National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[N] Evidence review for vitamin D

NICE guideline NG191

May 2022

Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

Objective 4
Review question 4
Methodology 4
Included studies 5
Results 12
Evidence to decision 15
Appendices 19
Appendix A: PICO table 19
Appendix B: Literature search strategy 22
Appendix C: PRISMA diagram 24
Appendix D: Included studies 25
Appendix E: Excluded studies at full text screening 26
Appendix F: Evidence tables 28
Appendix G: Forest Plots 72
Mortality 72
ICU admission 72
Mean duration of hospitalisation 72
Mechanical ventilation 72
Oxygen therapy 73
Appendix H: GRADE profile 74
Appendix I: Recommendations for research 77

Objective

This evidence review aims to assess the evidence on vitamin D supplementation for the treatment of COVID-19 in adults, young people and children.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19 in adults, young people and children?

Methodology

Search strategy

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The original NICE recommendations on the use of vitamin D supplementation for the treatment of COVID-19 were published in December 2020 (NG187). The following recommendation was made regarding the efficacy of vitamin D for the treatment of COVID-19:

- Do not offer a vitamin D supplement to people solely to treat COVID-19, except as part of a clinical trial.

Continuous surveillance of the literature using a broad COVID-19-wide search was undertaken weekly. The results were processed on a weekly basis and all records with relevance to COVID-19 and vitamin D, and which were added since the original review search was conducted, were brought together into a single group. Automated pattern matching was applied to the records in this group in order to further focus the results and identify the most relevant records for screening. The pattern matching code was created in Python using keywords relevant for the topic to enable automated study categorisation through natural language processing (see appendix B for full details).

All studies included by the pattern matching code were considered for inclusion in this review.

As quality assurance, the pattern matching code was run on all studies which were identified in the continuous surveillance, but had been excluded as not relevant to NICE's current reviews. No additional studies were identified through these checks.

Review protocol

A review protocol was developed by NICE for the effectiveness of vitamin D supplementation for treating COVID-19 (NG187) (published in December 2020). As part of the current update to this guideline, the existing review protocol was updated to include the following subgroups:

(i) baseline 25(OH)D levels

(ii) dosage >800 IU/day versus ≤800IU/day

(iii) single versus multiple doses

The updated protocol is presented in appendix A.

Included studies

Continual weekly surveillance searches up to the 26th May 2022 were used to identify studies for consideration in this update (see appendix B for full details). 382 relevant references were screened against the protocol using their titles and abstracts and 359 were excluded at title and abstract stage. 23 full text references were obtained and assessed for relevance at full text and 17 were excluded. Details of excluded studies at full text review stage are in appendix E.

In total, 7 studies are included in this updated evidence review, 6 of which are new to this review (Cannata-Andia 2022, Maghbooli 2021, Mariani 2022, Murai 2021, Rastogi 2020, Sanchez-Zuno 2021) and 1 of which was carried forward from the previous version of the evidence review (Entrenas Castillo 2020). A summary of the included studies is shown in Table 1.

Table 1: Summary of included studies

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Cannata-Andia 2022 New at this update 4 April 2020 to 22 April 2021 Argentina, Chile, Guatemala, Spain	RCT	People requiring hospitalisation for COVID-19 (referred to as moderate-severe in the paper). Criteria for hospitalisation: radiological evidence of pulmonary involvement compatible with the COVID19 disease, and/or moderate-severe flu-like syndrome having oxygen saturation lower than 94% breathing room air and/or additional risk factors (including cardiac disease).	543 participants. The median age of participants was 58 years (IQR 46 -68.8). The majority of participants were male (64.9%) with varying comorbidities such as hypertension (43.5%), diabetes (24.5%) and cardiovascular disease (20.2%). Baseline characteristics were balanced between both treatment groups.	Single dose 100,000 IU colecalciferol (D3)	No colecalciferol. Participants were prescribed enoxaparin, ceftriaxone, methylprednisolone, azithromycin, dexamethasone as standard care.	Death Admission to ICU Median length of hospitalisation

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Entrenas-Castillo 2020 29 April 2020 Spain	RCT	Hospitalised participants. Participants had acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1)	76 participants who were hospitalised with COVID-19. The mean age of participants was 53 years (SD 10), with the majority of participants being male (59%). There were slight differences in the prevalence of hypertension (24%) in the treatment group versus the standard care group (58%). Key exclusion criteria: pregnant women, people under the age of 18 years.	Day 1: 21,280 IU calcifediol; Day 3 & 7: 10,640 IU calcifediol; Then 10,640 IU weekly until hospital discharge or ICU admission. Type of calcifediol (D2 or D3) not reported in paper	All patients received standard care: Hydroxychloroquine - 400mg every 12 hours on the first day and 200mg every 12 hours for 5 days Azithromycin - 500mg orally for 5 days Patients with pneumonia and NEWS score =>5 a broad-spectrum antibiotic was added (ceftriaxone 2g every 24 hours for 5 days). This was also given to the intervention group	Death Admission to ICU
Mariani 2022 New at this update 01 August 2020 to 01 June 2021 Switzerland	RCT	Mild-moderate. Participants who were hospitalised with confirmed SARS-CoV-2 infection and/or, expected hospitalisation for at least 24	218 participants mild to moderate COVID-19 who have risk factors for severe disease progression. The mean age was 59.1 years (SD 10.7). The majority of participants were male (52.8%) and median baseline 25(OH)D was 81.25 [IQR: 68 to 110.5] nmol/L in the treatment group and 76.25 [IQR 56.25 to 90.5] nmol/L. Baseline characteristics were	Single oral dose of 500,000 IU of colecalciferol (D3)	Matching placebo. No further detail provided on standard care if any.	Death Admission to ICU Duration of ICU stay Invasive mechanical ventilation Oxygen therapy

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		hours, oxygen saturation >90%	balanced between treatment arms. Key exclusion criteria: women of childbearing age, participants with chronic kidney/liver disease			Duration of hospitalisation Adverse events
Maghbooli 2021 New at this update May 2020 to October 2020 Iran	RCT	Moderate-severe Disease severity of disease was considered based on the Centres for Disease Control and Prevention criteria: (1) dyspnoea, (2) respiratory frequency =>30/minute, (3) blood oxygen saturation < 93%, and/or (4) lung infiltrates > 50% of the lung field within 24 to 48 hours.	106 participants with 25(OH)D level <75 nmol/L. The mean age of participants was 49.1 years (SD 14.1). The majority of participants were male (60%) and average baseline 25(OH)D was 46.25 nmol/L for all participants. Baseline characteristics were balanced between treatment arms. Key exclusion criteria: pregnant or lactating women, chronic hepatic dysfunction and intestinal malabsorption syndromes.	1000 IU of calcifediol for 60 days (D3)	All patients received the same standard care: a combination of hydroxychloroquine, azithromycin, and, for patients with pneumonia, ceftriaxone was used	Death Hospitalisation duration Oxygen therapy Use of ventilator ICU admission ICU admission duration

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Murai 2021 New at this update 2 June 2020 to 27 October 2020 Brazil	RCT	Moderate-severe. Participants with computed tomography scan findings compatible with the disease (bilateral multifocal ground-glass opacities ≥50%); and diagnosis of flu syndrome with institutional criteria for hospitalisation on hospital admission, presenting respiratory rate greater than 24/min, saturation less than 93% while breathing room air, or risk factors for complications (eg, heart disease, diabetes, systemic arterial hypertension, neoplasms, immunosuppression, pulmonary	236 participants received either vitamin D3 or a placebo. The mean age of participants was 56.3 years (SD 14.4). The majority of participants were male (56.1%), with a majority having hypertension 52.8%. The average baseline 25(OH)D was 52.25 nmol/L (SD 9.1). Baseline characteristics were balanced between both treatment groups. Key exclusion criteria: pregnant or lactating women and participants with hypercalcaemia.	Single-dose of 200,000 IU vitamin D3	Standard care + Placebo (peanut oil solution). Standard care: participants also received anticoagulants, antibiotics, corticosteroids, antivirals, antihypertensives, proton-pump inhibitors, antiemetics, analgesics, hypoglycaemic, hypolipidemic and thyroid medication as standard care	Mortality Admission ICU Length of hospital stay Need for mechanical ventilation Mean duration of mechanical ventilation

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		tuberculosis, obesity) followed by COVID-19 confirmation.				
Rastogi 2020 New at this update 15 June 2020 to 21 April 2021 India	RCT	Asymptomatic or mildly symptomatic	40 participants with asymptomatic or mildly symptomatic COVID-19 and 25(OH)D levels <50nmol/L. The median age of participants in the intervention group was 50 years (IQR 36 - 51) and in the control group 47.5 years (IQR 39.3 - 49.2). The study included 50% females with baseline 25(OH)D was 21.3 nmol/L (IQR 17.75 - 32.75) in the intervention arm and 23.9nmol/L (IQR 20.25 - 25) in the control arm. Baseline characteristics between participant groups were balanced. Key exclusion criteria: participants with significant comorbidities.	60,000 IU colecalciferol per day. 25(OH)D levels were assessed at day 7 and a weekly supplementation of 60,000 IU provided to those with 25(OH)D >125 nmol/L or else continued on daily vitamin D 60,000 IU supplementation for another 7 days up until day-14 in participants with 25(OH)D <125 nmol/L.	Placebo. No further detail reported.	Proportion who became SARS-CoV-2 negative within 3 weeks Mean duration of SARS-CoV-2 negativity
Sanchez-Zuno 2021 New at this update Mexico	RCT	Asymptomatic or mildly symptomatic	42 participants with mild to asymptomatic COVID-19 disease in its analysis and the median age was 43 years (range 20 - 74). The study included 52.4% females while 16.7% had hypertension, 4.8% had diabetes and 2.4% had asthma.	10,000 IU vitamin D3 daily for 14 days	No vitamin D3. Standard care: treatment associated with COVID-19 (analgesics, antipyretics, anticoagulants, antibiotics	Positive PCR Test Presence of symptoms

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
					(azithromycin, erythromycin), antihistamines, beta-blockers, corticoids, anti-flu, and antiparasitic (ivermectin)).	

See appendix F for full evidence tables.

Results

Review question: What is the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19 in adults, young people and children?

There remains a high degree of uncertainty over whether vitamin D supplementation is more effective than placebo plus standard care or standard care for treating COVID-19. But, there is currently no clear evidence of benefit.

What is the evidence informing this conclusion?

This is an update to the December 2020 review. During this update, we have added 6 extra studies (Cannata-Andia 2022, Maghbooli 2021, Mariani 2022, Murai 2021, Rastogi 2020, Sanchez-Zuno 2021) and retained the existing study (Entrenas Castillo 2020).

Evidence comes from 7 randomised controlled trials that compared vitamin D supplementation with standard care (Cannata-Andia 2022, Entrenas-Castillo 2020, Maghbooli 2021, Rastogi 2020) or standard care plus placebo (Murai 2021, Mariani 2022 and Sanchez-Zuno 2021) in 1,262 people with COVID-19. Studies were conducted in Argentina, Brazil, Chile, Guatemala, India, Iran Mexico and Switzerland. All the studies were conducted in a hospital setting, regardless of disease severity.

All the trials included vitamin D doses higher than 800 IU/day. Three studies used a single-dose intervention of vitamin D (Cannata-Andia 2022, Mariani 2022 and Murai 2021). The remaining studies used a multiple-dose regimen (Entrenas-Castillo 2020, Maghbooli 2021, Rastogi 2020 and Sanchez-Zuno 2021). Two studies included only participants with vitamin D deficiency at baseline, defined as <75nmol/L (Maghbooli 20210) and <50nmol/L (Rastogi 2020) in the studies. It should be noted that these levels are not usually considered deficient in the UK.

Due to variability in dosage, disease severity and baseline vitamin D status, subgroup analyses were carried out to measure the effects of vitamin D supplementation.

Publication status

All studies are peer-reviewed manuscripts.

