eunethta

EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Gesundheit Österreich GmbH

"Rolling Collaborative Review" of Covid-19 treatments

HIGH-DOSE VITAMIN D FOR THE TREATMENT OF COVID-19

Project ID: RCR20

Monitoring Report

Template version June 2021

This Rolling Collaborative Review Living Document was started as part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020). Since EUnetHTA JA3 has ended in May 2021, the authors of this RCR are continuing on a voluntary basis staying committed to the agreed methodology of EUnetHTA Joint Action 3.

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**15/02/2021**	First version
V 2.0	**15/03/2021**	Second version
V 3.0	**17/05/2021**	Third version
V 4.0	**15/07/2021**	Forth version
V 5.0	**29/11/2021**	Fifth version

Major changes from previous version

Chapter, page no.	Major changes from version 4.0
Chapter 4, p. 14-29	3 RCTs have been added.
Chapter 4, p. 30-36	3 ongoing studies have been added, 1 has been removed because of the study being published, 1 has been removed because of the study being terminated.

Disclaimer

The content of this “Rolling Collaborative Review” (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA’s participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Rolling Collaborative Review team

Author(s)	Gesundheit Österreich GmbH (GÖG), Austria

Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

Copyright

How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR20) Authoring Team. High-Dose Vitamin D for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2021. [date of citation]. 43 pages. Report No.: RCR20, v5.0. Available from: https //www.eunethta.eu.

Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
AE	Adverse Event
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GÖG	Gesundheit Österreich GmbH
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
WP4	Work Package 4
VDR	Vitamin D-receptors

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against COVID-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on COVID-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on COVID-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA COVID-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month. As of May 2021, RCR 20 is updated on a bi-monthly basis.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

Description	Project Scope
	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	• Substances: Vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol) and their metabolites ercalcidiol, calcifediol, calcitriol and ercalcitriol* • Dosing (vitamin D2 and D3): “high-dose” interventions greater than 4,000 IU per day**
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and a minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

* Combined interventions of vitamin D and other substances are included if the interventions in two trial arms differ only by the presence or absence of vitamin D. ** There is no consensus definition of “high-dose” vitamin D. The adequate intake for adults recommended by EFSA is 600 IU/day, assuming minimal cutaneous production. [1] Various medical societies recommend different daily intake doses, including 2,000 IU or more. Generally, the upper intake level for Vitamin D can be assumed at 4,000 IU per day and continuing supplementation exceeding this level is recommended against by many experts. [2] We therefore provisionally applied this threshold to define “high-dose” vitamin D treatment. In the current version of the report, no published RCTs were excluded because of the dosing of vitamin D. One observational study was excluded that investigated a cohort of patients that had been using vitamin D supplementation at an average dosage of 1,800 IU/day.

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on two main mandatory sources and one optional source of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

The literature search is conducted in the following databases:

- MEDLINE, accessed via OVID
- PubMed

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology
- arXiv

In addition to the sources and strategies described above, registers of ongoing studies are screened. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Literature selection, data extraction, risk of bias assessment, data synthesis, certainty of evidence:

At least two reviewers are independently screening search results and assessing full texts of studies according to the pre-defined criteria (see Table 2-1) with disagreements solved by discussion with a third member of the review team. One reviewer extracts study characteristics and outcome data. Studies investigating a combination of vitamin D and other dietary supplements or medicines versus a comparator that does not include this combination therapy are excluded. Data extraction is checked by a second reviewer. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1. Two authors independently assess the risk of bias of the included studies using the Cochrane RoB tool v2.0 [3,4]. Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome. The standardised mean difference (SMD) is applied when studies used different instruments. Two reviewers independently use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [5], to evaluate the certainty of evidence.

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search was conducted on a monthly basis for versions 1.0 to 3.0, with the last search done on 3 May 2021. No relevant observational studies were identified until this date. The authoring team decided not to update the search for observational studies on a regular basis.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of GÖG is searching and extracting the data for the eligible studies. At least two reviewers are independently screening search results, with disagreements solved by discussion with a third member of the review team. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Appendix Table 6-2. Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Vitamin D is a generic term used for a group of seco-sterols, mostly referring to vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) and their metabolites. Both vitamins can be taken up by diet, whereas vitamin D3 is also produced endogenously from 7-dihydrocholesterol in sun-exposed skin. After absorption, vitamin D2 and D3 undergo hepatic and renal hydroxylation into 25-OH-D2 (ercalcidiol) and 25-OH-D3 (calcifediol) and hereafter into the biologically active forms 1,25-OH2- D2 (ercalcitriol) and 1,25-OH2-D3 (calcitriol). The effects of vitamin D are mediated through binding on vitamin D-receptors (VDR). [6,7]

In addition to the well-studied role of vitamin D in bone metabolism, it also modulates several immunomodulatory pathways both in the innate and adaptive immune system (VDR are, for example, expressed on macrophages, dendritic cells, T-cells, and B-cells). Vitamin D generally maintains a balance between effector responses and inflammatory processes. [6]

In acute infections, vitamin D plays a role in enhancing the innate immune system to defend against pathogens by immune cell activation and proliferation (macrophages, neutrophils, dendritic cells) resulting in controlled release of proinflammatory cytokines and antimicrobial peptides like cathelicidin. The role of vitamin D in initial immune response is physiologically beneficial and may also be relevant in COVID-19 infections.

However, excessive immune reactions, like acute respiratory distress syndrome (ARDS) in COVID-19, can result in cytokine storm, strong inflammation and herewith tissue damaging. It is postulated that vitamin D limits these destructive pathways by modulating adaptive and innate immune response towards anti-inflammatory, anti-proliferative processes. [8,9] In addition, vitamin D might interfere with viral entry into the host cells by downregulating ACE2 expression. [10,11]

3.2 Regulatory Status

The mutual recognition information (MRI) index[1] hosted by the Heads of Medicines Agencies (HMA) network of the EU lists over 70 approved vitamin D-containing mono-preparations that may be marketed in the member states under different domestic market names. The majority of those contain cholecalciferol, while only some preparations contain calcitriol, calcifediol or ergocalciferol. Vitamin D-containing preparations are available as capsules, tablets, oral drops/solution, and effervescent granules in various strengths ranging from 10 to 100,000 IU per unit. In addition, there are several combination preparations of cholecalciferol with calcium carbonate, calcium phosphate or bisphosphonates (used for the treatment of bone turnover disorders).

[1] https://mri.cts-mrp.eu/Human/. Last accessed 11.05.2021.

In addition to medicinal products, vitamin D may be marketed in the EU as food supplement.[2] These products can be marketed in several forms, such as capsules, powders or liquids and may contain either cholecalciferol or ergocalciferol. However, article 6 of the directive mandates that 'The labelling, presentation and advertising must not attribute to food supplements the property of preventing, treating or curing a human disease, or refer to such properties.'

3.3 Level of Evidence

The evidence for vitamin D for treatment of COVID-19 is still in early stage. There is currently no standardized or recommended level of what constitutes a (beneficial) "high dose". Nine RCTs [12-20] of varying size and quality have been published to date. We moreover identified 25 ongoing RCTs with estimated primary completion dates ranging from June 2020 to February 2023 (5 in 2020, 6 in 2021, 4 in 2022, 1 in 2023, 9 entries have no information on study completion date).

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

One RCT each is available for the following comparisons:

1) oral cholecalciferol vs. placebo, inpatients with mild or asymptomatic COVID-19 (Rastogi 2020 [13])[3];

2) intramuscular cholecalciferol vs. placebo, inpatients with COVID-19 infection (Soliman 2021[20])[4];

3) oral cholecalciferol plus standard treatment vs. standard treatment, outpatients with mild COVID-19 (Sánchez-Zuno 2021 [17]);

4) oral cholecalciferol plus standard treatment vs. placebo plus standard treatment, inpatients with moderate to severe COVID-19 (Murai 2020 [21]);

5) oral cholecalciferol plus standard treatment vs. standard treatment, inpatients with moderate to severe COVID-19 (Lakkireddy 2021 [16]);

6) comparison of two different dosages of cholecalciferol, inpatients and outpatients with mild to moderate disease (Sabico 2021 [15])[5];

7) calcifediol plus standard treatment vs. standard treatment, inpatients with COVID-19 infection (Castillo 2020 [12]);

8) calcifediol plus standard treatment vs. placebo plus standard treatment, inpatients with COVID-19 infection (Maghbooli 2021 [18]);

9) calcitriol plus standard treatment vs. standard treatment, inpatients with COVID-19 infection (Elamir 2021 [19]).

[2] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02002L0046-20170726#B-6. Last accessed: 11.05.2021.

[3] Additional standard treatment not explicitly mentioned in the publication.

[4] Additional standard treatment not explicitly mentioned in the publication.

[5] Additional standard treatment not explicitly mentioned in the publication. Clinical symptoms of outpatients (e.g., fever) are reported to have been managed by supportive care.

All cholecalciferol studies used different dosing regimens, the two calcifediol studies also used different dosing regimens. Also, the proportion of patients with vitamin D deficiency varied between studies (when reported). In most of the studies additional standard treatment is mentioned and in some it is also described in some detail (varying also according to disease severity of included patients). Because of the differences between studies regarding intervention (form and dosing) and population, we decided against pooling the results.

