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Hospital Mortality Prognosis of COVID-19 Patients with Vitamin D Deficiency: An Evidence-based Case Report

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ABSTRACT

COVID-19 is one of the most devastating diseases in recent times. Many factors were suggested to contribute to COVID-19 mortality, including vitamin D deficiency. However, the relations between vitamin D deficiency and the prognosis of COVID-19 remains unclear. The present study aimed to understand the association between hipovitaminosis D and the prediction of COVID-19 outcomes, particularly of hospital mortality and its application to patients. Literature search has been conducted using several biomedical databases. Cohort studies and systematic reviews of cohort studies were selected based on predetermined selection criteria. The studies were then evaluated for their validity, importance, and applicability of the results. Three retrospective cohort studies were selected. Two out of the three studies were scored as moderate validity, and one study was rated with low validity. Two studies found that vitamin D deficiency with 20 ng/mL cut-off had been linked to a higher risk of a severe course of COVID-19 and death. At the same time, one study had found that severe vitamin D deficiency vs. non-deficiency patients resulted in 50% vs. 5% for the probability of 10-day survival. The above three studies concluded that patients with vitamin D deficiency have an increased risk of mortality and severe disease courses. Therefore we conclude that COVID-19 confirmed adult patients with vitamin D deficiency have a poor prognosis regarding the hospital mortality versus patients with adequate plasma vitamin D concentrations.

Keywords: COVID-19, SARS-CoV-2, hypovitaminosis D, prognosis, mortality

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CLINICAL SCENARIO

A 56-years-old female patient came to the clinic with fever and dry cough complaints since three days prior and shortness of breath that got worse since the previous day. According to the patient, the fever is not too high, and she often leaves her home during the pandemic. After a nasopharyngeal swab examination, the patient was confirmed positive for COVID-19. The patient has gone through menopause for a year and had a fracture history on her left femur six months ago. The physician suspected that she also suffered from vitamin D deficiency, and so a laboratory examination was carried out.

Further investigation was as follows; physical examination: temperature: 38.2°C, height: 158 cm, bodyweight: 73 kg, muscle weakness, *genu valgum*; laboratory findings: total plasma 25-hydroxyvitamin D concentration was 9.9 ng/mL; x-ray findings: low bone density. As the laboratory finding confirmed the hypovitaminosis status, the patient asked whether her condition will affect her infection in the future. To plan appropriate treatment, healthcare providers needed to predict the course of a COVID-19 case with vitamin D deficiency. Although quite prevalent, the specific relationship between hipovitaminosis D and COVID-19 is yet to be discovered. Therefore, we searched for evidence to determine the patient's prognosis.

INTRODUCTION

COVID-19 is a debilitating disease caused by SARS-CoV-2 and currently is classified as an ongoing pandemic. Up to date, COVID-19 has driven over 2 million deaths worldwide.[1] Recent studies had suggested that vitamins and micronutrients such as vitamin C, vitamin D, selenium, zinc, and glutamine play an essential role in immune system activation against infections. Studies also suggested that micronutrients deficiency might be a risk factor that potentially affects mortality and morbidity COVID-19 patients.[2-5]

Vitamin D is well known for its mechanism on genes expressed in immune cells among vitamins and micronutrients. Vitamin D is known for its benefit on the skeletal system by regulating calcium by increasing epithelial calcium channel expression and enhancing the intestinal absorption of calcium. Vitamin D also has a lot of benefits on extraskeletal systems. Vitamin D activates the expression of pro-apoptotic proteins and decreases expressions of anti-apoptotic proteins. Vitamin D is beneficial for our immune system by stimulating our innate immunity, enhancing macrophages' phagocytic activity, and enhancing the antimicrobial properties of macrophages and monocytes. As stated before, Vitamin D regulates calcium homeostasis.[4-8]

Vitamin D deficiency is commonly found in the elderly, obese, or people with darker skin. However, the deficit can be easily corrected by adding supplements.[6-9] Recent study had shown that correcting vitamin D insufficiency resulted in the reduced the expression of dipeptidyl peptidase-4 (DPP-4/CD26),[10] which can connect with the S1 domain of SARS-CoV-2 spike glycoprotein and may act as a significant virulence factor of COVID-19.[11] Maintaining vitamin D concentration on normal level may also reduce unfavorable immunological sequelae such as the increased of interleukin 6 (IL-6) and delayed response of interferon-gamma (IFN-γ). All the above events leads to a poorer clinical outcomes in COVID-19 patients. Therefore, some studies had suggest hipovitaminosis D to be a negative prognostic marker in COVID-19 patients.[12-13]

Therefore, we aimed to investigate whether patients infected by COVID-19 with hypovitaminosis D might have a poorer hospital mortality prognosis due to a less effective immune system regulation.

