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Review

“Vitamin D supplementation and COVID-19 treatment: A systematic review and meta-analysis”



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ABSTRACT

Background: Vitamin-D is an immune-modulator which might be linked to disease severity by SARS-CoV-2.

Methods: Meta-analysis of RCTs and quasi-experimental studies, evaluating the role of vitamin-D supplementation in COVID patients was done.

Results: Total 5 studies (3 RCTs and 2 Quasi-experimental) including n = 467 patients were included. Vitamin D didn't reduce mortality (RR 0.55, 95%CI 0.22 to 1.39, p = 0.21), ICU admission rates (RR 0.20, 95% CI 0.01–4.26, p = 0.3) and need for invasive ventilation (RR 0.24, 95% CI 0.01–7.89, p = 0.42).

Conclusion: No significant difference with vitamin-D supplementation on major health related outcomes in COVID-19. Well-designed RCTs are required addressing this topic.

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1. Introduction

Currently the entire globe is suffering from third major outbreak caused by the family of beta-Coronavirus. Globally, till 18th May 2021 there have been 163,312,429 confirmed cases and 3,386,825 case fatality incidences, among which, 8.23% (2,78,719) case fatality incidences have been reported by India [1]. Despite being a tropical country and having plenty of sunshine, most of the Indian population are deficient in vitamin D [2]. The Severe Acute Respiratory syndrome virus (SARS-CoV-2) induces an inflammatory state, evidenced by raised acute markers like interleukin-6 (IL-6), c-reactive protein (CRP), ferritin, d-dimer etc. and may lead to lung damage especially in the second week of illness owing to the 'cytokine storm' [3]. This upsurge of inflammation has been linked to the occurrence of coronavirus induced acute respiratory distress syndrome (COVID ARDS) [4,5]. Vitamin D acts as an immune-modulator, which via various mechanisms e.g. ACE-2 receptor modulation, maintenance of pulmonary barrier function, enhancing neutrophil activity, reduces the damage

caused by pro-inflammatory cytokines [6]. This vitamin boosts the innate immune response during the initial viremic phase and shifts the adaptive immune response to a more T helper cell-2 (Th2) type [7]. Thus, it's regular supplementation was found to have beneficial role in preventing acute respiratory infections (ARI) as well as reduce its complications [8,9]. Different observational studies have shown a decreased COVID severity in patients without vitamin D deficiency, however contradictory evidences also exist [10,11]. Although few small scale studies showed vitamin D supplementation to reduce disease severity and/or attain earlier recovery [12–15], a large trial showed no added benefit with vitamin D supplementation [16]. Therefore, we aim to investigate the role of supplementation of Vitamin D among COVID-19 patients on their disease outcomes.

2. Aims and objectives

The study is aimed to assess the impact of Vitamin-D supplementation on clinical outcomes (mortality, ICU admission,

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mechanical ventilation, and change in inflammatory markers) in patients diagnosed with COVID-19.

3. Methodology

Preferred reporting items for systematic review and meta-analysis (PRISMA) statement for conducting meta-analysis was followed [17].

3.1. Search strategy

A comprehensive literature search was carried out using the pre-defined keywords (mentioned below) of articles published on PubMed, Embase and Scopus from inception till May 18, 2021.

Manual search was done to retrieve other articles using the keywords: (((covid 19) AND (vitamin D)) AND (supplementation)); ((covid 19 [Title/Abstract]) AND (vitamin D [Title/Abstract])) AND (supplementation [Title/Abstract]); (((vitamin D) AND (COVID)) AND (Coronavirus)) AND (covid-19).