Rastogi et al. [13] used a dosage of 60,000 IU cholecalciferol daily during the first week and thereafter weekly for those with 25(OH)D >50 ng/ml (and continuing daily for the others). They report 10 of 16 patients in the cholecalciferol group reaching SARS-CoV-2 negativity (primary outcome) before week 3 compared to 5 of 24 patients in the placebo group. SARS-CoV-2 negativity was determined by PCR but no cut-off Ct-value was reported. They do not report baseline characteristics on important risk factors such as obesity. Also, sample size calculation was done with regard to the secondary outcome (serum level of inflammatory marker).

Sánchez-Zuno et al. [17] used 10,000 IU of cholecalciferol per day for 14 days in outpatients and compared with no treatment. They report SARS-CoV-2 negativity by RT-PCR on day 7 and day 14 and find no significant differences.

Murai et al. [14] used a single dose of 200,000 IU cholecalciferol. They report on four relevant outcomes, mortality, length of hospital stay, admission to intensive care unit and mechanical ventilation. They find no significant effects in either direction, neither in the overall group, nor in the subgroup with vitamin D deficiency.

Lakkireddy et al. [16] used 60,000 IU of cholecalciferol per day for 8 days in patients with BMI of 18-25 and for 10 days in patients with BMI >25 in conjunction with standard treatment and compared to standard treatment alone. They report no significant differences in length of hospital stay, ICU admission rate or mortality.

Castillo et al. [12] used a dosage of 0.532 mg calcifediol on day 1, 0.266 mg on day 3 and 7, then weekly until discharge or admission to intensive care unit. They conducted an open label pilot trial with 76 patients. The study publication refers to a planned bigger trial with over 1,000 patients, registered in ClinicalTrials.gov (NCT04366908) with an estimated study completion date in August 2020. However, no publication could be found. They report only 1 of 50 calcifediol patients requiring admission to intensive care unit compared to 13 of 26 patients in the control group. Two patients died in the control group, none in the calcifediol group. These results remained statistically significant when adjusted for the two risk factors with significant baseline differences, hypertension and diabetes mellitus type 2. However, data on obesity were not collected (nor on vitamin D deficiency, see above).

Sabico et al. [15] compared 5,000 IU of cholecalciferol with 1,000 IU of cholecalciferol per day for 14 days in inpatients and outpatients. They report no significant difference in the rate of ICU admission. One patient died in the 5,000 IU group, no one in the 1,000 IU group. They also report no significant difference in “days to discharge” but it is unclear if this refers only to the hospitalised patients or a composite endpoint of discharge from hospital of inpatients and deisolation of outpatients.

Soliman et al. [20] investigated 200,000 IU of cholecalciferol as a single dose (administered intramuscularly) in 40 inpatients of a general hospital and compared this with normal saline placebo in 16 age matched patients. They report no significant differences in mortality, need for intubation and recovery (however, the authors provided no definition for the outcome “recovery”). All patients had type 2 diabetes, were aged over 60 and vitamin D deficient. However, baseline characteristics show a significant difference between vitamin D levels of both groups in the first measurement of the study (10.4 ng/ml in the vitamin D-treated group vs. 21.17 in the placebo-treated group, p=0.001). This is not explained by the authors.

Elamir et al. [19] investigated the use of calcitriol with a dosage of 0.5 µg daily for 14 days (or until hospital discharge) in 25 inpatients, combined with standard care, and compared this with standard care alone in another 25 inpatients. They also found no significant difference in length of hospital stay, ICU admission, need for intubation, mortality and readmission within 30 days; however, they mention that “in each case, numerical results may favour calcitriol therapy”. One limitation of the study is that they did not measure 25-OH-D3-levels.

Maghbooli et al. [18] investigated calcifediol with a dosage of 0,025 mg daily for 60 days in 53 inpatients, with outpatient follow-up, combined with standard care. Another 53 patients received matched placebo and standard care. They only included vitamin D deficient patients (25-OH-D3 <30 ng/ml). They did not find significant differences between the two groups with regard to length of hospital stay, length of ICU stay, mortality, need for oxygen therapy, and need for intubation. During outpatient follow-up many patients were lost, reducing the number of participants in both groups to less than 50% at second follow-up. The authors do not give detailed dropout reasons, but state that „concern about COVID-19 reinfection was the main reason".

Lakkireddy et al. reported no significant difference in the median duration of symptoms (5 days vs. 5 days; Z=0.9, p=0.4). Sabico et al. report the average duration to resolution of 11 specific symptoms and find significant shorter durations in the 5,000 IU group for cough (6.2+/-0.8 days vs. 9.1+/-0.8 days; p=0.007) and ageusia (11.4+/-1.0 days vs. 16.9+/-1.7 days; p=0.035) but not for the other symptoms. Sánchez-Zuno et al. report the rate of patients with any, more than 1, more than 2 or more than 3 symptoms at baseline, at day 7 and at day 14. They find a significantly smaller rate of patients with more than 3 symptoms in the cholecalciferol group (0 of 22 patients vs. 4 of 20 patients, both at day 7 and day 14; p=0.04) but no difference in the other comparisons.

Regarding safety, Rastogi et al. reported that 'No episodes of hypercalcaemia were observed in either group' but did not provide any further information on adverse events. Murai et al. reported one patient who vomited directly after vitamin D administration. Elamir et al. report no events of hypercalcemia, hyperphosphatemia and renal calculus and 4 events of a reduction in glomerular filtration rate by >10% in the control group. Lakkireddy et al., Sabico et al. and Maghbooli et al. reported that no patients had any adverse reactions. Castillo et al., Sánchez-Zuno et al. and Soliman et al. did not report on adverse events.

4.2 Safety evidence from observational studies

No observational study on safety fulfilling inclusion criteria was identified during the search period 1 September 2020 to 3 May 2021.

4.3 Ongoing studies

253 hits were retrieved from database search, 232 of which remained after deduplication. Of these, 27 hits were included.

4.4 Scientific conclusion about status of evidence generation

Currently, nine RCTs for high dose vitamin D for COVID-19 have been published, and a considerable number of studies is still ongoing. The nine published RCTs are heterogeneous with regard to the form and dosage of vitamin D, baseline disease severity and risk factors (with relevant risk factors not always being reported/available). Overall, most studies do not show significant differences between vitamin D treated groups and no vitamin D / placebo groups. However, many of the studies are very small and certainty of evidence is mostly low or very low.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (cholecalciferol) compared to no Vitamin D for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with no Vitamin D	Risk with Vitamin D (cholecalciferol)				
All-cause Mortality Population: inpatients with moderate to severe COVID-19 % vitamin D deficient[6]: 100 (both groups)	77 per 1,000	31 per 1,000 (6 to 153)	RR 0.400 (0.081 to 1.990)	130 (1 RCT [16])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
ICU admission Population: inpatients with moderate to severe COVID-19 % vitamin D deficient[7]: 100 (both groups)	77 per 1,000	62 per 1,000 (17 to 219)	RR 0.800 (0.225 to 2.486)	130 (1 RCT [16])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
Viral burden (SARS-CoV-2 negativity) at day 7 Population: outpatients with mild COVID-19 % vitamin D deficient: not reported[8]	400 per 1,000	454 per 1,000 (224 to 620)	RR 1.136 (0.561 to 2.301)	42 (1 RCT[17])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
Viral burden (SARS-CoV-2 negativity) at day 14 Population: outpatients with mild COVID-19 % vitamin D deficient: not reported[9]	1,000 per 1,000	955 per 1,000 (871 to 1,000)	RR 0.955 (0.871 to 1.046)	42 (1 RCT[17])	⨁⨁◯◯ LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

[6] 25-hydroxyvitamin D < 30 ng/mL

[7] 25-hydroxyvitamin D < 30 ng/mL

[8] Baseline level in n = 42 (median (range)): 22.4 (12.1-45.9)

[9] Baseline level in n = 42 (median (range)): 22.4 (12.1-45.9)

Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (cholecalciferol) compared to placebo for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with Vitamin D (cholecalciferol)				
All-cause Mortality Population: inpatients with moderate to severe COVID-19 % vitamin D deficient[10]: 47.90 (VitD) / 49.15 (pbo)	50 per 1,000	74 per 1.000 (27 to 202)	RR 1.487 (0.547 to 4.048)	240 (1 RCT [14])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies
Length of hospital stay Population: inpatients with moderate to severe COVID-19 % vitamin D deficient[11]: 47.90 (VitD) / 49.15 (pbo)	-	-	HR 1.07 (0.82 to 1.39)	240 (1 RCT [14])	⊕⊕⊕◯ MODERATE	
Viral burden (SARS-CoV-2 negativity) before day 21 Population: inpatients with mild or asymptomatic COVID-19 % vitamin D deficient[12]: 100 (both groups)	208 per 1,000	625 per 1.000 (263 to 1.000)	RR 3.000 (1.260 to 7.142)	40 (1 RCT [13])	⊕◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
ICU admission Population: inpatients with moderate to severe COVID-19 % vitamin D deficient[13]: 47.90 (VitD) / 49.15 (pbo)	208 per 1,000	157 per 1.000 (91 to 269)	RR 0.754 (0.439 to 1.293)	240 (1 RCT [14])	⊕⊕⊕◯ MODERATE	Own calculation of RR based on reported frequencies
Mechanical ventilation Population: inpatients with moderate to severe COVID-19 % vitamin D deficient[14]: 47.90 (VitD) / 49.15 (pbo)	142 per 1,000	74 per 1.000 (35 to 160)	RR 0.525 (0.244 to 1.130)	240 (1 RCT [14])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; pbo = Placebo; RR = Risk ratio; VitD = Vitamin D

