sequence generation in 15 randomized controlled trials (RCTs) was deemed low risk of bias, while three cohort studies were classified as high risk, and three were uncertain. Regarding allocation concealment, 16 studies were considered low risk, one did not report allocation methods and was thus deemed uncertain, and four classified as high risk. Four RCTs did not employ blinding, four did not mention blinding, and none of the cohort or observational studies applied blinding. The risk of bias in outcome blinding assessment was generally low in the RCTs; specifically, 11 studies conducted double-blind trials, 5 did not implement double-blinding, and 5 did not clearly specify their blinding procedures. In cohort and observational studies, outcome blinding was not explicitly mentioned. A detailed summary of these findings is provided in Figures 2A,B.

3.3.3 Sensitivity analysis

We performed sensitivity analyses to evaluate the robustness of our findings by excluding studies with a high risk of bias or outliers. The results indicated that the main outcomes, such as mortality and ICU admission rates, remained consistent even after excluding these high-risk or extreme studies. This suggests that our findings are robust and not influenced by individual studies with a high risk of bias or extreme values.

3.4 Meta-analyses

3.4.1 Effect of oral vitamin D on the mortality rate of COVID-19-infected individuals

A To analyze the mortality rate, we included 19 studies with a total of 4,115 participants. We first conducted a heterogeneity test, which revealed an I^2 value greater than 50% ($I^2 = 54\%$, $p = 0.02$). As a result, we employed a random-effects model for statistical analysis. Data analysis showed a total relative risk (RR) of 0.72 (95% CI: 0.54–0.94), with a significance level of $p = 0.02$ (Figure 3).

B Subgrouped by administration method: For the subgroup analysis based on the mortality rate, we categorized the intervention groups into two subgroups according to the Vitamin D intake method: single dose or continuous dose. Studies administering Vitamin D only once upon admission were classified as the single dose group (dose frequency = 1), while those administering multiple doses after admission were classified as the continuous dose group (dose frequency ≧ 2). Seven studies employed a single-dose regimen, while 12 studies used a continuous-dose regimen. The combined relative risk (RR) for the single-dose subgroup of the intervention group

A

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ajay Singh2024	+	+	+	+	+	+	+
Alan L Fernandes 2022	+	+	+	+	+	+	+
Ce´dric Annweiler 2022	+	+	−	−	+	+	+
Igor H. Murai, 2021	+	+	+	+	+	+	+
Javier Mariani 2021	+	+	+	+	+	+	+
Jorge B Cannata–Andía 2022	+	+	+	+	+	+	+
Josipa Domazet Bugarin 2023	?	+	?	+	+	+	+
Juan F. Alcala–Diaz 2021	−	−	−	−	+	+	+
Marta Entrenas Castillo2020	+	+	+	+	+	+	+
Mehmet Güven 2021	?	?	?	−	+	?	+
Miguel Cervero 2022	+	+	+	−	+	+	+
MikhailV. Bychinin 2022	+	+	+	+	+	?	+
Mustafa Sait Gönen 2021	−	−	−	?	?	+	+
Neven Sarhan 2022	+	+	?	?	+	+	+
Pitchaya Dilokpattanamongkol 2024	+	+	?	?	+	+	+
Shaun Sabico 2021	+	+	−	−	+	+	+
Sophie De Niet 2022	+	+	+	+	+	+	+
Vito Fiore 2022	−	−	+	?	+	?	+
Xavier Nogues 2021	?	−	?	?	+	+	+
Yasmine M. Elamir 2022	+	+	−	−	?	+	+
Zhila Maghbooli 2021	+	+	+	+	+	+	+

FIGURE 2 (Continued)
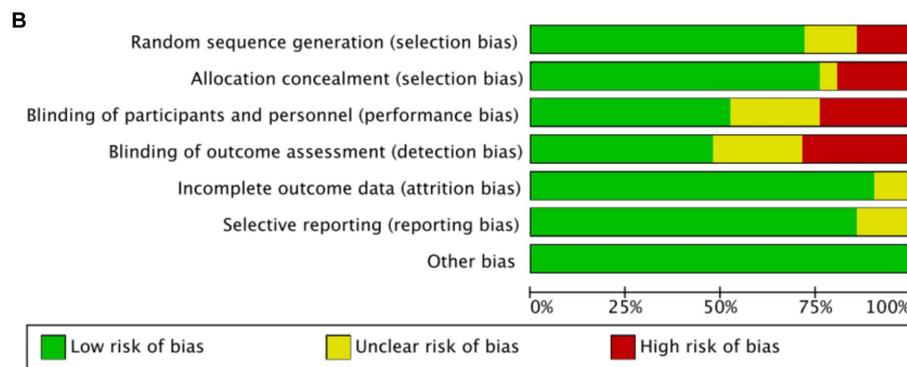
FIGURE 2
(A) Risk of bias summary: review authors' judgments about each risk of bias item for each included study. **(B)** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

was 0.88 (95% CI: 0.69–1.12), with an I^2 value of 21% and $p = 0.3$, indicating no statistically significant reduction in mortality. Conversely, the RR for the continuous-dose subgroup was 0.53 (95% CI: 0.34–0.83), with an I^2 value of 55% and $p = 0.006$, showing a statistically significant reduction in mortality (Figure 4).

C Subgrouped by dosage: For the second subgroup analysis based on mortality rate, we categorized the intervention groups according to the total Vitamin D intake. This was calculated according to the total dosage during the first 14 days of hospitalization. There were two groups: ≥100,000 International Units (IU and <100,000 IU). Of the selected studies, 12 administered total doses of ≥100,000 IU of Vitamin D in the intervention group, while seven administered <100,000 IU. The combined RR value for the ≥100,000 IU intake group was 0.85 (95% CI: 0.71–1.02), with an I^2 value of 1% and $p = 0.07$, indicating no statistically significant reduction in mortality. In contrast, the RR for the <100,000 IU intake group was 0.30 (95% CI: 0.21–0.44), with an I^2 value of 0% and $p < 0.0001$, showing a statistically significant reduction in mortality (Figure 5).

D Subgrouped by serum Vitamin D concentrations upon admission: For the third subgroup analysis based on mortality rate, we classified the studies according to the serum Vitamin D concentration restrictions applied to the included patients. The groups were divided into those with Vitamin D deficiency (serum 25 (OH)D (25-Hydroxyvitamin D) < 30 ng/mL) and those with no restrictions on serum Vitamin D concentrations. Of the selected studies, 9 limited inclusion to patients with serum 25 (OH) D < 30 ng/mL, while the other 10 studies had no restrictions on serum 25 (OH) D levels. The combined risk ratio (RR) for the group with serum 25 (OH) D < 30 ng/mL was 0.73 (95% CI: 0.59–0.89), with an I^2 value of 0% and $p = 0.002$, indicating a statistically significant reduction in mortality. In contrast, the RR for the group with no restrictions on serum 25 (OH) D concentrations was 0.73 (95% CI: 0.46–1.15), with an I^2 value of 73% and $p = 0.18$, suggesting no statistically significant reduction in mortality (Figure 6).

3.4.2 Effect of oral vitamin D dosage on the risk of ICU admission

A When assessing ICU admission rate as an outcome, a total of 13 studies involving 2,811 participants were included. The pooled relative risk (RR) was 0.58 (95% CI: 0.38–0.88), with significant heterogeneity ($I^2 = 74\%$, $p = 0.01$) (Figure 7).

B Subgrouped by administration method: Of the included studies, four applied single-dose administration, while nine used continuous administration. The combined RR value for the single-dose Vitamin D subgroup was 0.79 (95% CI: 0.61–1.03), with low heterogeneity ($I^2 = 22\%$, $p = 0.08$), indicating no statistically significant reduction in ICU admission rates. In contrast, the combined RR for the continuous administration subgroup was 0.44 (95% CI: 0.22–0.90), with substantial heterogeneity ($I^2 = 74\%$, $p = 0.02$), showing a statistically significant reduction in ICU admission rates (Figure 8).

C Subgrouped by dosage: The studies were further subdivided according to the Vitamin D dosage. Seven studies utilized Vitamin D dosages of ≥100,000 IU, while six offered dosages of <100,000 IU. The combined RR value for the ≥100,000 IU subgroup over 14 days was 0.86 (95% CI: 0.6–1.24), with moderate heterogeneity ($I^2 = 54\%$, $p = 0.42$), indicating no statistically significant reduction in ICU admission rates. However, the combined RR for the <100,000 IU subgroup was 0.31 (95% CI: 0.21–0.47), exhibiting low heterogeneity ($I^2 = 0\%$, $p = 0.001$), showing a statistically significant reduction in ICU admission rates (Figure 9).

D Subgrouped by serum Vitamin D concentrations upon admission: Among the selected studies, 6 restricted inclusion to patients with serum 25 (OH) D levels <30 ng/mL, while the remaining 7 studies imposed no restrictions on serum 25 (OH) D levels. The pooled risk ratio (RR) for the group with serum 25 (OH) D < 30 ng/mL was 0.63 (95% CI: 0.42–0.93), $I^2 = 0\%$, and $p = 0.02$, indicating a statistically significant reduction in ICU admission. Conversely, for the group with no restrictions on serum 25 (OH) D concentrations, the RR was 0.59 (95% CI: 0.32–1.11), ($I^2 = 86\%$) and $p = 0.1$, indicating no statistically significant reduction in ICU admission (Figure 10).

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
Ajay Singh2024	11	45	20	45	7.9%	0.55 [0.30, 1.01]	
Ce´dric Annweiler 2022	17	122	21	122	8.1%	0.81 [0.45, 1.46]	
Igor H. Murai, 2021	9	119	6	118	4.7%	1.49 [0.55, 4.05]	
Javier Mariani 2021	5	115	2	103	2.3%	2.24 [0.44, 11.29]	
Jorge B Cannata–Andía 2022	22	274	15	269	7.6%	1.44 [0.76, 2.72]	
Josipa Domazet Bugarin 2023	23	75	27	77	9.5%	0.87 [0.55, 1.38]	
Juan F. Alcala–Diaz 2021	4	79	90	458	4.9%	0.26 [0.10, 0.68]	
Marta Entrenas Castillo2020	0	50	2	26	0.8%	0.11 [0.01, 2.13]	
Mehmet Güven 2021	43	113	30	62	10.7%	0.79 [0.56, 1.11]	
Miguel Cervero 2022	1	41	1	44	0.9%	1.07 [0.07, 16.60]	
MikhailV. Bychinin 2022	19	52	27	54	9.6%	0.73 [0.47, 1.14]	
Mustafa Sait Gönen 2021	9	163	4	151	3.9%	2.08 [0.66, 6.63]	
Neven Sarhan 2022	26	58	30	58	10.4%	0.87 [0.59, 1.27]	
Shaun Sabico 2021	1	36	0	33	0.7%	2.76 [0.12, 65.41]	
Sophie De Niet 2022	1	21	3	22	1.4%	0.35 [0.04, 3.10]	
Vito Fiore 2022	3	58	11	58	3.6%	0.27 [0.08, 0.93]	
Xavier Nogues 2021	21	447	62	391	9.3%	0.30 [0.18, 0.48]	
Yasmine M. Elamir 2022	0	25	3	25	0.8%	0.14 [0.01, 2.63]	
Zhila Maghbooli 2021	3	53	5	53	3.0%	0.60 [0.15, 2.38]	
Total (95% CI)		**1946**		**2169**	**100.0%**	**0.72 [0.54, 0.94]**	
Total events	218		359				

Heterogeneity: Tau² = 0.15; Chi² = 39.53, df = 18 (P = 0.002); I² = 54%
Test for overall effect: Z = 2.41 (P = 0.02)

0.01 0.1 1 10 100
Favours [Vitamin D] Favours [control]

FIGURE 3
Forest plot of mortality rate.

