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ORIGINAL PAPER

Vitamin D serum level as a prognostic factor in predicting mortality of severe COVID-19 patients: An evidence based case report

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Abstract

Introduction: The mortality rate of COVID-19 is still high. Many prognostic factors have been studied to decrease the mortality rate. One of the many factors is vitamin D status, known for years as an immunomodulator and anti-inflammatory agent. Vitamin D deficiency could worsen the symptoms of COVID-19 and ultimately lead to mortality. However, some literature shows controversial results.

Methods: Literature research was conducted by advanced searching in Pubmed, Cochrane Library, Scopus, and ProQuest, using a combination of both MeSH Terms and Title/Abstract. After removing duplicates, these literature were screened according to the eligibility criteria. Appraisal and level of evidence of the final literature were determined based on Oxford Centre for Evidence-Based Medicine.

Results: Three selected literature were relevant to answer our clinical question. The first literature is a retrospective cohort study by Radujkovic et al. while the other two are prospective cohort studies by Bennouar et al. and Campi et al. All literatures show similar results that low vitamin D serum levels in severe COVID-19 patients can increase the in-hospital mortality risk.

Conclusion: Vitamin D is one of the prognostic factors that can predict the mortality rate of severe COVID-19 patients. We suggest that vitamin D serum level can be measured regularly in COVID-19 patients and administered to patients with such deficiencies. Adequate vitamin D deficiency management is expected to lower the COVID-19 mortality rate.

Keywords: COVID-19, SARS-CoV-2, vitamin D, 25-hydroxyvitamin-D, mortality, prognosis

Case Scenario

A 57-year-old man was admitted to the emergency department due to breathing difficulty since 3 days prior. The symptoms were worsened while doing activities and not relieved by rest. The patient also reported a dry cough. He did not have any history of chronic illnesses, except chronic obstructive pulmonary disease and recurrent pulmonary tuberculosis since 2011. The patient stated that he had never made any contact with COVID-19 patients, but recently, one of his neighbors tested positive for COVID-19. He regularly visited the hospital nearby to control his pulmonary condition.

Lung physical examination was remarkable for rhonchi at both lungs, with minimal vesicular sounds at the bases. Chest X-ray revealed a suspicion for tuberculosis infiltrate. He tested negative for GeneExpert MTB but positive for the nasopharyngeal SARS COV-2 RT-PCR swab. The patient was admitted to the intensive care unit, and as the condition deteriorated, he fell into a condition that required mechanical intubation. The patient was then consulted to a clinical nutrition physician to

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monitor his nutritional intake. Based on the anthropometric measurement, the patient's body mass index was 22.2 kg/m^2. The patient received liquid nutritional treatment and vitamin D 2x1000 IU. One of the patient's family members asked whether vitamin D deficiency can threaten the patient's condition.

Introduction

Based on WHO data in March 2021, it was reported that COVID-19 confirmed cases worldwide had exceeded 125 million cases with 2.7 million deaths, including Indonesia itself, which had more than 1 million confirmed cases and 40 thousand deaths. These data were considerably high in Asian countries.[1] COVID-19 has various clinical manifestations, ranging from asymptomatic to severe symptoms. A few risk factors had been known to worsen the COVID-19 infection, including older age, chronic illnesses such as hypertension, diabetes mellitus, obesity, and other cardiovascular or respiratory comorbidities.[2]

Vitamin D has been extensively studied in the last decade. Vitamin D deficiency is commonly found in chronic illnesses, such as obesity, diabetes mellitus, hypertension, and systemic infections.[2,3] Vitamin D has been known to have a significant role in the immune system as an immunomodulatory agent, which can increase innate immune response in the respiratory tract mucosal. Moreover, vitamin D is also vital in stimulating antimicrobial peptides that can reduce virus replication.[4]

A study by Radujkovic et al.[5] showed that among 185 COVID-19 patients, 22% of patients had vitamin D serum levels below 12 ng/mL. Some studies also showed that people with low 25(OH)Vitamin D serum have poorer clinical outcomes than those with normal vitamin D levels. A study conducted in Turkey showed a mean difference in patients with moderate and severe stage of COVID-19 26.3 ± 8.4 vs 10.1 ± 6.2, $p < 0.001$, respectively.[6,7] There was also a mean difference in vitamin D level in COVID-19 patients who survived, 19.3 ± 11.2 vs died 10.4 ± 6.4, $p < 0.001$.[7] Vitamin D supplementation can decrease pro-inflammatory cytokines, such as TNF-α, interferon-γ, and IL-6, while increasing inhibitory cytokines.[8,9] Adequate vitamin D level has been expected to lower the incidence of cytokine storm, which is generally found in severe COVID-19 patients and a cause of death in COVID-19.[9]

