Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Among patients with COVID-19, should Vitamin D be used as adjunctive treatment?

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RECOMMENDATION

There is insufficient evidence to recommend the use of Vitamin D supplementation as an adjunct treatment for patients with COVID-19 infection. *(Very low certainty of evidence)*

Consensus Issues
The panel members perceived that the quality of evidence, showing negligible benefit, is still very low. A panel member voted against using Vitamin D as an adjunct due to (1) the possibility of it being prescribed despite the inconclusive evidence of benefit, (2) additional expenses that would be incurred if prescribed, and (3) probable drug interactions with other medications.

PREVIOUS RECOMMENDATION

There is insufficient evidence to recommend the use of Vitamin D supplementation as adjunct treatment for patients with COVID-19 infection. *(Very low quality of evidence)*

Consensus Issues
There were no issues raised during the panel meeting.

What's New in this Version?

- This version includes eight randomized controlled trials, because of the addition of five new RCTs published in peer-reviewed journals, that were not yet available at the time of initial review.

Key Findings

We found eight randomized controlled trials of COVID-19 patients who were given vitamin D as adjunctive treatment. We found no significant benefit for the following outcomes: mortality, ICU admission, need for mechanical ventilation, hospital length of stay, clinical improvement, and

virologic clearance. Subgroup analysis revealed that vitamin D status did not significantly change our estimates. These results must be interpreted in the context of very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision among the included studies.

Introduction

At the start of the pandemic, nutritional supplements (e.g., vitamins A, C and D) were identified as potential treatments for COVID-19 based on indirect evidence of their effectiveness against respiratory viruses and other coronaviruses. Small cohort studies initially found a lower risk of progression of oxygen support requirement and lower risk of mortality among patients with COVID-19 who received oral vitamin D supplementation.[1,2] One early systematic review identified vitamin D deficiency as a significant risk factor for increase in COVID-19 severity.[3] However, a recent systematic review and meta-analysis with a search date until February 2021 showed that low levels of vitamin D was not significantly associated with increased risk for mortality.[4]

The SARS-CoV-2 virus upregulates renin and angiotensin- converting enzyme (ACE2) expression. This leads to a buildup of angiotensin II causing inflammation, enhanced lung permeability, and acute respiratory distress syndrome via the angiotensin 1 receptor pathway. Recent studies suggest that vitamin D lowers the risk of COVID-19 complications by attenuating cytokine release through lowering renin and angiotensin-converting enzyme expression. Vitamin D may also lower inflammation, fibrosis, and apoptosis.[5–7]

Currently, the evidence for benefit is based on observational studies. This review updates and summarizes the available evidence from randomized controlled trials to answer whether the use of vitamin D as adjunctive treatment has benefits in patients with COVID-19.

Review Methods

An updated systematic search was done from July 2021 until November 14, 2021. We included electronic databases (MEDLINE, Cochrane COVID-19 Study Register), trial registries (Chinese Clinical Trial Registry, Clinicaltrials.gov, EU Clinical Trials Register), and the COVID-NMA initiative. We also checked the included studies from other living guidelines or systematic reviews on COVID-19. Only randomized controlled trials that compared vitamin D against placebo or standard of care (SOC) were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, and adverse events. No limits were placed on age of patients, COVID-19 severity, hospitalization status, and dosing strategy of vitamin D. We performed sensitivity analysis to assess the robustness of the results when studies with serious risk of bias concerns were excluded. We also planned to do a subgroup analysis among patients with sufficient and low serum vitamin D levels, according to the sufficiency category given or defined by each study (see Appendix 2).

Results

The search yielded 302 records, of which eight were RCTs (N=740) and included in this review.[8–15] All eight RCTs used vitamin D as adjunct treatment among hospitalized patients with COVID-19 in Brazil, Egypt, India, Iran, Mexico, Spain, and USA. Sample size in the individual studies ranged from 40 to 240. At least four studies included COVID-19 severe cases.[8,9,12,13] Four studies [10,11,13,14] only included participants who had low serum level of vitamin D (below 20–30 ng/mL).

Seven studies administered oral vitamin D, while one study administered vitamin D through the intramuscular route.[14] Multiple oral forms and dosages of vitamin D were also used: two studies used calcifediol [9,13], one used calcitriol [12], three used cholecalciferol [10,11,15], and one was unspecified [8] (see Appendix 3).

Risk of bias was rated very serious in one out of eight studies and serious in three studies. All studies had adequate randomization. At least six of the eight studies had high risk for detection bias from unblinded assessors, and performance bias from unblinded investigators. Three studies had high risk for attrition bias due to incomplete data (see Appendix 4).

The overall certainty of evidence was rated very low for the outcomes of mortality, ICU admission, and clinical improvement due to serious risk of bias, serious inconsistency as reflected in the different dosages and forms of vitamin D, and serious imprecision from wide confidence intervals. For the outcomes of need for mechanical ventilation and hospital length of stay, certainty of evidence was rated as low because there was serious imprecision from the small number of event rates and the wide confidence interval (see Appendix 5).

Mortality and ICU admission

For overall mortality (pooled RR 0.73, 95% CI 0.38-1.40; I^2=11%, 6 RCTs) [8,9,11–14] and ICU admission (pooled RR 0.54, 95% CI 0.28-1.05; I^2=55%, 5 RCTs) [8,9,11–13], the pooled estimates for vitamin D were inconclusive. The pooled estimates in subgroup analysis according to serum vitamin D levels likewise yielded inconclusive results for the outcomes of overall mortality (pooled RR 0.65, 95% CI 0.30-1.45; I^2=0%, 3 RCTs) [11,13,14] and ICU admission (pooled RR 0.66, 95% CI 0.31-1.41; I^2=0%, 2 RCTs) [11,13] (see Appendix 6).