Study or Subgroup	vitamin D Events	vitamin D Total	Control Events	Control Total	Weight	Risk Ratio M–H, Random, 95% CI	Risk Ratio M–H, Random, 95% CI
3.2.3 single-dose group							
Ajay Singh2024	11	45	20	45	7.9%	0.55 [0.30, 1.01]	
Ce´dric Annweiler 2022	17	122	21	122	8.1%	0.81 [0.45, 1.46]	
Igor H. Murai, 2021	9	119	6	118	4.7%	1.49 [0.55, 4.05]	
Javier Mariani 2021	5	115	2	103	2.3%	2.24 [0.44, 11.29]	
Jorge B Cannata–Andía 2022	22	274	15	269	7.6%	1.44 [0.76, 2.72]	
Mehmet Güven 2021	43	113	30	62	10.7%	0.79 [0.56, 1.11]	
Neven Sarhan 2022	26	58	30	58	10.4%	0.87 [0.59, 1.27]	
Subtotal (95% CI)		**846**		**777**	**51.7%**	**0.88 [0.69, 1.12]**	
Total events	133		124				

Heterogeneity: Tau² = 0.02; Chi² = 7.56, df = 6 (P = 0.27); I² = 21%
Test for overall effect: Z = 1.04 (P = 0.30)

3.2.4 continuous-dose group							
Josipa Domazet Bugarin 2023	23	75	27	77	9.5%	0.87 [0.55, 1.38]	
Juan F. Alcala–Diaz 2021	4	79	90	458	4.9%	0.26 [0.10, 0.68]	
Marta Entrenas Castillo2020	0	50	2	26	0.8%	0.11 [0.01, 2.13]	
Miguel Cervero 2022	1	41	1	44	0.9%	1.07 [0.07, 16.60]	
MikhailV. Bychinin 2022	19	52	27	54	9.6%	0.73 [0.47, 1.14]	
Mustafa Sait Gönen 2021	9	163	4	151	3.9%	2.08 [0.66, 6.63]	
Shaun Sabico 2021	1	36	0	33	0.7%	2.76 [0.12, 65.41]	
Sophie De Niet 2022	1	21	3	22	1.4%	0.35 [0.04, 3.10]	
Vito Fiore 2022	3	58	11	58	3.6%	0.27 [0.08, 0.93]	
Xavier Nogues 2021	21	447	62	391	9.3%	0.30 [0.18, 0.48]	
Yasmine M. Elamir 2022	0	25	3	25	0.8%	0.14 [0.01, 2.63]	
Zhila Maghbooli 2021	3	53	5	53	3.0%	0.60 [0.15, 2.38]	
Subtotal (95% CI)		**1100**		**1392**	**48.3%**	**0.54 [0.34, 0.85]**	
Total events	85		235				

Heterogeneity: Tau² = 0.26; Chi² = 25.18, df = 11 (P = 0.009); I² = 56%
Test for overall effect: Z = 2.65 (P = 0.008)

Total (95% CI)		**1946**		**2169**	**100.0%**	**0.72 [0.54, 0.94]**	
Total events	218		359				

Heterogeneity: Tau² = 0.15; Chi² = 39.53, df = 18 (P = 0.002); I² = 54%
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Chi² = 3.47, df = 1 (P = 0.06), I² = 71.2%

0.01 0.1 1 10 100
Favours vitain D Favours [control]

FIGURE 4
Forest plot of mortality rate by administration method subgroup.

FIGURE 5
Forest plot of mortality rate by total Vitamin D dosage intake within the first 14 days of hospitalization.

3.4.3 Effect of oral vitamin D on hospitalization duration

A There were 15 studies involving 2,652 participants that assessed hospitalization duration as an outcome. The pooled results showed no significant difference between the Vitamin D group and the control group, with a standardized mean difference (MD) of −1 (95% CI: −2.16 to 0.16; $p = 0.13$) (Figure 11).

B Subgrouped by administration method: Six studies administered Vitamin D in single doses, while nine studies offered them continuously. There was a negligible difference between the single-dose subgroup and the control group, with an MD of −1.11 (95% CI: −2.35 to 0.13; $p = 0.08$). Similarly, there was no significant difference between the subgroup receiving continuous Vitamin D administration and the control group, with an MD of −0.50 (95% CI: −2.23 to 1.22; $p = 0.57$) (Figure 12).

C Subgrouped by dosage: Ten studies administered Vitamin D dosages of ≥100,000 IU, while three studies gave <100,000 IU. There was no significant difference between the subgroup receiving dosages of ≥100,000 IU and the control group, with an MD of −0.91 (95% CI: −1.83 to 0.01; $p = 0.05$). Similarly, there was an insignificant difference between the subgroup receiving <100,000 IU and the control group, with an MD of −0.97 (95% CI, −3.24 to 1.29; $p = 0.4$) (Figure 13).

D Subgrouped by serum Vitamin D concentrations upon admission: Among the selected studies, 8 restricted inclusion

to patients with serum 25(OH) D levels <30 ng/mL, while the remaining 7 studies imposed no restrictions on serum 25(OH) D levels, to evaluate the impact on the length of hospital stay. The pooled mean difference for the group with serum 25(OH) D < 30 ng/mL was −0.62 (95% CI: −2.17 to 0.92), with an I^2 of 72% and $p = 0.43$. For the group with no restrictions on serum 25(OH)D concentrations, the mean difference was −0.25 (95% CI: −1.12 to 0.62), with an I^2 of 75% and $p = 0.57$ (Figure 14).

3.4.4 Impact of oral vitamin D on endotracheal intubation rate

A In the analysis of endotracheal intubation, 10 studies involving 1,995 participants were included. The results indicated no significant difference between the Vitamin D group and the control group, with an RR value of 0.78 (95% CI: 0.56, 1.08; $p = 0.13$) (Figure 15).

B Subgrouped by administration method: Five studies involved one-time doses and five studies utilized continuous dosing. There was a negligible difference between the intervention group with one-time Vitamin D dosage and the control group. Specifically, the RR value was −0.10 (95% CI, −0.23, 0.03; $p = 0.13$). Similarly, no significant difference was observed between the intervention group with continuous Vitamin D dosage and the control group, with an RR value of −0.00 (95% CI: −0.04 to 0.04; $p = 0.87$) (Figure 16).
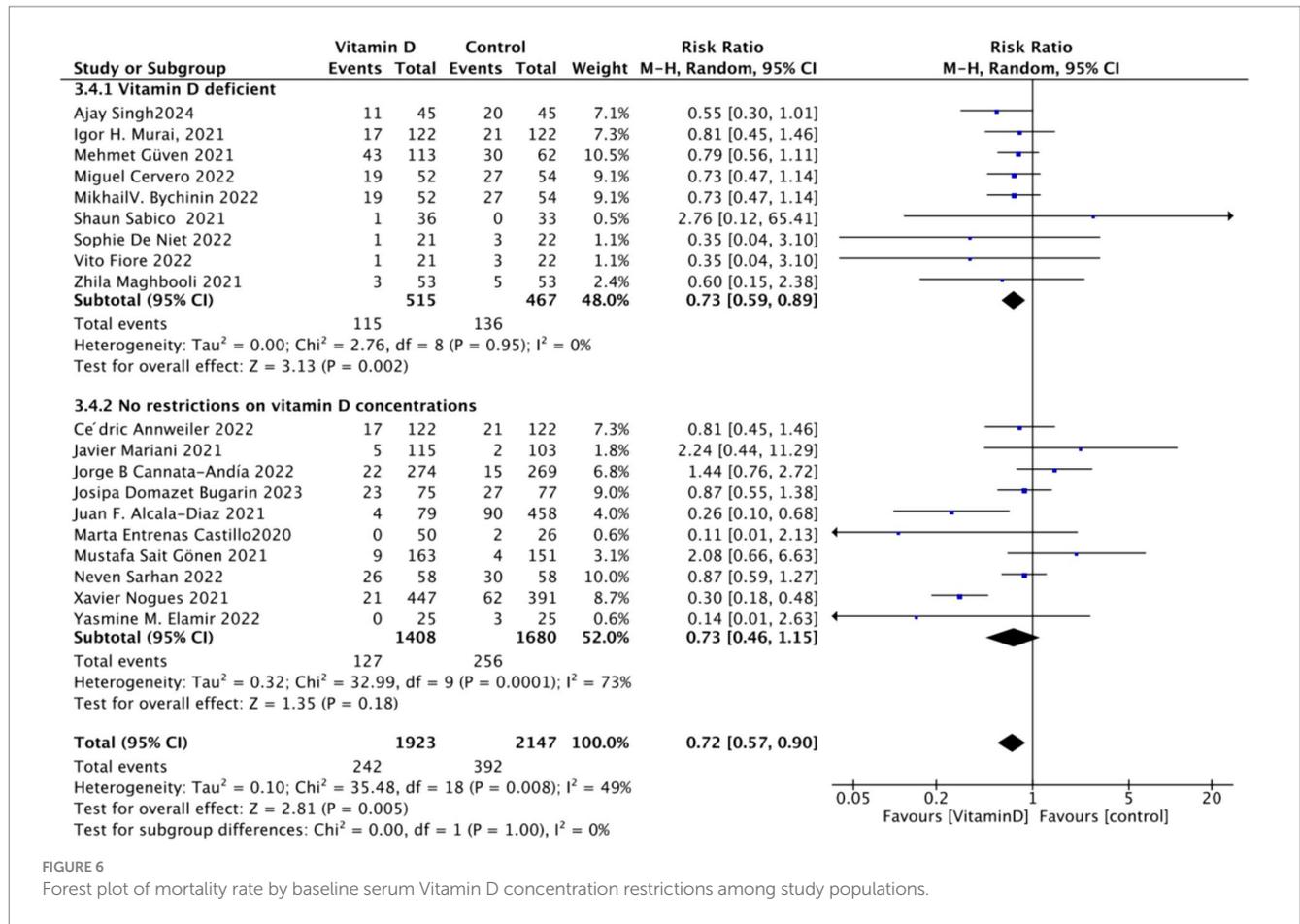
FIGURE 6
Forest plot of mortality rate by baseline serum Vitamin D concentration restrictions among study populations.
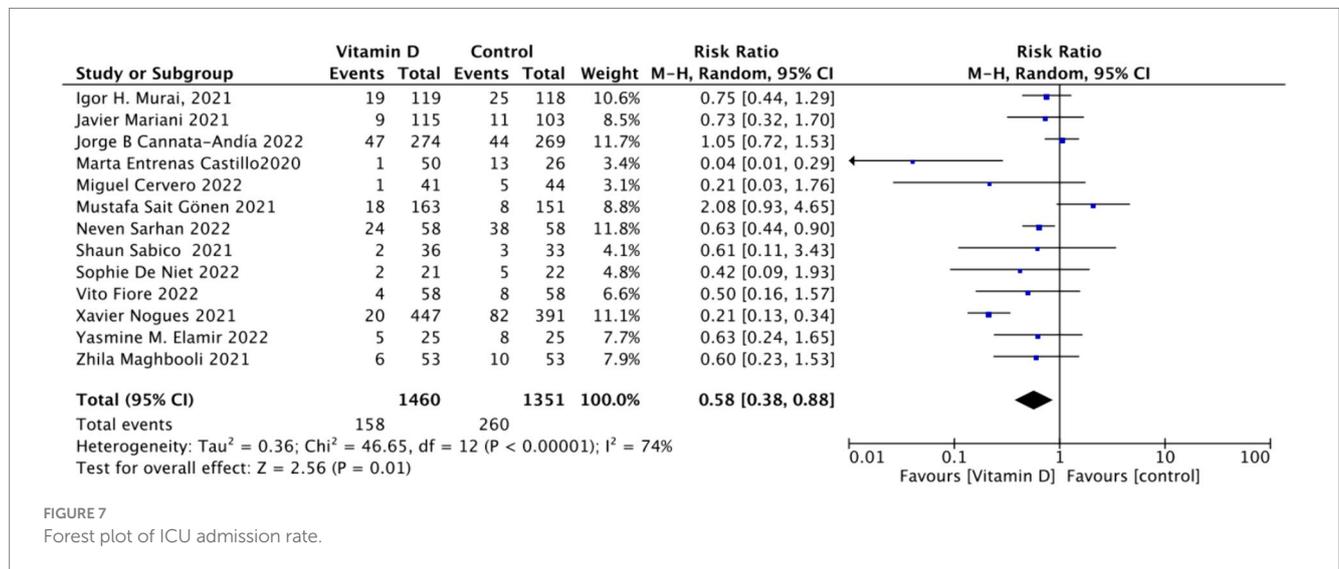
FIGURE 7
Forest plot of ICU admission rate.

C Subgrouped by dosage: Six studies included intervention groups with Vitamin D dosages ≥100,000 IU, while four studies involved groups with dosages <100,000 IU. There were no significant differences between the intervention group with dosages of ≥100,000 IU and the control group. The RR value was 0.59 (95% CI: 0.32, 1.09; $p = 0.09$). Equally, no noticeable differences were observed between the

intervention group with Vitamin D dosages of <100,000 IU and the control group, with an RR value of 0.96 (95% CI: 0.39–2.35; $p = 0.93$) (Figure 17).