Other factors are also likely to affect the severity of COVID-19, such as respiratory and cardiovascular disorders, obesity, and hypertension, which are also related to vitamin D deficiency. Therefore, the association between vitamin D and COVID-19 is unclear.[10,11] Some studies regarding the association between vitamin D levels and COVID-19 patients' mortality also showed mixed results. A study in Saudi Arabia showed that 74.7% of COVID-19 patients also experience vitamin D deficiency and have 7 times higher mortality incidents [HR 7.0 (CI 1.7-28.20; p=0.007].[12] Another study performed by Lohia et al.[4] showed that there was no significant association between vitamin D serum levels and mortality, ventilator utilization, and thromboembolic incidents in COVID-19. Based upon these controversial results, it is essential to perform further investigations to determine the relationship between vitamin D serum level and COVID-19 patients' mortality incidence, which will be discussed in this evidence based case report.

Indonesia's population is known to have a high vitamin D deficiency incidence. One of the studies investigating vitamin D levels among elderly women in 4 main hospitals in Jakarta and Bekasi showed a 35.1% prevalence of vitamin D deficiency.[13] This high vitamin D deficiency prevalence was suggested to affect the mortality of COVID-19 patients in Indonesia.

Clinical Question

"In adult patients with severe COVID-19, could vitamin D serum level affect the patient's mortality?"

P : Adult patients with severe COVID-19
I : Vitamin D serum level
C : -
O : Mortality

Methods

Literature searching was conducted by advanced searching using combination of both MesH Terms

and Title/Abstract in four databases, Pubmed, Cochrane Library, Scopus, and ProQuest. Keywords that were used include *"COVID-19", "SARS-CoV-2", "Vitamin D", "25 Hydroxyvitamin D", "Mortality",* and *"Death".* Authors used Oxford Centre for Evidence-Based Medicine as a guide to critically appraise the literature and determine the level of evidence.

Eligibility Criteria

Inclusion criteria

1. Patients aged 18-65 years old with severe COVID-19 diagnosis.
2. Vitamin D serum level was assessed during the patients' hospitalization.
3. The study output was COVID-19 patients' mortality.
4. Cohort studies, survival studies, or systematic review/meta-analysis of cohort or survival studies.
5. Articles were published in English.

Exclusion criteria

1. Studies were not conducted on humans.
2. The published article was not available in full text.

Results

The authors found 176 literatures from Pubmed database, 30 literatures from Cochrane Library, 106 literatures from Scopus and 23 literatures from ProQuest. Duplicates removal was done using Covidence application (Table 1). Lastly, literatures were assessed for eligibility based on PICO and eligibility criteria. (Figure 1) We finally selected 3 articles from Radujkovic et al.[5], Bennouar et al.[14], and Campi et al.[15] The level of evidence of these articles is 2 (Table 2). All of the articles were valid and relevant to answer our clinical question. (Table 3, Table 4)

Discussion

COVID-19 mortality continues to increase. Various prognostic factors have been studied to reduce COVID-19 mortality, including vitamin D levels. From the literature search, three studies by Radujkovic et al.[5], Bennouar et al.[14], and Campi et al.[15] showed similar results that vitamin D level is an important prognostic factor in estimating mortality in severe COVID-19.