[10] 25-hydroxyvitamin D < 20 ng/mL
[11] 25-hydroxyvitamin D < 20 ng/mL
[12] 25-hydroxyvitamin D < 20 ng/mL
[13] 25-hydroxyvitamin D < 20 ng/mL
[14] 25-hydroxyvitamin D < 20 ng/mL

Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (intramuscular cholecalciferol) compared to placebo for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with no Vitamin D	Risk with Vitamin D (cholecalciferol)				
All-cause Mortality Population: inpatients with COVID-19, type 2 diabetes, age > 60 years % vitamin D deficient[15]: 100 (both groups)	188 per 1.000	175 per 1.000 (52 to 594)	RR 0.933 (0.275 to 3.168)	56 (1 RCT [20])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
Mechanical ventilation Population: inpatients with COVID-19, type 2 diabetes, age > 60 years % vitamin D deficient[16]: 100 (both groups)	438 per 1,000	350 per 1,000 (174 to 704)	RR 0.800 (0.398 to 1.608)	56 (1 RCT [20])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

[15] 25-hydroxyvitamin D < 20 ng/mL

[16] 25-hydroxyvitamin D < 20 ng/mL

Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (cholecalciferol) 5000 IU compared to Vitamin D (cholecalciferol) 1000 IU for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Vitamin D (cholecalciferol) 1,000 IU	Risk with Vitamin D (cholecalciferol) 5,000 IU				
All-cause Mortality Population: inpatients and outpatients with mild to moderate disease % vitamin D deficient[17]: 55	0 per 1.000	0[18] per 1.000	not estimable	69 (1 RCT [15])	⊕◯◯◯ VERY LOW	No deaths in the 1,000 IU group, one death in the 5,000 IU group.
ICU admission Population: inpatients and outpatients with mild to moderate disease % vitamin D deficient[19]: 55	91 per 1,000	56 per 1,000 (10 to 312)	RR 0.611 (0.109 to 3.432)	69 (1 RCT [15])	⊕◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

Table 4-5 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (calcifediol) compared to no Vitamin D for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with no Vitamin D	Risk with Vitamin D (calcifediol)				
All-cause Mortality Population: consecutive inpatients with COVID-19 % vitamin D deficient: no data	77 per 1,000	0 per 1,000	not estimable	76 (1 RCT[12])	⊕◯◯◯ VERY LOW	No deaths in the Vitamin D group
ICU admission Population: consecutive inpatients with COVID-19 % vitamin D deficient: no data	500 per 1,000	20 per 1,000 (3 to 145)	RR 0.040 (0.006 to 0.289)	76 (1 RCT [12])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

[17] 25-hydroxyvitamin D < 20 ng/mL

[18] One person died.

[19] 25-hydroxyvitamin D < 20 ng/mL

Table 4-6 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (calcifediol) compared to placebo for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with no Vitamin D	Risk with Vitamin D (cholecalciferol)				
All-cause Mortality Population: inpatients with COVID-19 % vitamin D deficient[20]: 100 (both groups)	94 per 1.000	57 per 1.000 (14 to 225)	RR 0.600 (0.151 to 2.384)	106 (1 RCT [18])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
ICU admission Population: inpatients with COVID-19 % vitamin D deficient[21]: 100 (both groups)	189 per 1,000	113 per 1,000 (44 to 289)	RR 0.600 (0.235 to 1.533)	106 (1 RCT [18])	⨁⨁◯◯ LOW	Own calculation of RR based on reported frequencies
Mechanical ventilation Population: inpatients with COVID-19 % vitamin D deficient[22]: 100 (both groups)	94 per 1,000	38 per 1,000 (8 to 186)	RR 0.400 (0.081 to 1.971)	106 (1 RCT [18])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

[20] 25-hydroxyvitamin D < 30 ng/mL

[21] 25-hydroxyvitamin D < 30 ng/mL

[22] 25-hydroxyvitamin D < 30 ng/mL

Table 4-7 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (calcitriol) compared to no vitamin D for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with no Vitamin D	Risk with Vitamin D (cholecalciferol)				
All-cause Mortality Population: inpatients with COVID-19 % vitamin D deficient: no measured	120 per 1.000	0 per 1,000	not estimable	50 (1 RCT [19])	⨁◯◯◯ VERY LOW	No deaths in the Vitamin D group
ICU admission Population: inpatients with COVID-19 % vitamin D deficient: no measured	320 per 1,000	200 per 1,000 (76 to 528)	RR 0.625 (0.237 to 1.649)	50 (1 RCT [19])	⨁⨁◯◯ LOW	Own calculation of RR based on reported frequencies
Mechanical ventilation Population: inpatients with COVID-19 % vitamin D deficient: no measured	80 per 1,000	0 per 1,000	not estimable	50 (1 RCT [19])	⨁◯◯◯ VERY LOW	No cases of mechanical ventilation in the Vitamin D group

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

Table 4-8 Study characteristics of included RCTs – Rastogi 2020, Murai 2020, Castillo 2020, Lakkireddy 2021, Sánchez-Zuno 2021

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14,22-24], NCT04449718	Castillo 2020 [12], NCT04366908[23]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]
Study design	RCT	RCT	Pilot RCT, open label	RCT, open label	RCT, open label
Centres (single centre or multicentre), country, setting	Single centre, India, tertiary care hospital (inpatient)	Multicentre, Brazil, one quarternary hospital and one field hospital in Sao Paulo (inpatient)	Single centre, Spain, university hospital (inpatient)	Single centre, India, public teaching hospital (inpatient)	Single centre, Mexico, university hospital (outpatient)
Patient population (number of	n=40[25]	n=240	n=76	n=130 (allocated), n=87 (analysed)	n=42

[23] refers to a planned RCT with estimated study completion date in August 2020, for which no publication could be identified – Castillo 2020 report the results of a preceding pilot trial

[25] age and sex not reported for whole cohort

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14,22-24], NCT04449718	Castillo 2020 [12], NCT04366908[23]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]
included patients/ Mean age and sex/ Disease severity[24])	Intervention group: age (median, IQR): 50.0 (36-51); gender (% male): 37.5% Comparator group: age (median, IQR): 47.5 (39.3-49.2); gender (% male): 58.3% Severity: mild or asymptomatic COVID-19	age (mean, SD): 56.2 (14.4) gender (% male): 56.1% Severity: hospitalised patients with moderate to severe COVID-19	age (mean, SD): 53+/-10 gender (% male): 59.2% Severity: consecutive patients hospitalized with COVID-19 infection	age (mean, SD): 45+/-13 (n=87) gender (% male): 75% Severity: mild to moderate COVID-19	age (median, range): 43 (20-74) gender (% male): 47.7% Severity: mild disease
Inclusion criteria	• Individuals with SARS-CoV-2 infection who were mildly symptomatic or asymptomatic with or without comorbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) • Patients with vitamin D deficiency defined as 25 (OH)D level<20 ng/ml[26]	• adults aged 18 years or older • diagnosis of COVID-19 by either polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasopharyngeal swabs or computed tomography scan findings (bilateral multifocal ground-glass opacities ≥ 50%) compatible with the disease • diagnosis of flu syndrome with hospitalization criteria on hospital admission, presenting respiratory rate ≥ 24 breaths per minute, saturation < 93% on room air or risk factors for complications, such as heart disease, diabetes mellitus, systemic arterial hypertension, neoplasms,	• consecutive patients hospitalized with COVID-19 infection (acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB-65 severity scale recommending hospital admission	• Patients with confirmed COVID-19 above the age of 18 years with hypovitaminosis D (vit.D level below 30 ng/ml) and mild to moderate illness (SpO2 > 90%) as per the revised guidelines for COVID-19 issued by the Directorate General of Health Services, Government of India on 31-03-2020[27]	• individuals with mild disease, • over 18 years of age, • who were not taking any vitamin D supplementation at the recruiting time

[24] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[26] not consistent with study registry mentioning only „SARS-CoV-2 RNA positive Asymptomatic individuals“