D Subgrouped by serum Vitamin D concentrations upon admission: Among the selected studies, 6 restricted inclusion to patients with serum 25(OH)D levels <30 ng/mL, while the remaining 4 studies imposed no restrictions on serum 25(OH)
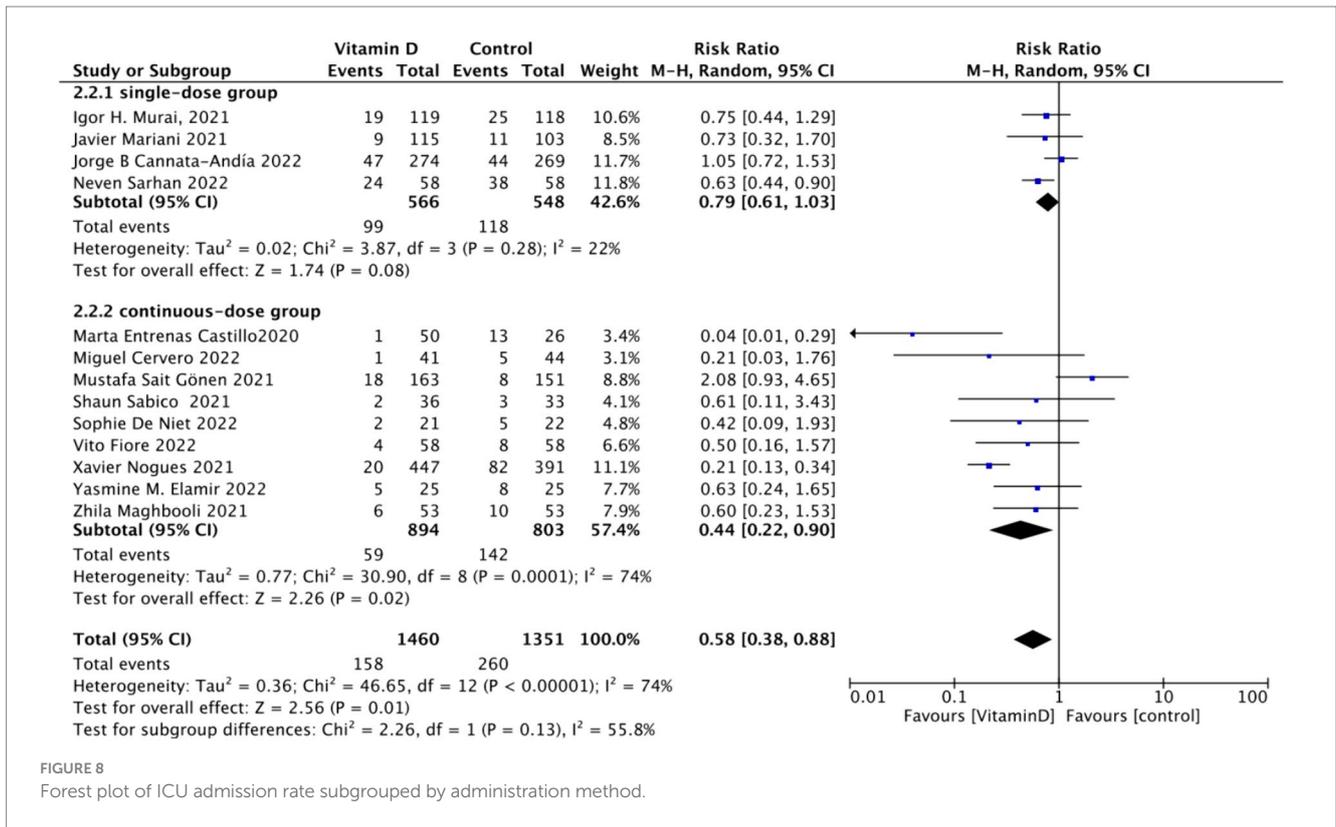
FIGURE 8
Forest plot of ICU admission rate subgrouped by administration method.
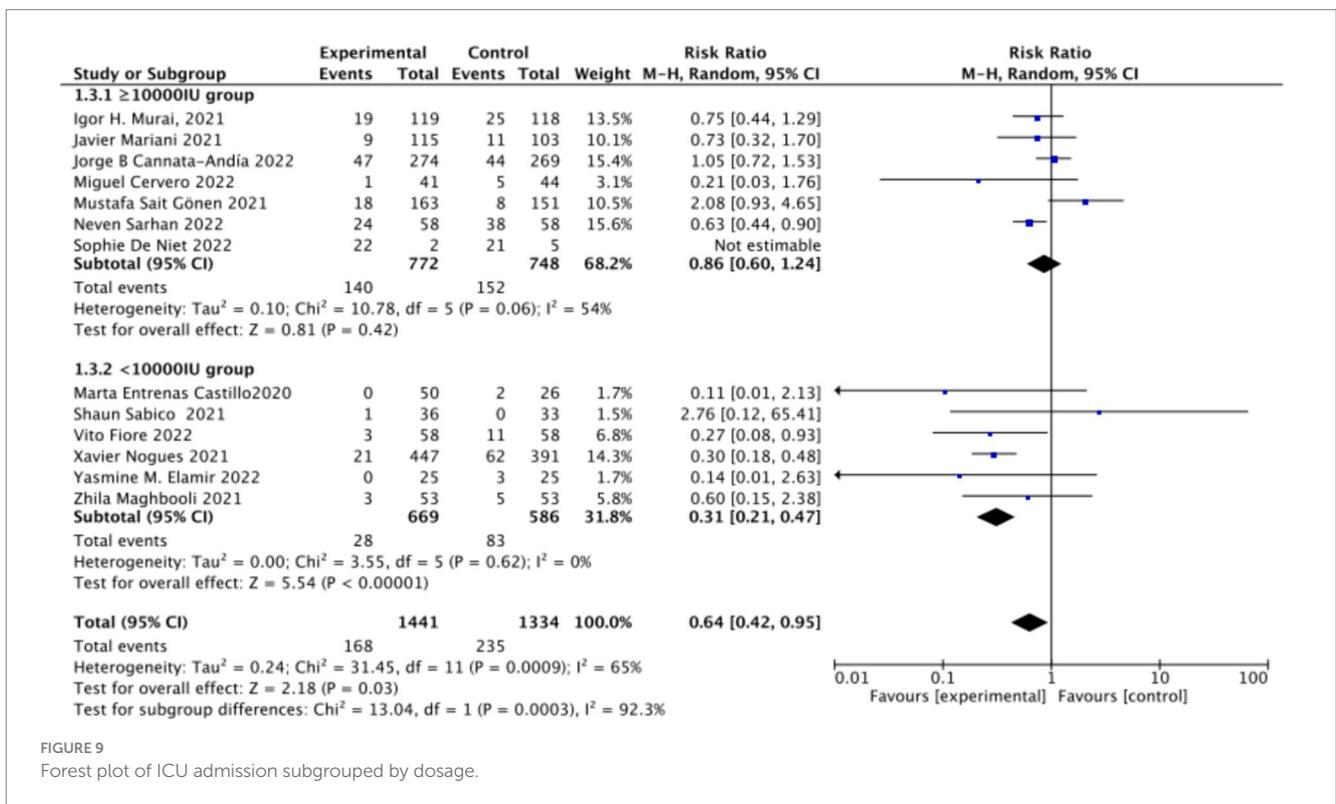
FIGURE 9
Forest plot of ICU admission subgrouped by dosage.

D levels, to evaluate the impact on the of intubation. The pooled risk ratio (RR) for the group with serum 25(OH) D < 30 ng/mL was 0.92 (95% CI: 0.61 to 1.37), with an I^2 of 36%

and $p = 0.67$. For the group with no restrictions on serum 25(OH)D concentrations, the RR was 0.78 (95% CI: 0.34 to 1.80), with an I^2 of 74% and $p = 0.57$ (Figure 18).
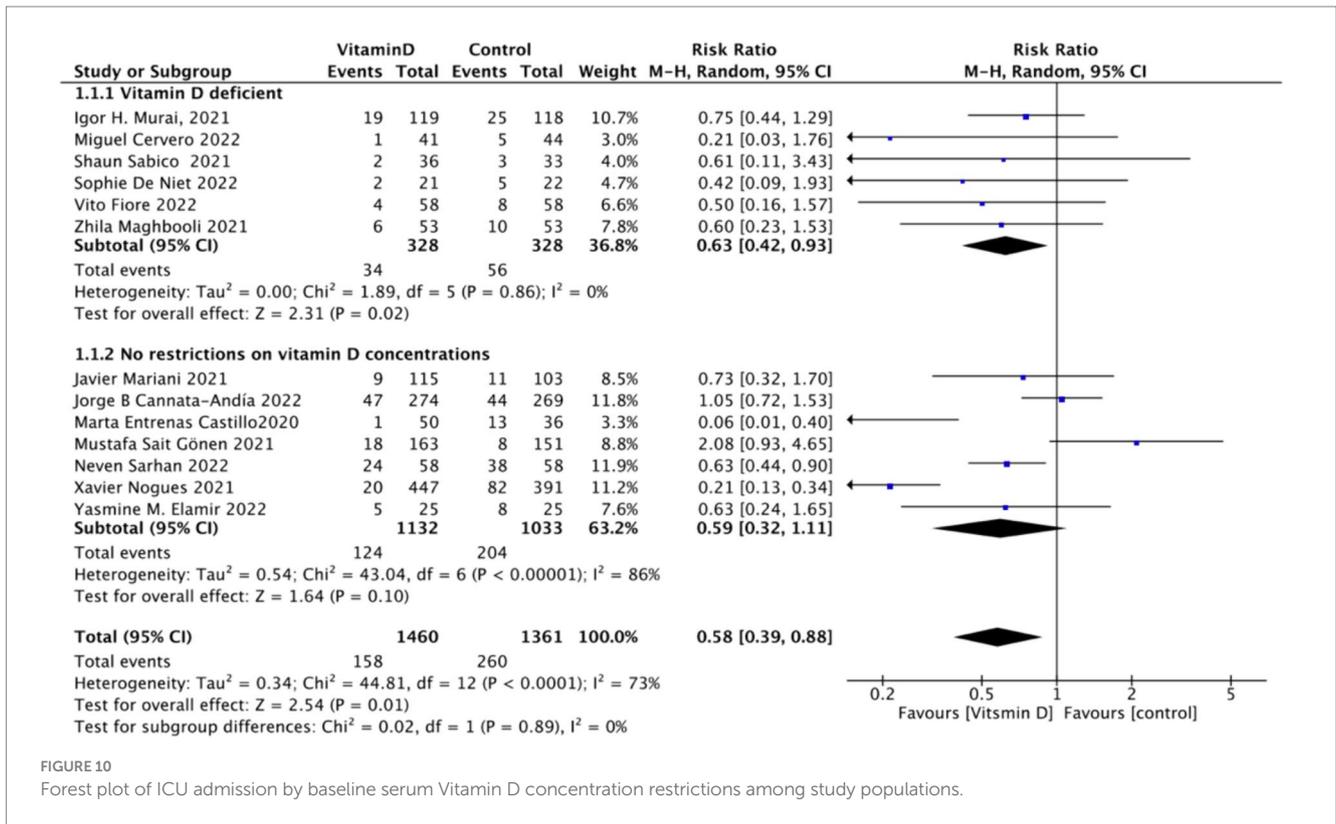
FIGURE 10
Forest plot of ICU admission by baseline serum Vitamin D concentration restrictions among study populations.
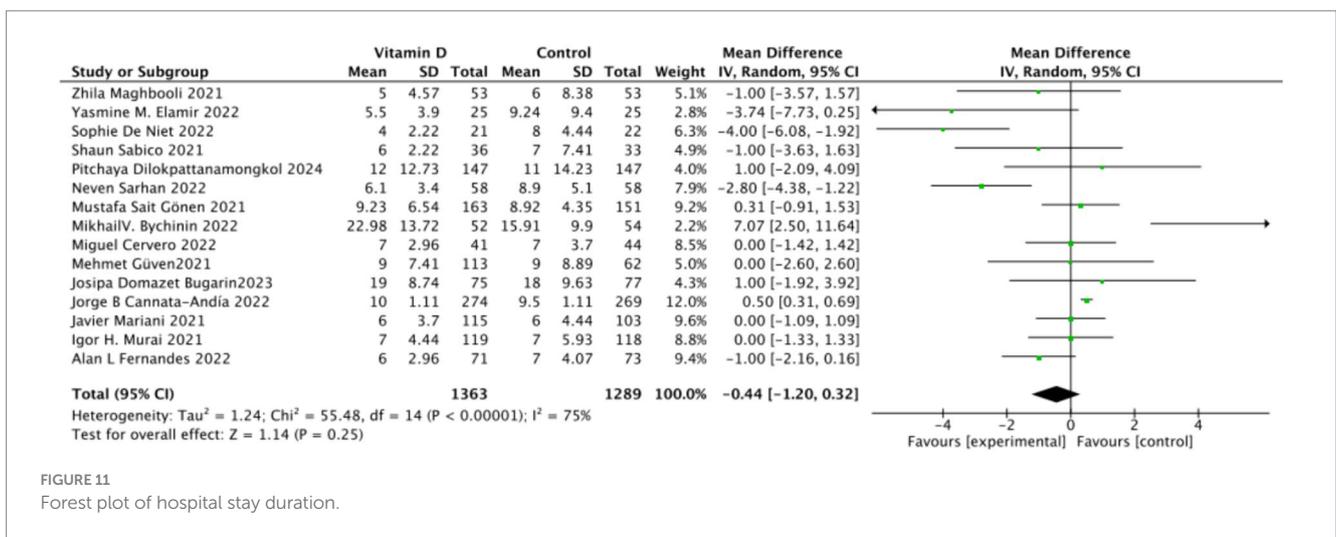
FIGURE 11
Forest plot of hospital stay duration.