The study by Radujkovic et al.[5] found that vitamin D deficiency was associated with a higher incidence of in-hospital death, both in the entire cohort (HR 14.73, CI 95% [4.16-52.9], $p < 0.001$) and in the inpatient group (HR 11.51, CI 95% [3.24-40.92]). The vitamin D deficiency group was also at a higher risk for mechanical ventilation, both in the entire cohort (HR 6.12, CI 95% [2.79-13.42], $p < 0.001$) and inpatient group (HR 4.65, CI 95% [2.11-10.25], $p < 0.001$). Bennouar et al.[14] also found that only the severe vitamin D deficiency group had a significant association with an increased risk of mortality (HR=6.9, 95% CI [2.0-24.1], p=0.002). Severe vitamin D deficiency also significantly reduced the survival rate ($P_{log\text{-}rank}$=0.009). Campi et al.[15] found that severely-symptomatic COVID-19 patients had lower vitamin D levels (18.2 ± 11.4 ng/mL) than mildly-symptomatic and non COVID-infected controls (30.3 ± 8.5 ng/mL and 25.4 ± 9.4 ng/mL, $p < 0.0001$). This study also showed that vitamin D deficiency is more common in group of patients requiring ICU admission than in those who did not. In addition, vitamin D levels was inversely correlated with in hospital mortality in severely-symtpomatic COVID-19 patients [RR 0.961, CI 95% (0.937 – 0.985, p value = 0.002]. A 1 ng/mL increase in 25(OH)D levels was associated with a reduction of 1% of ICU admission risk (95% CI 0 to 2%, p value = 0.011).

Although the confidence interval is quite wide due to the small number of samples, the results of these studies are in line with several previous studies examining the relationship between vitamin D and COVID-19. Several studies have suggested that vitamin D deficiency is associated with poor prognosis in COVID-19 patients. Recent studies have shown that many patients with severe COVID-19 have vitamin deficiency on admission.[4,7]

Table 1. Literature searching strategy

Database	Search Strategy	Hits	Selected article
Pubmed	(("covid 19"[MeSH Terms] OR "covid 19"[Title/Abstract] OR ("sars cov 2"[MeSH Terms] OR "sars cov 2"[Title/Abstract])) AND ("vitamin d"[MeSH Terms] OR "ergocalciferols"[MeSH Terms] OR "vitamin d"[Title/Abstract] OR ("calcifediol"[MeSH Terms] OR "25 hydroxyvitamin d"[Title/Abstract])) AND ("mortality"[MeSH Terms] OR "mortal*"[Title/Abstract] OR ("Death"[MeSH Terms] OR "Death"[Title/Abstract])))	176	20
Cochrane Library	#1 MeSH descriptor: [COVID-19] explode all trees #2 ("COVID 19"):ti,ab,kw #3 ("SARS COV 2"):ti,ab,kw #4 MeSH descriptor: [Vitamin D] explode all trees #5 ("vitamin D"):ti,ab,kw #6 ("25-hydroxy vitamin D"):ti,ab,kw #7 MeSH descriptor: [Mortality] explode all trees #8 (MORTALITY):ti,ab,kw #9 (DEATH):ti,ab,kw #10 MeSH descriptor: [Death] explode all trees #11 #1 OR #2 OR #3 #12 #4 OR #5 OR #6 #13 #7 OR #8 OR #9 OR #10 #14 #11 AND #12 AND #13	30	0
Scopus	*((TITLE-ABS-KEY ("COVID 19") OR TITLE-ABS-KEY ("SARS COV 2"))) AND ((TITLE-ABS-KEY ("VITAMIN D") OR TITLE-ABS-KEY ("25 HYDROXYVITAMIN D"))) AND ((TITLE-ABS-KEY (mortality) OR TITLE-ABS-KEY (death))) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (DOCTYPE , "ar"))*	106	6
ProQuest	(ti(COVID 19) OR ti(SARS COV 2)) AND (ti(VITAMIN D) OR ti(25 HYDROXYVITAMIN D)) AND (ti(MORTALITY) OR ti(DEATH))	23	2