[27] inclusion criteria not consistent with study registry

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14,22-24], NCT04449718	Castillo 2020 [12], NCT04366908[23]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]
		immunosuppression, pulmonary tuberculosis, and obesity, followed by COVID-19 confirmation before randomization	in case of total score > 1)		
Exclusion criteria	• patients unable to take oral supplementation like those requiring invasive ventilation or with significant comorbidities like uncontrolled hyperglycaemia or hypertension[28]	• patient unable to read and sign the written informed consent • patient already admitted under invasive mechanical ventilation • previous vitamin D3 supplementation (> 1,000 IU/day) • renal failure requiring dialysis or creatinine ≥ 2.0 mg/dL • hypercalcemia defined by total calcium > 10.5 mg/dL • pregnant or lactating women • patients with expected hospital discharge in less than 24 hours	• Patients younger than 18 years and pregnant women	• Patients with severe illness29 • Patients who have taken high dose vitamin D (60,000 IUs) in the last 3 months • Patients with active malignancy, chronic renal disease and HIV, pregnant and breastfeeding mothers were excluded	NR
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Cholecalciferol (day 1-7: 60,000 IU per day (5 ml oral solution in nano droplet form), day 8-14: weekly 60,000 IU cholecalciferol to those with	Cholecalciferol (single dose of 200,000 IU of dissolved in a 10 mL of peanut oil solution on day of randomization plus standard care[30])	Calcifediol (0.532 mg on day 1, 0.266 mg on day 3 and 7, then weekly until discharge or ICU admission plus standard care as per hospital protocol (see below)	Cholecalciferol (60,000 IU per day for 8 days for subjects with BMI of 18–25 and 10 days for subjects	Cholecalciferol (10,000 IU per day in soft capsule form for 14 days; in the morning with the company of a meal)

[28] slight inconsistencies with criteria in study registry: “Uncontrolled Diabetes Uncontrolled Hypertension Chronic Liver Disease Chronic obstructive Pulmonary disease Requiring Invasive Ventilation”

[29] exclusion criteria not consistent with study registry

[30] no further definition

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14,22-24], NCT04449718	Castillo 2020 [12], NCT04366908[23]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]
	25(OH)D >50 ng/ml or else continued daily 60,000 IU cholecalciferol) n=16, no subgroups reported	n=120 (randomised), n = 119 (mITT[31]), n=117 (per protocol), no subgroups reported	n=50, no subgroups reported	with BMI > 25[32]) plus standard treatment[33] n=65 (allocated), n=44 (analysed), no subgroups reported	plus standard treatment[34] n=22
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Placebo (5 ml distilled water) for 7 days n=24, no subgroups reported	Placebo (10 mL of peanut oil solution plus standard care[35]) n=120 (randomised), n = 118 (mITT[36]), n= 118 (per protocol), no subgroups reported	Standard care as per hospital protocol (hydroxychloroquine 400 mg every 12 h on the first day, and 200 mg every 12 h for the following 5 days combined with azithromycin 500 mg orally for 5 days; for patients with pneumonia and NEWS ≥ 5 additionally ceftriaxone 2 g intravenously every 24 h for 5 days)	Standard treatment[37] n=65 (allocated), n=43 (analysed), no subgroups reported	Standard treatment[38] n=20

[31] Patients that withdrew consent before receiving the intervention were excluded from analysis.

[32] dosing not consistent with study registry

[33] No further information in study publication; in study registry “according to physician's decision, based on the current recommendations”.

[34] Additional pharmacological treatment is reported for both groups.

[35] no further definition

[36] Patients that withdrew consent before receiving the intervention were excluded from analysis.

[37] No further information in study publication; in study registry “according to physician's decision, based on the current recommendations”.

[38] Additional pharmacological treatment is reported for both groups.

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14,22-24], NCT04449718	Castillo 2020 [12], NCT04366908[23]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]
			n=26, no subgroups reported		
Primary Outcome(s)	• Proportions of participants who turn SARS-CoV-2 negative (confirmed twice at 24-hour interval) before week 3 in the two groups	• Hospital length of stay, defined as the total number of days that patients remained hospitalized from the date of randomization until the date of hospital discharge[39]	• Rate of ICU admission • mortality	Relevant primary outcomes according to study registry: • Difference in two study groups with respect to the duration and severity of signs and symptoms • Time taken for double negative RT-PCR between the two study groups • Duration of hospital stay Relevant reported outcomes: • Duration of symptoms • Duration of hospital stay • Adverse reactions	• SARS-CoV-2 PCR positivity • Presence of symptoms[40]
Patient-relevant secondary outcome(s)	NR	• mortality • number of patients admitted to ICU • number of patients who needed mechanical ventilation and duration of mechanical ventilation	NR	Relevant secondary outcomes according to study registry: • ICU admission • Recovery	NR

[39] The criteria used for patient discharge were: 1) no need for supplemental oxygen in the last 48 hours; 2) no fever in the last 72 hours; and 3) oxygen saturation > 93% in room air without respiratory distress.

[40] Fever, headache, loss of smell, dry cough, sore throat, ageusia, runny nose, nausea or vomiting, tiredness, diarrhoea, myalgia, arthralgia, shortness of breath

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14,22-24], NCT04449718	Castillo 2020 [12], NCT04366908[23]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]
				• Composite of cumulative death, i.e., all causes and specific causes mortality Relevant reported outcomes: • ICU admission • Number of deaths	
Follow-up (days, months)	21 days (oropharyngeal swabs and SARS-CoV-2 RNA detection by PCR on days 5, 7, 10, 14, 18, 21)	Outcomes were assessed at baseline and on hospital discharge or death records.	Until ICU admission, hospital discharge or death	After treatment completion (9 or 11 days depending on BMI, see above)[41]	14 days
Sponsor/ lead institution	Department Of Internal Medicine, Nehru Hospital, PGIMER, Chandigarh 160012, India The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.	Clinical Hospital of the School of Medicine of the University of Sao Paulo, Ibirapuera Field Hospital supported by Sao Paulo Research Foundation (grants 20/05752-4; 19/24782-4; 20/11102-2; 16/00006-7; 17/13552-2; 15/26937-4; 19/18039-7) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (305556/2017-7).	Maimónides Biomedical Research Institute of Córdoba public funding (COVID-011-2020 Programa de Investigacion clínica en COVID-19 de Andalucía, Consejería de Salud y Familia, Fundacion Progreso y Salud, Fundacion para la Investigacion Biomedica de Cordoba)	Lead: Department of Orthopaedics/ Biochemistry/ Internal Medicine, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, India Sponsor: Pulse Pharmaceuticals	National Council of Science and Technology (CONACYT Ciencia Básica grant number A1-S-8774) and the Universidad de Guadalajara through Fortalecimiento de la Investigación y el Posgrado 2020

Abbreviations: BMI = body mass index, CURB = Confusion, Urea, Respiratory rate, Blood pressure; ICU = Intensive Care Unit; IU = international unit; mITT = modified intention to treat; mg = milligram; ml = per millilitre; NEWS = National Early Warning Score; ng = nanogram; NR = not reported; RCT = randomised clinical trial; SpO2 = saturation of peripheral oxygen

[41] Not consistent with study registry

Table 4-9 Study characteristics of included RCTs – Sabico 2021, Soliman 2021, Elamir 2021, Maghbooli 2021

Author, year, reference number/Study name/Study ID	Sabico 2021 [15], SCTR H-01-R-012	Soliman 2021 [20], NCT04733625	Elamir 2021 [19]	Maghbooli 2021 [18], NCT04386850
Study design	RCT, open label[42]	RCT	RCT, open label (pilot study)	RCT (pilot study)
Centres (single centre or multicentre), country, setting	Multicentre, Saudi Arabia, tertiary care hospitals (inpatient and outpatient)	Single centre, Egypt, general hospital (inpatient)	Single centre, Icahn School of Medicine at Mount Sinai Beth Israel, USA (inpatient)	Multicentre, Iran, general hospitals (inpatient and outpatient)
Patient population (number of included patients/ Mean age and sex/ Disease severity[43])	n=73 (allocated), n=69 (analysed) age (mean, SD): 49.8+/-14.3 (n=69) gender (% male): 49.3% Severity: mild to moderate disease	n=56 Intervention group: age (mean, SD): 71.30 (4.16); gender (% male): NR Comparator group: age (mean, SD): 70.19 (4.57); gender (% male): NR Severity: hospitalised patients with COVID-19 infection	n=50 Intervention group: age (mean[44], SD): 69 +/- 18; gender (% male): 48% Control group: age (mean[45], SD): 64 +/- 16; gender (% male): 52% Severity: hospitalised patients with COVID-19 infection	n=106 age (mean, SD): 49.1+/-14.1 gender (% male): 60.4% Severity: hospitalised patients with COVID-19 infection
Inclusion criteria	• Aged 20-75 years • RT-PCR confirmed SARS-CoV-2 (positive test no more than 3 days prior to inclusion) • Mild to moderate symptoms of COVID-19	• Type 2 diabetes • Age more than 60 years • Deficient serum vitamin D levels (less than 20 ng/mL[46]) • Diagnosis of COVID-19 confirmed by PCR using	• hospitalized adult patients with COVID-19	• Older than 18 years old • No medications or disorders that would affect vitamin D metabolism • Vitamin D deficiency/insufficiency (25-OH-D3 concentration of <30 ng/ml)

[42] Blinded data collector

[43] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[44] Not explicitly stated in the publication, but probably mean and SD