3.5 Administration method

Continuous, multiple-dose administration resulted in lower heterogeneity ($I^2 = 55\%$ for mortality, $I^2 = 74\%$ for ICU admissions) and significant reductions in both mortality ($p = 0.006$) and ICU admissions ($p = 0.02$). Single-dose administration, which showed higher heterogeneity and no significant improvements, underscores that continuous dosing provides more consistent and effective results.

Total Dosage Over 14 Days: Lower dosages (<100,000 IU) led to reduced heterogeneity ($I^2 = 0\%$ for both mortality and ICU admissions) and significant outcome improvements ($p < 0.0001$ for

mortality, $p = 0.001$ for ICU admissions). Higher dosages ($\geq 100,000$ IU) showed moderate heterogeneity and did not achieve similar benefits, indicating that moderate dosing not only improves outcomes but also provides more consistent results.

Baseline Vitamin D Status: Patients with Vitamin D deficiency (25OHD < 30 ng/mL) showed low heterogeneity and significant benefits from supplementation, including reduced mortality ($I^2 = 0\%$, $p = 0.002$) and ICU admission rates ($I^2 = 0\%$, $p = 0.02$). In contrast, high heterogeneity in the no-restriction group ($I^2 = 73\%$ for mortality, $I^2 = 86\%$ for ICU admission) with no significant benefits suggests that baseline deficiency is crucial for achieving effective outcomes (Table 2).
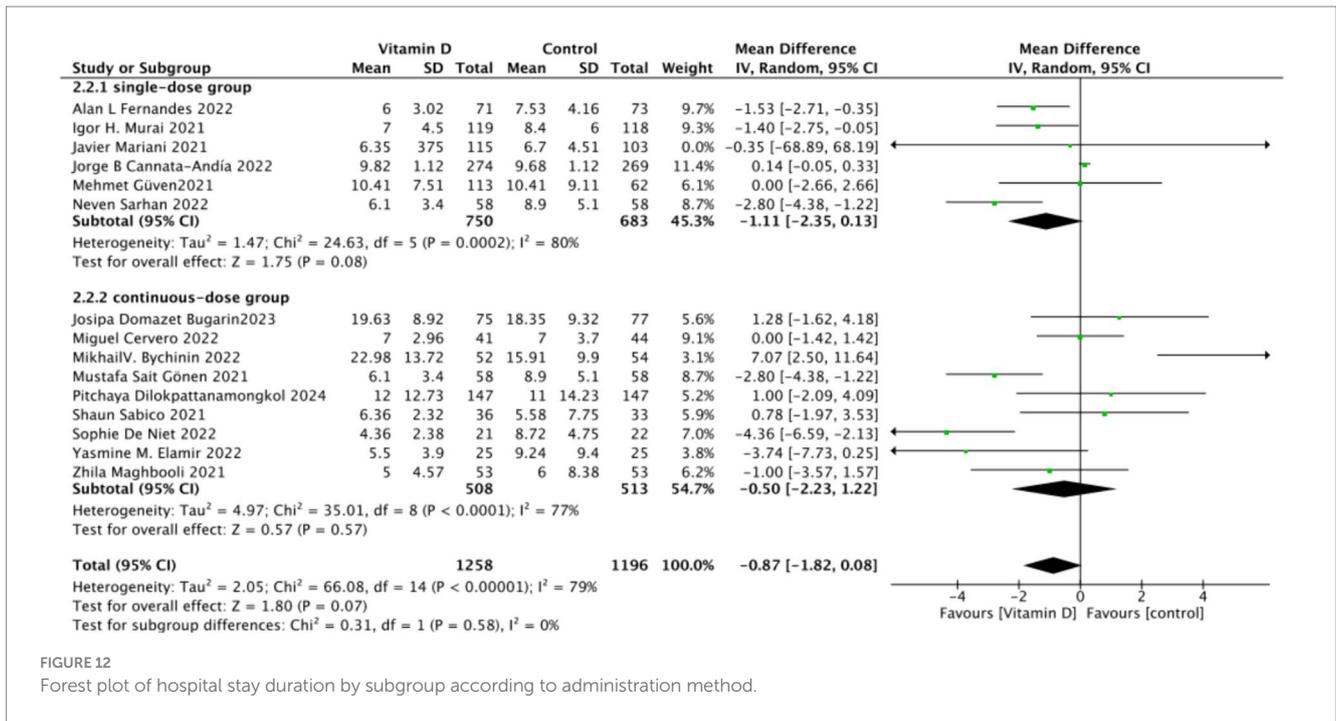
FIGURE 12
Forest plot of hospital stay duration by subgroup according to administration method.
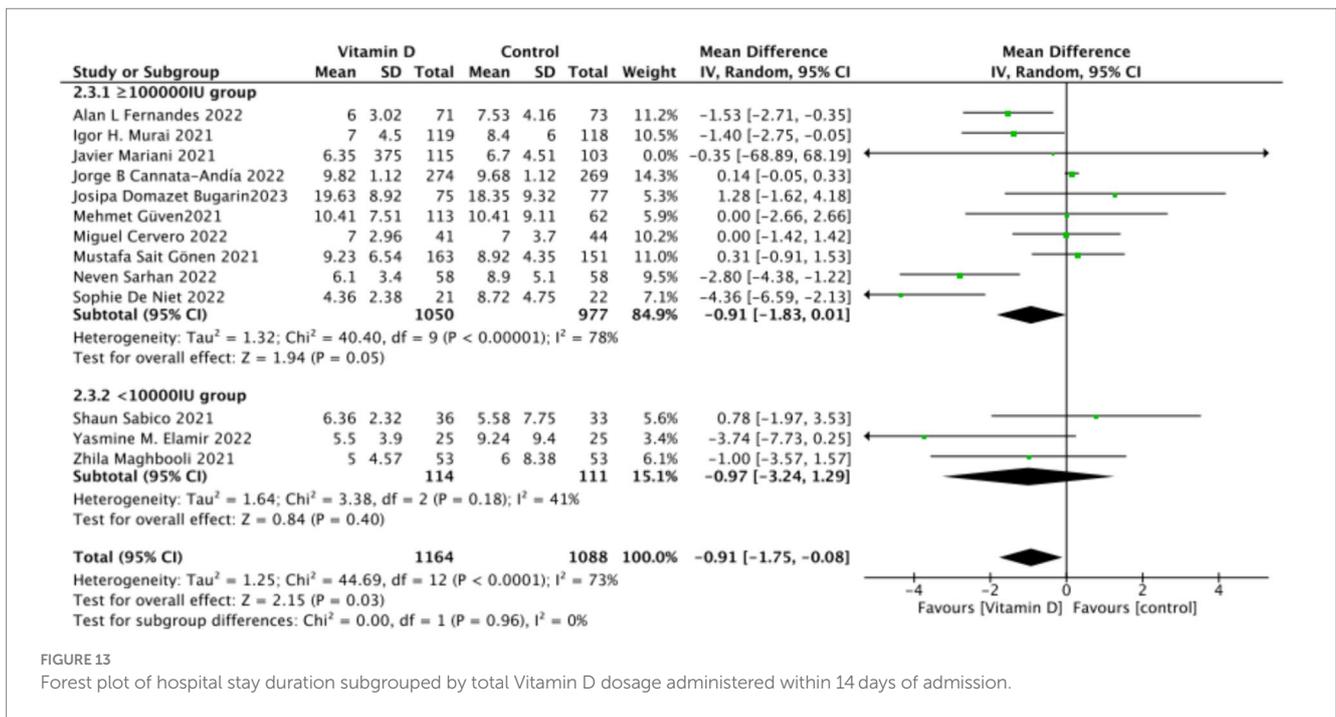
FIGURE 13
Forest plot of hospital stay duration subgrouped by total Vitamin D dosage administered within 14 days of admission.

3.6 Bias analysis

The funnel plots (Figures 19–22) are approximately symmetrical on both sides, indicating the absence of meaningful publication bias. Subsequently, we conducted a sensitivity analysis, systematically assessing the impact of removing individual studies. We established that no single study exerted substantial influence on the overall results, suggesting that our findings were robust.

