The Effect Vitamin D Supplementation on Severity and Mortality Risk of COVID-19: A Systematic Review

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Abstract

Vitamin D levels are associated with improved immunity dysregulation to prevent worsening of COVID-19 patients. However, studies regarding the effects of vitamin D on COVID-19 patients are still inconsistent. This study aimed to analyze vitamin D supplementation's effect on the severity and mortality risk of COVID-19 patients. Search was conducted in seven databases on September 2020. Studies assessing the topic were included without study design restrictions.

Four studies were included in this study. All reported risk of mortality, and three reported of severity degree. Two of the three found patients with vitamin D supplementation had a significantly lower risk of disease. One other found no significant difference, although a higher proportion of severe COVID-19 was recorded in the group without supplementation.

Three of the four reported supplementation as a protective factor against mortality in COVID-19 patients. One study reported that vitamin D supplementation group had a higher mortality than the group without, although it has low validity and high risk of bias. In conclusion, there were differences in the severity and mortality risk between COVID-19 patients given vitamin D supplementation and control patients. Vitamin D supplementation is a protective factor in the severity and mortality risk of COVID-19 patients.

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Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a positive single chain *ribonucleic acid* (RNA) virus that appears in late 2019, with signs and symptoms such as fever, difficulty breating, fatigue, cough and respiratory distress.[1] Currently, the approach to Coronavirus Disease-2019 (COVID-19) is symptomatic and supportive. There are several nutritional approaches considered to help prevent or cure COVID-19, such as zinc, vitamin A, C, D, and E.[2,3]

The role of vitamin D3 supplementation in respiratory disease has become the subject of many studies. Although, the benefit of vitamin D3 supplementation in COVID-19 is not exactly known. Liu et al.[4] stated that vitamin D3 supplementation of 300,000 IU/day is thought to have antiviral and anticoagulant effects and could enhance the immune system.

Although several studies try to identify the relationship between supplementation of vitamin D with increased immune system, recent clinical study shows a contradicting results.[4-8] Due to these inconsistencies in findings about the efficacy of vitamin D towards reduced mortality risk and COVID-19 disease severity, as well as the prevalence and mortality rate of COVID-19 patients, reviewer is interested to conduct a systematic review.

Materials and methods

The review utilises the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). This study has been approved by PROSPERO, with the registration number of CRD42020224330. Literature search was done using published sources on seven databases on 27 September 2020. The search was made using a combination of manual search and MeSH search with keywords of *("vitamin D" OR "cholecalciferol" OR "ergocalciferol") AND*

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("COVID 19" OR "novel coronavirus" OR "SARS-CoV-2" OR "2019-nCOV") in the databases other than PubMed. On PubMed, the search was made with keywords of "*COVID-19"[Supplementary Concept] AND "vitamin D"[Mesh].*

The inclusion criteria were: (1) interventional or observational studies; (2) involving COVID-19 populations of all ages; (3) uses vitamin D supplementation as intervention or independent variable; (4) reports of mortality and disease severity of patients as clinical outcomes; (5) written in English. Editorial, review, case reports, or case series were not included.

Bias anlaysis for the RCTs was done using the Cochrane 'Risk of Bias' tools assessing seven aspects of bias. Studies with interventional design with no randomization prior to the studies were assessed using the ROBINS-I tool. Observational studies was assessed using the Newcastle-Ottawa Scale. The study characteristic, critical appraisal, and risk of bias assessment table are provided in the supplement.