Study characteristics

The mean or median age in the studies ranged between 43 and 58 years and the proportion of men ranged between 50% and 65%. The severity of COVID-19 in 3 of the studies was reported as moderate-severe (Cannata-Andia 2022, Maghbooli 2021 and Murai 2021), mild to moderate in Mariani (2022) and asymptomatic-mildly symptomatic in Rastogi (2020) and Sanchez-Zuno (2021). Disease severity in one study was not clear (Entrenas-Castillo 2020).

The dose and duration of vitamin D supplementation varied across the trials. Three studies included a single dose of vitamin D of 100,000 IU (Cannata-Andia 2022), 200,000 IU (Murai 2021) or 500,000 IU (Mariani 2022). The remaining studies used multiple doses between 1000 IU/day and 60,000 IU/day for a duration ranging from 7 to 60 days.

Due to the variability in dosage, disease severity and baseline vitamin D concentration, subgroup analyses were conducted where the data allowed.

Children under 18 were excluded from the trials.

What are the main results?

Vitamin D supplementation does not result in statistically significant differences in mortality, ICU admission, requirement for oxygen therapy, adverse events, symptoms at day 7 or 14, PCR test results at day 7 or 14, or duration of: ICU stay, hospitalisation or mechanical ventilation.

Data on adverse events (for example cardiovascular or gastrointestinal serious adverse events) was only reported in one study (Mariani 2022).

The evidence suggests that, compared with control groups, there was a non-statistically significant reduction in mechanical ventilation and an increase in negative COVID-19 test results within 3 weeks in the vitamin D group.

Our confidence in the results

Overall, the studies are heterogeneous with both clinical and methodological diversity. Most studies were assessed to have some concerns with risk of bias due to insufficient reporting around randomisation and allocation and a lack of blinding in studies which did not use placebo.

Other reasons for downgrading evidence included inconsistency (for example, when point estimates varied widely between studies) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome). The variance in the duration of symptoms prior to randomisation across the studies may impact the certainty of outcomes as well as the effect of standard care regimens. The certainty of the evidence was moderate to very low for most outcomes.

Evidence to decision

Benefits and harms

All included trials compared the effects of vitamin D for treating COVID-19 with placebo or standard care. The trials included diverse populations with different COVID-19 severity, and used varying dosages of vitamin D. All trials compared the effects of vitamin D3 and not D2 for treating COVID-19.

The evidence shows no statistically significant difference in mortality, admissions to intensive care, hospitalisation or oxygen therapy in people having vitamin D compared with standard care or placebo. The panel noted that the certainty of the evidence for mortality and oxygen therapy was moderate, although certainty was lower for the other outcomes. The panel noted a non-statistically significant reduction in progression to mechanical ventilation (relative risk 0.55, 95% confidence interval 0.31 to 1.00) (Mariani 2022, Murai 2021 and Maghbooli 2021). While this result was at low risk for bias, the panel did not consider the result to be certain enough to justify recommending vitamin D.

The panel noted no statistically significant difference in presence of symptoms or positive polymerase chain reaction tests at 7 and 14 days. But in 1 study with 40 people there was increased SARS-CoV-2 negativity within 3 weeks (Rastogi 2020). This outcome was downgraded because of very serious risk of bias, and the panel did not think it represented a meaningful benefit, or that it could be attributed to treatment with vitamin D.

The panel were also presented with evidence on subgroup effects of vitamin D. These analyses show no statistically significant effect on admission to intensive care or mechanical ventilation of different numbers of doses (single or multiple), baseline vitamin D levels or COVID-19 severity. A meta-analysis of 5 studies (Cannata-Andia 2022, Mariani 2022, Murai 2021, Entrenas Castillo 2020, Maghbooli 2021) suggested an association between multiple doses of vitamin D and reduced mortality compared with single doses. But the difference was not statistically significant.

The panel had concerns about adverse events with the high doses of vitamin D used in the studies. Only 1 study reported adverse events as an outcome but showed no

statistically significant difference between vitamin D and placebo. The panel acknowledged that there are some well-known adverse effects of vitamin D overdose, including raised concentrations of calcium and phosphate in plasma and urine, and nausea and vomiting (for more details, please see the BNF). They agreed that treating COVID-19 with vitamin D at the dosages used in the included studies could have potential harms, and that more research is needed in this area.

The panel noted that the study populations did not include pregnant women or older populations who may be at more risk of severe COVID-19 outcomes. They also did not include children and young people under 18 years. So, they agreed that more research is also needed in the area.

Certainty of the evidence

Evidence comes from 7 randomised controlled trials (Cannata-Andia 2022, Entrenas Castillo 2020, Maghbooli 2021, Mariani 2022, Murai 2021, Rastogi 2020 and Sanchez-Zuno 2021).

All of the outcomes from the trials were rated as moderate to very low certainty, but the panel agreed that there was no clear evidence of benefit.

Outcomes from Maghbooli 2021, Mariani 2022 and Murai 2021 were assessed to be at low risk of bias. Outcomes from Cannata-Andia 2022 and Entrenas Castillo 2020 were downgraded because of insufficient detail on randomisation or the allocation process. Outcomes from Rastogi 2020 and Sanchez-Zuno 2021 were rated as at high risk of bias because neither trial reported details of study design and analysis plans.

The panel decided not to downgrade for indirectness despite reported vitamin D deficiency in the studies. This was because the deficiency threshold for vitamin D reported in the studies differed from the UK threshold. Vitamin D is a negative acute-phase reactant. This means its serum concentration falls during a systemic inflammatory response, which may occur with severe COVID-19. But, the panel noted that the potential mechanism of action of vitamin D in the context of COVID-19 is unknown. The effect of deficiency on COVID-19 outcomes is also unclear.

Overall, the panel noted that the evidence comes from diverse populations with varying care regimens and vitamin D doses. As such, evidence from the trials may not be generalisable to the UK.

The panel discussed the populations in different ongoing trials and noted that more research into specific subgroups of interest (for example, older people, children and pregnant women) could help determine the effects of vitamin D.

Values and preferences

The panel discussed that vitamin D3 (colecalciferol) supplements can be derived from an animal source. They noted that care providers need to consider people's concerns about using animal products because of a religious or ethical belief when they are discussing vitamin D products and their provision.

Resources

Vitamin D supplements are widely available in the NHS and public stores.

The panel discussed any resource implications that vitamin D provision for treating COVID-19 might have. They recognised that the doses from the trials are substantially higher than those used for daily supplementation in the UK. They agreed that, because vitamin D is not being recommended for this, there would be no resource implications.

Equity

The panel recognised the existing inequalities in vitamin D status, including those relating to location, health and family background. They noted that people who have dark skin and people who have low or no sunlight exposure, including people who spend more time indoors because of frailty or disability, are more likely to have vitamin D deficiency. They also acknowledged that people with dark skin are at greater risk of infection by SARS-CoV-2.

The panel also discussed that there is a lack of evidence on the effectiveness of vitamin D for COVID-19 in children, older people and when pregnant or breastfeeding, so the effect of treatment in these groups cannot be determined.

Acceptability

The acceptability of vitamin D for treating COVID-19 has not formed part of the evidence review. The panel believed that the lack of effect against COVID-19 shown in the studies and the limited information about adverse events may reduce the acceptability of vitamin D for treating COVID-19.

Feasibility

Vitamin D does not have marketing authorisation for the treatment of COVID-19.

Appendices

Appendix A: PICO table

PICO table

Review question: What is the effectiveness and safety of vitamin D supplementation for the treatment of COVID-19 in adults, young people and children?

Criteria	Notes
Population	Adults, young people and children with confirmed COVID-19.
Interventions	Vitamin D supplementation (all dosages, formulations and routes of administration). Note: Vitamin D supplementation as an adjunctive treatment will be included if other treatments are balanced out in the control arm.
Comparators	Placebo or standard care or no treatment
Outcomes	**Effectiveness outcomes** Mortality Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration) Hospitalisation (requirement and duration) Supplemental oxygen (requirement and duration) High-flow oxygen, continuous positive airway pressure or non-invasive ventilation (requirement and duration) Symptom resolution or clinical recovery (number and time until) Clinical worsening / deterioration (number and time until) Sustained recovery (development of long-term effects of COVID measured at least 4 weeks from onset of acute COVID-19) Virological clearance (negative PCR) / viral load

	Safety outcomes Adverse events Discontinuation due to adverse events **Definitions** The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings in which patients are managed for COVID-19 (primary or secondary care settings)
Subgroups	25(OH)D level at baseline (categorised as ≤25 nmol/L, 25-49 nmol/L, ≥50 nmol/L) Vitamin D dosage (categorised as ≤800 IU/day or >800 IU/day, as well as single versus multiple dose). Treatment settings (hospitalised or not hospitalised) Disease severity at baseline (mild/moderate/severe/critical) Adults > 50 years Children <12 years of age Gender Ethnic background Pregnant women

	Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • Non-randomised controlled trials • Systematic reviews of non-randomised controlled trials • Cohort studies • Before and after studies • Interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	Non-English language papers, studies that are only available as abstracts, and narrative reviews Animal studies Editorials, letters, news items, case reports and commentaries, conference abstracts and posters theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy

COVID-19 EPPI-R5 review

The search for the COVID-19 EPPI-R5 review was developed in compliance with section 8 of Appendix L of the NICE manual. EPPI-R5 is an application for systematic reviewing. Search results can be screened in EPPI-R5, and included studies are data extracted and assessed for risk of bias in the same application. The current version of Appendix L is: NICE (15 October 2020) Developing NICE guidelines: the manual. Process and methods [PMG20]. Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies.

The COVID-19 EPPI-R5 review contains papers published since 16 March 2020.

The development of the MEDLINE and Embase search strategy is detailed in the following preprint:

Levay, Paul; Finnegan, Amy (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. medRxiv 2021.06.11.21258749; doi:https://doi.org/10.1101/2021.06.11.21258749

The search is limited to those in the English language. Animal studies are removed from results. The following publication types are also excluded: MEDLINE: letter, historical article, comment, editorial, news, case reports Embase: letters, editorials, conferences, case reports.

From November 2020, the database search strategies were updated to include terms for the long-term effects of COVID-19. From August 2021, the database search strategies were updated to include terms for COVID-19 vaccines. The search results are managed in EPPI-R5. Duplicates are removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess ‘low-probability’ matches. All decisions made for the review can be accessed via the deduplication history. An automated process is used to download bioRxiv and medRxiv preprints. A daily RIS

file is automatically generated from the pre-sorted COVID-19 and SARS-COV-2 collection available on the website. This RIS file is uploaded to the EPPI-R5 review weekly. Since 10 August 2021, Europe PMC and NIH COVID-19 Portfolio are also searched weekly for preprints and deduplicated in EPPI-R5. The Information Services team at NICE peer reviewed the principal database strategies according to the standard NICE checklist that was adapted from the 2015 Peer review of electronic search strategies (PRESS) checklist.

Vitamin D searches

As this was a rapid evidence review, the surveillance repository* was used to identify evidence rather than running a bespoke evidence search. All records with relevance to COVID-19 and vitamin D, and which were added since the original review search was conducted, were brought together into a single group. Automated pattern matching was applied to the records in this group on 26 May 2022 in order to further focus the results and identify the most relevant records for screening.

The pattern matching code was created in Python using keywords relevant for the topic to enable automated study categorisation through natural language processing.