4 Discussion

In this systematic review and meta-analysis, we investigated the impact of oral Vitamin D supplementation on the prognosis of COVID-19 patients across 21 studies involving 4,553 individuals. Our findings suggest that Vitamin D administration following COVID-19 infection leads to improved mortality rates and reduced ICU admission rates. However, we did not observe
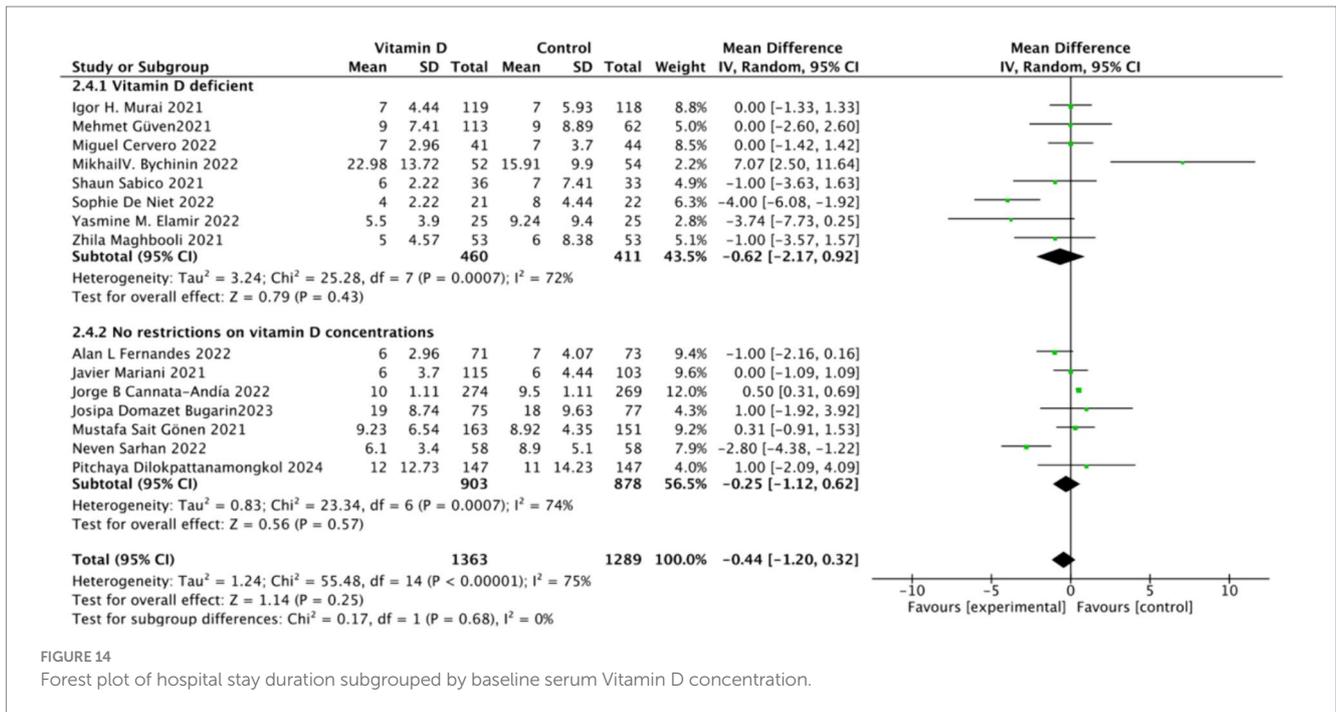
FIGURE 14
Forest plot of hospital stay duration subgrouped by baseline serum Vitamin D concentration.
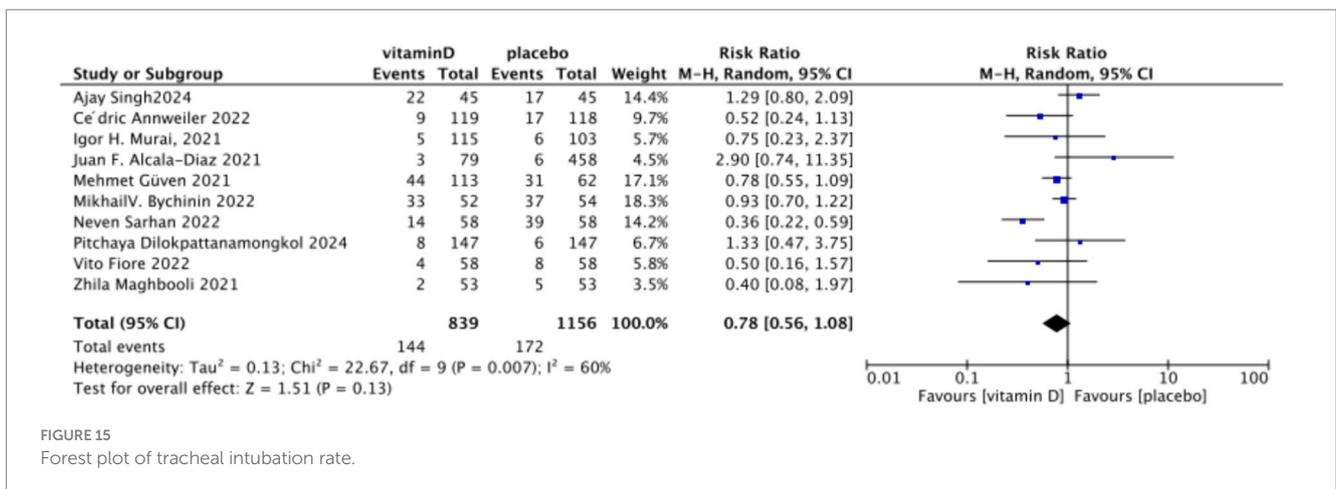
FIGURE 15
Forest plot of tracheal intubation rate.

any significant effects on hospital stay duration or intubation rates.

To achieve the optimal therapeutic effect of Vitamin D supplementation, we conducted various subgroup analyses. Patients were classified based on three main criteria: the mode of Vitamin D administration upon hospital admission (single-dose versus multiple-dose), the total Vitamin D dosage over 14 days (≥100,000 IU versus <100,000 IU), and baseline Vitamin D levels (serum 25(OH)D < 30 ng/mL versus no restriction). Our analysis revealed that continuous, multiple-dose administration and total dosages of <100,000 IU over 14 days were strongly associated with reduced mortality and ICU admission rates. In contrast, single-dose administration and total dosages ≥100,000 IU did not show noticeable improvements in outcomes. Furthermore, patients with baseline Vitamin D deficiency (25OHD < 30 ng/mL) experienced significant reductions in mortality and ICU admission rates following supplementation, while those without baseline restrictions did not show the same level of benefit.

By implementing strategic subgroup analyses, we effectively reduced heterogeneity and achieved more consistent results. For example, grouping patients by total Vitamin D dosage over 14 days and baseline Vitamin D levels significantly lowered heterogeneity. The <100,000 IU total dose subgroup and the Vitamin D deficiency subgroup (25OHD < 30 ng/mL) frequently showed heterogeneity values of zero in mortality and ICU admission outcomes (Table 2). These findings suggest that lower, continuous doses of Vitamin D are more effective than higher, single doses and that supplementation in Vitamin D-deficient populations leads to greater improvements in clinical prognosis. By highlighting the importance of dosing strategies and baseline Vitamin D status, our study provides a potential explanation for the conflicting results observed in previous research on Vitamin D supplementation and COVID-19 outcomes. The inconsistencies in earlier studies may be attributed to differences in patient selection, dosing regimens, and a lack of consideration for baseline Vitamin D status.
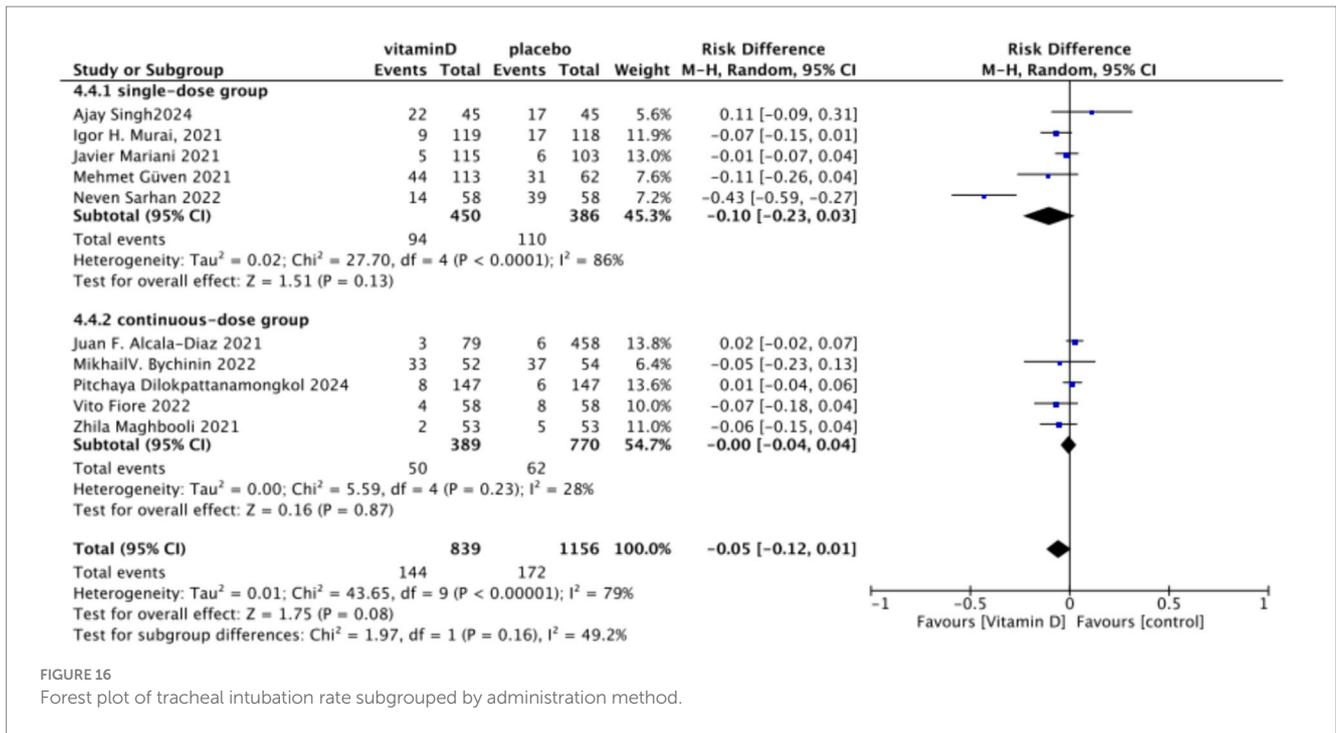
FIGURE 16
Forest plot of tracheal intubation rate subgrouped by administration method.
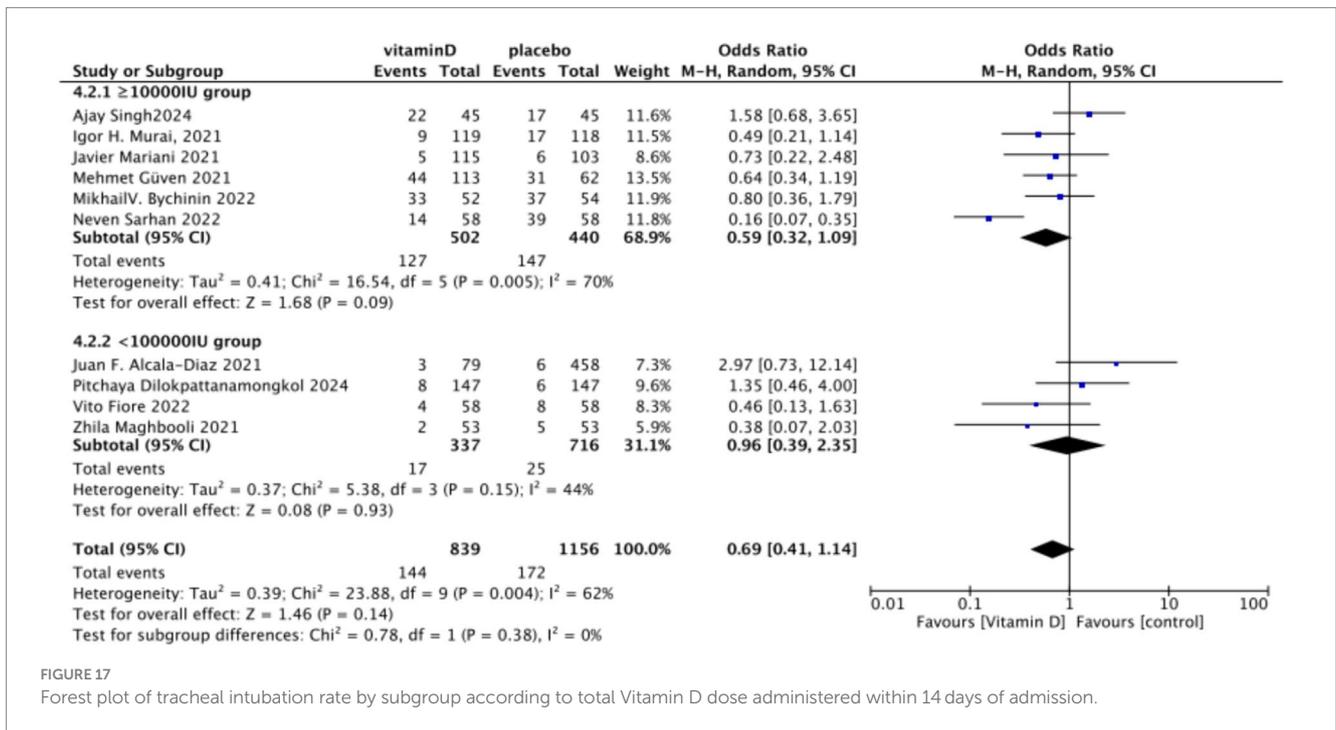
FIGURE 17
Forest plot of tracheal intubation rate by subgroup according to total Vitamin D dose administered within 14 days of admission.