Results

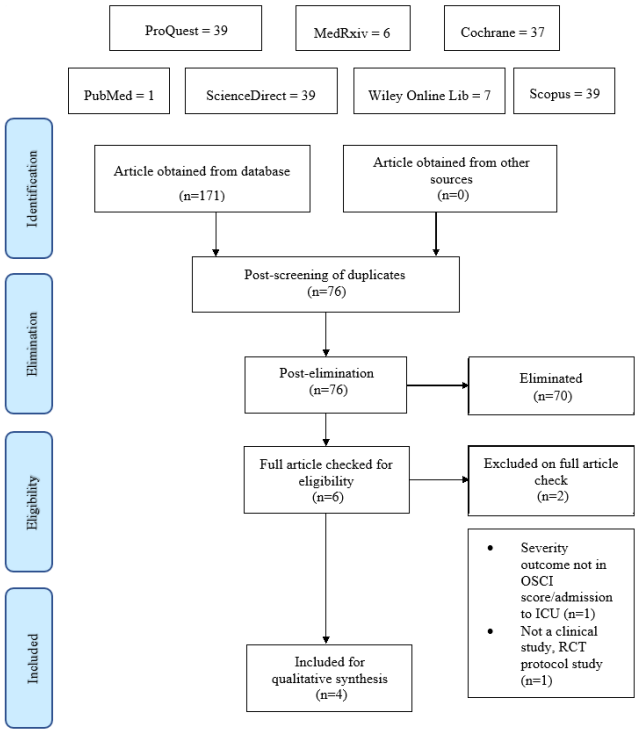

Figure 1. Study workflow and finding

Relationship of Vitamin D Supplementation and Degree of COVID-19 Severity

Three of four studies in this systematic review reported relations between vitamin D supplementation and the low degree of COVID-19 severity. Two of the three studies reporting this outcome used the score of OSCI ≥ 5 as severity threshold. One other study assumes that the patient suffered from a severe case of COVID-19 if the patient requires intensive care.[5-8]

One study shows no significant differences between patients given vitamin D3 supplementation of differing dosages and administration times with the control group. Although, Vitamin D supplementation is a relatively protective factor, with relative risk of 0.331 (0.101-1.086) for the group with an intervention of 50,000 IU vitamin D3 each month, or 80,000-100,000 IU vitamin D3 every 2-3 month. A quasi-experimental study by Annweiler et al., reported a significant difference in risk of severe COVID-19 (OSCI ≥5) between patients with 80,000 IU Vitamin D every 2-3 months and patients without supplementation. The relative risk of patients with vitamin D supplementation to suffer from severe COVID-19 is 0.316 (0.1596-0.625). This study and other previous quasi-experimental studies have a similar population characteristic, which is geriatric patients.[5,6]

Castillo et al's[7] study assess the difference in risk of patients with COVID-19 suffering from severe type with admission to intensive care as parameter. The result indicates a significant difference in risk between the intervention and control group to suffer from severe type of COVID-19.

From three studies that discussed the relations between supplementation of vitamin D with risk of severe type of COVID-19, two reported a significantly lower risk in the intervention group. The other study found that the risk in intervention group is lower compared to control group, although there was no significant difference.

Relationship between Mortality of COVID-19 and Vitamin D

According to Annweiler et al. (1)[5], supplementation of 50,000 IU vitamin D3/month or 80,000-100,000 IU vitamin D3/2-3 months significantly reduced the mortality risk of COVID-19 patients, with relative risk of 0.2207 (0.0527-0.924). Although, this result is not seen in 80,000 IU vitamin D3 supplementation several hours after COVID-19 diagnosis was made. Even so, the follow-up duration of this study to assess the

mortality outcome was only done in 14 days. In a longer follow-up duration, Annweiler et al. (2)[6] found that COVID-19 patients with a history of vitamin D3 80,000 IU/2-3 months had a significantly lower mortality risk compared to patients without a history of supplementation. The relative mortality risk of patients with COVID-19 with a history of supplementation is 0.316 (0.1404-0.71).

In study by Castillo et al.[7] no patients given calcifediol 0.532 mg died and all were discharged without complications. Cereda et al.[8] was the only study that reports of lower mortality risk in the control group, with relative mortality risk of COVID-19 patients with history of vitamin D supplementation of minimal 25.000 IU/month in the last 3 months is 1.78 (0.64-4.91).