METHODS

Search Strategy and Article Selection

We searched several biomedical article databases, including Pubmed, MEDLINE, Cochrane, and CINAHL, for relevant studies. We used the COVID-19 search string sample from the Canadian Agency for Drugs and Technologies in Health (CADTH) and added keywords for vitamin D deficiency and prognosis to specify the search. For the other 3 databases, we input our keywords for COVID-19, vitamin D deficiency, and prognosis. To add relevant articles, we add several synonyms for each keyword. The complete search strategy for each database is shown in Table 1.

We included cohort studies and systematic reviews of cohort studies that observed the effect of vitamin D deficiency on COVID-19 patients. Hits were screened for relevant articles based on their titles and abstracts. We included studies with confirmed COVID-19 patients of any severity that observed mortality outcomes in patients with vitamin D deficiency compared to those with a sufficient concentration of vitamin D. Deficiency was defined as serum total 25-hydroxyvitamin D concentration <20 ng/mL. We excluded studies without available full texts and those not available in English. Full-text articles were then further assessed using the same eligibility criteria to be analyzed in the report.

Table 1. Search Strategy

Database	Search Strategy
Pubmed	Search string for COVID-19 from CADTH[14] AND ((“Vitamin D” [MeSH Terms]) AND ((Hypovitaminosis) OR (Deficien*) OR (Deficit) OR (Short*) OR (Insufficien*) OR (Inadequa*) OR (Lack) OR (Absen*))))
MEDLINE	S1 (MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR (MH "COVID-19") S2 "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "corona-virus" OR "2019-novel coronavirus" OR "2019nCoV" OR "nCoV-2019" OR "nCoV2019" S3 (MH “Vitamin D Deficiency+”) S4 “Hypovitaminosis D” S5 (MH “Mortality+”) S6 (MH “Severity of Illness Indices”+) S7 (MH “Mortality”+) S8 “Prognosis” OR “Outcome” OR “Life Span” OR “Surviv*” OR “Mortal*” OR “Sever*” S9 S1 OR S2 S10 S3 OR S4 S11 S5 OR S6 OR S7 OR S8 S12 S9 AND S10 AND S11
Cochrane	#1 (prognosis):ti,ab,kw OR (outcome):ti,ab,kw OR (life span):ti,ab,kw OR (surviv*):ti,ab,kw OR (mortal*):ti,ab,kw OR (sever*):ti,ab,kw #2 (SARS-CoV-2):ti,ab,kw OR (COVID):ti,ab,kw OR (COVID-19):ti,ab,kw OR (nCoV*):ti,ab,kw #3 (vitamin D):ti,ab,kw AND ((hypovitaminosis):ti,ab,kw OR (deficien*):ti,ab,kw OR (short*):ti,ab,kw OR (insufficien*):ti,ab,kw OR (inadequa*):ti,ab,kw OR (lack):ti,ab,kw OR (absen*):ti,ab,kw) #4 #1 AND $2 AND #3
CINAHL	S1 (MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR (MH "COVID-19") S2 "COVID-19" OR "SARS-CoV-2" OR "2019-nCoV" OR "corona-virus" OR "2019-novel coronavirus" OR "2019nCoV" OR "nCoV-2019" OR "nCoV2019" S3 (MH “Vitamin D Deficiency+”) S4 “Hypovitaminosis D” S5 (MH “Mortality+”) S6 (MH “Severity of Illness”) OR (MH “Severity of Illness Indices”+) S7 (MH “Mortality”+) S8 “Prognosis” OR “Outcome” OR “Life Span” OR “Surviv*” OR “Mortal*” OR “Sever*” S9 S1 OR S2 S10 S3 OR S4 S11 S5 OR S6 OR S7 OR S8 S12 S9 AND S10 AND S11

Critical Appraisal

Selected articles were critically appraised using the University of Oxford CEBM Appraisal Tool of Prognostic Studies.[15] The appraisal was conducted by at least two assessors independently. Conflicts of results were solved by discussion.