Since the outbreak of the novel coronavirus infection in 2019, numerous studies have explored the relationship between Vitamin D supplementation and the prognosis for COVID-19 infection. However, results from clinical trials vary and meta-analyses on this topic also exhibit discrepancies. For instance, the majority of meta-analyses conclude that oral Vitamin D supplementation has a negligible impact on the mortality rate of COVID-19 patients (22, 43–51). Nevertheless, a few reports suggest that supplementation reduces COVID-19 patient mortality rates (52, 53). Similarly, most meta-analyses state that Vitamin D supplementation significantly lowers the ICU admission rate of COVID-19 patients (43, 46, 47, 49–51, 53), although some studies contradict these findings (22, 45). These discrepancies may be due to the Vitamin D supplementation dosage and method, necessitating further clinical trials and meta-analyses for deeper investigation. Our study evaluated the mortality rate, ICU admission rate, length of hospital stay, and intubation rate
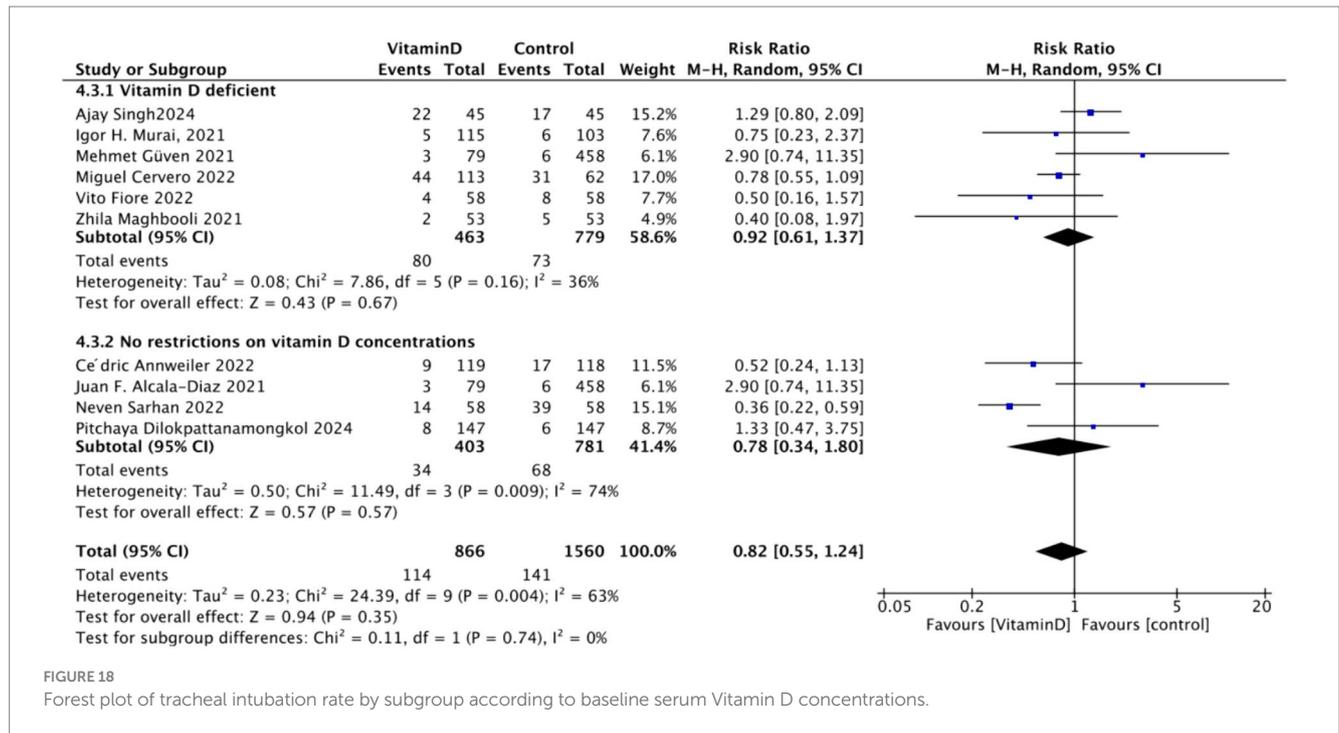
FIGURE 18
Forest plot of tracheal intubation rate by subgroup according to baseline serum Vitamin D concentrations.

TABLE 2 Summary table of subgroup analysis.

Subgroup criteria	Analysis type	Mortality			ICU admission			Length of hospital stay			Endotracheal intubation		
		RR (95% CI)	I^2	p value	RR (95% CI)	I^2	p value	MD (95% CI)	I^2	p value	RR (95% CI)	I^2	p value
	Total analysis	0.72 (0.54–0.94)	54%	0.02	0.58 (0.38–0.88)	74%	0.01	−1.00 (−2.16 to 0.16)	63%	0.13	0.78 (0.56–1.08)	60%	0.13
Subgroup by administration method	Single-dose	0.88 (0.69–1.12)	21%	0.3	0.79 (0.61–1.03)	22%	0.08	−1.11 (−2.35 to 0.13)	53%	0.08	−0.10 (−0.23 to 0.03)	42%	0.13
	Continuous dose	0.53 (0.34–0.83)	55%	0.006	0.44 (0.22–0.90)	74%	0.02	−0.50 (−2.23 to 1.22)	69%	0.57	−0.00 (−0.04 to 0.04)	45%	0.87
Subgroup by dosage	≥100,000 IU	0.85 (0.71–1.02)	1%	0.07	0.86 (0.60–1.24)	54%	0.42	−0.91 (−1.83 to 0.01)	57%	0.05	0.59 (0.32–1.09)	38%	0.09
	<100,000 IU	0.30 (0.21–0.44)	0%	<0.0001	0.31 (0.21–0.47)	0%	0.001	−0.97 (−3.24 to 1.29)	48%	0.4	0.96 (0.39–2.35)	34%	0.93
Subgroup by baseline vitamin D status	Vitamin D deficient (25OHD < 30 ng/mL)	0.73 (0.59–0.89)	0%	0.002	0.63 (0.42–0.93)	0%	0.02	−0.62 (−2.17 to 0.92)	72%	0.43	0.92 (0.61–1.37)	36%	0.67
	No baseline restriction	0.73 (0.46–1.15)	73%	0.18	0.59 (0.32–1.11)	86%	0.1	−0.25 (−1.12 to 0.62)	75%	0.57	0.78 (0.34–1.80)	74%	0.57

FIGURE 19
Funnel plot of mortality rate.

FIGURE 20
Funnel plot of ICU admission rate.

FIGURE 21
Funnel plot of hospital stay duration.
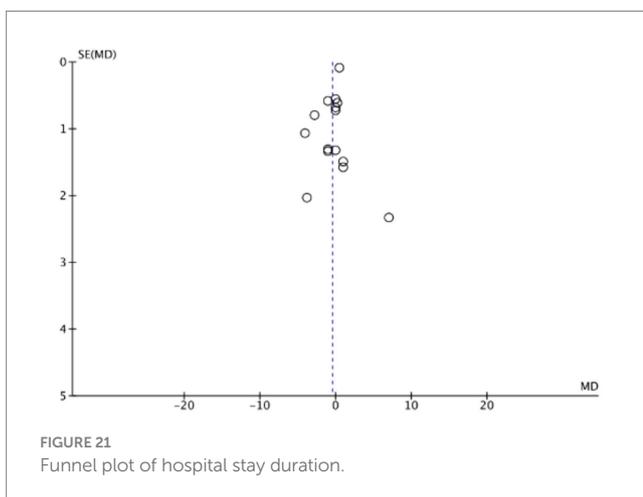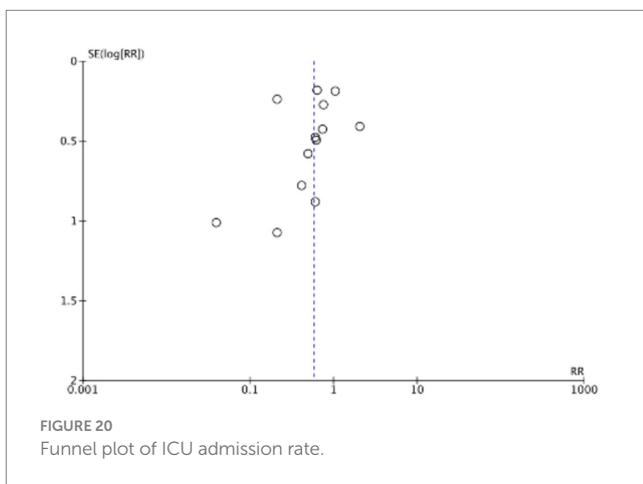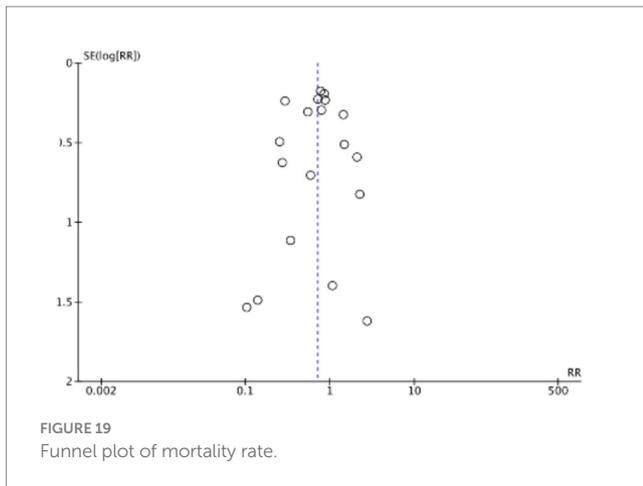
of hospitalized COVID-19 patients. The positive feature of this study is that we conducted subgroup analyses based on the mode of administration and 14-day total Vitamin D intake, which appreciably reduced the heterogeneity in some subgroups. Additionally, our study yielded new findings regarding total intake, partially clarifying the discrepancies encountered in previous meta-analyses.

Our conclusions regarding the impact of administration methods on the clinical outcomes of COVID-19 patients suggest that

continuous administration of Vitamin D is superior to one-time bolus intake. The relationship between Vitamin D supplementation methods and respiratory tract infections has been studied extensively in recent years. Numerous clinical trials have consistently shown that continuous low-dose Vitamin D supplementation is more effective than intermittent high-dose administration. In their respective meta-analyses of numerous randomized controlled trials, Martineau (54) and Jolliffe (6) both concluded that continuous low-dose maintenance Vitamin D supplementation produces a considerably greater protective effect against the risk of acute respiratory tract infections compared to high-dose intermittent dosing. Considering that COVID-19 is a respiratory infection，during the early stages of the COVID-19 pandemic, Griffin (55) recommended continuous administration of Vitamin D for COVID-19 patients based on the relationship between Vitamin D supplementation and respiratory tract infections. Elaborating on this, Feiner Solís et al. (56) conducted a systematic review, summarizing 11 relevant clinical trials. Six of the studies involved continuous Vitamin D administration and five studies involved a single bolus dose. His results revealed that continuous Vitamin D supplementation was associated with better clinical outcomes in patients with COVID-19, whereas a single bolus dose did not improve any clinical outcomes. Our study further corroborates these findings. From the perspective of Vitamin D metabolism, a plausible explanation is that its activation and metabolism are regulated by enzymes. Following a large bolus dose of Vitamin D, the enzyme 24-hydroxylase, which inactivates Vitamin D, may remain active for several weeks as a feedback response (57). This sustained elevation in 24-hydroxylase activity can paradoxically result in intracellular depletion of active Vitamin D, known as the rebound effect, particularly affecting immune cells. In contrast, daily low-dose supplementation maintains consistent Vitamin D activity by preventing the significant upregulation of 24-hydroxylase (58).