Discussion

Relationship between Vitamin D Supplementation and COVID-19 Severity

Studies which have analysed the correlation between the level of vitamin D with confirmed cases of COVID-19 concluded that normal vitamin D level has a protective effect towards SARS-CoV-2 infection.[9-17] Although, the exact mechanism behind this phenomenon is unknown.[9]

Vitamin D influence innate immunity through several measures. Vitamin D support the integrity of epithelial cells.[18,19] Vitamin D stimulates the production of antiviral molecules cathelicidin and β-defensins.[18-20] Vitamin D also affect zinc metabolism which may reduce viral replication.[21] It is also known to modulate the immune system through macrophage activity, dendritic and T cells.[22-24]

Castillo et al.,[7] explained the possibility that high doses of supplementation may activate receptors that reduce cytokine and chemokine storm, regulates RAS, maintain the epithelial barrier, stimulate epithelial repair, and reduces coagulation disturbance. Studies by Radujkovic et al.,[25] Hamza et al.,[26] and Karonova et al.,[27] found vitamin D deficiency relates to poor prognosis.

Recent studies shows adults with hypovitaminosis D have higher risk of SARS-CoV-2 infection (1.77, P<0.02).[13] Studies involving 20 Europe countries found a significant negative correlation between average serum concentration of 25(OH)D and COVID-19 cases.[16] In addition, hypovitaminosis D patients were also at higher risk for severe type of COVID-19 (1.59, p=0.02 if lacking vitamin D<30 ng/mL).[28]

Studies by Maghbooli et al.,[29] and Castillo et al.,[7] connects the clinical findings in studies of vitamin D deficiency (<30 ng/mL) with severe type of COVID-19. One of the reasons for the severity of COVID-19 in vitamin D deficiency may be caused by changes in the RAS pathway. RAS system regulates volume and blood pressure equilibrium with angiotensin peptide (AGT). In severe COVID-19, upregulation of ACE2 with downregulation of ACE are usually found.[30-35] This shifts the RAS system, producing more angiotensin 1-9 which are specifically produced by ACE2. Bradykinin are cytokines of the vasopressor system, it is degraded by ACE and its' production increased by angiotensin 1-9.

When activation of vitamin D receptor is inhibited, upregulation of ACE2 will follow, increasing bradykinin production. ACE, bradykinin degrader, is also downregulated. All of this resulted in an overproduction of bradykinin, creating an exaggerated vasodilatation. Resulting in vascular leakage and infiltration of inflammatory cells, characteristics of severe COVID-19.[2]

Relationship between Vitamin D Supplementation and COVID-19 Mortality

A number of studies agreed of a reduction in mortality risk of COVID-19 patients with vitamin D supplementation.[5,6] One RCT found that all patients given Calcifediol (Faes-Frama, Lejona, Spain) 0.532 mg, were discharged without complication. The same study also reported that 2 of 26 patients without vitamin D therapy died during care.[7] Another study reports vitamin D increases mortality risk in COVID-19 patients, although this research have low validity and high risk of bias.[8]

The reason for low mortality risk in patients with supplementation history is not exactly known. Although vitamin D is linked with prevention of ARDS, a major COVID-19 complication.[31-34] The receptor and enzyme activator of vitamin D is found in abundance along respiratory epithelium, hence the role of immunomodulation of vitamin D becomes important in the respiratory system.

