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# A systematic review of the role of hypovitaminosis D in coronavirus disease-19 (COVID-19) infection and mortality: Is there a role of recommending high dose vitamin D supplementation?☆

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ABSTRACT

There are several studies corelating Vitamin D deficiency and risk of poorer outcomes in coronavirus disease −19 (COVID-19) patients. Our aim was to perform systematic review of the existing literature on the role of vitamin D deficiency in COVID-19 infection and mortality and whether high dose vitamin D supplementation might be helpful in reducing risk and improving outcomes.

A systematic search was conducted in PubMed, EMBASE and Cochrane Library up to 5th June 2020. The quality of included studies was evaluated using the Downs and Black risk of bias scale. The available literature was critically appraised. 61 reports were shortlisted. After removing duplicates and reassessing eligibility, three articles were included in final review. The three included studies in this review scored from 10 to 17 (out of 31) on the risk of bias assessment tool; all of them scored low on the power criterion based on the low number of subjects included in these studies. On reporting and selection of bias, all the studies scored an average or above average. All studies failed to reach an average score on confounding. Two studies which showed positive correlation between Vitamin D levels and COVID-19 infection rates scored low on risk of bias assessment. Study showing no impact of Vitamin D scored average. There is only circumstantial evidence that links outcomes of COVID-19 and vitamin D status. Role of high dose Vitamin D against COVID-19 needs to be thoroughly evaluated in observational studies or high-quality randomized controlled studies before recommending it.

## 1. Introduction

Since the outbreak of coronavirus disease 2019 (COVID-19), only a section of its infectivity, clinical features and mortality related patterns have been identified. For a pandemic of global proportion, we have limited therapeutic options [2]. Reported overall intensive care unit (ICU) mortality rate is 25.7% [3]. Lack of any vaccine and definitive therapeutic drug has lead to cocktail of drugs as researchers try to find the best suited modality of treatment. Hence, evaluation of chemoprophylaxis and barrier methods is one of the main strategy to prevent the increasing infection and mortality. As vaccine development will take time, between 6 and 18 months, There is a lot of speculation on drugs like hydroxychloroquine, Vitamin D, Vitamin C and Zinc [4–8]. News and social media platforms have implicated dietary supplements in the

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treatment and prevention of coronavirus disease 2019 (COVID-19). During this pandemic when News and social media platforms implicate dietary supplements, contradicting messages and misinformation reach far and wide.

Vitamin D activity helps in the maintenance of cell physical barrier, antimicrobial peptide expression, activity of macrophages and monocytes, and activity of cells involved with innate and adaptive immunity, such as dendritic and T-cells through a complex mechanism [9,10]. Data from observational studies associate low vitamin D levels with acute respiratory tract infections [11]. Vitamin D through immune modulation may affects viral replication and also helps in immune regulation and theoretically can decrease infection rate and mortality. But the challenge is the translational impact of this model to actual clinical practice. There are studies from Italy and other countries highlighting the use of Vitamin D suggesting that ensuring adequate vitamin D levels through safe sun exposure, food, or vitamin D supplementation [12,13].

We aimed to systematically review the literature on the role of Vitamin D on infection and mortality of COVID-19 as whether taking daily vitamin D improves outcomes associated with COVID-19 is unknown.

## 2. Methods

We aimed to include all completed and published clinical studies, which reported the role of Vitamin D on COVID-19 infection and or mortality. Commentaries, reviews, viewpoints, or opinions were excluded.

### 2.1. Search strategy

PubMed, EMBASE and Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials [CENTRAL], and Cochrane Methodology Register) were searched from inception until 5th June 2020. We also searched the reference lists of included studies and previous reviews in this field. The search terms used in various combinations were: "Vitamin D", "Calcitriol", "hypovitaminosis D", "coronavirus", "coronavirus disease", "coronavirus disease-19", "COVID-19", "severe acute respiratory syndrome", "SARS-CoV-2".

