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**NARRATIVE REVIEW OF SYSTEMATIC REVIEWS ON THE ROLES OF VITAMIN D  
IN THE ERA OF COVID-19 PANDEMIC**

Short Running Title: Vitamin D in COVID-19 review of reviews

**MUHAMMAD FAKHRI MUMIN<sup>1</sup> and SHYH POH TEO<sup>2\*</sup>**

1. Clinical Dietetics Unit, Raja Isteri Pengiran Anak Saleha Hospital, Brunei Darussalam.
2. Geriatrics and Palliative Unit, Department of Internal Medicine, Raja Isteri Pengiran Anak Saleha Hospital, Jalan Putera Al-Muhtadee Billah, Bandar Seri Begawan Brunei Darussalam.

## NARRATIVE REVIEW OF SYSTEMATIC REVIEWS ON THE ROLES OF VITAMIN D IN THE ERA OF COVID-19 PANDEMIC

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**MUHAMMAD FAKHRI MUMIN<sup>1</sup> and SHYH POH TEO<sup>2\*</sup>**

3. Clinical Dietetics Unit, Raja Isteri Pengiran Anak Saleha Hospital, Brunei Darussalam.
4. Geriatrics and Palliative Unit, Department of Internal Medicine, Raja Isteri Pengiran Anak Saleha Hospital, Jalan Putera Al-Muhtadee Billah, Bandar Seri Begawan Brunei Darussalam.

\*Corresponding Author: [shyhpoh.teo@moh.gov.bn](mailto:shyhpoh.teo@moh.gov.bn)

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### ABSTRACT:

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) virus has caused a worldwide COVID-19 pandemic. Vitamin D deficiency and insufficiency may have a significant impact on respiratory viral infections. This narrative review of systematic reviews describes the roles of vitamin D on COVID-19 infection prognosis and whether vitamin D supplementation has any role in improving clinical outcomes of COVID-19 patients. A literature search of PubMed and Google Scholar was conducted in October 2021. Only systematic reviews published in the English language from January 2020 through October 2021 were included. Seven systematic reviews were identified. Five showed that low vitamin D levels increased the likelihood of contracting COVID-19 infections, admission into intensive care and increased mortality for severe vitamin D deficient individuals. Two reviewed the benefits of vitamin D supplementation and found an association between supplementation and a reduction in ICU admissions and mortality from COVID-19 infections. All of the systematic reviews identified a high prevalence of vitamin D deficiency in COVID-19 individuals, with a positive correlation between vitamin D deficiency and disease severity. Maintaining appropriate levels of vitamin D through oral supplementation or sunlight exposure may be beneficial to improve public resilience during this pandemic.

**Keywords:** COVID-19, Infection, Mortality, Vitamin D

### INTRODUCTION:

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) has had a tragic impact globally since the end of 2019 [1,2]. The pandemic is implicated in over 530 million confirmed cases, with more than 6.3 million deaths as of 8 June 2022 [3]. Medical therapies to treat COVID-19 are rapidly growing and evolving, ranging from supportive care,

antivirals to administration of anti-inflammatory agents [2]. While further research is required for highly effective treatment against the virus, the best strategy to contend with COVID-19 infections is still through prevention and vaccination to reduce the risk of acquiring infections and developing complications.

Over the last few years, vitamin D deficiency and insufficiency has garnered worldwide attention as a global health issue that instigated

numerous studies related to its impact on respiratory viral infections [4, 5]. A large number of epidemiological studies have demonstrated that individuals with low levels of vitamin D have a higher risk of developing severe respiratory infections, which may lead to death [1,6-9]. Vitamin D, Cholecalciferol (vitamin D3) and Ergocalciferol (vitamin D2), is a hormone precursor that plays a vital role in regulating the metabolism of calcium and phosphate [1]. The vitamin D biosynthetic pathway begins with ultraviolet B radiation of 7-hydrocholesterol on the bare skin exposed to sunlight. This process is deemed to be the primary source for vitamin D synthesis in humans, as there are very few foods that contain vitamin D [1]. This Vitamin D then undergoes several metabolic processes in the liver and kidneys transforming it into a metabolically active form of vitamin D known as 1,25-dihydroxyvitamin D [1]. There is evidence to suggest that the local synthesis of active vitamin D is crucial for the immuno-modulatory role of vitamin D against inflammation and microbes beyond the systemic level of 25-hydroxyvitamin D and bone [1]. A systematic review and meta-analysis also identified several studies demonstrating that vitamin D hinders lymphocyte proliferation, antibody production and cytokine synthesis through monocyte and cell-mediated immune stimulation [1].