Cardiovascular complications is also found in patients with severe infection.[35] The mechanism includes severe heart inflammation, hypoxia from

acute respiratory damage, SARS-CoV-2 invasion on cardiomyocytes, and microvascular dysfunction.[36] ACE2 is found in abundance on cardiomyocytes. While microvascular dysfunction is related to hyperactivity of bradykinin, which can be modulated by vitamin D receptor activation.[2] Another common complication in critical COVID-19 patients is vein and lung thromboembolism. Arterial thromboembolism is linked to myocardial stroke and infarct in COVID-19 patients with a prevalence of 1,6%.[37]

This systematic study has answered questions regarding the effect of vitamin D supplementation on the severity and mortality risk of COVID-19 patients. However, the study synthesis was conducted narratively. Ioannidis et al. (2008) summarized several reasons for avoiding meta-analyses, such as a high (statistical) heterogeneity of studies, variations in study designs, and the contrasting differences in patient characteristics among studies.[38] This study did not specify patient characteristics and study design as inclusion criteria, resulting in a reasonably high heterogeneity between studies. Studies with various designs were included. The high risk of bias in some studies was also taken into account hence quantitative data synthesis was not performed, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[39]

Implementation of Vitamin D Supplementation for COVID-19

One study suggest a significant correlation between the geographical distance of a country to the equator to COVID-19 mortality.[40] Endogenous vitamin D amongst people living in high sunlight exposure places is thought to be higher, and adequate endogenous vitamin D is related to better clinical outcome.[19,20]

Low level of vitamin D observed in people living in places lacking sunlight exposure such as prison or nursing homes, caused them to be at higher COVID-19 mortality risk. Hence, it can be said that countries with low sun exposure, farther from the equator, are more affected by the pandemic. However, many studies have proven things are not that simple. Living farther from the equator does not translate to vitamin D deficiency.[40]

There are two studies which supports this. Study done by Laird et al.[34] shows that low latitude countries have a higher level of vitamin D deficiency, higher infection and mortality rate. Another found that even though countries like Britain, Ireland, Spain, or North Italy is closer to the equator, the infection and mortality rate of COVID-19 in the Nordic countries are lower.[34] Although located far north, Scandinavian people have a higher intake of vitamin D, because vitamin D supplementation is imposed on fortified foods in their countries. Hence, aside from sunlight exposure, vitamin D supplementation is also important.[34]

Equatorial countries with sunlight all throughout the year are still at risk of vitamin D deficiency. A study by Setiati et al.,[41] in two Indonesian cities, shows that the prevalence of vitamin D deficiency in elderly women is around 35%. In other study, the prevalence of vitamin D deficiency in pregnant women is even higher (82.8%).[42] This further exemplifies that there are also other factors at play to fulfil vitamin D needs aside from geography.[21]

Several strategies may promote vitamin D intake in Indonesia. Health personnel and citizen should be educated about the recommended vitamin D intake.[43] Aside from that, education about the types of food rich in vitamin D should be done actively.[44] Not only that, lifestyle intervention must also be done. Periodic sunlight exposure of at least 15 minutes can increase the status of vitamin D. Direct sunlight of at least 30 minutes is enough to fulfil daily requirements.[45] Fortification of staple food is an economically sound and feasible solution to tackle vitamin D deficiency.[45] Last but not least, oral supplementation program can also be offered as a strategic solution. This was proven to be an effective modality in high-risk population such as pregnant and breastfeeding women. In a pandemic, especially in Indonesia, where vitamin D deficiency is prevalent, vitamin D supplementation ought to be beneficial for public health.[46] Singh et al.,[14] recommended proper dietary intake and supplementation of vitamin D to reduce risk for COVID-19, while D' Avolio et al.[13], recommended the use of 10,000 IU/ day Vitamin D for several weeks followed by 5,000 IU/day to reduce risk of infection.

In a pragmatic context, vitamin D supplementation to reduce COVID-19 burden in Indonesia may be implemented. Studies that have been done to analyse the cost and benefit from vitamin D supplementation program to prevent vertebral fracture, rickettsia, osteoporosis, and other diseases shows that the benefit are

much greater compared to the cost.[47] If vitamin D supplementation program is implemented in Indonesia, public health burden caused by COVID-19 might significantly reduce.