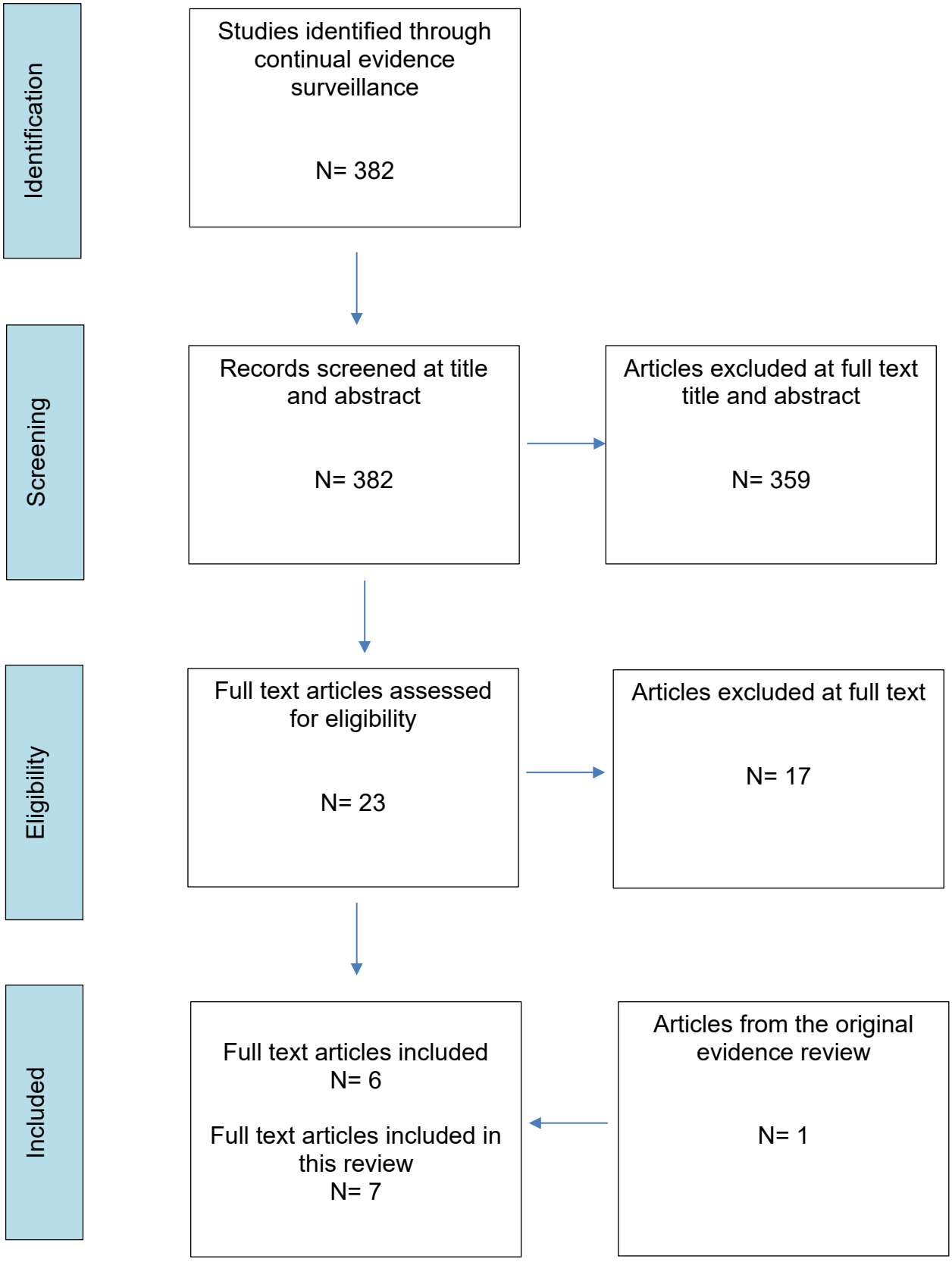
The steps implemented by the pattern matching code was as follows:

- Text pre-processing: Convert the words in title/abstracts to lower case and replace punctuations with space.
- Search the pre-processed titles/abstracts for the following patterns:
    - Containing either: vitamin D , calciferol
    - Exact words: vitamin D, vit D, ergocalciferol, cholecalciferol, calciferol

Testing was done on 30 May 2022 to test whether the vitamin D content in the COVID-19 EPPI-R5 review was comparable to evidence retrieved through vitamin D searches in MEDLINE and Embase. As quality assurance, the COVID-19 EPPI-R5 review excludes were exported and ran through the pattern matching code. No relevant studies for vitamin D were identified.

** The surveillance repository is an EPPI review that includes all search results from when surveillance searches for the COVID-19 health and social care emergency begin (March 2020) to current date.*

Appendix C: PRISMA diagram



Appendix D: Included studies

Cannata-Andia Jorge, B, Diaz-Sottolano, Augusto, Fernandez, Pehuen et al. (2022) 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 medicine 20(1): 83

Entrenas Castillo, Marta, Entrenas Costa, Luis Manuel, Vaquero Barrios, José Manuel et al. (2020) "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". The Journal of Steroid Biochemistry and Molecular Biology 203: 105751

Maghbooli, Zhila, Sahraian, Mohammad Ali, Jamali-Moghadam, Saeid Reza et al. (2021) Treatment with 25-hydroxyvitamin D3 (calcifediol) is associated with a reduction in the blood neutrophil-to-lymphocyte ratio marker of disease severity in patients hospitalized with COVID-19: a pilot, multicenter, randomized, placebo-controlled double blind clinical trial. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists

Mariani J, Antonietti L, Tajer C et al. (2022) High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: Multicentre randomized controlled clinical trial. PloS one 17(5): e0267918

Murai, Igor H, Fernandes, Alan L, Sales, Lucas P et al. (2021) Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. JAMA

Rastogi, Ashu, Bhansali, Anil, Khare, Niranjan et al. (2020) Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). Postgraduate medical journal

Sanchez-Zuno, Gabriela Athziri, Gonzalez-Estevez, Guillermo, Matuz-Flores, Monica Guadalupe et al. (2021) Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. Journal of clinical medicine 10(11)

Appendix E: Excluded studies at full text screening

Study	Reason for exclusion
Bishop, Charles, W, Ashfaq, Akhtar et al. Results From the REsCue Trial: A Randomized Controlled Trial with Extended-Release Calcifediol in Symptomatic Outpatients with COVID-19. medrxiv preprint	- No extractable outcomes
Bignardi Paulo, R, Castello Paula, Andrade, Aquino Bruno, Matos et al. Is the vitamin D status of patients with COVID-19 associated with reduced mortality?. medrxiv preprint	- Does not evaluate the role of vit D for treatment
BIGNARDI, PAULO; Castello, Paula; Aquino, Bruno (2022) Association between Vitamin D and COVID-19: a systematic review and meta-analysis.	- SR of observational trials
da Rocha, Aline Pereira, Atallah, Alvaro Nagib, Aldrighi, Jose Mendes et al. (2021) Insufficient evidence for Vitamin D use in COVID-19: A rapid systematic review. International journal of clinical practice: e14649	- Supporting evidence
Dissanayake Harsha, Anuruddhika, de Silva Nipun, Lakshitha, Sumanatilleke, Manilka et al. (2021) Prognostic and therapeutic role of vitamin D in COVID-19: systematic review and meta-analysis. The Journal of clinical endocrinology and metabolism	- Does not evaluate the role of vit D for treatment
Ghasemian, Roya, Shamshirian, Amir, Heydari, Keyvan et al. The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis Along with an Ecological Approach. medrxiv preprint	- Supporting evidence
Grove, Amy, Osokogu, Osemeke, Al-Khudairy, Lena et al. (2021) Association between vitamin D supplementation or serum vitamin D level and susceptibility to SARS-CoV-2 infection or COVID-19 including clinical course, morbidity and mortality outcomes? A systematic review. BMJ open 11(5): e043737	- SR of observational trials
Hosseini, B; El Abd, A; Ducharme F, M (2022) Effects of Vitamin D Supplementation on COVID-19 Related Outcomes: A Systematic Review and Meta-Analysis. Nutrients 14(10): 2134	- SR of observational trials *Includes a combination of randomised and non-randomised trials, only randomised trials were identified for inclusion*
Jolliffe, DA, Camargo, CA, Sluyter, JD et al. (2021) Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. The lancet diabetes and endocrinology 9(5): 276-292	- Does not evaluate the role of vit D for treatment
Kazemi, Asma, Mohammadi, Vida, Aghababaee, Sahar Keshtkar et al. (2021) Association of Vitamin D Status with SARS-CoV-2 Infection or COVID-19 Severity: A Systematic Review and Meta-analysis. Advances in nutrition (Bethesda, Md.)	- Does not evaluate the role of vit D for treatment
Nikniaz, Leila, Akbarzadeh Mohammad, Amin, Hosseinifard, Hossein et al. The impact of vitamin D supplementation on mortality rate and clinical outcomes of COVID-19 patients: A systematic review and meta-analysis. medrxiv preprint	- Relevant systematic review: included studies screened and included where relevant.
Rawat, Dimple, Roy, Avishek, Maitra, Souvik et al. (2021) "Vitamin D supplementation and COVID-19 treatment: A systematic review and meta-analysis". Diabetes & metabolic syndrome 15(4): 102189	- Relevant systematic review: included studies screened and included where relevant.
Shah, Komal, V, P, Varna et al. (2022) Does vitamin D supplementation reduce COVID-19 severity? - a systematic review. QJM : monthly journal of the Association of Physicians	- Primary studies included in data extraction
Stroehlein, Julia Kristin, Wallqvist, Julia, Iannizzi, Claire et al. (2021) Vitamin D supplementation for the treatment of COVID-19:	- Supporting evidence

a living systematic review. The Cochrane database of systematic reviews 5: cd015043	
Szarpak, Luiza, Filipiak, Krzysztof J, Gasecka, Aleksandra et al. (2021) Vitamin D supplementation to treat SARS-CoV-2 positive patients. Evidence from meta-analysis. Cardiology journal	- Primary studies included in data extraction
Teshome, Amare, Adane, Aynishet, Girma, Biruk et al. (2021) The Impact of Vitamin D Level on COVID-19 Infection: Systematic Review and Meta-Analysis. Frontiers in public health 9: 624559	- Does not evaluate the role of vit D for treatment
Varikasuvu Seshadri, Reddy, Thangappazham, Balachandar, Vykunta, Alekya et al. (2022) COVID-19 and Vitamin D (Co-VIVID Study): a systematic review and meta-analysis of randomized controlled trials. Expert review of anti-infective therapy	- Relevant systematic review: included studies screened and included where relevant.
Villasis-Keever Miguel, A, Lopez-Alarcon Mardia, G, Miranda-Novales, Guadalupe et al. (2022) Efficacy and Safety of Vitamin D Supplementation to Prevent COVID-19 in Frontline Healthcare Workers. A Randomized Clinical Trial. Archives of medical research	- Does not evaluate the role of vit D for treatment

Appendix F: Evidence tables

Cannata-Andia Jorge, 2022

Bibliographic Reference	Cannata-Andia Jorge, B; Diaz-Sottolano, Augusto; Fernandez, Pehuen; Palomo-Antequera, Carmen; Herrero-Puente, Pablo; Mouzo, Ricardo; Carrillo-Lopez, Natalia; Panizo, Sara; Ibanez Guillermo, H; Cusumano Carlos, A; Ballarino, Carolina; Sanchez-Polo, Vicente; Pefaur-Penna, Jacqueline; Maderuelo-Riesco, Irene; Calvino-Varela, Jesus; Gomez Monica, D; Gomez-Alonso, Carlos; Cunningham, John; Naves-Diaz, Manuel; Douthat, Walter; Fernandez-Martin Jose, L; COVID-VIT-D, trial; collaborators; 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 medicine; 2022; vol. 20 (no. 1); 83

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04552951
Study start date	04-Apr-2020
Study end date	22-Apr-2021
Aim of the study	To investigate if an oral bolus of cholecalciferol administered at hospital admission influences the outcomes of moderate-severe COVID-19 disease
Country/geographical location	Argentina, Chile, Guatemala, Spain
Study setting	Hospital
Population description	The study analysed data from 543 participants with moderate to severe COVID-19. The median age of participants was 58 years (IQR 46 -68.8). The majority of participants were male (64.9%) with varying comorbidities such as hypertension (43.5%), diabetes (24.5%) and cardiovascular disease (20.2%). Baseline characteristics were balanced between both treatment groups
Inclusion criteria	• Aged 18 years and older • Patients requiring hospitalisation for moderate-severe COVID-19 disease
Exclusion criteria	• Patients with dementia or not able to communicate • Patients who tested negative for SARS-CoV-2 despite clinical findings compatible with COVID-19 disease • Pregnant and lactating women • Patients who received any form of vitamin D in the previous 3 months • Patients allergic to vitamin D