RESULTS

Figure 1 showed the search process flow from four databases (PUBMED, CINAHL, MEDLINE, and COCHRANE). As a result, we found 50 articles from PUBMED, 17 manuscripts from CINAHL, 41 from MEDLINE, and 22 from COCHRANE. In summary, we found 90 papers with different titles. Then, we screened the titles and abstracts according to our eligibility criteria, resulting in 8 articles for full-text assessment. Further, five papers were excluded due to uneligible study designs, resulting in 3 articles to be included and appraised. Table 2 presented the study characteristics of the included studies, while the results of the validity appraisal of each research were shown in Table 3.

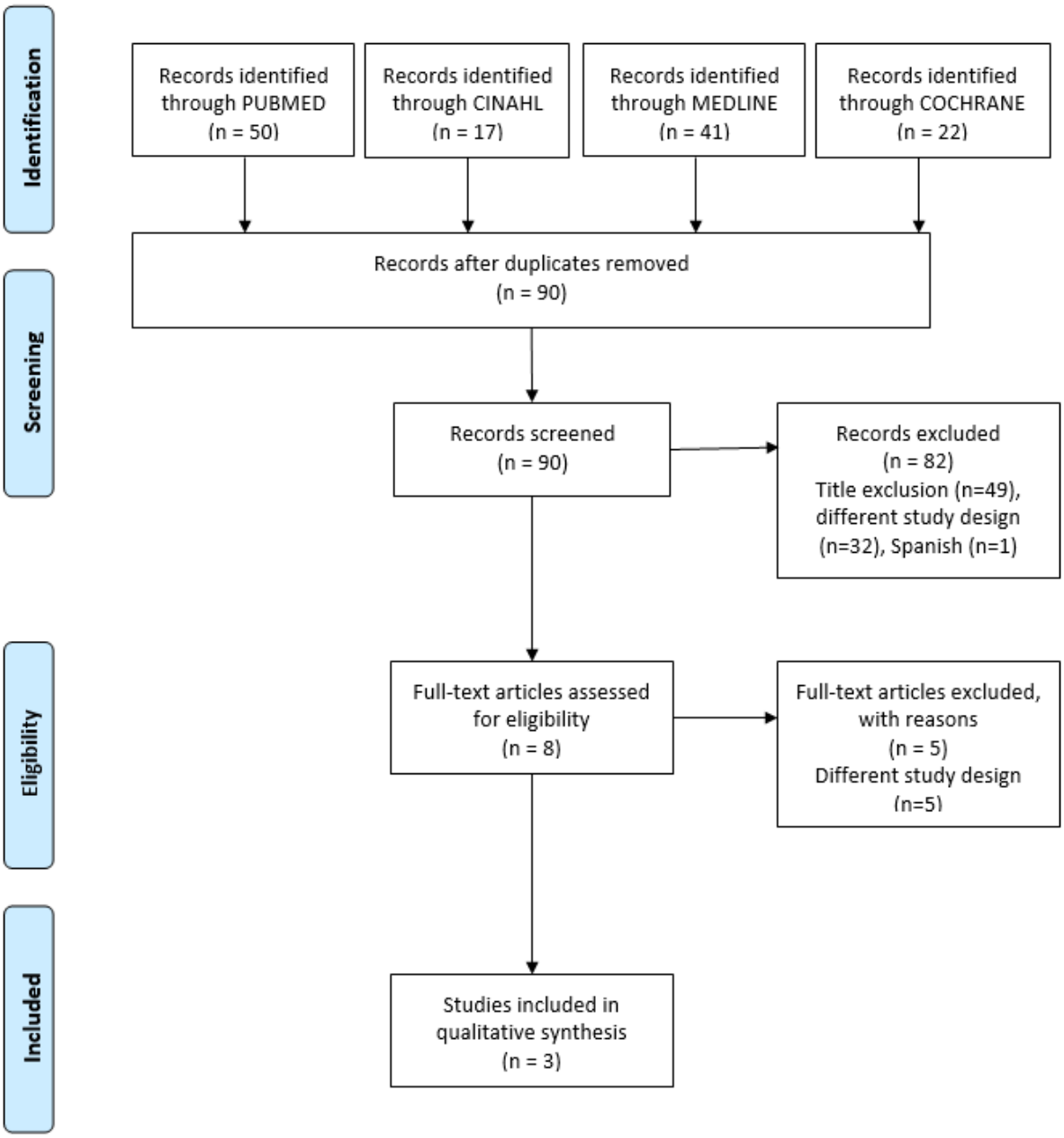

Figure 1. Flowchart of Article Search and Selection

Table 2. Study characteristics

Author	No. of Patients	Study Design	Study Population	Cut-off	Study Endpoint
Carpagnano et al. (2020)[16]	42	Retrospective Cohort	Patients diagnosed with acute respiratory failure due to COVID-19, treated in Respiratory ICU from March 11 to April 30, 2020	<10 ng/mL	Death within ten days of hospitalization
Macaya, et al. (2020)[17]	80	Retrospective Cohort	Patients from a tertiary hospital with positive RT-PCR for SARS-CoV-2 and an available value of serum 25(OH)D concentrations at admission or within the three previous months	<20 ng/mL	Severe disease course (death, admission to ICU, and need for higher oxygen flow)

Radujkovic et al. (2020)[18]	185	Retrospective Cohort	Symptomatic COVID-19 patients, with PCR positive SARS-CoV-2- patients, hospitalized between March 18 and June 18 2020	<12 ng/mL and <20 ng/mL	Severe disease course (requiring invasive mechanical ventilation and/or death)

Table 3. Critical appraisal of the included study

Author	Representative sample	Sufficient Follow-up	Objectivity/ Blinding	Adjustment for Confounders	Validity
Carpagnano, et al. (2020)[16]	No	No	No	Yes	Low
Macaya et al. (2020)[17]	No	Yes	No	Yes	Moderate