Conclusions

To conclude, vitamin D supplementation reduces disease severity and mortality risk of COVID-19 patients. Further double-blind, randomized controlled studies comparing the effectiveness of vitamin D supplementation with placebo in COVID-19 patients are warranted. It is necessary to analyse specific sub-groups in order to obtain results that are free of confounding factors. Clinical testing needs to be conducted to determine the need for a vitamin D supplementation policy in İndonesia.

Declaration of Interest

The authors report no conflict of interest.

No	Author	Year	Design	Location	Age	N	Intervention	Control	Aims	Outcome	Level of Evidence	Result
1	Annweiler et al. (1)[12]	November 2020	Quasi-experimental	Angers, France	A: 88 (87–93) B: 85 (84–89) C: 88 (84–92) p>0,05	77	A: regular vitamin D supplementation B: in-hospital vitamin D supplementation	No vitamin D supplementation	To determine whether bolus vitamin D supplementation taken either regularly over the preceding year or after the diagnosis of COVID-19 was effective in improving survival among hospitalized frail elderly COVID-19 patients.	14-day mortality, OSCI score in acute phase	2b	Mortality [RR (CI)]: - A: 0,2207 (0,0527–0,924) B: 0,436 (0,1354–1,406) OSCI score≥5 [RR (CI)]: - A: 0,331 (0,101–1,086) - B: 0,800 (0,297–2,157)
2	Annweiler et al. (2).[13]	November 2020	Quasi-experimental	Rhone, France	I: 87.7±9.3 C: 87.4±7.2 p≥0,05	66	Vitamin D3 80,000 IU every 2-3 months	No vitamin D supplementation	To determine whether bolus vitamin D3 supplementation taken during or just before COVID-19 was effective in improving survival among frail elderly nursing-home residents with COVID-19.	14-day mortality, OSCI score in acute phase	2b	Mortality [RR (CI)]: 0,316 (0,1404–0,71) OSCI score ≥5 [RR (CI)]: 0,316 (0,1596–0,625)
3	Castillo et al.[14]	Agustus 2020	RCT	Córdoba Spain	I: 53,14±10,77 C: 52,77±9,35 p>0,05	76	Kalsifediol (Faes-Farma, Lejona, Spain) 0,532 mg	No vitamin D supplementation	To evaluate the effect of kalsifediol treatment, on Intensive Care Unit Admission and Mortality rate among Spanish patients hospitalized for COVID-19	Mortality, ICU admission	1b	Mortality: All patients (50) in the intervention group recovered without complications. Two of the 26 control patients died. RR= 0,000 (CI could not be calculated) ICU admission [RR (CI)]: 0,040 (0,006–0,289)
4	Cereda et al.[11]	November 2020	Prospective observational study	Lombardy, Italy	I: 68,8±10,6 C: 70,5±13,1 p>0,05	324	Vitamin D 25.000 IU/month in the last 3 months [~800 IU/day])	No vitamin D supplementation	To evaluate whether vitamin 25OHD supplementation, which may be a better surrogate of real 25OHD status, is associated with prognosis in COVID-19 patients from the Italian outbreak area of Lombardy.	Mortality, dan hospitalization	2b	Mortality [RR (CI)]: 1,78 (0,64–4,91)

Table 1. Summary of Study Characteristics Involved.
Description:
A: 50,000 IU vitamin D3 monthly, or 80,000–100,000 IU vitamin D3 every 2–3 months
B: 80,000 IU vitamin D3 within a few hours of the diagnosis of COVID-19.
I: intervention; C: control; CI: confidence interval; N: total participant; RR: relative risk.