To date, there have been no clinical trials or meta-analyses that specifically analyze the effects of total intake within a certain timeframe on the prognosis of COVID-19 patients. In the context of respiratory tract infections and Vitamin D supplementation, the RCT study by Wall-Gremstrup et al. (59) proposed that the probability of respiratory tract infections is significantly higher in the high-dose Vitamin D group (supplemented with 300,000 IU on the first day followed by 1,500 IU/day for the next 150 days) than the non-supplemented group. This study supports the notion that high-dose supplementation does not enhance immunity in infected patients and may even impair innate immunity. Vieth (60) provided a possible explanation from a pharmacological mechanism perspective. They suggested that high-dose Vitamin D3 intake leads to an imbalance in Vitamin D regulatory enzymes including CYP27B1 and CYP24A1 (Cytochrome P450 family 24 subfamily B member 1 and cytochrome P450 family 24 subfamily A member 1), resulting in significant fluctuations in serum 25(OH) D3 concentrations. This results in a fall in the levels of active Vitamin D (1,25(OH)2D3), which assists the immune system in combating respiratory tract infections. Therefore, high doses of Vitamin D may impair immune function. Another possible cause is fibroblast growth factor23 (FGF23), which is increased by high doses of oral Vitamin D but not by sustained low doses of Vitamin D of 2,000 IU or less per day. High concentration of FGF23 in turn significantly inhibited the 1α-hydroxylation of 25(OH)D, resulting in reduced Vitamin D intracellular activation of 1,25(OH)2D,

FIGURE 22
Funnel plot of tracheal intubation rate.
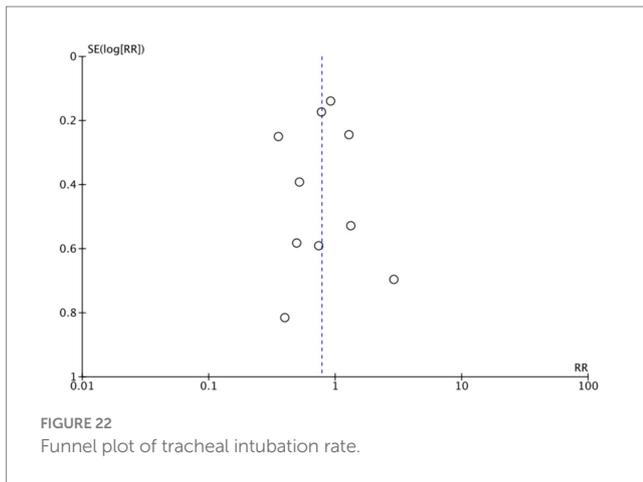
thereby attenuating the immune-enhancing effect of Vitamin D (61). Concerning supplementation dosage and the prognosis of COVID-19 patients, Tentolouris et al. (47) conducted a preliminary analysis in their meta-analysis. They performed a subgroup analysis on single high-dose and low-dose Vitamin D supplementation, concluding that low-dose supplementation reduces the mortality rate and ICU admission rate of COVID-19 patients, while high-dose supplementation does not. However, in their classification of high and low doses, they arbitrarily assigned studies with individual doses of 200,000 IU and 400,000 IU to the high-dose group, while the remainders were categorized as low doses. They did not consider whether the low-dose group was administered continuously, nor did they compare the total intake of Vitamin D within a certain timeframe between the single high-dose and single low-dose groups. As a result, this approach failed to exclude the influence of factors such as continuous application or total intake on clinical outcomes. Our study is currently the only meta-analysis that simultaneously includes an analysis of both the method of Vitamin D intake and the total dosage within a specific period. Thus, the conclusions of this meta-analysis may facilitate the determination of more appropriate dosages and methods of Vitamin D supplementation, thereby achieving better clinical outcomes.

Previous studies have indicated that Vitamin D deficiency is associated with an increased risk of COVID-19 infection and poor outcomes (5, 10, 52, 62), Consequently, supplementing Vitamin D in deficient populations is more likely to improve COVID-19 prognosis, a finding supported by recent meta-analyses (63). However, few randomized clinical trials have directly grouped patients based on baseline Vitamin D concentrations. In our study, which included 21 clinical trials, 9 did not specify baseline Vitamin D levels, while the remaining 12 included only Vitamin D-deficient individuals (25OHD < 30 ng/mL). Our subgroup analysis using this criterion found that Vitamin D supplementation significantly improved mortality and ICU admission rates in deficient populations, along with a notable reduction in heterogeneity. In contrast, the group without baseline restrictions showed no significant effect on mortality and a significant effect on ICU admission rates, but with high heterogeneity. This discrepancy may be attributed to differences in baseline Vitamin D concentrations. Therefore, selecting appropriate patient populations for Vitamin D supplementation is crucial for optimizing its therapeutic efficacy.

Due to the significant variations in vitamin D supplementation doses and effects in existing clinical trials, there is currently no clear recommendation or consensus for the use of vitamin D specifically for COVID-19 patients. These studies have not provided explicit guidance on the specific applications and dosages of vitamin D in the treatment of COVID-19. As a result, most recommendations focus primarily on the preventive use of vitamin D against COVID-19, drawing on guidelines from other diseases. The main goal is to enhance immune function by maintaining adequate vitamin D levels. For instance, in 2020, international nutritional guidelines recommended a daily intake of 400 IU of vitamin D as a preventive measure against COVID-19, particularly for individuals with limited sun exposure (64, 65). However, in 2022, Griffin G conducted a critical review of the role of vitamin D in the prevention and treatment of diseases such as rickets, tuberculosis, and respiratory infections. He argued that a daily intake of 400 IU is insufficient to achieve optimal serum vitamin D levels, suggesting an increased daily dosage of 800–1,000 IU. For individuals suspected of having vitamin D deficiency, he recommended a higher initial dose of 4,000 IU per day for the first 4 weeks (55, 66). Our study investigated the effects of vitamin D supplementation in COVID-19 patients, focusing on baseline vitamin D levels, supplementation methods, and dosage. The findings indicate that vitamin D supplementation is significantly more effective in individuals with vitamin D deficiency, with optimal results observed when the total supplementation over 14 days is less than 100,000 IU. Although specific guidelines for vitamin D supplementation during COVID-19 are currently limited, our study is the first to demonstrate that a lower cumulative dose of less than 100,000 IU over 14 days is associated with better outcomes.

This study has certain limitations. Firstly, most of the included trials did not report the baseline blood concentrations of Vitamin D among participants, which limited our ability to accurately compare the supplementation effects between individuals with low and high baseline levels. Moreover, there was considerable variation across studies in terms of Vitamin D dosage, patient populations, and methods of administration. To address these differences and better capture real-world scenarios, we employed a random-effects model. Additionally, differences in baseline health conditions, illness severity, and concurrent medications among participants may have influenced the observed effects of Vitamin D supplementation. As this study did not perform stratified analyses based on these patient characteristics, future research should aim to explore these factors to provide a more comprehensive understanding.

5 Conclusion

The findings of this review support the conclusion that Vitamin D supplementation has a positive impact on the clinical outcomes of patients with COVID-19. Our analysis of the mode and dosage of Vitamin D supplementation indicates that continuous intake is associated with greater improvements in COVID-19 patients compared to single-dose treatments. Additionally, a total Vitamin D supplementation of less than 100,000 IU over 14 days is more effective than higher doses of 100,000 IU or more. Furthermore, Vitamin D supplementation shows significantly greater efficacy in individuals with Vitamin D deficiency. To further validate these findings, high-quality, long-term follow-up randomized controlled trials (RCTs) are necessary.

Data availability statement

The authors confirm that the data supporting the findings of this study are available in the article.

Author contributions

XZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JW: Conceptualization, Writing – review & editing. HD: Methodology, Writing – review & editing. NS: Investigation, Writing – review & editing. YL: Software, Writing – review & editing. YZ: Data curation, Writing – review & editing. SG: Conceptualization, Funding acquisition, Writing – review & editing. XM: Conceptualization, Supervision, Writing – review & editing.

Funding

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnut.2024.1441847/full#supplementary-material

References

1. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol*. (2017) 27:e1909. doi: 10.1002/rmv.1909

2. Vaghari-Tabari M, Mohammadzadeh I, Qujeq D, Majidinia M, Alemi F, Younesi S, et al. Vitamin D in respiratory viral infections: a key immune modulator? *Crit Rev Food Sci Nutr*. (2023) 63:2231–46. doi: 10.1080/10408398.2021.1972407

3. Fabbri A, Infante M, Ricordi C. Editorial - vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections. *Eur Rev Med Pharmacol Sci*. (2020) 24:4048–52. doi: 10.26355/eurrev_202004_20876

4. Saraf R, Jensen BP, Camargo CAJr, Morton SMB, Jing M, Sies CW, et al. Vitamin D status at birth and acute respiratory infection hospitalisation during infancy. *Paediatr Perinat Epidemiol*. (2021) 35:540–8. doi: 10.1111/ppe.12755

5. Berry DJ, Hesketh K, Power C, Hyppönen E. Vitamin D status has a linear association with seasonal infections and lung function in British adults. *Br J Nutr*. (2011) 106:1433–40. doi: 10.1017/S0007114511001991

6. Jolliffe DA, Camargo CAJr, Sluyter JD, Aglipay M, Aloia JF, Ganmaa D, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol*. (2021) 9:276–92. doi: 10.1016/S2213-8587(21)00051-6

7. Vlieg-Boerstra B, de Jong N, Meyer R, Agostoni C, De Cosmi V, Grimshaw K, et al. Nutrient supplementation for prevention of viral respiratory tract infections in healthy subjects: a systematic review and meta-analysis. *Allergy*. (2022) 77:1373–88. doi: 10.1111/all.15136

8. Zhang Y, Fang F, Tang J, Jia L, Feng Y, Xu P, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ*. (2019) 366:l4673. doi: 10.1136/bmj.l4673

9. Annweiler G, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, et al. Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: the GERIA-COVID quasi-experimental study. *Nutrients*. (2020) 12:3377. doi: 10.3390/nu12113377

10. Ben-Eltriki M, Hopefl R, Wright JM, Deb S. Association between vitamin D status and risk of developing severe COVID-19 infection: a Meta-analysis of observational studies. *J Am Nutr Assoc*. (2022) 41:679–89. doi: 10.1080/07315724.2021.1951891

11. Dror AA, Morozov N, Daoud A, Namir Y, Yakir O, Shachar Y, et al. Pre-infection 25-hydroxyVitamin D3 levels and association with severity of COVID-19 illness. *PLoS One*. (2022) 17:e0263069. doi: 10.1371/journal.pone.0263069

12. Oscanoa TJ, Amado J, Vidal X, Laird E, Ghashut RA, Romero-Ortuno R. The relationship between the severity and mortality of SARS-CoV-2 infection and 25-hydroxyVitamin D concentration - a metaanalysis. *Adv Respir Med*. (2021) 89:145–57. doi: 10.5603/ARM.a2021.0037

13. Angelidi AM, Belanger MJ, Lorinsky MK, Karamanis D, Chamorro-Pareja N, Ognibene J, et al. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: a cohort of COVID-19 hospitalized patients. *Mayo Clin Proc*. (2021) 96:875–86. doi: 10.1016/j.mayocp.2021.01.001

14. Sabico S, Enani MA, Sheshah E, Aljohani NJ, Aldisi DA, Alotaibi NH, et al. Effects of a 2-week 5000 IU versus 1000 IU vitamin D3 supplementation on recovery of symptoms in patients with mild to moderate Covid-19: a randomized clinical trial. *Nutrients*. (2021) 13:2170. doi: 10.3390/nu13072170

15. Ling SF, Broad E, Murphy R, Pappachan JM, Pardesi-Newton S, Kong MF, et al. High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with COVID-19: a cross-sectional multi-Centre observational study. *Nutrients*. (2020) 12:3799. doi: 10.3390/nu12123799

16. Alcala-Diaz JF, Limia-Perez L, Gomez-Huelgas R, Martin-Escalante MD, Cortes-Rodriguez B, Zambrana-Garcia JL, et al. Calcifediol treatment and hospital mortality due to COVID-19: a cohort study. *Nutrients*. (2021) 13:1760. doi: 10.3390/nu13061760

17. Gonen MS, Alaylioglu M, Durcan E, Ozdemir Y, Sahin S, Konukoglu D, et al. Rapid and effective vitamin D supplementation may present better clinical outcomes in COVID-19 (SARS-CoV-2) patients by altering serum INOS1, IL1B, IFNg, cathelicidin-LL37, and ICAM1. *Nutrients*. (2021) 13:12. doi: 10.3390/nu13114047

18. Cervero M, Lopez-Wolf D, Casado G, Novella-Mena M, Ryan-Murua P, Taboada-Martinez ML, et al. Beneficial effect of short-term supplementation of high dose of vitamin D(3) in hospitalized patients with COVID-19: a multicenter, single-blinded, prospective randomized pilot clinical trial. *Front Pharmacol*. (2022) 13:863587. doi: 10.3389/fphar.2022.863587

19. De Niet S, Tremege M, Coffiner M, Rousseau AF, Calmes D, Frix AN, et al. Positive effects of vitamin D supplementation in patients hospitalized for COVID-19: a randomized, double-blind, placebo-controlled trial. *Nutrients*. (2022) 14:3048. doi: 10.3390/nu14153048

20. Guven M, Gultekin H. The effect of high-dose parenteral vitamin D(3) on COVID-19-related inhospital mortality in critical COVID-19 patients during intensive care unit admission: an observational cohort study. *Eur J Clin Nutr*. (2021) 75:1383–8. doi: 10.1038/s41430-021-00984-5

21. Maghbooli Z, Sahraian MA, Jamalimoghadamsiahkali S, Asadi A, Zarei A, Zendehdel A, et al. Treatment with 25-HydroxyVitamin D(3) (Calcifediol) is associated with a reduction in the blood neutrophil-to-lymphocyte ratio marker of disease severity in hospitalized patients with COVID-19: a pilot multicenter, randomized, placebo-controlled, double-blinded clinical trial. *Endocr Pract*. (2021) 27:1242–51. doi: 10.1016/j.eprac.2021.09.016