[45] Not explicitly stated in the publication, but probably mean and SD

[46] Less than 25 ng/mL according to registry entry

Author, year, reference number/Study name/Study ID	Sabico 2021 [15], SCTR H-01-R-012	Soliman 2021 [20], NCT04733625	Elamir 2021 [19]	Maghbooli 2021 [18], NCT04386850
		TaqPath RT-PCR COVID-19 Kit		• Ability and willingness to give informed consent and comply with protocol requirements
Exclusion criteria	• Severe disease • Children • Pregnant women • Baseline 25(OH)D level above 75 nmol/L	• Known history of renal stones • Diagnosis of hypercalcemia within the past year • Baseline serum total calcium level more than 10 mg/dl • Established diagnosis associated with increased risk of hypercalcemia (e.g., metastatic cancer, sarcoidosis, multiple myeloma, and primary hyperparathyroidism) • Cholecalciferol supplementation within last 6 weeks before recruitment • Known malignancy, organ transplant, known chronic autoimmune diseases, long-term systemic steroid use	• Admitted directly to the intensive care unit (ICU) • hypercalcemia and/or hyperphosphatemia on admission blood tests • untreated disorders of calcium metabolism including hyperparathyroidism • hypoparathyroidism • chronic renal insufficiency with glomerular filtration rate < 30 ml/min • prescription of calcitriol for any reason outside of the study	• Pregnant or lactating women • Severe underlying diseases, such as advanced malignant tumor 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 analogs • 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 absorption (anticonvulsants, antituberculosis medication glucocorticoids, HIV medications and cholestyramine) • History of an adverse reaction to orally administered vitamin D, vitamin D metabolites, or analogs • History of an elevated serum calcium concentration of >10.6 mg/dL that was corrected for albumin concentration or subjects with a history of hypercalciuria and kidney stones • History of conditions that could lead to high serum calcium concentrations, such as sarcoidosis, tuberculosis, and some lymphomas associated with activated macrophages, which increase the production of 1,25-OH2-D • Inability to give informed consent

Author, year, reference number/Study name/Study ID	Sabico 2021 [15], SCTR H-01-R-012	Soliman 2021 [20], NCT04733625	Elamir 2021 [19]	Maghbooli 2021 [18], NCT04386850
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Cholecalciferol (5,000 IU in tablet form per day for 14 days) n=38 (allocated), n=36 (analysed), no subgroups reported	Cholecalciferol (200,000 IU intramuscularly) once as a single dose during the period of the study n=40, no subgroups reported	Calcitriol (0.5 µg daily for 14 days or until hospital discharge) plus standard care (see below) n=25, no subgroups reported	Calcifediol (0.025 mg daily for 60 days) plus standard care (see below) n=53, no subgroups reported
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Cholecalciferol (1,000 IU in tablet form per day for 14 days) n=35 (allocated), n=33 (analysed), no subgroups reported	Matched placebo (normal saline) n=16, no subgroups reported	standard care: may include treatment with remdesivir (200 mg for 1 day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma, as well as supplemental O2 n=25, no subgroups reported	Matched placebo plus standard care (combination of hydroxychloroquine and azithromycin;, for patients with pneumonia, ceftriaxone was used) n=53, no subgroups reported
Primary Outcome(s)	• number of days to resolve symptoms	• mortality within 6 weeks of the diagnosis of COVID-19	• oxygen requirements (including need for endotracheal intubation) • length of hospital stay • need for ICU admission • mortality • readmission • adverse events	• severity of COVID-19 (SARS-CoV-2) infection: percentage of mild, moderate, and severe forms of COVID-19 based on the WHO criteria[47] • length of hospital stay • percentage of patients with COVID-19 who need oxygen support • rate of death due to COVID-19 during the study • lymphocyte count and percentage • serum 25-OH-D3 concentrations at baseline and after 30 and 60 days of starting oral 25-

[47] mentioned as an outcome, but no results presented

Author, year, reference number/Study name/Study ID	Sabico 2021 [15], SCTR H-01-R-012	Soliman 2021 [20], NCT04733625	Elamir 2021 [19]	Maghbooli 2021 [18], NCT04386850
				OH-D3 or placebo (first and second months of follow-up) • adverse events
Patient-relevant secondary outcome(s)	• days to discharge • ICU admission • mortality • adverse events	• number of patients who needed intubation • recovery • "death or need for intubation" as composite outcome	Not relevant[48]	Not relevant[49]
Follow-up (days, months)	7 days or on discharge day and 30 days after discharge and/or the last vitamin dose	6 weeks	For readmission: 30 days Other outcomes: not explicitly stated (probably 14 days or until hospital discharge)	60 days
Sponsor/ lead institution	Deanship of Scientific Research, Chair for Biomarkers of Chronic Diseases at King Saud University, Riyadh, KSA. Vitamin D supplements used in the intervention were provided by Synergy Pharma (Dubai, UAE). According to registry entry, Synergy Pharma was a sponsor	Internal Medicine Department, Kasr al Ainy School of Medicine Cairo University, Egypt	Icahn School of Medicine at Mount Sinai Beth Israel, USA	Tehran University of Medical Sciences, Iran; Boston University School of Medicine, USA Supported by Dishman Carbogen Amcis Ltd

Abbreviations: BMI = body mass index, CURB = Confusion, Urea, Respiratory rate, Blood pressure; ICU = Intensive Care Unit; IU = international unit; mITT = modified intention to treat; mg = milligram; ml = per millilitre; NEWS = National Early Warning Score; ng = nanogram; NR = not reported; RCT = randomised clinical trial; SpO2 = saturation of peripheral oxygen

[48] No distinction between primary and secondary outcomes in the publication, so all outcomes are listed above.

[49] No distinction between primary and secondary outcomes in the publication, so all outcomes are listed above.

Table 4-10 Ongoing trials of single agent: Vitamin D

Trial Identifier/registry ID(s)/contact	IRCT20200324046850N1 [25]	NCT04344041 [26]	NCT04621058 [27]	NCT04536298 [28]
Estimated study completion date	No information	May 2021	November 2021	Juni 2021
Study design, study phase	RCT, phase 3	RCT, phase 3	RCT, phase 3	RCT, phase 3
Recruitment status	Recruitment complete	Recruitment completed	Recruiting	Recruiting
Number of Patients, Disease severity[50]	100 patients diagnosed with COVID-19	260 high-risk COVID-19 Patients	108 patients with COVID-19 and pneumonia	2,700 Patients newly diagnosed with COVID-19 (inclusion within 72 hours of testing)
Setting (hospital, ambulatory...)	Hospital	Hospital, ambulatory, nursing home	Hospital	Ambulatory
Intervention (generic drug name and dosage)	Standard country protocol drugs with vitamin D3 ampoules of 50,000 units once a week and N-acetylcysteine placebo tablets every 12 hours[51]	High dose of vitamin D3 Drug: cholecalciferol 200,000 IU	If vitamin D deficiency < 30 ng/ml: treatment with 2 capsules of 0.266 mg If vitamin D deficiency < 40 ng/ml: treatment with 1 capsule of 0.266 mg	Vitamin D capsules including 3,200 IU of vitamin D3. Three capsules per day (9,600 IU/day) will be taken on days 1 and 2, and one capsule per day (3,200 IU/day) will be taken on days 3 through 28
Comparator (standard care or generic drug name and dosage)	Standard country protocol drugs with placebo vitamin D3 once a week and placebo tablets N-acetylcysteine every 12 hours[52]	Standard dose of vitamin D3, drug: cholecalciferol 50,000 IU	Placebo	Placebo
Primary Outcome(s)	Time to clinical improvement	Mortality	Mortality	Hospitalization or death in index cases
Sponsor/ lead institution, country (also country of recruitment if different)	Abadan University of Medical Sciences, Iran	CHU Angers, France	Bioaraba Health Research Institute Fundación Eduardo Anitua, Spain	Brigham and Women's Hospital, USA

Abbreviations: RCT = randomised clinical trial; IU = international unit; ICU = Intensive Care Unit; ng/ml = nanograms per millilitre; mg = milligram

[50] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[51] only relevant study arm displayed

[52] only relevant study arm displayed

Table 4-11 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04552951 [29]	NCT04641195 [30], CTRI/2021/04/032593 [31]	EudraCT: 2020-001960-28 [32]	NCT04363840 [33]
Estimated study completion date	December 2020	March 2022	No information	December 2020
Study design, study phase	RCT, phase 4	RCT (factorial design), phase 3	RCT , phase 3	RCT, phase 2
Recruitment status	Recruiting	Recruiting	No information	Not yet recruiting
Number of Patients, Disease severity[53]	80 patients diagnosed with COVID-19	700 adult COVID-19 patients with oxygen saturation level of 90 or above	108 patients diagnosed with COVID-19	1,080 patients newly diagnosed with COVID-19 (within 24 hours after diagnoses)
Setting (hospital, ambulatory...)	Not clear	Start as inpatient, continuation as outpatients	Hospital	Ambulatory
Intervention (generic drug name and dosage)	Cholecalciferol Single dose of 100,000 IU	Daily Vitamin D3 (2,000 IU) for 60 days, Bolus Vitamin D3 (180,000 IU) at enrolment Daily vitamin D3 (2,000 IU) and Zinc Gluconate (40 mg) for 60 days, Bolus Vitamin D3 (180,000 IU) at enrolment	Hidroferol 0.266 mg capsules	Aspirin 81 mg to be taken orally once daily for 14 days. In combination with Dietary Supplement: Vitamin D 50,000 IU to be taken orally once weekly for 2 weeks
Comparator (standard care or generic drug name and dosage)	No intervention / no vitamin D	Placebo maintenance dose for 60 days, Bolus Placebo at enrolment Daily Zinc Gluconate (40 mg) for 60 days, Bolus Placebo at enrolment	Placebo	Aspirin 81 mg to be taken orally once daily for 14 days.
Primary Outcome(s)	• Mortality • ICU admission • Time of hospitalization [54]	Time to recovery	Mortality ICU admission	Hospitalization
Sponsor/ lead institution, country (also country of recruitment if different)	Fundación para la Investigación Biosanitaria del Principado de Asturias, Spain	Department of Tuberculosis Mumbai, India; primary sponsor: University Health Network, Canada	Investigation Institute Bioaraba, Spain	Louisiana State University Health Sciences Center in New Orleans, USA