3.2. Inclusion criteria

We wanted to know the true effect of vitamin D supplementation in COVID infected individuals, hence, we included randomized trials and quasi-experimental studies published in English language, where vitamin D supplementation was done prospectively i.e. after the diagnosis of COVID. Observational and retrospective studies were excluded due to the risk of their biasness. Patients diagnosed with COVID-19 irrespective of the disease severity, who received vitamin D supplementation in any form and dose in addition to prevailing standard therapy, comprised the intervention arm. Patients who did not receive any form of vitamin D constituted the control arm. We assessed major health related outcomes which are, mortality till the longest follow up mentioned, ICU admission rates, need for mechanical ventilation and change in acute inflammatory markers.

3.3. Exclusion criteria

Articles/pre-prints which are not published in peer reviewed journals, study protocols and trials with incomplete data, retrospective & observational studies were excluded. Studies where vitamin D supplementation was done retrospectively were also excluded to avoid recall bias.

3.4. Study selection

The articles retrieved initially from the databases were screened for the titles and abstracts to identify all eligible articles bearing the above MeSH (medical sub-heading) terminologies. Two independent researchers AR and DR screened all the articles for the titles and abstract eliminating all irrelevant or duplicate articles, followed by full text assessment. Any disagreement on the inclusion of article was sought by another co-author (SM/VS).

3.5. Data extraction

Relevant data of each articles pertaining to the population studied, intervention implemented, and outcomes (acute serum marker change, mechanical ventilation days, ICU stay days, mortality) were extracted independently by AR and DR. A search was made for supplementary data against each article. A qualitative approach was used for evaluation and synthesis of key findings. A consensus was reached when conflict occurred.

3.6. Quality assessment

Two authors (AR and DR) independently assessed the methodological quality of the included studies as per Cochrane Systematic Review Guidelines, any disagreements were resolved through a discussion with third co-author (SM/VS.) Individual quality analysis were expressed via GRADE-PRO approach and risk of bias graph was made using Review Manager 5.4.

3.7. Statistical analysis

Effect measure used in this review was risk ratio (RR). Presence of heterogeneity among the included studies was assessed by I^2 . We employed random-effect model and a p-value less than 0.05 was considered to be statistically significant. Methodological quality of studies was assessed by the Guidelines recommended by the Cochrane guidelines using the Review Manager version. 5.4.

4. Results

4.1. Study characteristics

For the present review, our initial search identified a total of 673 articles using the database searching and thorough manual search strategies. 465 duplicate references to the same papers were removed manually. After screening the titles and abstracts of remaining articles ($n = 173$) with irrelevant topics or not fulfilling the selection criteria, irrelevant articles were excluded, resulting in a potential total of 41 articles. After evaluation of the full text of all selected articles among 41, 5 articles were eventually included the present review, meeting the inclusion criteria (Fig. 1; Table 1).

4.2. Description of the included studies

In the present review among all included studies, three were RCTs [12,13,16] and two were Quasi experimental [14,15], involving details from 467 subjects (sample size range 40–237). Among all, one study was from India [12] one from Brazil [16], one from Spain [13] and two from France [14,15].

In one of the study, the population were divided into three groups: group 1 received vitamin D supplementation in the preceding year, group 2 received vitamin D after diagnosis and group 3

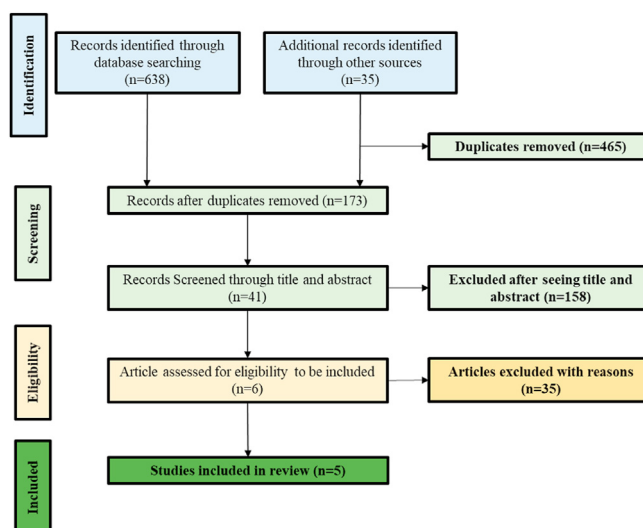


Fig. 1. Study flow diagram.