Need for Mechanical Ventilation and Length of Hospital Stay

For the outcome of need for mechanical ventilation, the pooled estimate for Vitamin D as adjunctive treatment showed that it may provide benefit or only be equivalent to standard of care (pooled RR 0.61, 95% CI 0.38-1.00; I^2=0%, 4 RCTs).[8,12–14] The effect of adjunctive treatment with vitamin D on the length of hospital stay was also inconclusive when compared to placebo or standard of care (MD -0.48, 95% CI -1.91-0.94; I^2=35%, 3 RCTs).[8,11,12] While it was noted that Maghbooli et al. reported no significant difference in hospital length of stay between participants who received vitamin D (median 5 days) compared to placebo (median 6 days), the results were not pooled due to inadequate data. Subgroup analysis according to serum vitamin D levels revealed inconclusive results for both mechanical ventilation (pooled RR 0.72, 95% CI 0.38-1.36; I2=0%, 2 RCTs)[13,14] and hospital length of stay (MD -0.17, 95% CI -1.97-1.63, 1 RCT).[11]

Clinical Improvement and Virologic Clearance

The estimates for the effect of Vitamin D on clinical improvement (RR 0.58, 95% CI 0.28-1.18, 1 RCT)[15] and virologic clearance (RR 0.58, 95% CI 0.19-1.79; I^2=16, 2 RCTs)[10,15] were inconclusive.

Safety outcomes / Adverse events

Among the eight RCTs that used vitamin D as adjunctive treatment, only one patient who received vitamin D was documented to have vomiting. No episodes of hypercalcemia or hyperphosphatemia were observed. Based on these studies, we report no adverse events directly attributable to vitamin D supplementation among COVID-19 patients.

Pediatric Population

We found no RCTs that used vitamin D as adjunctive treatment for COVID-19 in the pediatric population. We found only one systematic review that investigated the association between vitamin D levels and COVID-19 severity in children with search date until June 2021.[16] We found no additional observational studies from our literature search until November 4, 2021. Based on the systematic review, they found two small (n=40-103) retrospective cohort studies conducted in Turkey among children <18 years of age.[17,18] We analyzed both cohort studies and found that low serum vitamin D level (<30 ng/mL) was not significantly associated with a higher risk for COVID-19 severity (OR 2.66, 95% CI 0.94-7.55; I^2=0%, 2 studies). No mortalities were reported for both studies. We found insufficient evidence to determine whether vitamin D is associated with benefits or harms for COVID-19 in children; large well conducted randomized controlled trials are needed (see Appendix 7).

Evidence to Decision

Vitamin D is available locally in two forms (Calcitriol and Cholecalciferol). Based on the 2021 Drug reference price index, only the fixed dose combination of Calcium Carbonate 500/600mg + Cholecalciferol (vitamin D3) 400 IU at 4.00Php per tablet is registered in the Philippine National Formulary. Calcitriol and cholecalciferol are not included in the formulary list.

Vitamin D forms	
Calcitriol 0.25mcg/cap	₱32.00
Cholecalciferol 800 IU/cap	₱8.00

Recommendations from Other Groups

The recommendations of other groups on the use of vitamin D for the prevention or treatment of COVID-19 are summarized in the table below.

Group/Society/Network	Recommendations
US NIH (4 November 2021) [19]	Does not recommend for or against the use of vitamin D for the prevention or treatment of COVID-19
Australian COVID-19 Living CPG (3 November 2021) [20]	Does not recommend the use of vitamin D outside of trials [20]
NICE Guidelines (3 November 2021)	Does not recommend the use of vitamin D in the prevention or treatment of COVID-19.
Cochrane Systematic Review (March 2021) [21]	There is insufficient evidence to determine the benefits or harms of vitamin D supplementation as treatment for COVID-19.

Research Gaps

As of September 2021, there are 24 ongoing clinical trials investigating the efficacy of vitamin D as adjunctive treatment for COVID-19 that are listed in COVID-19 NMA database [22] (see Appendix 8).

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 5)

FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No	Yes (5)					COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate	Small (2)	Uncertain (3)			• Benefit: Inconclusive results for the following outcomes: mortality, ICU admission, need for mechanical ventilation, hospital length of stay, clinical improvement, and virologic clearance; even Vitamin D status did not significantly change our estimates.
Harm	Large	Small (4)	Uncertain (1)	Varies			• One patient who received vitamin D had vomiting. • No episodes of hypercalcemia or hyperphosphatemia were reported. • We generally found no adverse events directly attributable to vitamin D supplementation among COVID-19 patient
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			• These results must be interpreted in the context of very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision among the included studies.
Balance of effects	Favors Vitamin D (3)	Does not favor Vitamin D (1)	Uncertain (1)	Varies			
Values	Important uncertainty or variability	Possibly important uncertainty or variability (1)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost	Moderate Costs (2)	Negligible costs or savings	Moderate savings (3)	Large savings	• Vitamin D is available locally in two forms (Calcitriol and Cholecalciferol). Only the fix dose combination of calcium carbonate 500/600mg + cholecalciferol (vitamin D3) 400 IU at 4.00 php per tablet is registered in the Philippine National Formulary.

FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
							• Calcitriol and cholecalciferol are not included in the formulary list. Calcitriol 0.25mcg/cap = ₱32.00. Cholecalciferol 800 IU/cap = ₱8.00
Certainty of evidence of required resources	No included studies (5)	Very low	Low	Moderate	High		• No research evidence found on cost-effectiveness of vitamin D as an adjunctive treatment for COVID-19.
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			• No research evidence found on cost-effectiveness of vitamin D as an adjunctive treatment for COVID-19.
Equity	Uncertain (4)	Reduced	Probably no impact (1)	Increased			• No research evidence found.
Acceptability	Uncertain (4)	No	Yes (1)	Varies			• No research evidence found.
Feasibility	Uncertain (2)	No	Yes (3)	Varies			• Vitamin D is available locally in two forms (calcitriol and cholecalciferol).

Appendix 2. Search Strategy (as of 4 November 2021)

Information Source	Search Strategy	Yield	Eligible
MEDLINE (PubMed)	((Vitamin D OR "Vitamin D"[Mesh] OR (Ergocalciferol OR Cholecalciferol)) AND ((("COVID-19" [Supplementary Concept] OR "COVID-19 diagnostic testing" [Supplementary Concept] OR "COVID-19 drug treatment" [Supplementary Concept] OR "COVID-19 serotherapy" [Supplementary Concept] OR "COVID-19 vaccine" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sars cov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2") OR ((19[tiab] OR 2019[tiab] OR "2019-nCoV" OR "Beijing" OR "China" OR "Covid-19" OR epidem*[tiab] OR epidemic* OR epidemy OR new[tiab] OR "novel"[tiab] OR "outbreak" OR pandem* OR "SARS-CoV-2" OR "Shanghai" OR "Wuhan") AND ("Coronavirus Infections"[Mesh] OR "coronavirus"[MeSH Terms] OR coronavirus*[all] OR corona-virus*[all] OR cov[tiab] OR pneumonia-virus*[tiab])))) AND 2019/12/1:3000/12/31[PDAT]))))	Nov 4: 239	3
Cochrane COVID-19 Study Register	“Vitamin D”; Limits: randomized controlled trials & reporting results	Nov 4: 20	0
COVID-NMA initiative https://covid-nma.com/		Nov 4: 5	0
ClinicalTrials.gov https://clinicaltrials.gov/	Condition or disease: COVID Other terms: Vitamin D OR Ergocalciferol OR Cholecalciferol Filter: Completed	Nov 4: 36	1
Chinese Clinical Trial Registryhttp://www.chictr.org.cn/searchprojen.aspx	Intervention: Vitamin D, Cholecalciferol Target Disease: COVID	Nov 4: 0	0
EU Clinical Trials Register https://www.clinicaltrialsregister.eu/	“Covid-19 AND Vitamin D” Filter: Trial with results	Nov 4: 2	0

Appendix 3. Characteristics of Included Studies

Table 2. Adjunctive treatment with Vitamin D versus placebo or standard care (8 RCTs)

No.	Clinical Trial ID/ Title	Population	Sample Size	Intervention	Comparator	Outcomes
1	Murai 2020 Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19 Brazil	Hospitalized patients with mild to severe COVID-19 Adults aged 18>yrs Positive for SARS-CoV-2 PCR or positive CT scan findings compatible with COVID-19	N=240	200,000 IU of vitamin D3 per orem given on day of admission (N=120)	Placebo (N=120)	Length of Hospital stay Mortality ICU admission Need for mechanical ventilator Duration of mechanical ventilator Serum vitamin D levels
2	Entrenas Castillo 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 Spain	Hospitalized patients with moderate to severe COVID-19 infection clinical picture of acute respiratory infection confirmed by a radiographic pattern of viral pneumonia positive SARS-CoV-2 PCR with CURB65 severity scale (recommending hospital admission in case of total score > 1).	N=76	Day of admission: 2 capsules of calcifediol (0.266 mg/cap). 1 capsule on days 3, 7, 14, 21, 28 until discharge or ICU admission. Plus standard of care (N=50)	Standard of care (N=26) defined as: 1) Hydroxychloroquine 400mg every 12 hours on first day and 200 mg every 12 hours for the following 5 days 2) Azithromycin 500 mg orally for 5 days, 3) For patients with pneumonia and NEWS score >5, Ceftriaxone 2 g intravenously every 24 hours was given for 5 days.	ICU admission Mortality
3	Rastogi 2020 Short term, high-dose vitamin D supplementation forCOVID-19 disease: a randomized, placebo-controlled, study (SHADE study) India	Hospitalized patients with asymptomatic to mild COVID-19 with or without co-morbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease)	N=40	Daily 60,000 IU of cholecalciferol (5 ml oral solution in nano droplet form) for 7 days with the aim to achieve 25 (OH)D level>50 ng/ml (N=16) Subsequently, 25(OH)D levels were assessed at	Placebo (5 ml distilled water) (N=24) Plus standard of care	Proportion of participants who turn SARS-CoV-2 RNA negative at days 5, 7, 10, 14,18 and 21 (real-time PCR, CFX-96 IVD, Bio-Rad)