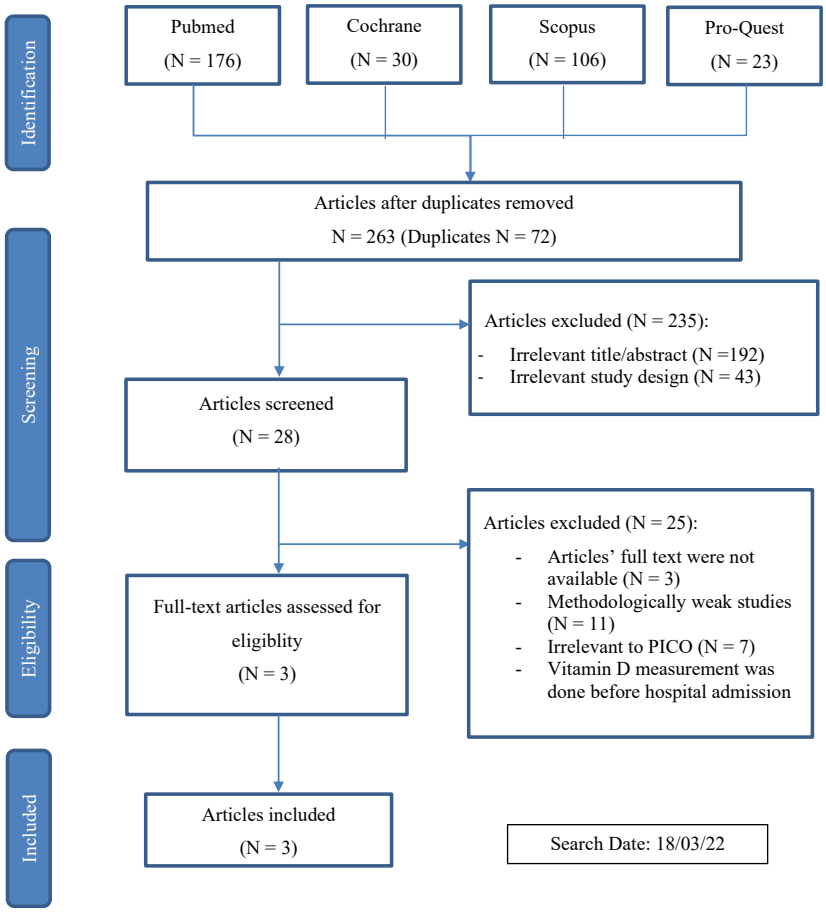

Figure 1. Prisma's flow chart

Tabel 2. Study charactheristic

Articles	Study design	Population	Outcome
Radujkovic, et al, (2020)[5]	Retrospective cohort study	185 patients, >18 years old diagnosed with COVID-19, had been tested for vitamin D levels on admission. Patients were divided into subgroups: mild symptoms (outpatient) and severe (inpatients). Based on vitamin D levels, patients were classified into: Deficiency (<12ng/mL), control (≥12 ng/mL)	Mortality rate and the use of an invasive mechanical ventilator
Bennouar et al, (2020)[14]	Prospective cohort study	120 patients, >18 years old diagnosed with severe COVID-19, had been tested for vitamin D levels on admission. Based on vitamin D level, patients were classified into: Optimal (>78 nmol/ l or >10 μg/l), insuffiency (52-75 nmol/l or 20-29 μg/l), deficiency (26-52 nmol/l or 10-20 μg/l) and severe (< 26 nmol/l or < 10 μg/l)	In-hospital mortality within 28 days of admission

Tabel 2. Study charactheristic

Articles	Study design	Population	Outcome
Campi et al. (2021)[15]	Prospective cohort study	361 patients, >18 years old diagnosed with COVID-19, had been tested for vitamin D levels. Patients were divided into subgroups: mildly symptomatic, severely symptomatic and non SARS-CoV-2 infected controls . Based on vitamin D levels, patients were classified into: Deficiency (≤12ng/mL), control (>12 ng/mL)	The need of admission to ICU and in-hospital mortality

Table 3. Validity criteria

Relevance										
Article	Common point	Follow up	Outcome	Adjustment	Outcome over time	Precision	Applicability	Clinically important	Result	Level of Evidence
Radujkovic, et al.[5]	+	+	+	+	+	+	+	+	A	2
Bennouar, et al.[14]	+	+	+	+	+	+	+	+	B	2
Campi, et al.[15]	+	+	+	+	+	+	+	+	C	2

A: inpatient with vitamin D deficiency group had a significantly higher mortality rate (HR = 11.51, CI 95% [3.24-40.92], p<0.001).
B: inpatient with severe vitamin D deficiency group had a significantly higher mortality rate than the vitamin D deficiency and insufficiency groups (HR = 6.9, 95% CI [2.0-24.1], p=0.002). Patients with severe vitamin D deficiency had a significantly reduced likelihood of survival ($P_{log\text{-}rank}$=0.009)
C: vitamin D levels inversely correlated with mortality rate (RR 0.97, 95% CI [0.95-0.99], p=0,011)

Table 4. Relevance criteria

1.	Similarity Population	Similarity Determinant	Similarity Outcome
Radujkovic et al. [5]	+	+	+
Bennouar et al. [14]	+	+	+
Campi et al. [15]	+	+	+