Two authors carried out the first step of the screening process independently which involved reading the titles and the abstracts using broad criteria. Each study was classified as include, exclude or unclear. Disagreement resolution was done with a third author. The systematic review protocol could not be pre-registered as the current pandemic is an ongoing public health emergency, thereby resulting in a paucity of time to permit pre-registration.

### 2.2. Study selection and appraisal

Studies were selected on the basis of pre-determined criteria. The Downs and Black assessment tool was used to assess the methodological quality of the included studies by two reviewers at the study level. Once

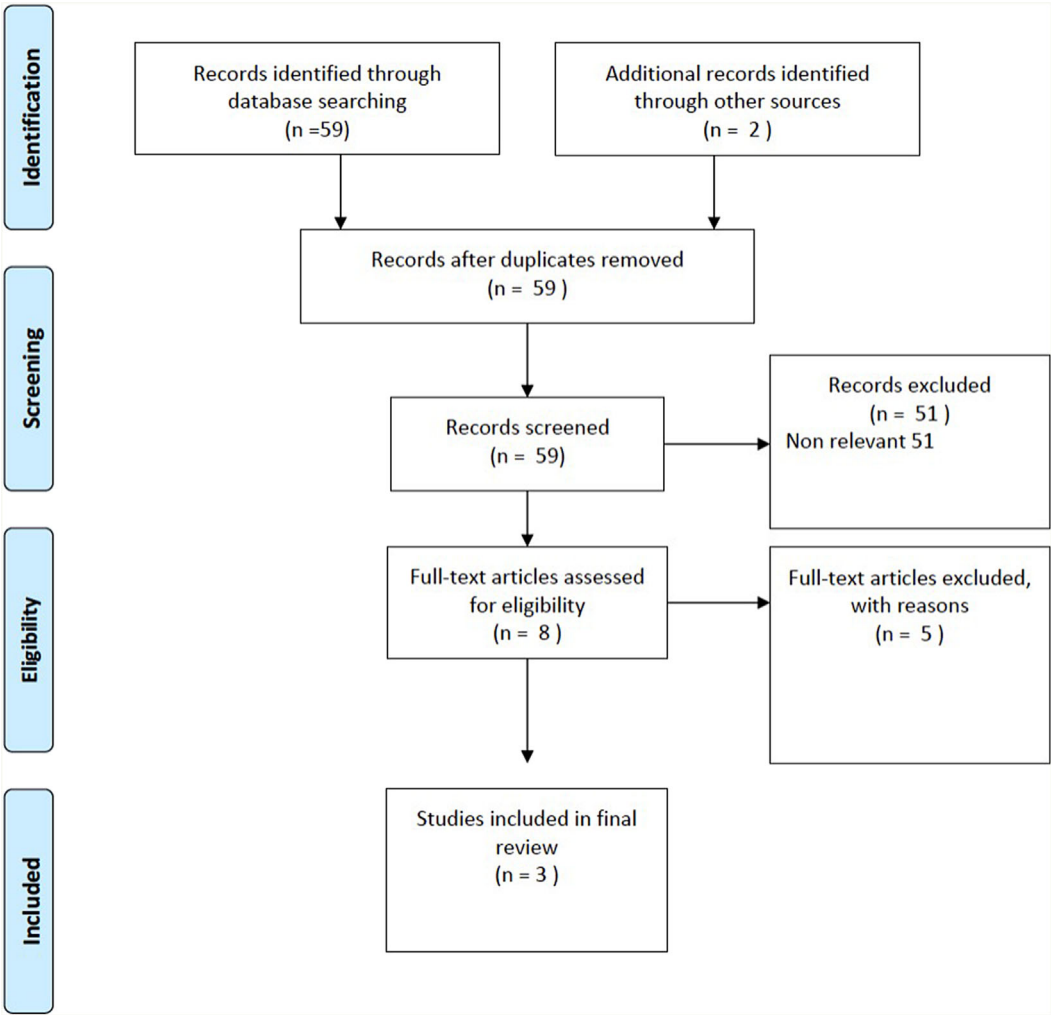


**Fig. 1.** PRISMA flow diagram of search and selection strategy.

again, all disagreements were resolved via third party adjudication performed by a third author.