		with vitamin D deficiency defined as levels below 20 ng/ml		day 7 and a weekly supplementation of 60,000IU provided to those with 25(OH)D >50 ng/ml or else continued daily vitamin D 60,000 IU supplementation for another 7 days up until day-14 in participants with 25(OH)D <50 ng/ml Plus standard of care		
4	Lakkireddy 2021 Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease India	Hospitalized patients with mild to moderate COVID-19 with vitamin D defined as levels below 30 ng/mL	N=130	60,000 IU of cholecalciferol (aqueol nano solution/Deksel) per orem daily for 8 days if with body mass index (BMI) between 18-25 and for 10 days if with BMI more than 25 (N=65) Plus standard of care	Standard of care (N=65)	Inflammatory markers and vitamin D levels before and after intervention (vitamin D levels, CRP, LDH, IL6, Ferritin, N/L ratio) Mortality ICU admission Mean hospital stay Adverse events
5	Elamir 2021 A randomized pilot study using calcitriol in hospitalized COVID-19 patients USA	Hospitalized patients with COVID-19 with moderate to severe COVID-19	N=50	Calcitriol 0.5 ug daily for 14 days or discharge whichever came first. Plus standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma	Standard of care Standard of care: remdesivir (200 mg for one day followed by 100 mg for 4 days), dexamethasone (6 mg daily for 10 days), or convalescent plasma	Oxygen requirements Length of hospital stay Need for ICU admission Mortality Readmission.
6	Maghbooli 2021 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	Hospitalized patients with moderate to severe COVID-19	N=106	Calcifediol 25 mg per orem once daily for 30 days Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia	Placebo Plus standard of care: a combination of hydroxychloroquine, azithromycin, and ceftriaxone for patients with pneumonia	Length of Stay Need for Mechanical Ventilation Mortality ADE Admission to ICU

	Iran					
7	Soliman 2021 Impact of Vitamin D Therapy on the Progress COVID-19: Six Weeks Follow-Up Study of Vitamin D Deficient Elderly Diabetes Patients Egypt	Hospitalized elderly diabetes patients with SARS-CoV-2 with vitamin D deficiency.	N=56	200,000 units of high dose cholecalciferol single dose IM	Placebo	Mortality Need for Mechanical Ventilation
8	Sánchez-Zuno 2021 Vitamin D Levels in COVID-19 Outpatients from Western Mexico: Clinical Correlation and Effect of Its Supplementation	Outpatient adults with mild COVID-19	N=42	10,000 IU daily of vitamin D3 in soft capsule form for 14 days	Standard of care	Clinical Improvement (D7) Virologic Clearance (D14)

Appendix 4. Methodological Quality Assessment of Included Studies

*Green: not serious; Yellow: serious; Red: very serious

Studies	Risk of bias	Random assignment	Allocation concealment	Similar baseline characteristics	Patients blinded	Caregivers blinded	Assessors blinded[1]	Intention-to-treat analysis	Adequate follow-up rate	Peer-reviewed
1. Murai	Serious	Yes	Yes	Yes	Yes	Yes	Yes	No	No[1]	Yes
2. Entrenas Castillo	Not serious	Yes	Unclear	Yes[2]	No	No	No	Yes	Yes	Yes
3. Rastogi	Not serious	Yes	Unclear	Yes[3]	No	Unclear	Unclear	Yes	Yes	Yes
4.Lakkireddy	Very serious	Yes	Unclear	No[4]	No	No	No	No	No[5]	Yes
5. Elamir	Not serious	Yes	No	Yes	No	No	No	Yes	Yes	Yes
6. Maghbooli	Serious	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	No[6]	Yes
7. Soliman	Not serious	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
8. Sánchez-Zuno	Serious	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Yes

[1] Vitamin D group 119/120 analyzed, Placebo group 118/120 analyzed, 3 drop out
[2] Except for high blood pressure and diabetes mellitus
[3] Except for serum calcium level
[4] Vitamin D group had higher inflammatory markers (CRP, LDH, IL-6, Ferritin, N/L ratio) at the start of the study despite randomization.
[5] High drop-out rate for the vitamin D group 19/65 (29%) and the control group 18/65 (28%) with only 87 participants in the final analysis. Reasons as follows: discharged prior to repeat analysis of inflammatory markers (n= 35) and non-adherence (n=2)
[6] High drop-out rate for the vitamin D group 16/53 (30%) and the control group 21/53 (40%) at 1 month follow up. No reasons were provided.

Appendix 5. GRADE Evidence Profile

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Question: Should Vitamin D supplements compared to placebo in adjunct treatment for COVID-19?
Bibliography: Murai, Entrenas-Castillo, Rastogi, Lakkireddy, Elamir, Maghbooli, and Soliman

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Should Vitamin D supplements	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality (ITT) (follow-up: range 30 days to 60 days)												
6[a]	randomised trials	serious[b]	serious[c]	not serious	serious[d]	none	21/353 (5.9%)	24/305 (7.9%)	**RR 0.73** (0.38 to 1.40)	**21 fewer per 1,000** (from 49 fewer to 31 more)	⨁◯◯◯ Very low	CRITICAL
ICU admission (ITT) (follow-up: range 30 days to 60 days)												
5	randomised trials	serious[e]	serious[c,f]	not serious	serious[g]	none	35/313 (11.2%)	61/289 (21.1%)	**RR 0.54** (0.28 to 1.05)	**97 fewer per 1,000** (from 152 fewer to 11 more)	⨁◯◯◯ Very low	CRITICAL
Need for Mechanical Ventilation (ITT) (follow-up: range 30 days to 60 days)												
4	randomised trials	not serious	serious[a,c]	not serious	serious[g]	none	25/238 (10.5%)	31/214 (14.5%)	**RR 0.61** (0.38 to 1.00)	**56 fewer per 1,000** (from 90 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Hospital length of stay												
3	randomised trials	not serious	serious[c]	not serious	serious[d]	none	210	210	-	MD **0.48 days lower** (1.91 lower to 0.94 higher)	⨁⨁◯◯ Low	CRITICAL
Clinical Improvement (follow-up: mean 7 days)												
1	randomised trials	very serious[h]	not serious	not serious	serious[g]	none	7/21 (33.3%)	11/19 (57.9%)	**RR 0.58** (0.28 to 1.18)	**243 fewer per 1,000** (from 417 fewer to 104 more)	⨁◯◯◯ Very low	CRITICAL
Virologic Clearance (follow-up: range 14 days to 21 days)												