22. Rawat D, Roy A, Maitra S, Shankar V, Khanna P, Baidya DK. Vitamin D supplementation and COVID-19 treatment: a systematic review and meta-analysis. *Diabetes Metab Syndr*. (2021) 15:102189. doi: 10.1016/j.dsx.2021.102189

23. Cannata-Andía JB, Díaz-Sottolano A, Fernández P, Palomo-Antequera C, Herrero-Puente P, Mouzo R, et al. A single-oral bolus of 100,000 IU of cholecalciferol at hospital admission did not improve outcomes in the COVID-19 disease: the COVID-VIT-D-a randomised multicentre international clinical trial. *BMC Med*. (2022) 20:83. doi: 10.1186/s12916-022-02290-8

24. Mariani J, Antonietti L, Tajer C, Ferder L, Inserra F, Sanchez Cunto M, et al. High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: multicentre randomized controlled clinical trial. *PLoS ONE*. (2022) 17:e0267918. doi: 10.1371/journal.pone.0267918

25. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. (2021) 372:n71. doi: 10.1136/bmj.n71

26. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. (2018) 27:1785–805. doi: 10.1177/0962280216669183

27. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. (2014) 14:135. doi: 10.1186/1471-2288-14-135

28. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. (2011) 343:d5928. doi: 10.1136/bmj.d5928

29. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. (2019) 366:l4898. doi: 10.1136/bmj.l4898

30. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane handbook for systematic reviews of interventions. *Cochrane Database Syst Rev*. (2019) 10:Ed000142. doi: 10.1002/14651858.ED000142

31. Annweiler C, Beaudenon M, Gautier J, Gonsard J, Boucher S, Chapelet G, et al. High-dose versus standard-dose vitamin D supplementation in older adults with COVID-19 (COVIT-TRIAL): a multicenter, open-label, randomized controlled superiority trial. *PLoS Med*. (2022) 19:e1003999. doi: 10.1371/journal.pmed.1003999

32. Bychinin MV, Klypa TV, Mandel IA, Yusubalieva GM, Baklaushev VP, Kolyshkina NA, et al. Effect of vitamin D3 supplementation on cellular immunity and inflammatory markers in COVID-19 patients admitted to the ICU. *Sci Rep*. (2022) 12:18604. doi: 10.1038/s41598-022-22045-y

33. Dilokpattanamongkol P, Yan C, Jayanama K, Ngamjanyaporn P, Sungkanuparph S, Rotjanapan P. Impact of vitamin D supplementation on the clinical outcomes of COVID-19 pneumonia patients: a single-center randomized controlled trial. *BMC Complement Med Ther*. (2024) 24:97. doi: 10.1186/s12906-024-04393-6

34. Domazet Bugarin J, Dosenovic S, Ilic D, Delic N, Saric I, Ugrina I, et al. Vitamin D supplementation and clinical outcomes in severe COVID-19 patients-randomized controlled trial. *Nutrients*. (2023) 15:1234. doi: 10.3390/nu15051234

35. Elamir YM, Amir H, Lim S, Rana YP, Lopez CG, Feliciano NV, et al. A randomized pilot study using calcitriol in hospitalized COVID-19 patients. *Bone*. (2022) 154:116175. doi: 10.1016/j.bone.2021.116175

36. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcala Diaz JF, Lopez Miranda J, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. *J Steroid Biochem Mol Biol*. (2020) 203:105751. doi: 10.1016/j.jsbmb.2020.105751

37. Fernandes AL, Sales LP, Santos MD, Caparbo VF, Murai IH, Pereira RMR. Persistent or new symptoms 1 year after a single high dose of vitamin D(3) in patients with moderate to severe COVID-19. *Front Nutr*. (2022) 9:979667. doi: 10.3389/fnut.2022.979667

38. Fiore V, De Vito A, Bagella P, Princic E, Mariani AA, Denti L, et al. Effectiveness of vitamin D supplements among patients hospitalized for COVID-19: results from a monocentric matched-cohort study. *Healthcare (Basel)*. (2022) 10:956. doi: 10.3390/healthcare10050956

39. Murai IH, Fernandes AL, Antonangelo L, Gualano B, Pereira RMR. Effect of a single high-dose vitamin D3 on the length of hospital stay of severely 25-HydroxyVitamin D-deficient patients with COVID-19. *Clinics (São Paulo)*. (2021) 76:e3549. doi: 10.6061/clinics/2021/e3549

40. Nogues X, Ovejero D, Pineda-Moncusí M, Bouillon R, Arenas D, Pascual J, et al. Calcifediol treatment and COVID-19-related outcomes. *J Clin Endocrinol Metab*. (2021) 106:e4017–27. doi: 10.1210/clinem/dgab405

41. Sarhan N, Abou Warda AE, Sarhan RM, Boshra MS, Mostafa-Hedeab G, ALruwaili BF, et al. Evidence for the efficacy of a high dose of vitamin D on the hyperinflammation state in moderate-to-severe COVID-19 patients: A randomized clinical trial. *Medicina (Kaunas)*. (2022) 58:1358. doi: 10.3390/medicina58101358

42. Singh A, Rastogi A, Puri GD, Ganesh V, Naik NB, Kajal K, et al. Therapeutic high-dose vitamin D for vitamin D-deficient severe COVID-19 disease: randomized, double-blind, placebo-controlled study (SHADE-S). *J Public Health (Oxf)*. (2024) 46:256–66. doi: 10.1093/pubmed/fdae007

43. Shah K, Saxena D, Mavalankar D. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. *QJM*. (2021) 114:175–81. doi: 10.1093/qjmed/hcab009

44. Beran A, Mhanna M, Srour O, Ayesh H, Stewart JM, Hjouj M, et al. Clinical significance of micronutrient supplements in patients with coronavirus disease 2019: a comprehensive systematic review and meta-analysis. *Clin Nutr ESPEN*. (2022) 48:167–77. doi: 10.1016/j.clnesp.2021.12.033

45. Kümmel LS, Krumbein H, Fragkou PC, Hünerbein BL, Reiter R, Papathanasiou KA, et al. Vitamin D supplementation for the treatment of COVID-19: a systematic review and meta-analysis of randomized controlled trials. *Front Immunol*. (2022) 13:1023903. doi: 10.3389/fimmu.2022.1023903

46. Szarpak L, Filipiak KJ, Gasecka A, Gawel W, Koziel D, Jaguszewski MJ, et al. Vitamin D supplementation to treat SARS-CoV-2 positive patients. Evidence from meta-analysis. *Cardiol J*. (2022) 29:188–96. doi: 10.5603/CJ.a2021.0122

47. Tentolouris N, Samakidou G, Eleftheriadou I, Tentolouris A, Jude EB. 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. *Diabetes Metab Res Rev*. (2022) 38:e3517. doi: 10.1002/dmrr.3517

48. Chen J, Mei K, Xie L, Yuan P, Ma J, Yu P, et al. Low vitamin D levels do not aggravate COVID-19 risk or death, and vitamin D supplementation does not improve outcomes in hospitalized patients with COVID-19: a meta-analysis and GRADE assessment of cohort studies and RCTs. *Nutr J*. (2021) 20:89. doi: 10.1186/s12937-021-00744-y

49. Zaazouee MS, Eleisawy M, Abdalalaziz AM, Elhady MM, Ali OA, Abdelbari TM, et al. Hospital and laboratory outcomes of patients with COVID-19 who received vitamin D supplementation: a systematic review and meta-analysis of randomized controlled trials. *Naunyn Schmiedeberg's Arch Pharmacol*. (2023) 396:607–20. doi: 10.1007/s00210-022-02360-x

50. Sartini M, Del Puente F, Oliva M, Carbone A, Bobbio N, Schinca E, et al. Preventive vitamin D supplementation and risk for COVID-19 infection: a systematic review and Meta-analysis. *Nutrients*. (2024) 16:679. doi: 10.3390/nu16050679

51. Sîrbu AC, Sabin O, Bocşan IC, Vesa ŞC, Buzoianu AD. The effect of vitamin D supplementation on the length of hospitalisation, intensive care unit admission, and mortality in COVID-19-a systematic review and Meta-analysis. *Nutrients*. (2023) 15:3470. doi: 10.3390/nu15153470

52. D'Ecclesiis O, Gavioli C, Martinoli C, Raimondi S, Chiocca S, Miccolo C, et al. Vitamin D and SARS-CoV2 infection, severity and mortality: a systematic review and meta-analysis. *PLoS One*. (2022) 17:e0268396. doi: 10.1371/journal.pone.0268396

53. Hosseini B, El Abd A, Ducharme FM. Effects of vitamin D supplementation on COVID-19 related outcomes: a systematic review and meta-analysis. *Nutrients*. (2022) 14:2134. doi: 10.3390/nu14102134

54. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. (2017) 356:i6583. doi: 10.1136/bmj.i6583

55. Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, et al. Perspective: vitamin D supplementation prevents rickets and acute respiratory infections when given as daily maintenance but not as intermittent bolus: implications for COVID-19. *Clin Med (Lond)*. (2021) 21:e144–9. doi: 10.7861/clinmed.2021-0035

56. Feiner Solís Á, Avedillo Salas A, Luesma Bartolomé MJ, Santander Ballestín S. The effects of vitamin D supplementation in COVID-19 patients: a systematic review. *Int J Mol Sci*. (2022) 23:12424. doi: 10.3390/ijms232012424

57. Ketha H, Thacher TD, Oberhelman SS, Fischer PR, Singh RJ, Kumar R. Comparison of the effect of daily versus bolus dose maternal vitamin D(3) supplementation on the 24,25-dihydroxyVitamin D(3) to 25-hydroxyVitamin D(3) ratio. *Bone*. (2018) 110:321–5. doi: 10.1016/j.bone.2018.02.024

58. Kundu R, Chain BM, Coussens AK, Khoo B, Noursadeghi M. Regulation of CYP27B1 and CYP24A1 hydroxylases limits cell-autonomous activation of vitamin D in dendritic cells. *Eur J Immunol*. (2014) 44:1781–90. doi: 10.1002/eji.201344157

59. Wall-Gremstrup G, Holt R, Yahyavi SK, Jorsal MJ, Juul A, Jørgensen N, et al. High-dose vitamin D(3) supplementation shows no beneficial effects on white blood cell counts, acute phase reactants, or frequency of respiratory infections. *Respir Res*. (2024) 25:11. doi: 10.1186/s12931-023-02642-9

60. Vieth R. How to optimize vitamin D supplementation to prevent cancer, based on cellular adaptation and hydroxylase enzymology. *Anticancer Res*. (2009) 29:3675–84.

61. Bacchetta J, Sea JL, Chun RF, Lisse TS, Wesseling-Perry K, Gales B, et al. Fibroblast growth factor 23 inhibits extrarenal synthesis of 1,25-dihydroxyVitamin D in human monocytes. *J Bone Miner Res*. (2013) 28:46–55. doi: 10.1002/jbmr.1740

62. Coudray MS, Hansel S, Alesci S, Meyer WA3rd, Christenson RH, Landry LG, et al. Vitamin D levels and SARS-CoV-2 infection among medically underserved populations in the minority and rural coronavirus insights study. *Viruses*. (2024) 16:639. doi: 10.3390/v16040639

63. Meng J, Li X, Liu W, Xiao Y, Tang H, Wu Y, et al. The role of vitamin D in the prevention and treatment of SARS-CoV-2 infection: a meta-analysis of randomized controlled trials. *Clin Nutr.* (2023) 42:2198–206. doi: 10.1016/j.clnu.2023.09.008

64. Grant WB, Al Anouti F, Boucher BJ, Dursun E, Gezen-Ak D, Jude EB, et al. A narrative review of the evidence for variations in serum 25-HydroxyVitamin D concentration thresholds for optimal health. *Nutrients.* (2022) 14:639. doi: 10.3390/nu14030639

65. Cawood AL, Walters ER, Smith TR, Sipaul RH, Stratton RJ. A review of nutrition support guidelines for individuals with or recovering from COVID-19 in the community. *Nutrients.* (2020) 12:3230. doi: 10.3390/nu12113230

66. Griffin G, Hewison M, Hopkin J, Kenny RA, Quinton R, Rhodes J, et al. Preventing vitamin D deficiency during the COVID-19 pandemic: UK definitions of vitamin D sufficiency and recommended supplement dose are set too low. *Clin Med (Lond).* (2021) 21:e48–51. doi: 10.7861/clinmed.2020-0858