Intervention dosage (loading)	Single-dose of 100,000 IU cholecalciferol upon admission
Intervention dosage (maintenance)	Not applicable
Intervention scheduled duration	Not applicable
Intervention actual duration	Not applicable
Intervention route of administration	Oral bolus at hospital admission
Comparator (where applicable)	No cholecalciferol. Participants were prescribed enoxaparin, ceftriaxone, methylprednisolone, azithromycin, dexamethasone as standard care.
Methods for population selection/allocation	Participants were randomised using a computer-generated list in a 1:1 ratio. This was a single-blinded study where participants were not informed of the treatment arm they were randomised in and medical staff were blinded to calcidiol levels at admission.
Methods of data analysis	Continuous variables were described by using median and interquartile range (IQR), and categorical variables were summarised using absolute and relative frequencies. Differences between groups were tested using the Kruskal-Wallis or Mann-Whitney test for continuous variables, and chi-squared test or Fisher's exact test (frequencies less than five), for categorical variables. Patients were described according to initial calcidiol levels (≤10, 10–15, 15–20, 20–25 and >25 ng/mL). The association between the serum calcidiol levels at hospital admission and length of hospitalisation was assessed using linear regression analysis. Binary logistic regression was used to study the association between calcidiol levels and pulmonary involvement and Cox regression was used for admission to ICU, and mortality. Multivariate adjustments with ten variables: demographics (N=2), comorbidities (N=5) and serum biochemical parameters (N=3) were performed in patients in whom at least 70% of these variables were collected. A complete set of gender, age-matched and control group analyses was performed. All statistical analyses were done using R statistical software version 4.0.4.
Attrition/loss to follow-up	Not reported
Source of funding	• Fondo Europeo de Desarrollo Regional • Plan de Ciencia, Tecnologia e Innovacion del Prinicipado de Asturias
Study limitations (Author)	The study did not analyse the time between symptom onset and administration of vitamin D. The study was not controlled by placebo which could introduce bias. Lastly, the trial population may have been heterogeneous due to the site/location differences.
Study limitations (Reviewer)	Adverse event data were not collected during the trial duration and at follow-up, as such safety profile of treatment is unclear. The study did not account for the effect of co-interventions administered to patients in the trial and there may have been significant

	differences in the populations from the trial centres and this site variation was not adjusted for in the analysis.
Other details	Not applicable

Study arms

Cholecalciferol (100,000 IU) (N = 274)

Control (N = 269)

Characteristics

Arm-level characteristics

Characteristic	Cholecalciferol (100,000 IU) (N = 274)	Control (N = 269)
Age Median (IQR)	59 (49 to 70)	57 (45 to 67)
Males No of events	n = 181 ; % = 66.1	n = 172 ; % = 63.9
Hypertension No of events	n = 114 ; % = 41.6	n = 124 ; % = 46.1
Diabetes No of events	n = 58 ; % = 21.2	n = 76 ; % = 28.3
Cardiovascular disease No of events	n = 55 ; % = 20.1	n = 60 ; % = 22.3
Asthma No of events	n = 14 ; % = 5.1	n = 16 ; % = 5.9
COPD No of events	n = 14 ; % = 5.1	n = 9 ; % = 3.3
Enoxaparin No of events	n = 210 ; % = 77.8	n = 191 ; % = 72.3
Ceftriaxone No of events	n = 100 ; % = 36.9	n = 94 ; % = 35.6
Methylprednisolone No of events	n = 99 ; % = 36.5	n = 94 ; % = 35.5
Azithromycin	n = 88 ; % = 32.4	n = 97 ; % = 36.6

Characteristic	Cholecalciferol (100,000 IU) (N = 274)	Control (N = 269)
No of events		
Dexamethasone No of events	n = 83 ; % = 30.5	n = 78 ; % = 29.4
Baseline calcidiol concentration (ng/mL) Median (IQR)	17 (11.8 to 22)	16.1 (11.5 to 22)

Outcomes

Cholecalciferol vs control

Outcome	Cholecalciferol (100,000 IU), , N = 274	Control, , N = 269
Median length of hospitalisation (days) Custom value	Median 10, 95% CI 9 to 10.5	Median 9.5, 95% CI 9 to 10.5
Admission to ICU No of events	n = 47 ; % = 17.2	n = 44 ; % = 16.4
Death No of events	n = 22 ; % = 8	n = 15 ; % = 5.6

Critical Appraisal - Cannata-Andia Jorge, 2022

Median length of hospitalisation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Insufficient detail on randomisation and concealment methods)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(No information on attrition or missing data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for	Some concerns *(Trial not blinded to assessors)*

Section	Question	Answer
	measurement of the outcome	
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Study is open label and there is a risk of confounding bias arising from differences between the population and symptom onset within the population. There is also a risk of confounding arising from the unadjusted effect of co-administered interventions on the outcome/effects of vitamin D)*
Overall bias and Directness	Overall Directness	Directly applicable

Admission to ICU

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Insufficient detail on randomisation and concealment methods)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(No information on attrition or missing data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Trial not blinded to assessors)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Study is open label and there is a risk of confounding bias arising from differences between the population and symptom onset within the population. There is also a risk of confounding arising from the unadjusted effect of co-administered*

Section	Question	Answer
		interventions on the outcome/effects of vitamin D)
Overall bias and Directness	Overall Directness	Directly applicable

Death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Insufficient detail on randomisation and concealment methods)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(No information on attrition or missing data)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Trial not blinded to assessors)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(Study is open label and there is a risk of confounding bias arising from differences between the population and symptom onset within the population. There is also a risk of confounding arising from the unadjusted effect of co-administered interventions on the outcome/effects of vitamin D)*
Overall bias and Directness	Overall Directness	Directly applicable

Entrenas Castillo, 2020

Bibliographic Reference	Entrenas Castillo, Marta; Entrenas Costa, Luis Manuel; Vaquero Barrios, José Manuel; Alcalá Díaz, Juan Francisco; López Miranda, José; Bouillon, Roger; Quesada Gomez, José Manuel; “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"; The Journal of Steroid Biochemistry and Molecular Biology; 2020; vol. 203; 105751

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04366908
Study start date	29-Apr-2020
Aim of the study	To assess the clinical effectiveness of calcifediol for patients hospitalised with COVID-19 in early stages.
Country/geographical location	Spain
Study setting	Hospital
Population description	The study randomised 76 participants who were hospitalised with COVID-19. The mean age of participants was 53 years (SD 10), with the majority of participants being male (59%). At baseline, there were slight differences in the prevalence of hypertension in the proportion of people who received calcifediol (24%) versus standard care (58%).
Inclusion criteria	• Patients hospitalised with COVID-19
Exclusion criteria	• Patients under the age of 18 years • Pregnant women
Intervention dosage (loading)	Patients received 0.532 mg calcifediol orally upon admission
Intervention dosage (maintenance)	0.266 mg capsule on days 3 and 7 and then weekly until hospital discharge
Intervention scheduled duration	Varied – until hospital discharge.
Intervention actual duration	Varied – until hospital discharge.
Intervention route of administration	Oral capsules
Comparator (where applicable)	Per hospital protocol: • Hydroxychloroquine - 400mg every 12 hours on the first day and 200mg every 12 hours for 5 days • Azithromycin - 500mg orally for 5 days • Patients with pneumonia and NEWS score =>5 a broad-spectrum antibiotic was added (ceftriaxone 2g every 24 hours for 5 days) This was also given to the intervention group.

Methods for population selection/allocation	Eligible participants were allocated at a 2:1 ratio using electronic randomisation prepared by statisticians. The list was accessible only to nonmasked specialists in the study in an attempt to minimise observation bias. The patients' data were recorded in the hospital's electronic medical record, with blind access by the technical data collectors and the statistician who carried out the study.
Methods of data analysis	Descriptive statistics were used for demographic, laboratory, and clinical prognostic factors related to COVID-19 for each treatment arm. The comparison between groups of quantitative variables were performed by using *t*-test for qualitative variables, χ2 tests and Fisher exact tests (with frequencies <5) were used. Univariate and multivariate logistic regressions were used to estimate the Odds ratio and 95 % CIs for the probability of admission to ICU. Significant p-value was considered when $p < 0.05$. All the analysis has been done using IBM SPSS Statistics software (SPSS).
Attrition/loss to follow-up	None
Source of funding	Not reported
Study limitations (Author)	The study is not a double-blinded placebo. The study did not collect BMI data and there could not evaluate the association of obesity as a prognostic factor for severe COVID-19. The study did not collect serum vitamin D levels at baseline or during treatment, so the extent of the effect of vitamin D could not be fully elucidated especially in patients who may have been deficient/insufficient.
Study limitations (Reviewer)	The study did not collect information on baseline vitamin D levels or during treatment, therefore the comparative efficacy of vitamin D as a treatment based on baseline vitamin D levels cannot be determined. There were also some variations between baseline characteristics in treatment groups, mainly hypertension and diabetes, which may have introduced confounding bias to the outcomes measured. Information on randomisation and allocation concealment was limited. Safety outcomes from follow-up patients were not fully reported for data extraction.
Other details	None

Study arms

Calcifediol (N = 50)

Standard care (N = 26)

Characteristics

Arm-level characteristics

Characteristic	Calcifediol (N = 50)	Standard care (N = 26)
Age Mean (SD)	53.14 (10.77)	52.77 (9.35)

Characteristic	Calcifediol (N = 50)	Standard care (N = 26)
Males No of events	n = 27 ; % = 54	n = 18 ; % = 69
Females No of events	n = 23 ; % = 46	n = 8 ; % = 31
Hypertension No of events	n = 11 ; % = 24.2	n = 15 ; % = 57.7
Cardiovascular disease No of events	n = 2 ; % = 4	n = 1 ; % = 3.9
Lung disease No of events	n = 4 ; % = 8	n = 2 ; % = 7.7
At least one risk factor No of events	n = 24 ; % = 48	n = 16 ; % = 61.6

Outcomes

Calcifediol vs control

Outcome	Calcifediol, , N = 50	Standard care, , N = 26
Proportion requiring ICU admission No of events	n = 1 ; % = 2	n = 13 ; % = 50
Death within proportion admitted to ICU No of events	n = 0 ; % = 0	n = 2 ; % = 15.4

Critical appraisal - Entrenas Castillo, 2020

Proportion requiring ICU admission

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(There were significant differences prevalence of hypertension in either treatment arm. Secondly there was insufficient detail on the randomisation process and allocation and it was not clear whether there was concealment or not)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of	Risk of bias for deviations from the intended interventions	Some concerns *(It is not clear whether the allocation was concealed or not and therefore there may be risk for bias)*

Section	Question	Answer
assignment to intervention)	(effect of assignment to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(It was unclear whether the allocation was concealed or not and there were variations between baseline characteristics such as hypertension and diabetes mellitus in treatment arms which may have impacted outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(It was unclear whether the allocation was concealed or not and there were variations between baseline characteristics such as hypertension and diabetes mellitus in treatment arms which may have impacted outcomes. Authors did not evaluate the effect of variations in baseline characteristics on mortality.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(It is not clear whether the allocation was concealed or not and therefore there may be risk for bias)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for	Low

Section	Question	Answer
	selection of the reported result	
Overall bias and Directness	Risk of bias judgement	High *(It was unclear whether the allocation was concealed or not and there were variations between baseline characteristics such as hypertension and diabetes mellitus in treatment arms which may have impacted outcomes. Authors did not evaluate the effect of variations in baseline characteristics on mortality.)*
Overall bias and Directness	Overall Directness	Directly applicable