Vitamin D has a vital role as an immunomodulator, which can increase immune reactions in the respiratory tract mucosa through the formation of antimicrobial peptides. Low vitamin D levels will affect the immune defense system, thereby increasing the risk of disease severity and mortality due to COVID-19. Calcitriol, which is the active form of vitamin D, can bind to vitamin D receptors presenting on T and B immune cells, antigen-presenting cells (APC) and respiratory epithelium. The binding between vitamin D and its receptor will form an antimicrobial peptide, namely cathelicidins, which can damage bacterial or viral cell membranes, including the SARS CoV-2 virus and defensins that function to induce inflammatory chemotaxis cells by increasing capillary permeability.[6] Vitamin D deficiency significantly increases the risk of pneumonia and the occurrence of thrombotic episodes that are frequently seen in

COVID-19 patients.[9] Low vitamin D levels may exacerbate the incidence of cytokine storm, which is one of the leading causes of death in severe COVID-19, through increased mechanisms of inflammatory cytokines, such as TNF-α, interferon-γ, and IL-6 and decreased inhibitory cytokines.[6]

Based on Lohia et al.[4] study, the groups with higher risk vitamin D deficiency were the elderly, obese, and men. The highest COVID-19 mortality rate is also known to occur in these groups. This was also found in Radujkovic et al.[5], where 63% of patients in the entire cohort with vitamin D deficiency were aged 60. However, there was no significant difference in vitamin D levels in men and women. Bennouar et al.[14] also found that most of the subjects were male (69.2%) with a mean age of 62.3±17.6 years old and most had low levels of vitamin D, in the vitamin D insufficiency group (19.2%), vitamin D deficiency (29.2%) and the severe deficiency (26.7%). Several literatures recommend maintaining a minimum vitamin D level of 30 ng/mL to have optimal health conditions and it will hopefully prevent from COVID-19 infection.[4] Vitamin D is known to prevent cytokine storms, and ARDS events which are the leading cause of death in COVID-19 because of its role in the immune system.[6] Campi et al also showed that vitamin D serum levels were inversely associated with IL-6 in severely symptomatic COVID-19 patients (IL-6, r = -0.282, p-value = 0.004).[15]

All studies by Radujkovic et al.[5], Bennouar et al.[14], and Campi et al.[15] have several advantages. First, all of these studies have representative subjects of the existing population. In Radujkovic et al.[5] and Campi et al.[15] studies, COVID-19 patients were divided based on mild clinical symptoms and severe symptoms; therefore, they had ruled out the severity of COVID-19 as a confounder. Bennouar et al.[14] study only used severe COVID-19 patients. Second, vitamin D levels were measured on hospital admission, unlike some studies that used vitamin D levels several months/years earlier. Third, the objective measurement of hospital mortality and adjusted analysis of several confounding factors in these studies further illustrated the relationship between vitamin D levels and patient mortality. However, there are also some weaknesses in these studies, such as the sample size being not too large and is a single-center design. In Bennouar et al.[14] study, the amount of mortality that occurred after 28 days was unknown, and other risk factors for mortality in COVID-19 patients related to vitamin D deficiency such as obesity, ethnicity, and socioeconomic status were also unknown. These factors may be associated with mortality in severe COVID-19 patients.

Based on the critical review from these literature, we believe that a longitudinal study is needed with a longer duration, with a larger number of research subjects involving other factors that could potentially be confounding factors such as body mass index, socioeconomic status, comorbid disease, or ethnicity. Therefore, the relationship between vitamin D levels and mortality in severe COVID-19 patients would be more accurate, leading to a decrease in COVID-19 patients mortality rate.

Conclusion

Based on the critical review for both articles, it was found that vitamin D is one of the prognostic factors for mortality in severe COVID-19 patients. Severe COVID-19 patients with severe vitamin D deficiency have a higher risk of death. We recommend vitamin D levels assessment to be one of the routine examinations in COVID-19 patients to predict the prognosis. Furthermore, administering vitamin D supplementation to COVID-19 patients is also essential to maintain vitamin D levels to improve the immune system and provide better outcomes for patients. Maintaining vitamin D levels in optimum range is also essential for the prevention of COVID-19. However, further research is needed to assess the relationship between vitamin D levels and mortality in COVID-19 patients more accurately by involving other confounding factors.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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