Table 1
Summary of the included articles in this review.

S. No.	Author and Year	Study design	Country (Study Setting)	Age (Mean ± SD)	Sample Size (I/ C)	Participants	Intervention	Control/ Placebo	Outcome	Remark	Outcomes studied
	Rastogi et al. 2020 [12]	Randomised, placebo controlled, study	India (Tertiary care hospital in north India)	—	16/24	Asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive vitamin D deficient (25(OH) D < 20 ng/ml) individuals.	Daily 60,000 IU of cholecalciferol (5 ml oral solution in nano droplet form) for 7 days. Then weekly supplementation of 60,000 IU (if 25(OH)D > 50 ng/ml) else continued 60,000 IU for another 7 days up until day-14 in participants with 25(OH) D < 50 ng/ml	Placebo (5 ml distilled water for 7 Days)	Proportion of patients with SARS CoV-2 RNA negative before day-21 and change in inflammatory markers (D-dimer, fibrinogen, CRP, Prolactin)	Short term high-dose cholecalciferol supplementation	<ul style="list-style-type: none"> • D-dimer • CRP
	Murari et al. 2020 [16]	Multicentre, double-blind, parallel-group, randomized, placebo-controlled trial	Brazil (Clinical Hospital of the School of Medicine of the University of Sao Paulo (a quaternary referral teaching hospital) and from the Ibirapuera field hospital)	56.2 ± 14.4	119/118	Hospitalized patients with COVID-19 who were moderately to severely ill at the time of enrollment.	A single, oral dose of 200,000 IU of vitamin D3 dissolved in a 10-ml peanut oil solution	Placebo (10 ml of a peanut oil solution)	Length of stay, in-hospital mortality, ICU admission to mechanical ventilation requirement	Single high dose of vitamin D3	<ul style="list-style-type: none"> • Mortality • ICU admission • Mechanical ventilation • D-dimer • CRP
	Castillo et al. 2020 [13]	Parallel Pilot randomized, open label, double-masked clinical study	Spain (Reina Sofia University Hospital, Cordoba, Spain EU)	53 ± 10	50/26	Hospitalized patients with COVID-19 clinical picture of acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB65 severity scale.	Oral Calcifediol (0.532 mg soft capsules on day of admission; and 0.266 mg on day 3 and 7, and then weekly until discharge or ICU admission	Usual Care	ICU admission; — Death	—	<ul style="list-style-type: none"> • Mortality • ICU admission • Mechanical ventilation
	Annweiler C. et al. 2020 [14]	Quasi-experimental study	France (Nursing home in Rhone, South East of France)	87.7 ± 9.3	57/9	Elderly nursing-home residents with COVID-19 and/or with physical disabilities, major neurocognitive and psychiatric disorders.	An oral bolus of 80,000 IU vitamin D3 either in the week following the suspicion or diagnosis of COVID-19, or during the previous month.	Usual Care	Mortality and Ordinal Scale for Clinical Improvement (OSCI) score in acute phase.	Single oral dose of 80,000 IU vitamin D3, either in the week following the suspicion or diagnosis of COVID-19, or during the previous month	<ul style="list-style-type: none"> • Mortality
	Annweiler G. et al. 2020 [15]	Quasi-Experimental Study	France (Angers University Hospital, France)	88 ± 5	16/32	Patients admitted for COVID-19 in a geriatric unit	Oral Vitamin D3 supplement of 80,000 IU within a few hours of the diagnosis of COVID-19	Usual Care	14-Day COVID-19 Mortality; Ordinal Scale for Clinical Improvement (OSCI) Score for COVID-19 in Acute Phase	80,000 IU vitamin D3 within a few hours of the diagnosis of COVID-19.	<ul style="list-style-type: none"> • Mortality

no supplementation [15]. Owing to our study inclusion criteria, we extracted data of group 2 and 3 of the above study. One RCT [12] included mild/asymptomatic middle aged vitamin D deficient individuals, whereas other two RCTs [13,16] included moderately to severely ill patients aged between 50 and 60 years. Both the quasi-experimental study groups included elderly nursing home individuals aged >80 years [14,15].