Maghbooli, 2021

Bibliographic Reference	Maghbooli, Zhila; Sahraian, Mohammad Ali; Jamali-Moghadam, Saeid Reza; Asadi, Asma; Azadeh Zarei, M D; Zendehdel, Abolfazl; Varzandi, Tarlan; Mohammadnabi, Sara; Alijani, Neda; Karimi, Mehrdad; Shirvani, Arash; Holick, Michael F; Treatment with 25-hydroxyvitamin D3 (calcifediol) is associated with a reduction in the blood neutrophil-to-lymphocyte ratio marker of disease severity in patients hospitalized with COVID-19: a pilot, multicenter, randomized, placebo-controlled double blind clinical trial.; Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04386850
Study start date	May-2020
Study end date	Oct-2020
Aim of the study	To investigate the therapeutic efficacy of calcifediol in improving vitamin D status in vitamin D-deficient/vitamin D-insufficient patients infected with SARS-CoV-2 virus
Country/geographical location	Iran
Study setting	Hospital
Population description	The study recruited 106 participants with vitamin D deficiency at baseline. The mean age of participants was 49.1 years (SD 14.1). The majority of participants were male (60%) and average baseline serum vitamin D was 18.5 ng/mL for all participants. Baseline characteristics were balanced between treatment arms.
Inclusion criteria	• Older than 18 years old

	• No medications or disorders that would affect vitamin D metabolism • Vitamin D deficiency/insufficiency (serum vitamin D concentration <30ng/mL) • Ability and willingness to give informed consent and comply with protocol requirements
Exclusion criteria	• Pregnant or lactating women • Severe underlying diseases, such as advanced malignant tumour and end-stage lung disease • Chronic hepatic dysfunction and intestinal malabsorption syndromes including inflammatory bowel disease • Ongoing treatment with pharmacologic doses of vitamin D, vitamin D metabolites or analogues • Supplementation with over the counter formulations of vitamin D2 or vitamin D3 • Use of tanning bed or artificial ultraviolet exposure within the last 2 weeks • Consuming medication affecting vitamin D metabolism or absorptions • History of an adverse reaction to orally administered vitamin D, vitamin D metabolites or analogues • History of an elevated serum calcium concentration of >10.6 mg/dL or subjects with a history of hypercalciuria and kidney stones • History of conditions that could lead to high serum calcium concentration and some lymphomas that increase production of 1,25(OH)2D • Inability to give informed consent
Intervention dosage (loading)	25ug once a day
Intervention dosage (maintenance)	Not reported
Intervention scheduled duration	60 days
Intervention actual duration	60 days
Intervention route of administration	Oral capsule
Comparator (where applicable)	Placebo. All patients received the same standard care; a combination of hydroxychloroquine, azithromycin, and, for patients with pneumonia, ceftriaxone was used.
Methods for population selection/allocation	Participants were randomised with a ratio of 1:1 using a computer-generated randomisation program on the day of admission.
Methods of data analysis	Data were analysed using SPSS statistical software (version 20). Continue variables are presented as mean (standard deviation) for normally distributed data or median (interquartile range [IQR]) for nonnormally distributed data. The parametric and nonparametric

	tests, including the independent t-test and Mann-Whitney U test, were used to compare differences between continuous variables where appropriate. Categorical variables are presented as percentages. The chi-square or Fisher exact test was used to examine the percentage differences in the sign and symptoms, need for mechanical ventilation, need for intensive care, and hospital mortality rates in the treated and placebo groups. The standardised mean difference (SMD) was used to express the size of the intervention effect on increasing the circulating vitamin D concentrations in the treatment group compared with the placebo group. The logistic regression model was used to consider an independent association of the neutrophil-to-lymphocyte ratio (NLR) and clinical outcomes. All tests were 2-sided, and P values of <.05 were considered significant.
Attrition/loss to follow-up	Lost to follow up in the first month: Treatment: 16 Placebo: 21 Lost to follow up in the second month: Treatment: 13 Placebo: 12
Source of funding	Tehran University of Medical Sciences
Study limitations (Author)	The study included small sample size and it is suggested that although the dose used is higher than Endocrine Society recommendations, it was not high enough to improve vitamin D concentrations rapidly.
Study limitations (Reviewer)	The study included a small sample size and did not report on safety events and data during follow-up. The study only recruited participants with vitamin D deficiency (<30ng/mL) and therefore data is not generalisable to rest of the population. The study was underpowered to test for clinical significance.
Other details	Study only recruited participants who have vitamin D deficiency.

Study arms

Calcifediol 25ug/day (N = 53)

Placebo (N = 53)

Characteristics

Arm-level characteristics

Characteristic	Calcifediol 25ug/day (N = 53)	Placebo (N = 53)
Age Mean (SD)	50 (15)	49 (13)
Female No of events	n = 22 ; % = 41	n = 20 ; % = 38
Male No of events	n = 31 ; % = 59	n = 33 ; % = 62
Hypertension No of events	n = 18 ; % = 34	n = 15 ; % = 28
Cardiac disorder No of events	n = 5 ; % = 9	n = 8 ; % = 15
Diabetes No of events	n = 14 ; % = 26	n = 11 ; % = 21
Immunologic chronic disease No of events	n = 2 ; % = 4	n = 0 ; % = 0
Liver chronic disease No of events	n = 1 ; % = 1.9	n = 0 ; % = 0
Renal chronic disease No of events	n = 2 ; % = 4	n = 1 ; % = 2
Neurologic chronic disease No of events	n = 2 ; % = 4	n = 0 ; % = 0
Lung chronic disease No of events	n = 4 ; % = 7.5	n = 7 ; % = 13
Baseline serum vitamin D concentration (ng/mL) Mean (SD)	19 (8)	18 (8)

Outcomes

Calcifediol vs placebo

Outcome	Calcifediol 25ug/day, , N = 53	Placebo, , N = 53
Death No of events	n = 3 ; % = 6	n = 5 ; % = 9
Hospitalisation duration (days) Median (IQR)	5 (3)	6 (5.5)
Oxygen therapy No of events	n = 32 ; % = 60	n = 34 ; % = 64
Use of ventilator No of events	n = 2 ; % = 4	n = 5 ; % = 9
ICU admission No of events	n = 6 ; % = 11	n = 10 ; % = 19
ICU admission duration Median (IQR)	7 (0 to 7)	11 (0 to 11)

Critical appraisal - Maghbooli, 2021

Death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Hospitalisation duration

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Oxygen therapy

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Use of ventilator

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ICU admission

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ICU admission duration

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mariani, 2022

Bibliographic Reference	Mariani J; Antonietti L; Tajer C; Ferder L; Inserra F; Sanchez Cunto M; Brosio D; Ross F; Zylberman M; López DE; Luna Hisano C; Maristany Batisda S; Pace G; Salvatore A; Hogrefe JF; Turela M; Gaido A; Rodera B; Banega E; Iglesias ME; Rzepeski M; Gomez Portillo JM; Bertelli M; Vilela A; Heffner L; Annetta VL; Moracho L; Carmona M; Melito G; Martínez MJ; Luna G; Vensentini N; Manucha W; High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: Multicentre randomized controlled clinical trial.; PloS one; 2022; vol. 17 (no. 5)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04411446
Study start date	01-Aug-2020
Study end date	01-Jun-2021
Aim of the study	To evaluate whether a single high dose of vitamin D3 supplementation can prevent respiratory worsening among hospitalised people with mild-to-moderate COVID-19 who have risk factors for disease progression.
Country/geographical location	Switzerland
Study setting	Hospital
Population description	Adults in general wards in hospital with mild-to-moderate COVID-19 and risk factors for disease progression.
Inclusion criteria	18 or older patients and either gender, who had been admitted to general wards in the last 24 hours, with SARS-CoV-2 confirmed infection by reverse transcriptase–polymerase chain reaction, an expected hospitalisation for at least 24 hours, oxygen saturation ≥90% (measured by pulse oximetry) breathing ambient air, and at least one of the following conditions: • Age 45 or older (age 45 or older was selected to ensure that the study was adequately powered) • Hypertension • Diabetes • Chronic obstructive pulmonary disease • Asthma (at least moderate) • Cardiovascular disease (history of myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting or valve replacement surgery) • Body mass index ≥30 • Obesity was added as risk condition on October 13, 2020, since it was recognised as risk factor after the study began.
Exclusion criteria	• ≥72 hours hours since admission • Women of childbearing age

	• Requirement for >5 litres/minute of oxygen or mechanical ventilation • chronic kidney disease requiring haemodialysis • chronic liver failure • chronic supplementation with pharmacological vitamin D • treatment with anticonvulsants • sarcoidosis • malabsorption syndrome • hypercalcemia • life expectancy <6 months • allergy to study medication • any condition at precludes giving informed consent
Intervention dosage (loading)	A single oral dose of 500,000 IU of vitamin D3 soft gel capsules (5 capsules of 100,000 IU)
Intervention dosage (maintenance)	N/A
Intervention scheduled duration	1 dose only
Intervention actual duration	1 dose only
Intervention route of administration	Oral
Comparator (where applicable)	Matching placebo
Methods for population selection/allocation	Participants were randomly assigned in a 1:1 ratio to receive vitamin D3 (colecalciferol) or matching placebo, using an interactive web response system with permuted blocks of size 16 and 24. Randomisation was stratified by study site, diabetes (yes vs no) and age (≤60 vs >60 years).
Methods of data analysis	For the first stage, it was estimated that 168 patients would give the trial 80% power to detect a between study groups difference of one point in the change of rSOFA, assuming a standard deviation (SD) of 2, and a type I error of 5%. The sample size was increased to 200 patients to account for non-adherence with the protocol. Analyses were conducted according to the intention to treat principle. Continuous data are expressed as means and SD in cases where normal distribution held, and medians and interquartile ranges otherwise. Categorical data are presented as frequencies and percentages. To compare continuous variables, the Student's T-test or the Mann-Whitney U test, as appropriate, was used. Normality assumption was assessed using histograms and Shapiro-Wilk's test. Categorical variables were compared using Pearson's Chi2 test or Exact Fisher's test, as appropriate. Continuous outcomes are presented as differences in medians with the corresponding 95% confidence

	intervals (95% CI). Differences in medians and the confidence intervals for these differences were generated using smoothed bootstrap with 5000 replicates. Categorical outcomes are presented as risk ratios and 95% CIs. For primary outcome, the Wilcoxon-Mann-Whitney odds (WMWOdds) with the corresponding 95% CIs was computed. Pre-specified subgroups included age (≥60 vs <60 years), gender, diabetes, hypertension, cardiovascular disease, body mass index (>30 vs ≤30) and smoking status (current vs former or never). Subgroup analyses were carried out using ordinal regression models with an interaction term of the subgroup indicator variable by treatment. For primary outcome (change in the Sepsis related Organ Failure Assessment (rSOFA) between baseline and the highest rSOFA recorded up to day 7), a sensitivity analysis using ordinal regression models was carried out, adjusting the estimated treatment effects for stratification variables (site, diabetes and age). Also, a post-hoc adjusted analysis using a ordinal regression model to account for imbalances in COPD and asthma distribution was carried out. All tests are 2-sided and a p value <0.05 was considered as statistically significant. Analyses were conducted using R.
Attrition/loss to follow-up	None. No participants were lost to follow-up.
Source of funding	The National Agency for the Promotion of Research, Technological Development and Innovation. Vitamin D3 and placebo were donated by Raffo S.A., an argentinian pharmaceutical company.
Study limitations (Author)	A single high dose of vitamin D3 was chosen to ensure rapid and persistent high plasma levels of 25-OH VitD. However, it is possible that multiple dosing regimens could have different biological effects. The primary outcome assessed the effects of the treatment on the respiratory system, precluding to detect other potentially relevant effects. The follow-up was limited to hospital stay, longer follow-up would be necessary to detect relevant effects on recovery after discharge. Also, the study was underpowered to detect differences between groups on clinically important events (in other words, intensive care unit admission, mechanical ventilation, mortality). Participants were admitted with a median of 7 days from symptoms onset and most of them with established pneumonia; whether treatment earlier in the course of disease could modify the subsequent clinical course has yet to be determined. In the present study, the measured serum 25-OH VitD levels among the participants with blood samples were sufficient, whether different results would be obtained among a vitamin D deficient population remains to be determined.

	The SpO2/FiO2 ratio used as primary outcome have been validated as surrogate of PO2/FiO2. Although validation studies of SpO2/FiO2 ratio did not included patients with COVID19, the absence of effects on other measures of respiratory worsening besides rSOFA, gives reassurance to study results. Since women of childbearing age were excluded from the study our results are not generalizable to this population.
Study limitations (Reviewer)	Nothing further to add.
Other details	We did not add the outcomes 'duration of hospital stay' and 'duration of ICU stay' to the meta-analyses because this data was given as medians and IQR (this data was not given as mean averages).