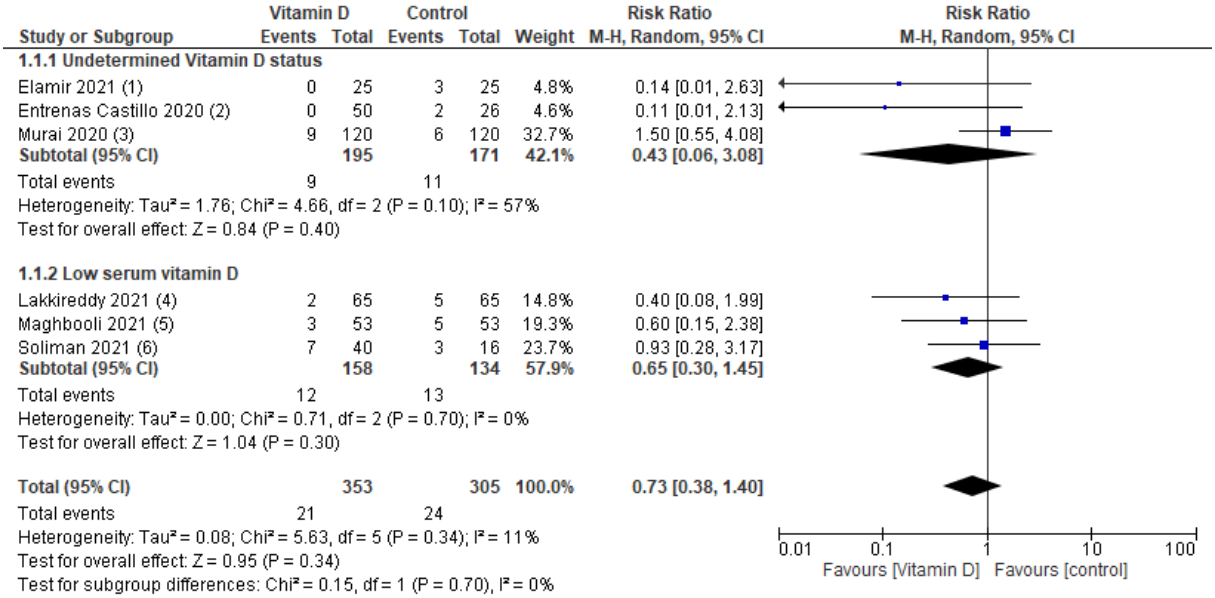
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Should Vitamin D supplements	placebo	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[i]	not serious	not serious	serious[g]	none	7/38 (18.4%)	19/44 (43.2%)	**RR 0.58** (0.19 to 1.79)	**181 fewer per 1,000** (from 350 fewer to 341 more)	⨁⨁◯◯ Low	IMPORTANT

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

Explanations

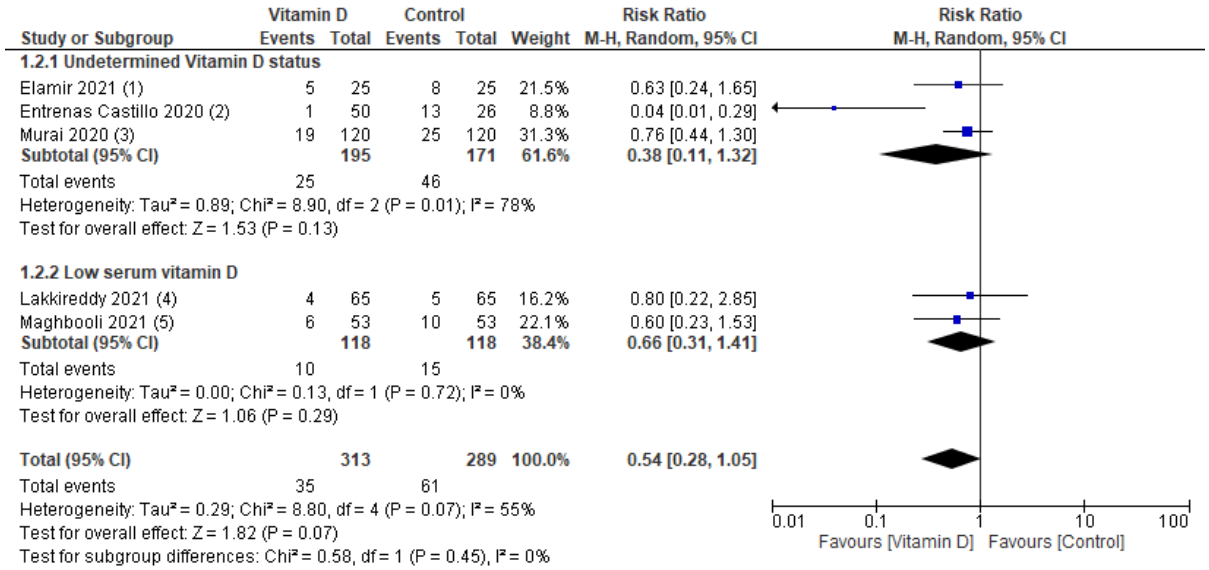
a. Serious inconsistency due to different direction of effect by one study Murai which contributed to 32.7% of the over all effect and with risk of bias rated as not serious.
b. serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 66.8% of the overall treatment effect
c. Serious inconsistency due to differences in dosage and formulation of vitamin D.
d. serious imprecision due to wide confidence interval
e. serious risk of bias due to high drop out rate in the study of Murai, Lakkireddy and Maghbooli which contributed to 69.7% of the overall treatment effect
f. serious risk for inconsistency; high heterogeneity I2=55%
g. Imprecision downgraded by 1 level: due to low number of event rate and wide confidence interval.
h. serious risk of bias due to unblinded patients and outcome assessors which may have affected how symptoms were reported
i. Risk of bias downgraded by 1 level: some concerns due to unclear randomization and allocation concealment, and lack of blinding in participants and personnel.