Considerable heterogeneity was noted in the dosages applied in

the intervention arm, whereas control arm received standard therapy i.e., steroids, antibiotics etc. as per available guidelines. The follow up period ranged from a minimum of 7 days [12] to a maximum of around 37 days [14].

One RCT [12] measured SARS-CoV-2 RNA negative status (tested twice with a gap of 24 h within 3 weeks) as primary outcome and change of inflammatory markers as secondary outcomes, whereas rest two RCTs [13,16] analysed ICU admission rates, mortality as

outcome measures. The quasi-experimental studies measured an objective Ordinal Scale of Clinical Improvement (OSCI) score to signify disease severity along with mortality [14,15,18]. Detailed characteristics are given in Table 1.

4.3. Methodological quality of study

Risk of bias graph, review authors judgements about each risk of bias item presented as percentages and risk of bias summary based on Cochrane Systematic Review Guidelines for each included study (green for low risk of bias, yellow for unclear risk of bias and red for high risk of bias) for randomised control trials and Quasi-experimental study are presented in Figs. 2 and 3 [19].

The overall rating for the quality of evidence for the role of vitamin D supplementation in patients with COVID-19 is shown in the GRADE summary of finding Table 2 [20]. GRADE summary reported the certainty of evidence as very low for the outcome's mortality, ICU admission and mechanical ventilation which means that any estimate of effect is very uncertain and we have little confidence in the effect.

4.4. Efficacy outcomes

4.4.1. Heterogeneity

Due to significant heterogeneity random-effects models were

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Annweiler C. et al., 2020	+	+	+	?	+	+
Annweiler G. et al, 2020	+	+	+	?	+	+
Castillo ME. et al., 2020	+	+	?	+	+	+
Murari IH. et al., 2020	+	+	+	+	+	+
Rastogi A. et al., 2020	?	?	?	?	+	?

Fig. 2. Risk of bias summary based on Cochrane Systematic Review Guidelines for each included study (green for low risk of bias, blank for unclear risk of bias and red for high risk of bias) included in this review.

used for outcome mortality ($I^2 = 58%$) [13–16] mechanical ventilation ($I^2 = 91%$) [13,16] and ICU admission ($I^2 = 89%$) [13,16] (Fig. 4).

4.5. Mortality outcome

Mortality was reported in four studies [13–16] involving 427 subjects (242 intervention and 185 control/placebo) among which two studies reported mortality benefit [13,14] and other didn't [15,16]. In the present review pooled analysis of the mortality rate in the intervention group (3.43% less mortality) as compared to placebo/controls was observed to be lower, although it was not statistically significant (Risk Ratio 0.55, 95% CI 0.22 to 1.39; $I^2 = 0.91$; $P = 0.21$) (Fig. 4a).

4.6. Mechanical ventilation outcome (MVO)

Only two studies [13,16] reported the MVO outcome involving 313 subjects (169 intervention and 144 control/placebo). In the present meta-analysis pooled data did not show a statistically significant improvement in the intervention group, although reduction in 9% requirement for MVO by the intervention group was observed (Risk Ratio 0.24, 95% CI 0.01 to 7.89; $P = 0.42$) (Fig. 4b).

4.7. Admission to ICU

This outcome was reported by two studies involving 313 subjects (169 intervention and 144 control/placebo) [13,16]. In the present review pooled data failed to show a statistically significant reduction in ICU admission in the intervention group. [Reduction in 14.55% in the intervention group (Risk Ratio 0.20, 95% CI 0.01 to 4.26; $P = 0.30$)] (Fig. 4c).