Abbreviations: RCT = randomised clinical trial; IU = international unit; ICU = Intensive Care Unit

[53] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[54] only relevant primary outcome measures displayed

Table 4-12 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT03188796 [34]	NCT04525820 [35]	CTRI/2020/06/026189 [36]
Estimated study completion date	February 2023	November 2021	February 2022
Study design, study phase	RCT, phase 3	RCT, Phase: no information	RCT, phase 2
Recruitment status	Recruiting	Recruiting	Not yet recruiting
Number of Patients, Disease severity[55]	2400 critical ill patients including patients infected with COVID-19	80 hospitalized patients diagnosed with COVID-19	210 patients with mild to moderate COVID- 19
Setting (hospital, ambulatory...)	Hospital, ambulatory	Hospital	COVID care facility
Intervention (generic drug name and dosage)	Cholecalciferol oral/enteral loading dose of 37.5 ml MCT including 540,000 IU vitamin D3 followed by 10 drops daily (4,000 IU) for 90 days	Single high dose vitamin D one dose orally of 140,000 IU (7 ml) followed by vitamin D 800 IU per day (treatment as usual)	Standard COVID-19 treatment, and Vitamin D 400,000 IU single dose plus Magnesium Glycinate 250 mg BD for 14 days
Comparator (standard care or generic drug name and dosage)	Placebo	Single dose of a placebo solution followed by vitamin D 800 IU per day (treatment as usual)	Standard COVID-19 treatment, and Vitamin D 60,000 IU single dose plus Magnesium Glycinate 250mg BD for 14 days
Primary Outcome(s)	Mortality	Length of hospitalization	• Negative RT- PCR test for COVID 19 infection • Improvement in Signs and symptoms of COVID 19 infection, use of ventilator, length of stay in ICU • Reduction in CRP levels • Reduction in rate of COVID -19 complication. • Speed of recovery and duration to becoming asymptomatic • Length of hospital stay
Sponsor/ lead institution, country (also country of recruitment if different)	Medical University of Graz, Austria, Belgium	Prof. Dr. Jörg Leuppi, Cantonal Hospital Baselland Liestal, Switzerland	Suraksha Pharma Private Limite, India

Abbreviations: RCT = randomised clinical trial; IU = international unit; mcg = microgram

[55] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-13 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04334005 [37]	NCT04385940 [38]	NCT04636086 [39]	NCT04411446 [40]	EudraCT: 2020-002119-23 [41]
Estimated study completion date	June 2020	December 2020	February 2022	July 28, 2021	No information
Study design, study phase	RCT, Phase: no information	RCT, Phase 3	RCT, Phase 4	RCT, Phase 4	RCT
Recruitment status	Not yet recruiting	Not yet recruiting	Recruiting	completed	No information
Number of Patients, Disease severity[56]	200 non-severe symptomatic patients diagnosed with COVID-19	64 patients diagnosed with COVID-19	100 patients diagnosed with COVID-19	1264 patients diagnosed with COVID-19	80 oncological patients in active oncological treatment diagnosed with Covid-19, non-hospitalized
Setting (hospital, ambulatory...)	Ambulatory	Ambulatory	Hospital	Hospital	Ambulatory
Intervention (generic drug name and dosage)	25,000 IU of vitamin D supplement in addition to usual care	High dose vitamin D: 50,000 IU, Oral Vitamin D3	25,000 IU/ml of cholecalciferol: one ampoule on Day 1, Day 2, Day 3, Day 4, Day 8, Day 15, Day 22, Day 29 and Day 36	5 capsules of 100,000 IU Vitamin D orally given all at once	Cholecalciferol, oral drops, 10,000 IU
Comparator (standard care or generic drug name and dosage)	Usual care	Low dose vitamin D: Vitamin D3 1,000 IU	Placebo	Placebo	Placebo
Primary Outcome(s)	Composite of cumulative death (i.e. mortality) for all causes and for specific causes	Symptoms recovery	Vitamin D serum concentration[57]	Respiratory organ failure assessment score (SOFA) Need of a high dose of oxygen or mechanical ventilation.	Rate of hospitalization due to COVID-19 related pneumonia
Sponsor/ lead institution, country (also country of recruitment if different)	Universidad de Granada, Spain	University of Alberta, USA	University of Liege, Belgium	Vitamin D Study Group; Ag Nac Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación, Argentinia	Istituto europeo di oncologia, Italy

Abbreviations: RCT = randomised clinical trial; IU = international unit; mcg = microgram

[56] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[57] Mortality is mentioned as secondary outcome measure.

Table 4-14 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04828538 [42]	EudraCT: 2020-001903-17 [43]	IRCT20200411047024N1 [44]	IRCT20140305016852N4 [45]
Estimated study completion date	November 30, 2021	No information	No information	No information
Study design, study phase	RCT	RCT, Phase 3b	RCT, no information	RCT, no information
Recruitment status	Active, not recruiting	No information	Recruitment complete	Recruitment complete
Number of Patients, Disease severity[58]	1,800 patients diagnosed with COVID-19	120 patients in a moderate to severe degree (4-7 in WHO severity scale) needing oxygen therapy	100 COVID-19 patients with vitamin D deficiency	30 Patients with COVID-19
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Factorial 1: 4000 IU Vitamin D (vs. placebo) Factorial 2: 1000mg Omega DHA/EPA (vs. placebo) Factorial 3: Combination 1000 mg Vitamin C, Vitamin B complex** and Zinc Acetate, 100 mg/day (vs. placebo)	Vitamin D3 (Cholecalciferol) single dose, 200,000 UI / 1 ml, solution for injection, plus Tocilizumab (solution for injection/infusion)	intramuscularly Injections of 300 mg of vitamin D at the beginning of the first week, as well as another dose at the beginning of the second week	Group one: 50,000 units of vitamin D daily for one week and routine treatment under the supervision of an infectious disease specialist Group two: 500 mg vitamin C daily for one week and routine treatment under the supervision of an infectious disease specialist
Comparator (standard care or generic drug name and dosage)	Placebo	Tocilizumab (solution for injection/infusion)	No intervention	Routine treatment under the supervision of a specialist
Primary Outcome(s)	• mortality • ICU admission • intubation • mechanical ventilation	number of patients with fatal outcome	Clinical course, paraclinical findings, in-hospital outcome (not clearly reported in the registry)	Complete recovery of clinical COVID-19 symptoms, normalization of chest symptoms in CT scan
Sponsor/ lead institution, country (also country of recruitment if different)	Hospital de la Soledad, Mexico	Hospital Universitario de Móstoles, Spain, Support by Madrilenian Health Service	Shahroud University of Medical Sciences, Iran	Sabzevar University of Medical Sciences, Iran

Abbreviations: RCT = randomised clinical trial; IU = international unit; ml = millilitre

[58] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-15 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04883203 [46]	NCT04952857 [47]	EUCTR2020-001793-30-DK [48]	NCT05092698 [49]
Estimated study completion date	October 31, 2020	December 31, 2021	No information	January 2022
Study design, study phase	RCT, Phase 3	RCT, Phase 4	RCT, Phase 4	RCT, not applicable
Recruitment status	Recruitment complete	Not yet recruiting	Recruitment ongoing or finished	Recruiting
Number of Patients, Disease severity[59]	130 patients with asymptomatic to mild COVID-19	90 patients with moderate to severe COVID-19	480 SARS-CoV-2-positive patients ≥ 50 without immediate need for hospitalisation	100 adult patients with COVID-19 admitted to the ICU with vitamin D deficiency[60]
Setting (hospital, ambulatory...)	No information	No information	Ambulatory	Hospital
Intervention (generic drug name and dosage)	A single vial of Cholecalciferol (1 ml) (200,000 IU / 1 ml), Oral form	Cholecalciferol 600,000 IU	Cholecalciferol single dose (25,000 IU)	Cholecalciferol (60,000 IU) dissolved in 45 ml herbal oil orally or via feeding tube, weekly until discharge or death.
Comparator (standard care or generic drug name and dosage)	Placebo (a single vial of physiological saline oral form)	Placebo equal volume/ weight	Placebo (soft capsule)	Patients will receive 45 ml of herbal oil orally or via feeding tube, weekly until discharge or death.
Primary Outcome(s)	Delay between the first positive RT-PCR and the second negative RT-PCR	Sequential Organ Failure Assessment (SOFA) score	Combined endpoint of death and duration of hospitalization, calculated as Days Alive and Out of Hospital (DAOH) in a Time Frame of 6 weeks (42 days)	Various laboratory values Secondary outcomes: mortality, mechanical ventilation duration, non-invasive Mechanical ventilation duration, length of stay in the ICU, length of stay in the hospital, infection complications
Sponsor/ lead institution, country (also country of recruitment if different)	University of Monastir, Tunisia	Postgraduate Institute of Medical Education and Research, India	Department of Cardiology, Copenhagen University Hospital of Bispebjerg, Denmark	Federal Research Clinical Center of Federal Medical & Biological Agency, Russia