Appendix 6. Forest Plots from Studies that Enrolled Adult Participants (November 4 2021)



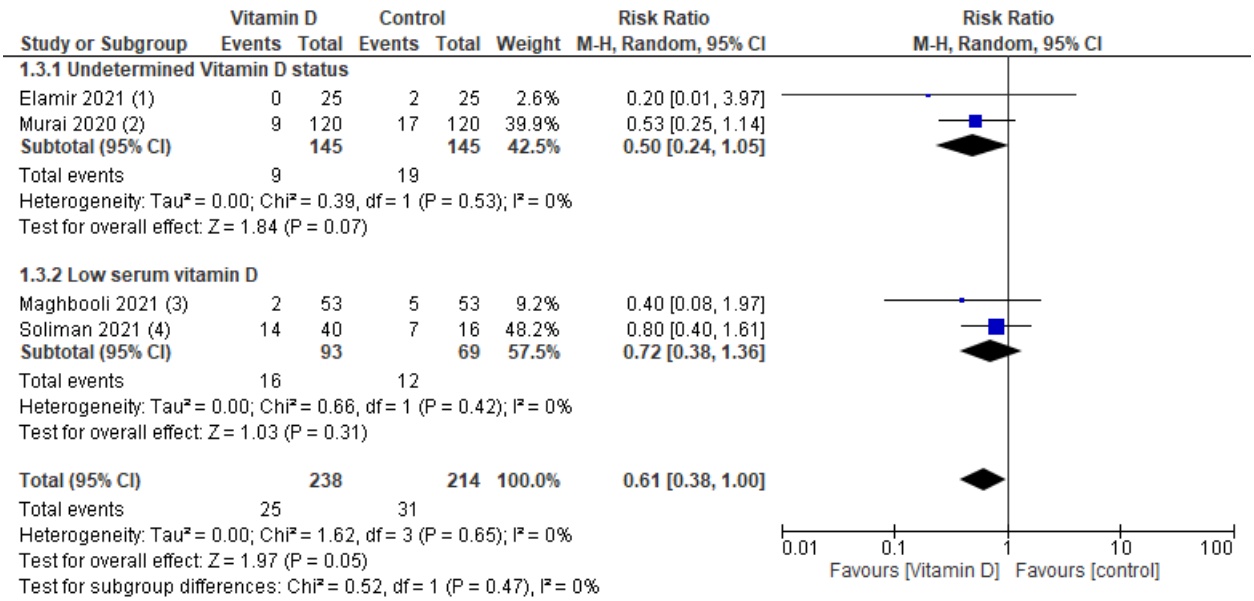
Footnotes
(1) moderate to severe
(2) moderate to severe
(3) mild to severe; vitamin D group (mean 21.2 ng/mL; SD 10.1); control group (mean 20.6 ng/mL; SD 8.1)
(4) mild to moderate; vitamin D <30 ng/mL
(5) moderate to severe; vitamin D <30 ng/mL
(6) severity not stated; vitamin D <20 ng/mL

Figure 1.1. Mortality, overall (ITT)



Footnotes
(1) moderate to severe
(2) moderate to severe
(3) mild to severe; data converted from percentage VitD 16% & control 21.2%;vitamin D group (mean 21.2 ng/mL; SD 10.1); control group (mean...
(4) mild to moderate; vitamin D <30 ng/mL
(5) moderate to severe; vitamin D <30 ng/mL

Figure 1.2. ICU admission (ITT)