Study arms

Vitamin D3 500,000 IU (N = 115)

Placebo (N = 103)

Characteristics

Arm-level characteristics

Characteristic	Vitamin D3 500,000 IU (N = 115)	Placebo (N = 103)
Mean age (SD) (years) Mean (SD)	59.8 (10.7)	58.3 (10.6)
Women (%) No of events	n = 51 ; % = 44.3	n = 52 ; % = 50.5
Median body mass index (kg/m²) Median (IQR)	28.4 (25.8 to 32.8)	27.7 (25.6 to 31.6)
Hypertension No of events	n = 47 ; % = 40.9	n = 47 ; % = 45.6
Diabetes No of events	n = 32 ; % = 27.8	n = 26 ; % = 25.2
Asthma or chronic obstructive pulmonary disease No of events	n = 17 ; % = 14.8	n = 9 ; % = 8.7
Cardiovascular disease No of events	n = 6 ; % = 5.2	n = 4 ; % = 3.9

Characteristic	Vitamin D3 500,000 IU (N = 115)	Placebo (N = 103)
Hypothyroidism No of events	n = 14 ; % = 12.2	n = 11 ; % = 10.7
Baseline vitamin D levels (nmol/L) Median (IQR)	81.25 (68 to 110.5)	76.25 (56.25 to 90.5)

Outcomes

Study timepoints

- 30 day (Clinical and adverse events were recorded until either day 30, discharge, or death - whichever occurred first.)

Outcomes

Outcome	Vitamin D3 500,000 IU, 30 day, N = 115	Placebo, 30 day, N = 103
Mechanical ventilation No of events	n = 5 ; % = 4.3	n = 6 ; % = 5.8
Oxygen therapy No of events	n = 17 ; % = 14.8	n = 15 ; % = 14.6
Mortality No of events	n = 5 ; % = 4.3	n = 2 ; % = 1.9
ICU admission No of events	n = 9 ; % = 7.8	n = 11 ; % = 10.7
People who experienced at least 1 adverse event No of events	n = 17 ; % = 14.8	n = 12 ; % = 11.7
Duration of Hospitalisation (days) Median (IQR)	6 (4 to 9)	6 (4 to 10)
Duration of ICU stay (days) Median (IQR)	9 (5 to 11.1)	9 (4 to 10.8)

Critical appraisal – Mariani 2022

Mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Oxygen therapy

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

ICU admission

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

People who experienced at least 1 adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Duration of hospitalisation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Duration of ICU stay

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Murai, 2021

Bibliographic Reference	Murai, Igor H; Fernandes, Alan L; Sales, Lucas P; Pinto, Ana J; Goessler, Karla F; Duran, Camila S C; Silva, Carla B R; Franco, Andre S; Macedo, Marina B; Dalmolin, Henrique H H; Baggio, Janaina; Balbi, Guilherme G M; Reis, Bruna Z; Antonangelo, Leila; Caparbo, Valeria F; Gualano, Bruno; Pereira, Rosa M R; Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial.; JAMA; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04449718
Study start date	02-Jun-2020
Study end date	27-Oct-2020
Aim of the study	To investigate the effect of a single high dose of vitamin D on hospital length of stay in patients with COVID-19
Country/geographical location	Brazil
Study setting	Hospital
Population description	The study analysed results from 236 participants with moderate to severe COVID-19 disease to receive either vitamin D3 or a placebo. The mean age of participants was 56.3 years (SD 14.4).

	The majority of participants were male (56.1%), with a majority having hypertension 52.8%. The average baseline serum vitamin d concentration was 20.9 ng/mL (SD 9.1). Baseline characteristics were balanced between both treatment groups
Inclusion criteria	• Patients aged 18 years and over • Diagnosis of COVID-19 via PCR testing or computed tomography scan findings compatible with disease • Diagnosis of flu syndrome with institutional criteria for hospitalisation on hospital admission • Respiratory rate greater than 24/min, oxygen saturation less than 93% • Risk factors for complications (e.g. heart disease, diabetes, systemic arterial hypertension, neoplasms, immunosuppression, pulmonary tuberculosis, obesity)
Exclusion criteria	• Patients who were unable to read and sign the written informed consent form • Patients who were already admitted and receiving invasive mechanical ventilation • Patients who received vitamin D supplementation >1000IU/day • Had kidney failure requiring dialysis or creatinine fo at least 2 mg/dL • Hypercalcaemia (calcium >10.5 mg/dL) • Pregnant or lactating women • Had expected hospital discharge in less than 24 hours
Intervention dosage (loading)	Single-dose of 200,000 IU
Intervention scheduled duration	Not applicable
Intervention actual duration	Not applicable
Intervention route of administration	Oral dose (dissolved in peanut oil solution)
Comparator (where applicable)	Placebo (peanut oil solution). Some information was provided on concomitant medications received but unclear standard care regime.
Methods for population selection/allocation	Patients were assigned in a 1:1 ratio to the vitamin D3 group or the placebo group. The randomisation list was created using a computer-generated code with block sizes of 20. A staff member who had no role in the study managed the randomisation. Outcomes were assessed at baseline and on hospital discharge. The vitamin D3 group received a single, oral dose of 200 000 IU of vitamin D3 dissolved in a 10-mL peanut oil solution. This selected dose is in the recommended range for effectively treating patients with 25-hydroxyvitamin D deficiency.16 Patients from the placebo group received 10 mL of a peanut oil solution. The solutions were identical in colour, taste, smell, consistency, and container. They were prepared by the pharmacy unit of the Clinical Hospital and labelled by a staff member who did not participate in the study.

	Patients and investigators remained blinded to randomization until the final analysis.
Methods of data analysis	The number of participants was chosen on the basis of feasibility, based on resources, the capacity of research staff and facility, and available patients, in line with current recommendations. Approximately 200 patients were expected to be enrolled, with the expectation of 16 to 17 eligible patients per week in both centres. Although the actual enrolment was approximately 20 patients per week, the planned date for ending enrolment was not changed to increase the study power, resulting in a larger final sample size than originally anticipated. The minimal clinically important difference between groups for the length of stay among patients with COVID-19 is unknown. The log-rank test was used to compare the Kaplan-Meier estimate curves for the length of stay, with deaths being right-censored in the analysis. Post hoc adjusted analyses for the primary outcome of length of stay was performed using Cox regression models to estimate hazard ratios (HRs) with corresponding 2-sided 95% CIs, considering potential confounders that were not fully balanced by randomization, prespecified as $P < .20$ for baseline comparisons between groups. These confounders were joint pain, sore throat, hypertension, diabetes, parathyroid hormone, and creatinine. The proportionality assumption for Cox regression models was confirmed by assessing Schoenfeld residuals. Generalised estimating equations for repeated measures were used for testing possible differences in laboratory parameters and duration of mechanical ventilation (using death as a covariate for the latter), assuming group and time (when applicable) as fixed factors, with marginal distribution, and a first-order autoregressive correlation matrix to test the main and interaction effects. Bonferroni adjustment was performed for generalised estimating equation analyses to maintain a family-wise 2-sided significance threshold of .05, considering 6 pairwise comparisons for all secondary endpoints. Percentages were compared between groups using $\chi 2$ and Fisher exact tests for mortality, admission to the intensive care unit, and mechanical ventilation requirement. All analyses were performed according to the patient randomisation group, with retention of all patients in the analyses except for those who withdrew consent before receiving the intervention. There was no imputation for missing data. For laboratory parameters, missingness was handled by generalised estimating equation models, assuming that missingness was at random based on the nonsignificant differences between groups for the proportion of missing data. Statistical analyses were performed with IBM-SPSS software, version 20.0. The significance level was set at 2-sided $\alpha = .05$.
Attrition/loss to follow-up	Not reported
Source of funding	• FAPSEP • Conselho Nacional de Desenvolvimento Cientifico e Tecnologico

Study limitations (Author)	The small sample size of the trial indicates that it was not powered to detect clinically meaningful differences in the effects of treatment. The results could have also been affected by heterogeneity in the treatment regimens of pre-existing conditions and the percentage of patients with vitamin D deficiency in the trial was not prominent. Patients received vitamin D supplementation after a long time from symptom onset (mean 10.3 days).
Study limitations (Reviewer)	The study included a small sample size and did not adjust for heterogeneity between treatment regimens and the effect of co-administered interventions on the effect of vitamin D3. Data from the follow-up period of the study was not presented and adverse events data were not reported in the supplement.
Other details	Not applicable

Study arms

Vitamin D 200,000 IU (N = 119)

Placebo (N = 118)

Characteristics

Arm-level characteristics

Characteristic	Vitamin D 200,000 IU (N = 119)	Placebo (N = 118)
Age Mean (SD)	56.5 (13.8)	56 (15)
Male No of events	n = 70 ; % = 58.8	n = 63 ; % = 53.4
Female No of events	n = 49 ; % = 41.2	n = 55 ; % = 46.6
White No of events	n = 62 ; % = 52.1	n = 68 ; % = 57.6
Pardo (mixed ethnicity) No of events	n = 37 ; % = 31.1	n = 36 ; % = 30.5
Black No of events	n = 19 ; % = 16	n = 14 ; % = 11.9

Characteristic	Vitamin D 200,000 IU (N = 119)	Placebo (N = 118)
Asian No of events	n = 1 ; % = 0.8	n = 0 ; % = 0
Oxygen supplementation No of events	n = 86 ; % = 72.3	n = 95 ; % = 80.5
No oxygen therapy No of events	n = 16 ; % = 13.4	n = 9 ; % = 7.6
Non-invasive ventilation No of events	n = 17 ; % = 14.3	n = 14 ; % = 11.9
Hypertension No of events	n = 67 ; % = 56.3	n = 58 ; % = 49.2
Diabetes No of events	n = 49 ; % = 41.2	n = 35 ; % = 29.7
Cardiovascular disease No of events	n = 16 ; % = 13.4	n = 16 ; % = 13.6
Rheumatic disease No of events	n = 13 ; % = 10.9	n = 10 ; % = 8.5
Asthma No of events	n = 7 ; % = 5.9	n = 7 ; % = 5.9
Chronic obstructive pulmonary disease No of events	n = 7 ; % = 5.9	n = 5 ; % = 4.2
Chronic kidney disease No of events	n = 2 ; % = 1.7	n = 0 ; % = 0
Baseline serum vitamin D concentration (ng/mL) Mean (SD)	21.2 (10.1)	20.6 (8.1)

Outcomes

Vitamin D3 vs Placebo

Outcome	Vitamin D 200,000 IU, , N = 119	Placebo, , N = 118
Length of hospital stay (days) Median (IQR)	7 (4 to 10)	7 (5 to 13)
Mortality No of events	n = 9 ; % = 7.6	n = 6 ; % = 5.1
Admission to ICU No of events	n = 19 ; % = 16	n = 25 ; % = 21.2
Need for mechanical ventilation No of events	n = 9 ; % = 7.6	n = 17 ; % = 14.4
Mean duration of mechanical ventilation (days) Nominal	14	12.8

Critical appraisal - Murai, 2021

Mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Details on randomisation and allocation methodology well described)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and assessors were blinded to allocation therefore risk of bias is low, there was one incident of a deviation in treatment protocol where one participant received an extra dose of vitamin D3 as part of a fracture treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 237/240 randomised participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Study was double-blinded and therefore any risk of bias is mitigated)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Details on randomisation, outcome measurement and effect of adherence and assessment of the intervention are adequately and accurately reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Length of hospital stay

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Details on randomisation and allocation methodology well described)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and assessors were blinded to allocation therefore risk of bias is low, there was one incident of a deviation in treatment protocol where one participant received an extra dose of vitamin D3 as part of a fracture treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all participants 237/240 randomised)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Study was double-blinded so bias was mitigated)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low *(Details on randomisation, outcome measurement and effect of adherence and assessment of the intervention are adequately and accurately reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Admission to ICU