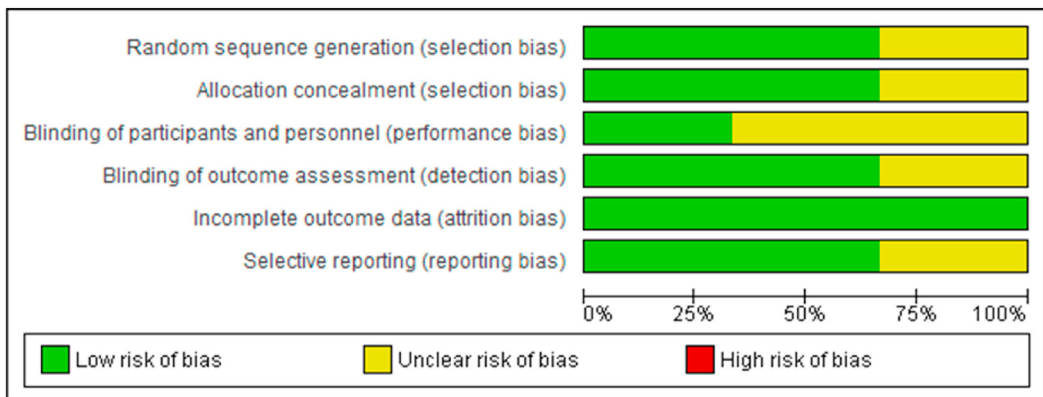
4.8. Acute markers

Only one study [12] evaluated all the inflammatory markers like fibrinogen, ferritin, d-dimer, CRP and it showed significant reduction of fibrinogen values [change of fibrinogen Δ fibrinogen -0.64 (-1.41 to 0.11) in intervention group vs. 0.06 (0.01 – 0.51) in control group]. Rest all values were insignificant. Due to paucity of data, we were unable to include quantitative data for two markers i.e. d-dimer and CRP hence only qualitative data were taken out of two studies [total 277 subjects, $n = 135$ for intervention and $n = 142$ for control] [12,16].

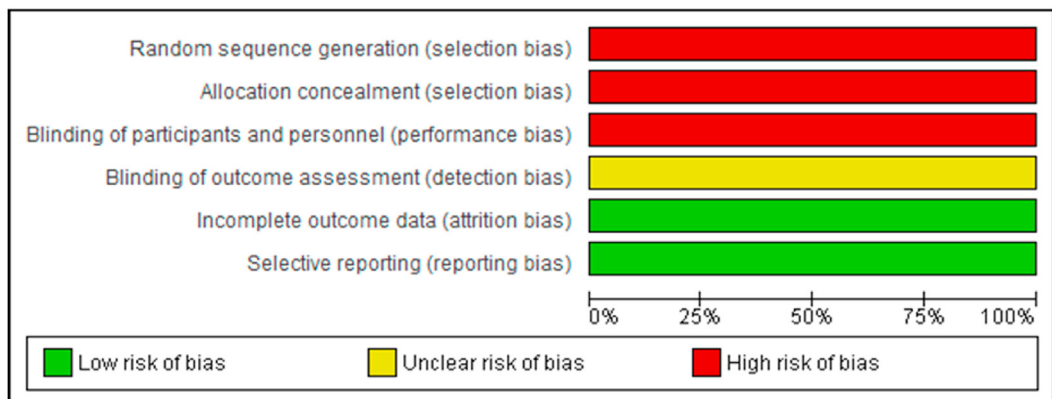
5. Discussion

The present systematic review and meta-analysis showed that administration of vitamin D after diagnosis of SARS-CoV-2 infection did not reduce major health outcomes like mortality, ICU admission and need for invasive ventilation. The included studies suffered from significant baseline heterogeneity with respect to drug dosing and population characteristics.