SARS-CoV 2 infections in COVID-19 patients trigger a surge of cytokine production in the pulmonary tract that prompts an uncontrolled

production and infiltration of pro-inflammatory cytokines and chemokines [10]. This event subsequently activates an abnormal adaptive immune response that builds into acute respiratory distress syndrome (ARDS), identified radiologically and histologically as widespread of inflammation in the lungs [2, 10]. It is hypothesised that Vitamin D plays a role in easing this abnormal cytokine production by triggering alveolar macrophages and/or airway epithelia to express the CYP27B1 gene and vitamin D receptor (VDR), which is a natural response following a viral infection [11]. While these metabolic processes seem to occur for respiratory infections, the application of this mechanism in coronaviruses remain uncertain and requires further investigation [12]. Currently, active research is being undertaken to review the role of Vitamin D in COVID-19 infections, ranging from clinical observations to randomised controlled trials. The current hypothesis is that the risk for contracting COVID-19 infections is higher in individuals with low vitamin D status [1,2,13]. It is also hoped that vitamin D supplementation may have a potential therapeutic role in improving clinical outcomes in COVID-19 patients [1, 2].

The aim of this narrative review of systematic reviews is to provide insight into the role of vitamin D on the prognosis of COVID-19 infections and whether there is a potential benefit of vitamin D supplementation on adverse clinical outcomes in COVID-19 patients.

**METHODS:**

A literature search of PubMed and Google Scholar using the terms 'vitamin D' and 'COVID-19' was carried out in October 2021. For this review, only systematic reviews published in the English language between January 2020 and October 2021 were included.

**RESULTS:**

Seven systematic reviews were identified that evaluated the association of vitamin D status and COVID-19 infections, of which two investigated the benefits of vitamin D supplementation on COVID-19 outcomes.

A systematic review by Yisak et al evaluated nine studies (1,005,042 participants) on the effects of vitamin D levels on the prognosis of COVID-19 infections [14]. The authors found that vitamin D deficiency was associated with hospitalisation of COVID-19 patients. Individuals with low levels of vitamin D had increased odds of contracting COVID-19 infections (OR 1.77, 95% CI 1.07-2.93). The likelihood for Intensive Care Unit (ICU) admission following COVID-19 infections were also greater in vitamin D deficient individuals (OR 2.55, 95% CI 1.28-5.08), with a higher mortality risk observed in severely vitamin D deficient patients (OR 5.681, 95% CI 1,114–28,974; P=0.037) [14]. The authors acknowledged that two of the nine studies failed to demonstrate an association between vitamin D status and COVID-19 infection. However, it was important to note that

the vitamin D levels measured in these two studies were acquired long before patients were infected with COVID-19, thus may not reflect the level of vitamin D during the COVID-19 infection [14]. The authors concluded that based on their findings, the likelihood of contracting COVID-19 including severity and mortality rate were strongly associated with vitamin D status. These findings were consistent with the systematic reviews conducted by Teshome et al [4], Ghasemia et al [5], Liu et al [1], and Periera et al [15]. Teshome et al examined 14 studies (91,120 participants) to review the impact of vitamin D levels on COVID-19 infections, which found that individuals deficient in vitamin D had an 80% higher risk of acquiring COVID-19 infections [4]. This review initiated the consideration of vitamin D supplementation to reduce the risk of contracting COVID-19, including severe infections and mortality rate [4]. In Ghasemia et al, 23 studies (11,901 participants) were evaluated to identify the link between vitamin D status and COVID-19 infections [5]. It was found that 41% and 42% of the COVID-19 patients had deficiency and insufficiency in vitamin D respectively, with vitamin D deficiency individuals having five times higher probability to develop severe COVID-19 [5]. The odds of getting infected with COVID-19 were 3.3 times higher in individuals with vitamin D deficiency [5], supporting the importance of having optimal levels of vitamin D. However, in contrast with the review findings of Yisak et al [14] and Teshome et al [4], Ghasemia

et al [5] did not find a significant association between vitamin D deficiency and mortality rates in COVID-19 patients.

The systematic review and meta-analysis by Liu et al consisting of 10 articles covering 361,934 participants also had similar outcomes [1]. In this review, although generally low levels of vitamin D were associated with a higher risk of COVID-19 infections, one of the studies did not demonstrate this link. However, the data on vitamin D levels for this study was collected between 2006 and 2010. When the authors conducted a sensitivity analysis to distinguish the overall effect estimate by removing this study from the meta-analysis, there were no significant changes in the results. The overall findings still supported the association that individuals infected with COVID-19 had lower vitamin D levels compared to COVID-19 negative counterparts. The authors suggested the need for future research to evaluate the benefits of vitamin D supplementations in improving clinical severity and prognosis of COVID-19 patients [1]. The systematic review and meta-analysis by Pereira et al (27 articles, 8,176 participants) observed similar findings [15]. While this review did not find an association between vitamin D deficiency and increased risk of COVID-19 infections, it identified that a higher prevalence of vitamin D deficiency was seen in COVID-19 positive patients. An association was also observed between vitamin D deficiency and COVID-19 severity, especially in the elderly [15]. The authors proposed, from these findings, that

the assessment of vitamin D levels should be considered as routine clinical practice by healthcare professionals in the management of COVID-19 infections, including vitamin D supplementation in those with vitamin D deficiency and insufficiency [15].