## 3. Results

### 3.1. The literature search

Our database search yielded 59 records and hand search of relevant articles, and previous systematic reviews added 2 more records. After the removal of duplicates, 59 records were identified for the first step of the screening process. Through our initial titles and abstracts screen, 51 records were excluded. For the remaining 8 articles included in the full-text review, 5 articles were subsequently excluded (Fig. 1). Of the three articles that met the inclusion criteria, no randomized control trials were identified. One study was a retrospective, one was retrospective-prospective and another was review [13–15].

The three included studies in this review scored from 10 to 17 (out of 31) on the risk of bias assessment tool; all of them scored low on the power criterion based on the low number of subjects included in these studies. On reporting and selection of bias, all the studies scored an average or above average. All studies failed to reach an average score on confounding. Table 1 summarizes the results of the risk of bias in the three studies included in this review.

### 3.2. Qualitative review of the included articles

Table 2 enumerates the brief description of the studies. Ilie at al [13]. conducted a review of studies from European countries describing mean Vitamin D levels in their population. They showed negative correlations between mean levels of vitamin D (average 56 mmol/L, standard deviation (SD) 10.61) in each European country and the number of COVID-19 cases/1-million (mean 295.95, SD 298.7, and mortality/1 million (mean 5.96, SD 15.13). Hastie et al. [14] analysed decade old UK biobank's baseline vitamin D concentration and COVID-19 test results. Univariable and multivariable logistic regression analyses were performed for the association between Vitamin D and confirmed COVID-19 and they found that Vitamin D was associated with COVID-19 infection univariably (Odds Ratio = 0.99; 95% CI 0.99–0.999; p = 0.013), but not after adjustment for confounders (Odds Ratio = 1.00; 95% CI - 0.998–1.01; p = 0.208). D'Avolio et al. [15] did a retrospective analysis the 25-hydroxyvitamin D (25(OH)D) concentrations in plasma obtained from a cohort of patients from Switzerland. In this cohort, significantly lower 25(OH)D levels (p = 0.004) were found in positive COVID-19 cases (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL).

Studies by Ilie et al. [13] and D'Avolio et al. [15] which showed positive correlation between Vitamin D levels and COVID-19 infection rates scored low on risk of bias assessment. Study by Hastie et al. [14] scored average (16) on risk of bias assessment.

## 4. Discussion

Data from observational studies associate low vitamin D levels with acute respiratory tract infections [11] which has lead to interest in possible role of Vitamin D levels to COVID-19 infection rate and mortality. Multiple randomized controlled trials (RCTs) have evaluated the role of Vitamin D supplementation and risk of upper respiratory tract infections due to influenza [16–18]. Two RCTs have reported protective effect of Vitamin D supplementation on influenza infection [17,18]. Based on these results, researchers have adjudicated the supplementation of Vitamin D against COVID-19. However, three studies included in this review gave conflicting results and all of them have major limitations. In the absence of robust clinical evidence, it is early to recommend high dose Vitamin D supplementation to general population. Quarantine, social distancing, and personal hygiene are only effective preventive measures against COVID-19 [19].

There is only circumstantial evidence that links outcomes of COVID-19 and vitamin D status. COVID-19, emerged and spread when the Northern hemisphere was experiencing winters (end of 2019) and levels of 25-hydroxyvitamin D are at their lowest [20]. These countries continue to witness greater number of cases and mortality. Although, one could argue that countries like Norway, Sweden and Finland which receive less sunlight than Southern Europe have lower incidence and mortality but their population has much higher mean 25(OH)D and thus relatively vitamin D sufficient owing to widespread fortification of foods [21]. On the other hand, Italy and Spain being lower latitude nations are also exceptions, but prevalence of vitamin D deficiency in these populations is surprisingly common [21,22]. Similarly, races with darker skin like Black and minority ethnic people who are more likely to be vitamin D deficient due to lower absorption of Ultra Violet-B (UVB), seem to be worse affected than fair skinned people races [21–23].