Abbreviations: RCT = randomised clinical trial; IU = international unit; mg = milligram; ml = millilitre

[59] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[60] 25-hydroxyvitamin ≤ 30 ng/ml

Table 4-16 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	CTRI/2021/03/032385 [50]
Estimated study completion date	No information
Study design, study phase	RCT, no information
Recruitment status	Not yet recruiting
Number of Patients, Disease severity[61]	160 adult hospitalized patients with moderate to severe COVID-19
Setting (hospital, ambulatory...)	Hospital
Intervention (generic drug name and dosage)	Cholecalciferol (60,000 IU) + Magnesium Glycinate (250 mg) for 7 days[62] plus standard treatment Cholecalciferol (60,000 IU) for 7 days[63] plus standard treatment Day 1, 2: Cilnidipine (5-10mg) + Telmisartan (20-40 mg) + Vitamin D3 (30,000 IU) + Magnesium Glycinate (125mg); Day 3-7: Cilnidipine (5mg) + Telmisartan (20 mg) + Cholecalciferol (30,000 IU) + Magnesium Glycinate (125mg)[64]
Comparator (standard care or generic drug name and dosage)	Standard treatment Cilnidipine (10mg) + Telmisartan (40 mg) for 7 days[65] plus standard treatment
Primary Outcome(s)	Reduction in severity of COVID-19 disease using non-invasive measurement of Arterial Stiffness as a clinical marker
Sponsor/ lead institution, country (also country of recruitment if different)	Department of CTVS Nodal Officer COVID-19 AIIMS Patna, India

Abbreviations: RCT = randomised clinical trial; IU = international unit; mg = milligram; ml = millilitre

[61] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[62] Dosage/frequency depending on arterial stiffness level, not quite clear

[63] Dosage/frequency not explicitly stated

[64] Dosage/frequency depending on arterial stiffness level, not quite clear

[65] Dosage/frequency depending on arterial stiffness level, not quite clear

5 REFERENCES

[1] EFSA. Dietary reference values for vitamin D. 2016.

[2] Simonson W. Vitamin D dosing considerations in COVID-19. Geriatric Nursing. 2020;41(5): 648-9.

[3] Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: http://www.training.cochrane.org/handbook.

[4] Higgins J, Savovic J, Page M, Sterne J. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). RoB2 Development Group; 2019.

[5] Balshem H HM, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology. 2011;64: 401-6.

[6] Sassi F, Tamone C, D'Amelio P. Vitamin D: Nutrient, Hormone, and Immunomodulator. Nutrients. 2018;10(11). Epub 2018/11/08.

[7] Lehmann U, Hirche F, Stangl GI, Hinz K, Westphal S, Dierkes J. Bioavailability of vitamin D(2) and D(3) in healthy volunteers, a randomized placebo-controlled trial. J Clin Endocrinol Metab. 2013;98(11): 4339-45. Epub 2013/09/05.

[8] Kalia V, Studzinski GP, Sarkar S. Role of vitamin D in regulating COVID-19 severity—An immunological perspective. Journal of Leukocyte Biology.n/a(n/a).

[9] Bilezikian JP, Bikle D, Hewison M, Lazaretti-Castro M, Formenti AM, Gupta A, et al. MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19. European Journal of Endocrinology. 2020;183(5): R133.

[10] Arboleda JF, Urcuqui-Inchima S. Vitamin D Supplementation: A Potential Approach for Coronavirus/COVID-19 Therapeutics? Frontiers in Immunology. 2020;11(1523).

[11] Jakovac H. COVID-19 and vitamin D—Is there a link and an opportunity for intervention? American Journal of Physiology-Endocrinology and Metabolism. 2020;318(5): E589-E.

[12] Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcala Diaz JF, Lopez Miranda J, Bouillon R, et al. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". The Journal of steroid biochemistry and molecular biology. 2020;203: 105751.

[13] Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). Postgrad Med J. 2020: 1-4. Epub 2020/11/14.

[14] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. 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. Journal of the American Medical Association, published online: 17 February 2021. 2021.

[15] Sabico S, Enani MA, Sheshah E, Aljohani NJ, Aldisi DA, Alotaibi NH, et al. Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with Mild to Moderate Covid-19: A Randomized Clinical Trial. Nutrients. 2021;13(7). Epub 2021/07/03.

[16] Lakkireddy M, Gadiga SG, Malathi RD, Karra ML, Raju I, Ragini, et al. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. Sci Rep. 2021;11(1): 10641. Epub 2021/05/22.

[17] Sánchez-Zuno GA, González-Estevez G, Matuz-Flores MG, Macedo-Ojeda G, Hernández-Bello J, Mora-Mora JC, et al. Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation. Journal of Clinical Medicine. 2021;10(11): 2378.

[18] Maghbooli Z, Sahraian MA, Jamalimoghadamsiahkali S, Asadi A, Zarei A, Zendehdel A, et al. Treatment With 25-Hydroxyvitamin D3 (Calcifediol) Is Associated With a Reduction in the Blood Neutrophil-to-Lymphocyte Ratio Marker of Disease Severity in Hospitalized Patients With COVID-19: A Pilot Multicenter, Randomized, Placebo-Controlled, Double-Blinded Clinical Trial. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2021.

[19] Elamir YM, Amir H, Lim S, Rana YP, Lopez CG, Feliciano NV, et al. A randomized pilot study using calcitriol in hospitalized COVID-19 patients. Bone. 2021;154: 116175.

[20] Soliman Ar ATSFA. Impact of Vitamin D Therapy on the Progress COVID-19: six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients. Proceedings of singapore healthcare. 2021.

[21] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of Vitamin D3 Supplementation vs Placebo on Hospital Length of Stay in Patients with Severe COVID-19: a Multicenter, Double-blind, Randomized Controlled Trial (preprint). Medrxiv; 2020. p. 2020.11.16.20232397.

[22] Murai IH. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19. Data Sharing Statement. Journal of the American Medical Association, published online: 17 February 2021. 2021.

[23] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19. Supplement 2. eTable 1. Baseline laboratory values. Journal of the American Medical Association, published online: 17 February 2021. 2021.

[24] Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19. Supplement 1. Trial protocol and statistical analysis plan. 2021.

[25] Abadan University of Medical S. Comparison of vitamin D3 and N-acetylcysteine prescription in COVID-19 patients and their effect on recovery process. ICTRP; 2020.

[26] Annweiler C, Beaudenon M, Gautier J, Simon R, Dubee V, Gonsard J, et al. COvid-19 and high-dose VITamin D supplementation TRIAL in high-risk older patients (COVIT-TRIAL): study protocol for a randomized controlled trial. In: Aidoud A AGACA-VAAMBJBFBGBJBBABSB-N, editor. Trials. England; 2020. p. 1031.

[27] Bioaraba Health Research I, Fundación Eduardo A. Efficacy of Vitamin D Treatment in Mortality Reduction Due to COVID-19. 2021.

[28] Brigham, Women's H. Vitamin D and COVID-19 Trial. ClinicalTrialsgov; 2020.

[29] Fundación para la Investigación Biosanitaria del Principado de A, Hospital Universitario Central de A, Instituto de Investigación Sanitaria del Principado de A. Effect of Vitamin D on Morbidity and Mortality of the COVID-19. 2020.

[30] Harvard School of Public H. Vitamin D and Zinc Supplementation for Improving Treatment Outcomes Among COVID-19 Patients in India. ClinicalTrialsgov; 2020.

[31] University Health N. Vitamin D and Zinc for COVID-19 patients. ICTRP. 2021. CTRI/2021/04/032593.

[32] Investigation Institute B. Efficacy of vitamin D treatment in patients diagnosed with pneumonia who require hospital admission and have vitamin D deficiency and a positive diagnosis for SARS-Cov-2 (COVID-19). ICTRP; 2020.

[33] Louisiana State University Health Sciences Center in New O. The LEAD COVID-19 Trial: Low-risk, Early Aspirin and Vitamin D to Reduce COVID-19 Hospitalizations. ClinicalTrialsgov; 2020.

[34] Medical University of G. The VITDALIZE Study: Effect of High-dose Vitamin D3 on 28-day Mortality in Adult Critically Ill Patients. ClinicalTrialsgov; 2017.