Radujkovic, et al. (2020)[18]	No	Yes	Yes	Yes	Moderate

All three included studies assessed vitamin D levels retrospectively.[16-18] Macaya et al. and Radujkovic et al. observed patients' outcomes up to their last contact, each with their endpoints.[17-18] The primary endpoint of Radujkovic et al.'s study is the need for invasive mechanical ventilation and/or death (IMV/D), while the secondary endpoint is death.[18] On the other hand, Macaya et al. defined their endpoint as severe disease courses, which included death, admission to ICU, and the need for higher oxygen flow. Both studies show a potential relationship between vitamin D deficiency and poor outcomes of COVID-19, as shown in Table 4. Study by Carpagnano et al. compared mortality probability based on a survival analysis between 2 groups of patients after ten hospitalization days. However, the number of outcomes in each group (25(OH)D <10 ng/mL and ≥10 ng/mL) was not reported.[16]

Table 4. Key findings and applicability of the included studies

Author	Key Findings		Similarity to patient in the case presentation	Clinical Importance
Carpagnano, et al. (2020)[16]	Severely vitamin D deficient patients have a 50% mortality probability, while patients with 25(OH)D level ≥10 ng/mL have a 5% mortality probability (RR=10).		No	Yes
Macaya et al. (2020)[17]	**Entire Cohort** Severe Disease Course RR 1.41 (95% CI 0.79-2.55)	**<67 years-old Subgroup** Severe Disease Course RR 15.75 (95% CI 0.99-251.47)	Yes	Yes
Radujkovic, et al. (2020)[18]	<12 ng/mL Cut-off		Yes	Yes
	Entire Cohort IMV/D: HR 6.12 (95% CI; 2.79-13.42) Death: HR 14.73 (95% CI 4.16-52.19)	**Inpatient Subgroup** IMV/D: HR 4.65 (95% CI 2.11-10.25) Death: HR 11.51 (95% CI 3.24-40.92)		
	<20 ng/mL Cut-off			
	Entire Cohort IMV/D: HR 5.75 (95% CI 1.73-19.09) Death: HR 11.27 (95% CI 1.48-85.55)	**Inpatient Subgroup** IMV/D: HR 3.99 (95%CI 1.2-13.28) Death: HR 7.97 (95%CI 1.05-60.6)		