Hariyanto et al [2] and Pal et al [13] both specifically investigated the impact of vitamin D supplementation on the clinical outcomes of COVID-19 infections. Hariyanto et al conducted a systematic review and meta-analysis of 11 studies (2,265 participants), in which vitamin D supplementation was found to be associated with a reduction in ICU admissions and mortality from COVID-19 infections [2]. These findings are similar to the systematic review and meta-analysis done by Pal et al (13 studies with 2,933 participants) [13]. Pal et al further discovered a reduction in the risk of adverse outcomes following vitamin D supplementation, with improved clinical outcomes in patients receiving the vitamin after diagnosis of COVID-19 [13]. However, most of the studies reviewed did not specify consistent or any baseline levels of vitamin D in their patients prior to supplementation. Therefore, it was difficult to propose whether the response obtained would be different in those with optimal versus deficient vitamin D levels. However, the positive outcomes still supported the use of vitamin D supplementation for the management of patients with COVID-19. The authors also suggested a need for further research directed towards identifying the appropriate dose of vitamin D

supplementation, including the duration and mode of administration [13].

#### **DISCUSSION:**

The above mentioned systematic reviews and meta-analyses indicated the importance of understanding the roles of vitamin D in managing COVID-19. The risk of acquiring COVID-19 infections was higher in individuals with low levels of serum vitamin D [1, 4, 5, 14], suggesting a vital role vitamin D has in potentially preventing COVID-19 infections. Following COVID-19 infections, the likelihood for ICU admissions was observed to be higher in patients who were vitamin D deficient [14]. The disease severity was especially linked to lower levels of serum vitamin D in older people [15]. Mortality rate was also higher in COVID-19 patients who have vitamin D deficiency [4, 14]. All these indicated that it was imperative to maintain optimal levels of vitamin D, including after contracting COVID-19 infections, as it is associated with overall clinical COVID-19 disease outcomes. Vitamin D supplementation was also potentially beneficial in treating COVID-19, as it lowered the risk of adverse outcomes in terms of ICU admission and mortality [2, 13].

Overall, these findings lend support towards the clinical practice of incorporating assessment of vitamin D levels and supplementation in the treatment of COVID-19 cases.

There are several limitations of this narrative review of identified systematic reviews and meta-analyses.

Firstly, the studies included were retrospective in nature, therefore unknown or unaccounted confounding factors may influence the results. A correlation does not confirm causation and only prospective studies controlling for potential biases can establish a true causal relationship [16].

Secondly, the different studies used different testing strategies for COVID-19 infections. The definitions for vitamin D deficiency and insufficiency were also not clearly stated or reported. For instance, among seven of the systematic reviews included, only Liu et al [1] and Ghasemian et al [5] reported their definition for vitamin deficiency and insufficiency being serum levels of 25-hydroxyvitamin D ([25(OH)D]) below 20 ng/mL and 21-29 ng/mL respectively. Thus, it is difficult to comment on the reliability and comparability of the data from the studies. Thirdly, COVID-19 severity may also be affected by other variables such as age, sex, existing comorbidities [15], and other immunomodulatory factors (e.g., vitamin C, zinc, selenium etc) [5], all of which were not explicitly discussed or included in the literature. Finally, it is possible that there is publication bias, as studies with negative associations are less likely to be published [1]. Thus, while there is a demonstrated association between vitamin D status and acquiring COVID-19 infection, disease severity and mortality, caution should

be exercised when interpreting these results. Larger prospective clinical trials that consider different age groups and climate conditions, following similar COVID-19 diagnostic criteria and vitamin D classifications should be developed in future studies to evaluate causality of vitamin D status and COVID-19 outcomes.

### CONCLUSION:

The present literature confirms a high prevalence of vitamin D deficiency in COVID-19 positive individuals, with a positive association between vitamin D deficiency and disease severity. Maintaining appropriate levels of vitamin D, either via oral supplementation or sunlight exposure may be beneficial to improve public resilience during this pandemic. The use of vitamin D supplementation may be beneficial in COVID-19 patients with vitamin D deficiency and insufficiency. Large prospective trials are still needed to confirm these findings.

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