[35] Prof. Dr. Jorg L. High Dose Vitamin-D Substitution in Patients With COVID-19: a Randomized Controlled, Multi Center Study. ClinicalTrialsgov; 2020.

[36] Suraksha Pharma Private L. To Compare the safety and efficacy of Vitamin D, with Magnesium in mild to moderate Covid 19 patients. ICTRP; 2020.

[37] Universidad de G. Vitamin D on Prevention and Treatment of COVID-19. 2020.

[38] University of A. Vitamin D and COVID-19 Management. ClinicalTrialsgov; 2020.

[39] University of L, Laboratoires SSA. Effect of Vitamin D on Hospitalized Adults With COVID-19 Infection. 2021.

[40] Vitamin DSG. Cholecalciferol to Improve the Outcomes of COVID-19 Patients. ClinicalTrialsgov; 2020.

[41] Istituto Europeo Di O. prevention of complications from COVID-19 in cancer patients under active treatment. ICTRP. 2020. EUCTR2020-002119-23-IT.

[42] Vitamin D, Omega-3, and Combination Vitamins B, C and Zinc Supplementation for the Treatment and Prevention of COVID-19.

[43] Hospital Univeristario De M. Effects of Tocilizumab and its combination with Vitamin D to treat the increased defensive response in COVID-19. ICTRP. 2020. EUCTR2020-001903-17-ES.

[44] Shahroud University of Medical S. Evaluation effect of treatment with IM D3 on clinical, paraclinical symptoms and signs and inhospital outcome at patient admitted with coovid19. ICTRP. 2020. IRCT20200411047024N1.

[45] Sabzevar University of Medical S. Comparison of three methods of treatment in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with and without coronavirus positive test. ICTRP. 2020. IRCT20140305016852N4.

[46] University of M. The Effect of Vitamin D Supplementation on COVID-19 Recovery. ClinicalTrialsgov. 2021. NCT04883203.

[47] Postgraduate Institute of Medical E, Research. Short Term, High Dose Vitamin D Supplementation in Moderate to Severe COVID-19 Disease. ClinicalTrialsgov. 2021. NCT04952857.

[48] Copenhagen University Hospital of B. High dose Vitamin D in Preventing Aggravation of COVID-19. ICTRP. 2020. EUCTR2020-001793-30-DK.

[49] Federal Research Clinical Center of Federal M, Biological Agency R. The Efficacy of Vitamin D Supplementation in Patients With Severe and Extremely Severe COVID-19. ClinicalTrialsgov. 2021. NCT05092698.

[50] Patna A. Use of three different drugs for reduction in severity of COVID-19 disease using Arterial Stiffness as a clinical marker. ICTRP. 2021. CTRI/2021/03/032385.

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

GÖG is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). GÖG performed a search in Medline and PubMed (Appendix Table 6-1) and searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane COVID-19 Study Register (covid-19.cochrane.org), ClinicalTrials.gov (www.clinicaltrials.gov) ISRCTN registry (www.isrctn.com) and EU Clinical Trials Register (www.clinicaltrialsregister.eu) were searched in addition. We applied no restriction on language of publication.

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. ((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV- 2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS- CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))OR "seafood market*"[Title/Abstract] OR "food market*"[Title/Abstract]) AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*[Title/Abstract])))) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*[Title/Abstract]) AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*[Title/Abstract]))) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND ((vitamin D[Title/Abstract] OR vitamin D3[Title/Abstract] OR vitamin D2[Title/Abstract] OR ergocalciferol[Title/Abstract] OR ercalcitriol[Title/Abstract] OR calcitriol[Title/Abstract] OR high-dose Vitamin D[Title/Abstract]) OR Calcifediol or (vitamin D[MeSH Major Topic]))	12/7/2021 until 4/11/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1 exp coronavirus/ 2 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ab,kw,ti. 3 (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARSCov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ab,kw,ti. 4 (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ab,kw,ti. 5 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ab,kw,ti. 6 "severe acute respiratory syndrome* ".ab,kw,ti. 7 or/1-6 8 randomized controlled trial.pt. 9 controlled clinical trial.pt. 10 "random*".ab. 11 placebo.ab. 12 clinical trials as topic.sh. 13 random allocation.da,sh. 14 trial.ti. 15 or/8-14 16 exp animals/ not humans.sh. 17 15 not 16 18 7 and 17 19 limit 18 to yr="2019 -Current" 20 exp Vitamin D/ 21 (vitamin D or Vitamin D3 or Vitamin D2 or Calcifediol or ergocalciferol or ercalcitriol or calcitriol).ab,kw,ti. 22 high-dose Vitamin C.ab,kw,ti. 23 20 or 21 or 22 24 18 and 23	12/7/2021 until 4/11/2021

6.2 Search strategy to identify ongoing studies

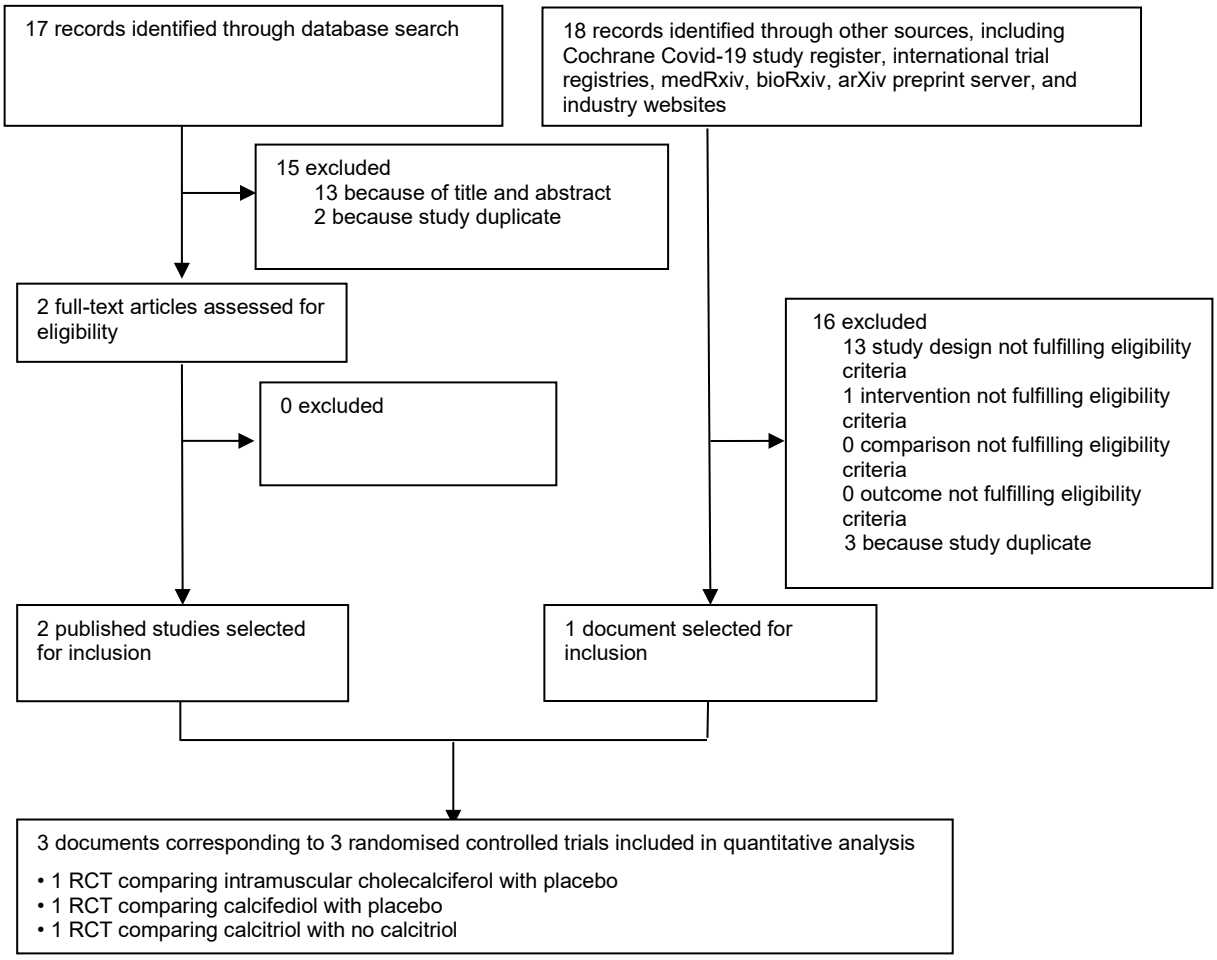
GÖG is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Vitamin D are described in Table 6-2.

Table 6-2 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 or corona Terms used at "other terms": • vitamin D or Vitamin D2 OR Vitamin D3 OR Calcifediol or ergocalciferol or ercalcitriol or calcitriol	12/7/2021 until 4/11/2021	7 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and Vitamin D	12/7/2021 until 4/11/2021	0
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and Vitamin D	12/7/2021 until 4/11/2021	1 new

***** In "Basic Search mode", one term was added to the field "condition or disease" and one term in the field "other terms".

6.3 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

RCT = randomised controlled trial