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Details on randomisation and allocation methodology well described)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of	Risk of bias for deviations from the intended interventions	Low *(Participants and assessors were blinded to allocation therefore risk of bias is low, there was one incident of a*

Section	Question	Answer
assignment to intervention)	(effect of assignment to intervention)	*deviation in treatment protocol where one participant received an extra dose of vitamin D3 as part of a fracture treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 237/240 participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Study was double-blinded and therefore risk of bias is mitigated)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low *(Details on randomisation, outcome measurement and effect of adherence and assessment of the intervention are adequately and accurately reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Need for mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Details on randomisation and allocation methodology well described)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and assessors were blinded to allocation therefore risk of bias is low, there was one incident of a deviation in treatment protocol where one participant received an extra dose of vitamin D3 as part of a fracture treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 237/240 participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low *(Details on randomisation, outcome measurement and effect of adherence*

Section	Question	Answer
		and assessment of the intervention are adequately and accurately reported)
Overall bias and Directness	Overall Directness	Directly applicable

Mean duration of mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Details on randomisation and allocation methodology well described)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Participants and assessors were blinded to allocation therefore risk of bias is low, there was one incident of a deviation in treatment protocol where one participant received an extra dose of vitamin D3 as part of a fracture treatment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for 237/240 participants)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low *(Details on randomisation, outcome measurement and effect of adherence and assessment of the intervention are adequately and accurately reported)*
Overall bias and Directness	Overall Directness	Directly applicable

Rastogi, 2020

Bibliographic Reference	Rastogi, Ashu; Bhansali, Anil; Khare, Niranjan; Suri, Vikas; Yaddanapudi, Narayana; Sachdeva, Naresh; Puri, G D; Malhotra, Pankaj; Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study).; Postgraduate medical journal; 2020

Study details

Study design	Randomised controlled trial (RCT)

Trial registration (if reported)	NCT04459247
Study start date	15-Jun-2020
Study end date	21-Apr-2021
Aim of the study	To determine the effect of high dose colecalciferol supplementation on SARS-CoV-2 viral clearance
Country/geographical location	India
Study setting	Hospital
Population description	The study analysed results from 40 participants with asymptomatic or mildly symptomatic COVID-19 and vitamin deficiency. The median age of participants in the intervention group was 50 years (IQR 36 - 51) and in the control group 47.5 years (IQR 39.3 - 49.2). The study included 50% females with baseline vitamin D concentration was 8.5 ng/mL (IQR 7.1 - 13.1) in the intervention arm and 9.54 ng/mL (IQR 8.1 - 12.5) in the control arm. Baseline characteristics between participant groups were balanced.
Inclusion criteria	• Patients with SARS-CoV-2 infection who were symptomatic or asymptomatic • Patients without comorbidities
Exclusion criteria	• Patients requiring invasive mechanical ventilation • Patients with significant comorbidities • Patients unable to take oral supplementation like those requiring invasive ventilation • Or with significant comorbidities like uncontrolled hyperglycaemia or hypertension
Intervention dosage (loading)	60,000 IU colecalciferol once per day
Intervention dosage (maintenance)	60,000 IU colecalciferol once per day for 7 days
Intervention scheduled duration	7 days
Intervention actual duration	Varied as patients who after 7 days had vitamin D serum concentration <50 ng/mL continued the treatment for 7 more days
Intervention route of administration	Oral solution in nano droplet form
Comparator (where applicable)	Placebo (5ml distilled water for 7 days). All participants received standard care for the SARS-CoV-2 infection and pre-existing co-morbidities as per institute protocol
Methods for population selection/allocation	Not reported - Supplementary material not found
Methods of data analysis	A modified intention-to-treat analysis was performed. The normality of the data was assessed by Kolmogorov–Smirnov test and mean ± SD is used to depict data following a normal gaussian pattern

	and median and inter-quartile range for skewed data. Student T-test was used to compare the means of two groups for parametric variables and Mann–the Whitney U-test for non-parametric variables. The proportion of participants achieving SARS-CoV-2 RNA negativity in the two groups was compared with Fischer Exact (2 by 2 tailed) test. SPSS version 22 was used for data analysis and a p-value <0.05 was considered significant.
Attrition/loss to follow-up	None
Source of funding	None
Study limitations (Author)	Only mildly symptomatic or asymptomatic participants were enrolled and therefore the findings cannot be generalised to severe cases of COVID-19. The placebo used in the study was not matched in taste and consistency to the intervention. Lastly follow-up data on the toxicity of high dose of vitamin D was not studied.
Study limitations (Reviewer)	The study does not include safety data from participants and included a small sample size. Most of the baseline characteristics were matched between participant groups except for serum calcium concentration. Secondly, the placebo was not properly concealed from participants or controlled in a similar way to the intervention, therefore, introducing bias. Insufficient detail on the randomisation and allocation methods (supplementary material not found). Time between SARS-CoV-2 positive PCR and treatment allocation not reported.
Other details	Not applicable

Study arms

Colecalciferol 60,000 IU/day (N = 16)

Placebo (N = 24)

Characteristics

Arm-level characteristics

Characteristic	Colecalciferol 60,000 IU/day (N = 16)	Placebo (N = 24)
Age Median (IQR)	50 (36 to 51)	47.5 (39.3 to 49.2)
Male No of events	n = 6 ; % = 37.5	n = 14 ; % = 58.3
Female	n = 10 ; % = 62.5	n = 10 ; % = 41.7

Characteristic	Colecalciferol 60,000 IU/day (N = 16)	Placebo (N = 24)
No of events		
Baseline vitamin D concentration (ng/mL) Median (IQR)	8.6 (7.1 to 13.1)	9.54 (8.1 to 12.5)

Outcomes

Colecalciferol vs Placebo

Outcome	Colecalciferol 60,000 IU/day, , N = 16	Placebo, , N = 24
Proportion who became SARS-CoV-2 negative within 3 weeks No of events	n = 10 ; % = 62.5	n = 5 ; % = 20.8

Critical appraisal - Rastogi, 2020

Proportion of patients who became SARS-CoV-2 negative within 3 weeks

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(The study protocol and design details are not available online and therefore details on study randomisation and allocation concealment is lacking)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Due to insufficient detail on study randomisation and blinding, the effect on assignment to intervention cannot be elucidated.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No information on study plan and protocol is available)*
Overall bias and Directness	Risk of bias judgement	High *(The study supplemental material*

Section	Question	Answer
		which may include further detail on study design and analysis was not found therefore information on randomisation process on analysis plans was not found)
Overall bias and Directness	Overall Directness	Directly applicable

Mean duration to SARS-CoV-2 negativity

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(The study protocol and design details are not available online and therefore details on study randomisation and allocation concealment is lacking)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Due to insufficient detail on study randomisation and blinding, the effect on assignment to intervention cannot be elucidated.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No information on study plan and protocol is available)*
Overall bias and Directness	Risk of bias judgement	High *(The study supplemental material which may include further detail on study design and analysis was not found therefore information on randomisation process on analysis plans was not found)*
Overall bias and Directness	Overall Directness	Directly applicable

Sanchez-Zuno, 2021

Bibliographic Reference	Sanchez-Zuno, Gabriela Athziri; Gonzalez-Estevez, Guillermo; Matuz-Flores, Monica Guadalupe; Macedo-Ojeda, Gabriela; Hernandez-Bello, Jorge; Mora-Mora, Jesus Carlos; Perez-Guerrero, Edsaul Emilio; Garcia-Chagollan, Mariel; Vega-Magana, Natali; Turrubiates-Hernandez,

Francisco Javier; Machado-Sulbaran, Andrea Carolina; Munoz-Valle, Jose Francisco; Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation.; Journal of clinical medicine; 2021; vol. 10 (no. 11)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	Not reported
Aim of the study	To evaluate the effects of supplementation with 10,000 IU/daily of vitamin D3 in mildly symptomatic or asymptomatic COVID-19 patients and its relationship with biochemical parameters and clinical features.
Country/geographical location	Mexico
Study setting	Primary care/Community
Population description	The study included 42 participants with mild to asymptomatic COVID-19 disease in its analysis and the median age was 43 years (range 20 - 74). The study included 52.4% females while 16.7% had hypertension, 4.8% had diabetes and 2.4% had asthma.
Inclusion criteria	• Mild disease • Over 18 years of age • Not taking any vitamin D supplementation at recruitment
Exclusion criteria	Not reported
Intervention dosage (loading)	10,000 IU vitamin D3
Intervention dosage (maintenance)	10,000 IU vitamin D3
Intervention scheduled duration	14 days
Intervention actual duration	14 days
Intervention route of administration	Oral capsules in the morning to accompany a meal
Comparator (where applicable)	Control (did not receive supplementation). No further detail on standard care received.
Methods for population selection/allocation	Details on randomisation and allocation not reported
Methods of data analysis	Quantitative variables are expressed as medians (ranges), and qualitative characteristics are described as frequencies (%). The chi-square test (or Fisher's exact test) was used for comparison proportions between groups. Comparisons of quantitative variables

	between outpatients with sufficient vitamin D and insufficient vitamin D serum levels, as well as comparisons of outpatients with and without supplementation, were performed using the Mann-Whitney U test. Spearman's test identified the correlations between vitamin D serum levels and clinical variables. The comparison of vitamin D serum levels in patients with supplementation and those without supplementation was performed using the Wilcoxon Rank-Sum Test. To identify factors associated with a high number of symptoms at baseline, we performed a logistic regressions analysis. We used R version 4.0.3 to perform the statistical analyses and ggplot2 package for graphics. A p-value ≤ 0.05 was considered statistically significant
Attrition/loss to follow-up	Not reported
Source of funding	National Council of Science and Technology Universidad de Guadalajara (Fortalecimiento de la Investigacion y el Posgrado)
Study limitations (Author)	Serum vitamin D levels were not reported in day 14 in control subjects. The study was not designed as double blind.
Study limitations (Reviewer)	The study included a small number of participants and insufficient detail on participant selection, randomisation and allocation were provided. The study did not report the time between symptom onset and receipt of treatment which could affect the analysed outcomes. Lastly the study did not report any safety outcomes.
Other details	None

Study arms

Vitamin D3 10,000 (N = 22)

Control (N = 20)

Characteristics

Arm-level characteristics

Characteristic	Vitamin D3 10,000 (N = 22)	Control (N = 20)
Age Median (IQR)	44 (20 to 71)	43 (21 to 78)
Female No of events	n = 7 ; % = 31.8	n = 6 ; % = 30

Characteristic	Vitamin D3 10,000 (N = 22)	Control (N = 20)
Arterial hypertension No of events	n = 4 ; % = 18.2	n = 3 ; % = 15
Diabetes mellitus No of events	n = 0 ; % = 0	n = 2 ; % = 10
Smoking No of events	n = 2 ; % = 9.1	n = 2 ; % = 10
Asthma No of events	n = 1 ; % = 2.4	n = 0 ; % = 0
Total vitamin D at baseline (ng/mL) Median (IQR)	20.2 (12.2 to 45.9)	23.4 (12.1 to 45.6)

Outcomes

Vitamin D vs Control

Outcome	Vitamin D3 10,000 , , N = 22	Control, , N = 20
Positive PCR Test Day 7 No of events	n = 13 ; % = 59.1	n = 9 ; % = 45
Positive PCR Test Day 14 No of events	n = 14 ; % = 63.6	n = 8 ; % = 40
Presence of symptoms Day 7 No of events	n = 12 ; % = 60	n = 12 ; % = 54.5
Presence of symptoms Day 14 No of events	n = 1 ; % = 5	n = 0 ; % = 0

Critical appraisal - Sanchez-Zuno, 2021

Positive PCR test Day 7

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Randomisation and allocation methods are not available)*
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended	Some concerns *(Participants and trial*

Section	Question	Answer
interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*assessors were not blinded and no information was provided on experiment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Study design, analysis plan and full protocol not available.)*
Overall bias and Directness	Risk of bias judgement	High *(Study design, analysis plan not available. It is not clear whether assessors were blinded or not)*
Overall bias and Directness	Overall Directness	Directly applicable