Footnotes

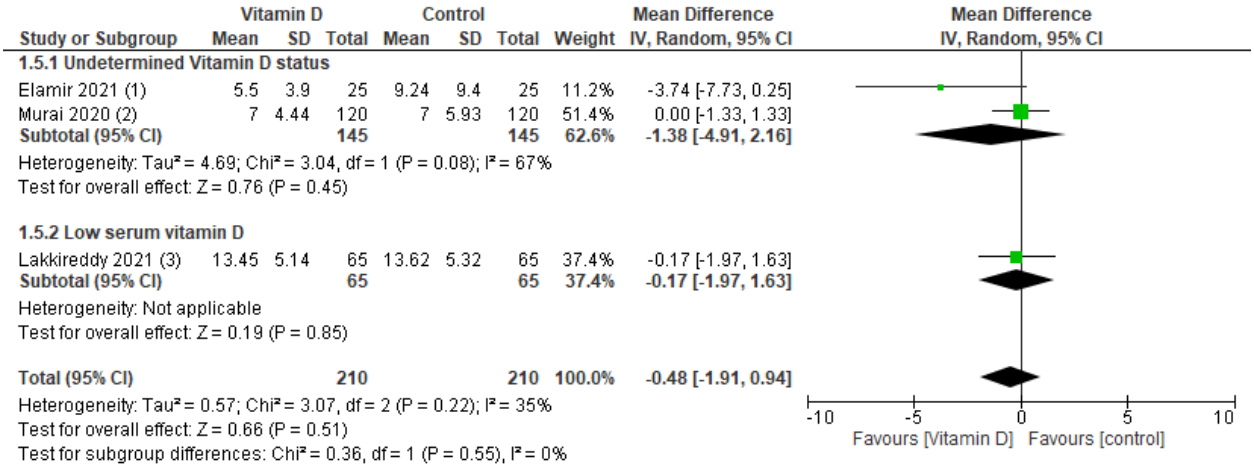
(1) moderate to severe

(2) mild to severe; data converted from percentage VitD 7.6% & control 14.4%; vitamin D group (mean 21.2 ng/mL; SD 10.1); control group...

(3) moderate to severe; vitamin D <30 ng/mL

(4) severity not stated; vitamin D <20 ng/mL

Figure 1.3. Need for Mechanical Ventilation (ITT)



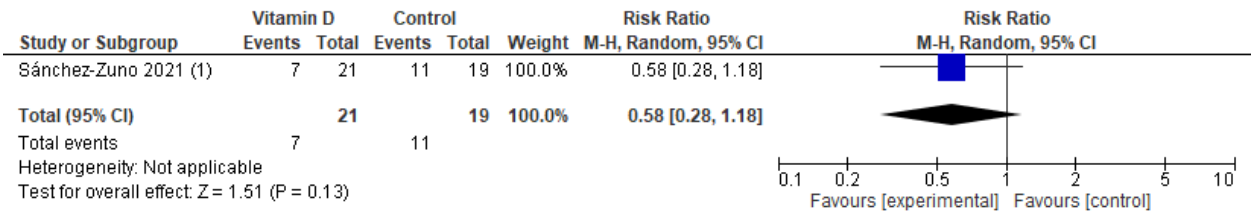
Footnotes

(1) moderate to severe

(2) mild to severe; data converted from IQR; vitamin D group (mean 21.2 ng/mL; SD 10.1); control group (mean 20.6 ng/mL; SD 8.1)

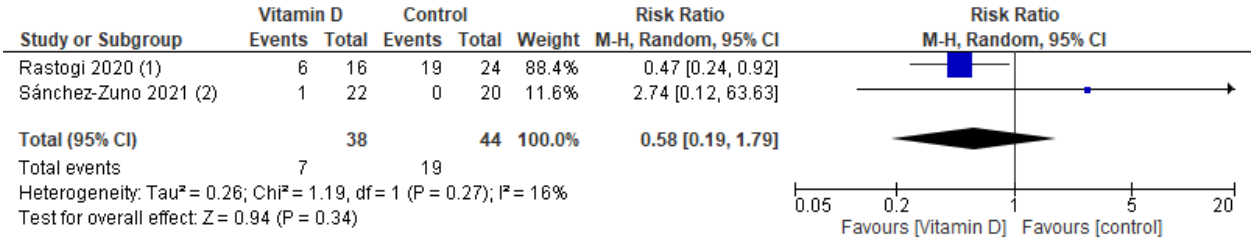
(3) mi vitamin D <30 ng/mL

Figure 1.4. Length of Hospital Stay (ITT)



Footnotes
(1) Defined as proportion of patients who became asymptomatic at day 14

Figure 1.5. Clinical Improvement (ITT)



Footnotes
(1) Proportion of patients who remained positive at Day 21
(2) Proportion of patients who remained positive at Day 14

Figure 1.6. Virologic Clearance (ITT)

Appendix 7. Forest Plot from Studies that Enrolled Pediatric Participants (November 4 2021)

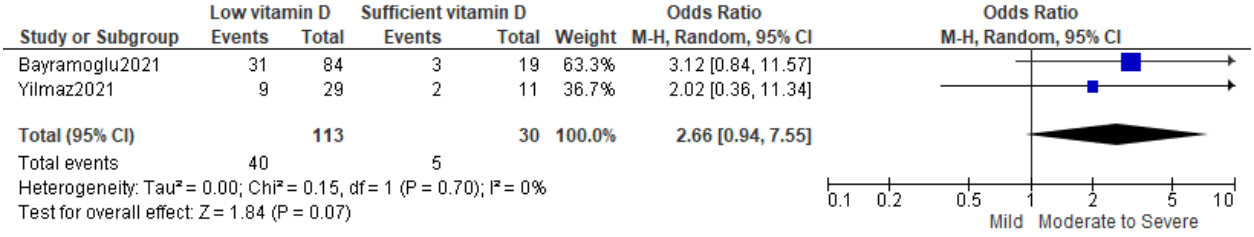


Figure 2.1. COVID-19 Severity

Appendix 8. Table of Ongoing Studies (September 2021)