	Study	Annweiler et al. (1).[5]	Annweiler et al. (2).[6]	Castilo et al.[7]	Cereda et al.8
V	Are patient allocation randomized?	No	No	Yes	No
	Are randomized list hidden?	No	No	Yes	No
	Are follow up complete?	Yes	Yes	Yes	Yes
	And are they analysed to their appropriate group?	Yes	Yes	Yes	Yes
	Are patient and doctors remain 'blinded' to treatment received?	No	No	No	No
	Other than experimental treatment, are the group treated the same?	Unclear	Unclear	Yes	Unclear
	Are the groups similar prior to study?	Yes	Yes	Yes	Yes
I	How large is the intervention effect? (Mortality outcome)	RR=0,221	RR=0,316	0,000	1,78

	How accurate is the estimate of intervention effect?	0,0527–0,924	0,1404–0,71	-	0,64–4,91
A	Is there a possibility that treatment benefit is equal ot potential hazard and cost?	Benefit NNT=8	Benefit NNT=3	Benefit NNT=1	Dangerous NNH=8

Table 2. Result of Critical Appraisal of Each Studies.
Description: V: validitty; I: Importance; A: applicability.

Tool			
	Parameter	**Annweiler et al. (1)**	**Annweiler et al. (2)**
Pre-intervention	Bias due to confounders	Low risk	Low risk
	Bias due to selection of participant	Low risk	Low risk
During intervention	Bias due to classification of intervention	Low risk	Low risk
Post intervention	Bias due to deviation from intended intervention	Moderate risk	Moderate risk
	Bias due to missing data	Low risk	Low risk
	Bias due to outcome assessment	Low risk	Low risk
	Bias due to selection of reported outcome	Low risk	Low risk
	Parameter	Annweiler et al. (1)	Annweiler et al. (2)
Pre-intervention	Bias due to confounders	Low risk	Low risk
	Bias due to selection of participant	Low risk	Low risk
During intervention	Bias due to classification of intervention	Low risk	Low risk
Post intervention	Bias due to deviation from intended intervention	Moderate risk	Moderate risk
	Bias due to missing data	Low risk	Low risk
	Bias due to outcome assessment	Low risk	Low risk
	Bias due to selection of reported outcome	Low risk	Low risk
	Parameter	Annweiler et al. (1)	Annweiler et al. (2)
Pre-intervention	Bias due to confounders	Low risk	Low risk
	Bias due to selection of participant	Low risk	Low risk
During intervention	Bias due to classification of intervention	Low risk	Low risk
Post intervention	Bias due to deviation from intended intervention	Moderate risk	Moderate risk
	Bias due to missing data	Low risk	Low risk
	Bias due to outcome assessment	Low risk	Low risk
	Bias due to selection of reported outcome	Low risk	Low risk
	Parameter	Annweiler et al. (1)	Annweiler et al. (2)
Pre-intervention	Bias due to confounders	Low risk	Low risk
	Bias due to selection of participant	Low risk	Low risk

	Parameter		Cereda et al (2020).
Selection bias	Bias due to confounders		Not fulfilled
	Bias due to selection of participant		Not fulfilled
	Measurable intervention		Fulfilled
	Absence of outcomes prior to study		Fulfilled
Comparability	Able to compare intervention with study design/analysis used		Not fulfilled
Outcome	Accurate outcome measures		Fulfilled
	Adequate follow-up duration		Fulfilled
	Adequate follow-up number of patients		Fulfilled
During intervention	Bias due to classification of intervention	Low risk	Low risk
Post intervention	Bias due to deviation from intended intervention	Moderate risk	Moderate risk
	Bias due to missing data	Low risk	Low risk
	Bias due to outcome assessment	Low risk	Low risk
	Bias due to selection of reported outcome	Low risk	Low risk

Table 3. Risk of Bias Assessment of Observational Studies using Newcastle-Ottawa Scale (NOS)

Parameter	Castillo et al. (2020)
Random sequence generation	Low Risk
Allocation concealment	Low Risk
Patient and personnel blinding	High Risk
Blinding of outcome measures	Low Risk
Outcome data is not complete	Low Risk
Data reporting selectivity	High Risk

Tabel 4. Risk of Bias in RCT using Cochrane Risk of Bias (RoB)

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