DISCUSSION

Our evidence-based case report aimed to determine the hospital mortality in adult COVID-19 patients with vitamin D deficiency. Our literature search resulted in three cohort studies. We found a variety of results between the three studies. However, each tends to show an increased risk of mortality and severe disease courses in patients with vitamin D deficiency. The three authors applied different cut-off points of total serum 25-hydroxyvitamin D levels.[16-18] Radujkovic et al. defined vitamin D deficiency as 25(OH)D level <12 ng/mL with an additional analysis toward another cut-off point of <20 ng/mL, which was the same cut-off point set by Macaya et al.[17,18] Carpagnano et

al. focused on 25(OH)D level <10 ng/mL reflecting severe vitamin D deficiency.[16]

According to Radujkovic et al., hipovitaminosis D deficiency was associated with a higher IMV/D (Hazard Ratio of 6.2; 95% CI: 2.79-13.42) and mortality risk (Hazard Ratio of 14.73, 95% CI: 4.16-52.19) when adjusted for age, gender, and presence of comorbidities. A similar, albeit weaker, the association was also observed with the 20 mg/mL cut-off (Hazard Ratio of 5.75, 95%CI: 1.73-19.09 for IMV/D and Hazard Ratio of 11.27, 95%CI: 1.48-85.55 for mortality risk). The association was weaker when analyzed in the inpatient subgroup due to more inferior prognostic factors.[18] Although statistically insignificant, the study by Macaya et al. also showed a tendency toward a higher risk of severe courses of COVID-19, including death, in patients with vitamin D deficiency (RR 1.41, 95%CI: 0.79-2.55). A higher association was shown by a subgroup analysis of patients <67 years old, suggesting that vitamin D deficiency may have a more significant impact on the younger subset of patients.[17]

In contrast to the two studies mentioned earlier, Carpagnano et al. observed that vitamin D deficiency impacts a more advanced stage of COVID-19 (patients with acute respiratory failure), which indicates a poorer prognosis.[16] In this study, patients with severe vitamin D deficiency had a 50% mortality probability, while patients with 25(OH)D ≥10 ng/mL had a 5% probability based on a survival analysis after ten days of hospitalization resulting in relative risk of 10.[16]

Overall, the studies included in this report have a low-to-moderate level of validity. The strength of the association is inconsistent from study to study. However, all tend to show a positive association between vitamin D deficiency status and the risk of severe courses of COVID-19. The results' low precision levels may arise from small sample sizes and unadjusted potential confounders in each study. Notable potential factors associated with COVID-19 severity and mortality include age, sex, co-infections, and comorbidities such as hypertension, diabetes, cardiovascular diseases, and respiratory system diseases.[19-22] Moreover, vitamin D plasma concentrations are not routinely measured in the general patient population but rather in the elderly and patients with comorbidities, leading to potential selection biases in these retrospective studies. Therefore, a prospective cohort study with a larger sample size would be needed to confirm these findings. However, since there is no available causal treatment for COVID-19, identification, and modification of prognostic factors such as vitamin D level may improve outcomes. Radujkovic et al. show the most significant result, have the lowest risk of bias, and be best applied to our patient.[17] Despite the low precision levels, these findings warrant the intervention recommendation. Definite results from some ongoing intervention trials with a high dose of vitamin D in COVID-19 patients currently are still anticipated.[23,24] Regarding the patient in our case, since all three studies showed that vitamin D deficiency might lead to poorer hospital prognosis, it is recommended that the physician give vitamin D supplementation to the patient and try to increase the serum concentration above 20 ng/mL.

CONCLUSION

The prognosis of a COVID-19 confirmed adult patient with vitamin D deficiency in terms of mortality is likely to be lower than those without vitamin D deficiency. However, with extensive intervention trials with greater validity to strengthen the evidence, modification of this prognostic factor is potentially beneficial in the lack of a causal treatment. Hence, supplementation of vitamin D supplementation is recommended to maintain a vitamin D level in the normal range (>20 ng/mL) to improve clinical outcomes and reduce mortality risk.

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