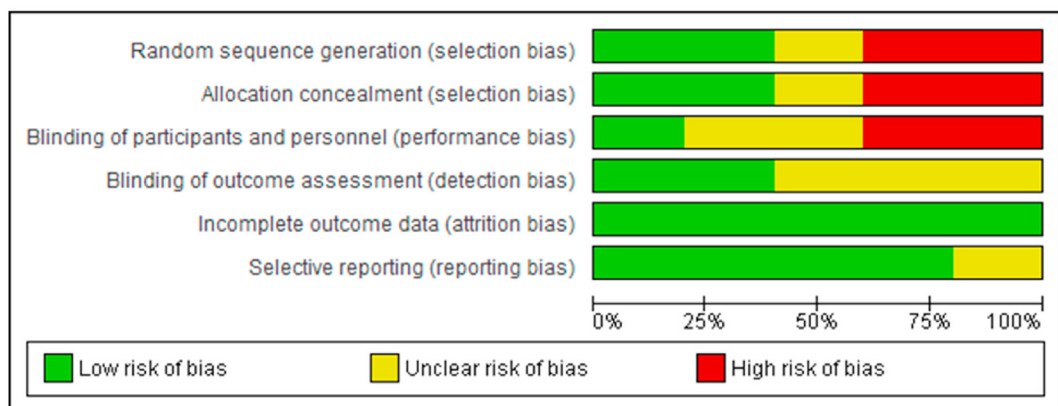
The SARS-CoV-2 may induce a pro-inflammatory state and in a subgroup of patients may lead to 'cytokine storm', which has been linked to worse outcomes [3,21]. Dysregulated delayed adaptive immune response leads to raised pro-inflammatory cytokines {interleukin-6, TNF-alpha, interferon etc.} which subsequently may lead to potentially dreaded complications like ARDS, thrombosis of major vascular bed due to pro-coagulant state etc [4,5]. Infection associated molecular response elements e.g. toll-like receptors (TLR) induce 1-alpha hydroxylase to increase the active form of vitamin D i.e. 1,25-hydroxy cholecalciferol (DHCC), which in turn induces defensin group of proteins like beta-defensin 2, cathelicidin via its receptor (vitamin D receptor-VDR) [22]. These proteins help in autophagy, and apoptosis of infected cell and



3a) Randomised control trials



3b) Quasi-experimental studies



3c) All included studies (n=5): Randomised control trials (n=3) and Quasi-experimental studies (n=2)

Fig. 3. (3a-3c): Risk of bias graph review authors judgements about each risk of bias item presented as percentages across various study designs.

strengthen innate immune system. Till date multitude of infections both by bacteria and viruses have been linked to vitamin D deficiency (VDD) [23]. Individual patient data (IPD) analysis of nearly 10,000 patients across 25 RCTs by Martineau et al. also revealed almost 11% reduction of incidence of ARI with vitamin D

supplementation, and that regular supplementation among the sub-group with VDD may have additional benefit [8]. Researchers have gone on to correlate the historical influenza pandemic of 1918–1919 to VDD [24]. By suppressing delayed dendritic cell activation and driving the ‘T’ cell response towards an anti-

Table 2
The overall rating for the quality of evidence profile for COVID-19 related health outcomes based on the grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group methodology.

№ of studies	Study design	Certainty assessment					№ of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mortality	placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	randomised trials	serious ^a	serious ^b	serious ^c	very serious ^d	none	22/242 (9.1%)	23/185 (12.4%)	RR 0.55 (0.22 to 1.39)	56 fewer per 1,000 (from 97 fewer to 48 more)	⊕○○○ VERY LOW	CRITICAL
Mechanical Ventilation												
2	randomised trials	not serious	very serious ^e	serious ^c	very serious ^d	none	20/169 (11.8%)	30/144 (20.8%)	RR 0.24 (0.01 to 7.89)	158 fewer per 1,000 (from 206 fewer to 1,000 more)	⊕○○○ VERY LOW	CRITICAL
Admission to ICU												
2	randomised trials	not serious	very serious ^f	serious ^c	very serious ^d	none	20/169 (11.8%)	38/144 (26.4%)	RR 0.20 (0.01 to 4.26)	211 fewer per 1,000 (from 261 fewer to 860 more)	⊕○○○ VERY LOW	CRITICAL