Positive PCR test Day 14

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Randomisation and allocation methods are not available)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and trial assessors were not blinded and no information was provided on experiment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Study design, analysis plan not available)*
Overall bias and Directness	Risk of bias judgement	High *(Study design, analysis plan not available. It is not clear whether assessors were blinded or not)*
Overall bias and Directness	Overall Directness	Directly applicable

Presence of symptoms - day 7

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Randomisation and allocation methods are not available)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and trial assessors were not blinded and no information was provided on experiment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Study design, analysis plan and full protocol not available)*
Overall bias and Directness	Risk of bias judgement	High *(Study design, analysis plan not available. It is not clear whether assessors were blinded or not)*
Overall bias and Directness	Overall Directness	Directly applicable

Presence of symptoms - day 14

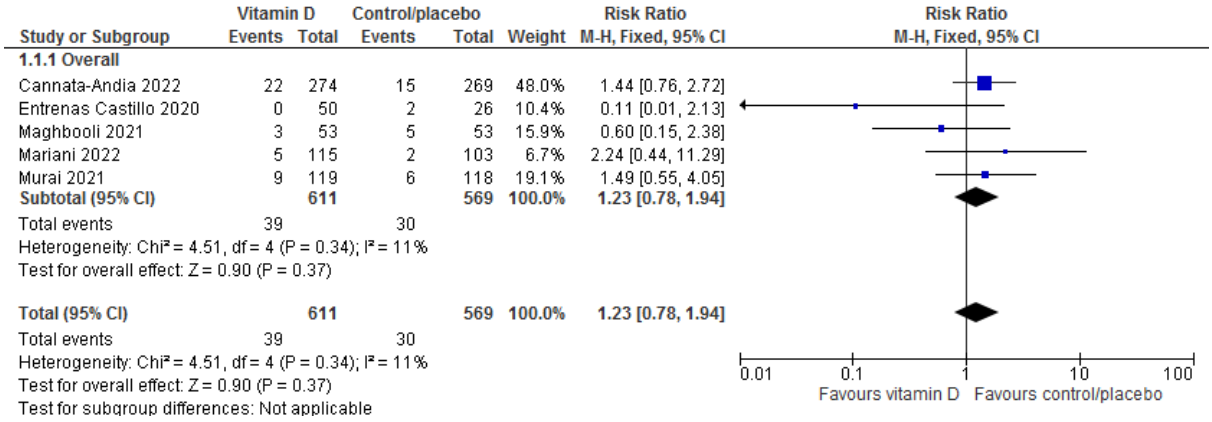
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	High *(Randomisation and allocation methods not available)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Participants and trial assessors were not blinded and no information was provided on experiment)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Study design, analysis plan and full protocol not available)*
Overall bias and Directness	Risk of bias judgement	High *(Study design, analysis plan*

Section	Question	Answer
		not available. It is not clear whether assessors were blinded or not)
Overall bias and Directness	Overall Directness	Directly applicable

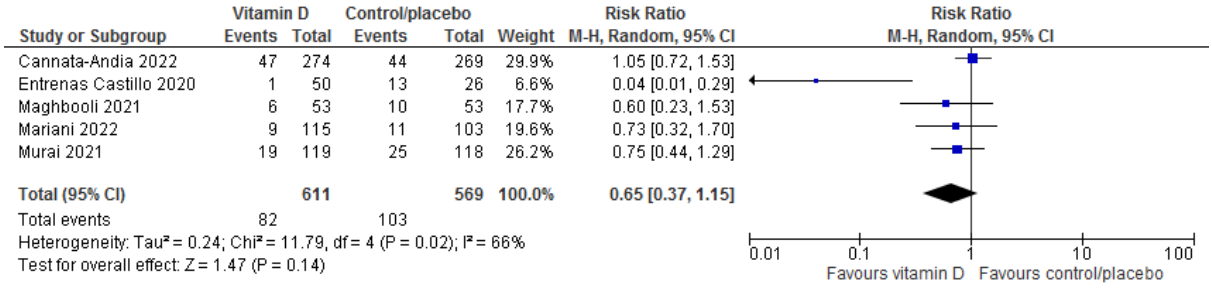
Appendix G: Forest Plots

Forest plots were produced where raw data was reported in the study.

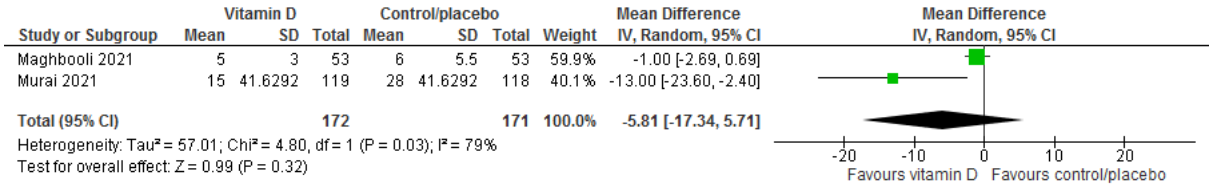
Mortality



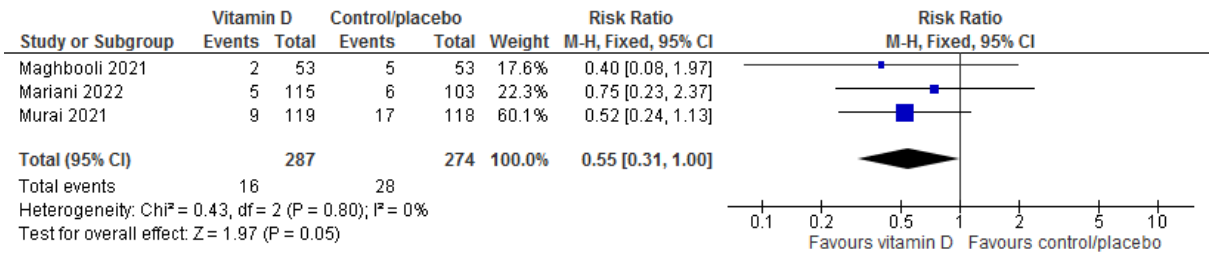
ICU admission



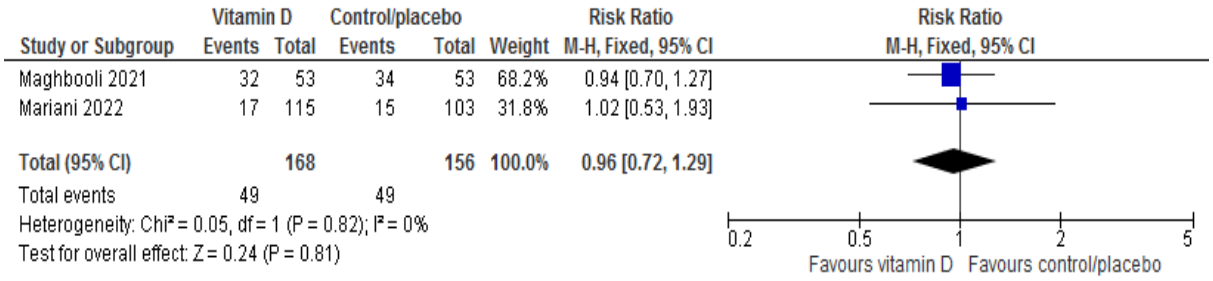
Mean duration of hospitalisation



Mechanical ventilation



Oxygen therapy



Appendix H: GRADE profile

Vitamin D compared to standard care for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard care	With Vitamin D		Risk with standard care	Risk difference with Vitamin D
Mortality											
1180 (5 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	30/569 (5.3%)	39/611 (6.4%)	**RR 1.23** (0.78 to 1.94)	53 per 1,000	**12 more per 1,000** (from 12 fewer to 50 more)
ICU admission											
1180 (5 RCTs)	serious[b]	not serious	not serious	serious[a]	none	Low	103/569 (18.1%)	82/611 (13.4%)	**RR 0.65** (0.37 to 1.15)	181 per 1,000	**63 fewer per 1,000** (from 114 fewer to 27 more)
Mechanical Ventilation											
561 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	28/274 (10.2%)	16/287 (5.6%)	**RR 0.55** (0.31 to 1.00)	102 per 1,000	**46 fewer per 1,000** (from 71 fewer to 0 fewer)
Oxygen therapy											

Certainty assessment							Summary of findings				
324 (2 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	49/156 (31.4%)	49/168 (29.2%)	**RR 0.96** (0.72 to 1.29)	314 per 1,000	**13 fewer per 1,000** (from 88 fewer to 91 more)
Presence of symptoms - Day 7											
42 (1 RCT)	very serious[c]	not serious	not serious	very serious[d]	none	Very low	9/20 (45.0%)	13/22 (59.1%)	**RR 1.31** (0.72 to 2.38)	450 per 1,000	**140 more per 1,000** (from 126 fewer to 621 more)
Presence of symptoms - Day 14											
42 (1 RCT)	very serious[c]	not serious	not serious	very serious[d]	none	Very low	8/20 (40.0%)	14/22 (63.6%)	**RR 1.59** (0.85 to 2.97)	400 per 1,000	**236 more per 1,000** (from 60 fewer to 788 more)
Positive PCR test - Day 7											
42 (1 RCT)	very serious[c]	not serious	not serious	very serious[d]	none	Very low	12/20 (60.0%)	12/22 (54.5%)	**RR 0.91** (0.54 to 1.53)	600 per 1,000	**54 fewer per 1,000** (from 276 fewer to 318 more)
Positive PCR test - Day 14											
42 (1 RCT)	very serious[c]	not serious	not serious	very serious[d]	none	Very low	1/20 (5.0%)	0/22 (0.0%)	**RR 0.30** (0.01 to 7.07)	50 per 1,000	**35 fewer per 1,000** (from 50 fewer to 304 more)
SARS-CoV-2 negativity within 3 weeks											

Certainty assessment							Summary of findings				
40 (1 RCT)	very serious[c]	not serious	not serious	not serious	none	Low	5/24 (20.8%)	10/16 (62.5%)	**RR 3.00** (1.26 to 7.14)	208 per 1,000	**417 more per 1,000** (from 54 more to 1,000 more)

Mean time until SARS-CoV-2 negativity

40 (1 RCT)	very serious[e]	not serious	not serious	very serious[d]	none	Very low	24	16	-		MD **0** (3.94 lower to 3.94 higher)

Mean duration of hospitalisation

343 (2 RCTs)	serious[f]	not serious	not serious	serious[a]	none	Low	171	172	-		MD **5.81 lower** (17.34 lower to 5.71 higher)

Mean duration of mechanical ventilation

237 (1 RCT)	not serious	not serious	not serious	serious[a]	none	Moderate	118	119	-		MD **2.2 higher** (8.4 lower to 12.8 higher)

Mean duration of hospitalisation

543 (1 RCT)	serious[f]	not serious	not serious	serious[a]	none	Low	Difference : 0.5 more (95% CI 17.34 lower - 5.71 more)				

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Confidence interval includes line of no effect
b. Insufficient reporting around randomisation
c. No information on study design and analysis were available. It is not clear from manuscript whether assessors were blinded or not.
d. Confidence interval includes line of no effect, with a small sample size
e. Study design and randomisation information not available.
f. Some concerns due to the presence of confounding from the lack of adjustment for co-administered interventions

Appendix I: Recommendations for research

Question	**What is the clinical effectiveness and safety of vitamin D for treating COVID-19 in children, young people and adults?**
Population	People with COVID-19, particularly groups for which current evidence is lacking, for example: • in pregnancy and breastfeeding • people 65 years and over • children and young people under 18 • people from minority ethnic family backgrounds • people with risk factors for severe COVID-19
Intervention(s)	Vitamin D (800 IU/day or less and more than 800 IU/day; single or multiple doses)
Comparator(s)	• standard care • placebo
Outcomes	**Effectiveness outcomes:**

	• all-cause hospitalisation • all-cause mortality • need for mechanical ventilation • need for non-invasive respiratory support • admission to intensive care • symptom alleviation • adherence to therapy • long-term effects of COVID-19 (at least 4 weeks from acute COVID-19 onset) **Safety outcomes:** • any adverse event • adverse event leading to trial discontinuation • serious adverse events