A recently published review discusses the role of vitamin D in reducing influenza and how supplementation might be a useful measure to reduce risk of acquiring COVID 19 [11,24]. Several conclusions have been drawn from the case-fatality rate studies (CFRs) conducted by the United States Public Health Service during the 1918–1919 influenza pandemic. The pneumonia CFR was 28.8 per 100 for whites and 39.8 per 100 for “coloreds” and communities in the southwest had lower CFR than those in the northeast because of higher summertime and wintertime solar UVB doses [24,25].

In a recent double blind RCT, conducted on ventilated intensive care unit patients evaluated effect of high-dose vitamin D therapy on hospital length of stay, readmission rate, sepsis and mortality. Subjects (n = 31) were administered either placebo, 50,000 International Units (IU) cholecalciferol (Vitamin D3) or 100,000 IU vitamin D3 daily for 5 consecutive days enterally (total vitamin D3 dose = 250,000 IU or 500,000 IU, respectively). There was a significant decrease in hospital length of stay over time in the 250,000 IU and the 500,000 IU vitamin D3 group, compared to the placebo group ($25 \pm 14$ and $18 \pm 11$ days compared to $36 \pm 19$ days, respectively; p = 0.03). Other clinical parameters did not show significant difference [26,27].

The importance of correcting hypovitaminosis D cannot be overemphasized in certain communities that are at high risk of hospital acquired infections, namely, frontline workers, medical and health care personnel, patients and visitors. Serum 25(OH)D concentrations of at least 40–50 ng/mL (100–125 nmol/L) are indicated on the basis of observational studies [11,28].

## 5. Conclusion

There is only circumstantial evidence that links outcomes of COVID-19 and vitamin D status. The overall cost of Vitamin D testing and subsequent supplementation also presents a significant financial burden on most people in developing countries. Role of high dose Vitamin D against COVID-19 needs to be thoroughly evaluated in observational studies or high-quality randomized controlled studies before recommending it.

**Table 1**
Results of the risk of bias assessment using the Downs and Black assessment tool.

| Study | Reporting (10*) | External validity (3)* | Bias (7)* | Confounding (6)* | Power (5)* | Total (31)* |
|---|---|---|---|---|---|---|
| Ilie et al. | 4 | 1 | 2 | 1 | 1 | 10 |
| Hastie et al. | 7 | 2 | 3 | 2 | 2 | 16 |
| D'Avolio et al. | 6 | 1 | 3 | 2 | 1 | 13 |

**Table 2**
Summary of study characteristics.

| Study | n | Design | Primary outcome | Secondary outcome | Description of study |
|---|---|---|---|---|---|
| Ilie et al. | Data given as per million population | Review | Mortality | Infection rate | Mean vitamin D levels in various European countries and mortality the number of cases of COVID-19 evaluated. Negative correlation between levels of mean vitamin D and number of cases and the number of deaths caused by COVID-19/1 Million |
| Hastie et al. | 1474 | Prospective retrospective | Infection rate | None | Vitamin D was associated with COVID-19 infection univariably (Odds Ratio = 0.99; 95% CI 0.99–0.999; p = 0.013), but not after adjustment for confounders (Odds Ratio = 1.00; 95% CI = 0.998–1.01; p = 0.208). |
| D'Avolio et al. | 107 | Retrospective | Infection rate | None | Significantly lower 25(OH)D levels (p = 0.004) were found in positive COVID-19 cases (median value 11.1 ng/mL) patients compared with negative patients (24.6 ng/mL) |

## Author contributions

Sanjay Kumar Yadav, Sanjeet Kumar, Goonj Johri-literature search, figures, study design, data collection, data analysis, data interpretation, writing.

C K Jha, N Yadav- Revision and editing of manuscript.

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## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## Informed consent

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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