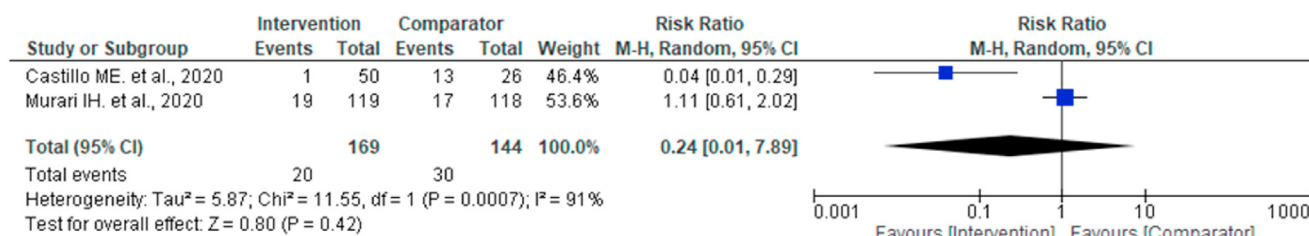
CI: Confidence interval; RR: Risk ratio; SMD: Standard mean difference

Explanations

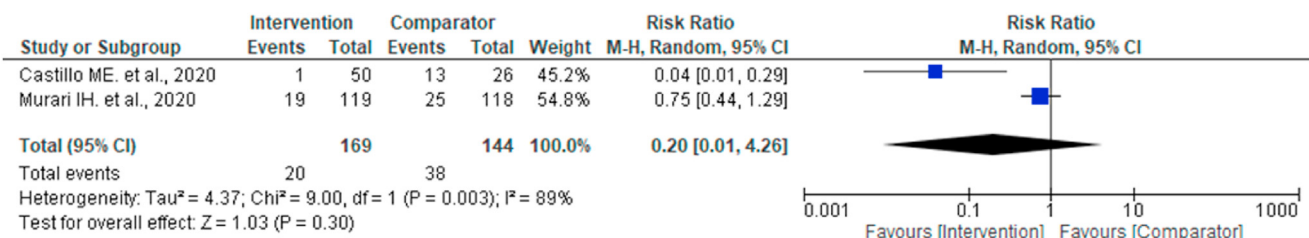
- (a) Some concern with method of randomization used (n=2), allocation concealment (n=3), blinding of participants (n=4), blinding of outcome assessment (n=3) and selective reporting (n=1).
 (b) I²=58%; Variation in effect size; (c) There were differences in the follow up time points to measure the outcomes and Vitamin D dosages and duration; (d) Confidence Interval were not narrow enough for us to be confident that this is the effect or does it really reduce and have no effect; (e) I²=91%; (f) I²=89%.



4a) Mortality



4b) Mechanical Ventilation



4C) Admission to ICU

Fig. 4. (a–c): Forest plot random effect model for vitamin D supplementation for various outcomes.

inflammatory (Th2/T-reg) domain rather than pro-inflammatory (Th1/Th17) one, vitamin may be instrumental for curtailing maladaptive cytokine storm seen with COVID-19, as observed in vitro studies [25,26].