	Treatment (per arm)	Sample size	Severity at enrollment	Reg. number
1	To Study the Role of Vitamin D in the Treatment of Confirmed COVID-19 Infection (1) Vitamin D vs (2) Standard of care	100	Moderate/severe	CTRI/2020/12/030083
2	Prevention and treatment with Calcifediol of respiratory problems caused by COVID-19	1008	No restriction on type of patients	EUCTR2020-001717-20-ES

	(1) Vitamin D vs (2) Standard of care			
3	High dose Vitamin D in Preventing Aggravation of COVID-19 (1) Vitamin D vs (2) Placebo	480	Mild	EUCTR2020-001793-30-DK
4	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) (1) Vitamin D vs (2) Placebo	108	Moderate/severe	EUCTR2020-001960-28-ES
5	Evaluation of the likely beneficial effects of vitamin D on infection with coronavirus (1) Vitamin D3 vs (2) Standard of care	60	No restriction on type of patients	EUCTR2020-002274-28-ES
6	Clinical trial, randomized, open-label, to evaluate the efficacy of high-dose vitamin D in patients with COVID-19 pneumonia (1) Vitamin D vs (2) Vitamin D	82	Moderate/severe	EUCTR2020-002312-43-ES
7	Effect of vitamin D supplementation in novel corona virus 2019 (1) Vitamin D vs (2) Vitamin D vs (3) Vitamin D	210	Mild/moderate	IRCT20110726007117N11
8	Evaluation of the efficacy of oral 25-hydroxyvitamin D3 on COVID-19 (1) Vitamin D vs (2) Placebo	260	Mild	IRCT20200401046909N1
9	Effect of Vitamin D Administration on Prevention and Treatment of Mild Forms of Suspected Covid-19 (1) Vitamin D vs (2) Standard of care	200	Mild	NCT04334005
10	COvid-19 and Vitamin D Supplementation: a Multicenter Randomized Controlled Trial of High Dose Versus Standard Dose Vitamin D3 in High-risk COVID-19 Patients (CoVitTrial) (1) Vitamin D vs (2) Vitamin D	260	Moderate/severe	NCT04344041
11	High-dose vitamin D versus placebo to prevent complications in COVID-19 patients: A structured summary of a study protocol for a randomized controlled trial (CARED-TRIAL) (1) Vitamin D vs (2) Placebo	1264	Moderate	NCT04411446
12	The Effect of Weekly 50,000 IU Vitamin D3 Supplements on the Serum Levels of Selected Cytokines Involved in Cytokine Storm of Covid-19; A Randomized Clinical Trial in the Covid-19 Uninfected Jordanian People With Vitamin D Deficiency (1) Vitamin D3 vs (2) Standard of care	100	Healthy volunteers	NCT04476745
13	The Role of Vitamin D in Mitigating COVID-19 Infection Severity: Focusing on Reducing Health Disparities in South Carolina (1) Vitamin D3 vs (2) Vitamin D3 vs (3) Placebo	140	Mild	NCT04482673
14	Efficacy of Vitamin D Treatment in Pediatric Patients Hospitalized by COVID-19: Open Controlled Clinical Trial (1) Vitamin D vs (2) Standard of care	40	No restriction on type of patients	NCT04502667
15	High Dose Vitamin-D Substitution in Patients With COVID-19: a Randomized Controlled, Multi Center Study	80	Moderate/severe/critical	NCT04525820

	(1) Vitamin D vs (2) Placebo			
16	Effect of Vitamin D on Morbidity and Mortality of the COVID-19 (1) Vitamin D3 vs (2) Standard of care	80	No restriction on type of patients	NCT04552951
17	Efficacy of Treatment With Vitamin D in Patients Diagnosed With Pneumonia Requiring Hospital Admission and Presenting Vitamin D Deficit and Positive Diagnosis for SARS-Cov-2 (1) Vitamin D vs (2) Placebo	108	Moderate/severe	NCT04621058
18	Vitamin D Supplementation and Covid-19: a Randomized, Double- Blind, Controlled Study (1) Vitamin D vs (2) Placebo	100	No restriction on type of patients	NCT04636086
19	The Effect of Vitamin D Therapy on Morbidity and Mortality in Patients With SARS-CoV 2 Infection (1) Vitamin D3 vs (2) Placebo	56	No restriction on type of patients	NCT04733625
20	Vitamin D3 Levels in COVID-19 Outpatients From Western Mexico: Clinical Correlation and Effect of Its Supplementation (1) Vitamin D3 vs (2) Standard of care	42	No restriction on type of patients	NCT04793243
21	Short Term, High Dose Vitamin D Supplementation in Moderate to Severe COVID-19 Disease (1) Vitamin D vs (2) Placebo	90	Severe	NCT04952857
22	The effect of vitamin D and magnesium supplementation on clinical symptoms, inflammatory markers and oxidative stress in patients with COVID-19: double-blind randomized control clinical trial (1) Vitamin D vs (2) Vitamin D3 + magnesium sulfate vs (3) Magnesium sulfate vs (4) Placebo	104	Mild/moderate	IRCT20210702051763N1
23	A study of vitamin D supplementation on clinical outcome of COVID-19 infected patients with pneumonia (1) Vitamin D vs (2) Standard of care	400	Moderate/severe	TCTR20210906005
24	A prospective, double-blind, parallel assignment, randomized controlled study to evaluate the effectiveness and safety of high dose Vitamin D supplementation and effects and associations of low vitamin D levels in patients with symptomatic SARS CoV-2 infection (1) Vitamin D vs (2) Placebo	258	Mild/moderate	SLCTR/2021/019