A recent systematic review and meta-analysis consisting of 43 observational studies and nearly 6 lakh patients concluded that, vitamin D deficient individuals (<20 ng/ml) had 50% higher risk of infection with COVID as compared to replete individuals [OR 1.5, 95% CI 1.08–2.08, p = 0.02] [27]. Observational study including 10 articles and nearly 3 lakh patients done by Liu et al. (Dec 2020) showed that low vitamin D levels were associated more frequently with COVID positivity [10]. In a similar meta-analysis [28] which included two RCTs [13,16] similar to our study along with a retrospective case control study [29], it was concluded that vitamin D supplementation had reduction of ICU admission rates but insignificant effect on mortality [28]. The different result from this study as compared to ours could be attributable to the inclusion of retrospective study [29]. Another study showed reduced ICU admission rates and mortality with vitamin D supplementation [30], however, their study could not include data from the RCT which had the largest weightage and influence in our study [16]. The findings of our study corroborated with one large study which

included a total of 34 peer reviewed observational studies and RCTs [31]. Though VDD was positively correlated with COVID disease, there was insignificant reduction of mortality/ICU admission/hospital admission etc [31]. Systematic review and meta-analysis of effect of vitamin D on elderly frail people revealed that vitamin D had protective role against the viral infection and also reduced primary health related outcomes i.e. mortality, ICU admission etc. in them [32].

Despite its sentinel role in controlling respiratory infections, there is speculation that this late suppression of adaptive response by attenuating dendritic cell mediated pro-inflammatory drive, may be counterproductive and rather increase chance of ARIs [26]. Vitamin D supplementation failed to show all-cause mortality except cancer related deaths in a meta-analysis by Zhang et al. (25). One recently conducted RCT, which is included in the present meta-analysis failed to show beneficial effects of vitamin D in moderate to severe COVID patients [33]. Another study evaluated the effect of recent (<3 month prior) supplementation of vitamin D in hospitalized patients by dividing them into three sub-groups [patients with Parkinson's disease (PD), their caregivers and hospitalized patients (n = 127)], and showed that higher vitamin D levels not associated with either reduced hospital admission or mortality

[unadjusted OR 1.30,95% CI 0.51–3.31, $P = 0.56$ for hospitalization and 1.78, 5%CI 0.64–4.91, $P = 0.26$ for mortality] [34].

Out of the of 5 studies included, two studies [12,16] showed significant increase in DHCC levels with vitamin D supplementation. While four out of five studies were carried out on symptomatic individuals [13–16], one study included mildly symptomatic patients [12]. All the studies included the active form of vitamin D i.e. DHCC except one [13], who used calcifediol. Although four studies [13–16] reported major outcomes like mortality, ICU admission etc., one study [12] reported COVID negativity as their primary outcome, clinical significance of which are questionable [35,36]. This later study also had discrepancy in the published data and data provided via supplementary material [12]. Therefore, a significant heterogeneity exists in their study design as well as methodology, which rendered them 'critical/very low' status as per the GRADE-PRO approach [20].

6. Conclusion

Vitamin D supplementation did not reduce major health related outcomes like mortality, ICU admission rates and mechanical ventilation. The studies differed significantly with respect to their design, drug dosage, and population characteristics. The intrinsic heterogeneity of the included studies and small sample size make it difficult to interpret and extrapolate this data on to a large population. Thus, well-designed RCTs with uniform study population characteristics, methodology, and uniform drug dosing are warranted to determine the efficacy of treatment with vitamin D on COVID-19 patients.

7. Limitations

Our study has certain limitations. Firstly, outcomes like mortality were assessed without taking into account time frame. A longer follow up, taking into account delayed mortality might have bearing on the result. Secondly, significant heterogeneity across the studies indicate divergent population at baseline. There was heterogeneity in the intervention with respect to dosage of Vitamin-D also. Drawing conclusions based on such heterogeneous population can be fraught with misinformation. Lastly, Studies were limited (<10) for any of outcome measures, hence meta-regression was not possible. In future, if more RCTs are published with different conclusion, findings of this review will be changed.

Hitherto, due to significant non-uniformity regarding various factors governing vitamin D administration, no conclusive evidence could be drawn. Hence, trials comprising of larger sample size and uniform methodology with an aim to focus on specific, time bound clinical outcomes, should pave the way forward.

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Ethical approval

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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