Association between Vitamin D and COVID-19: a systematic review and meta-analysis

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Abstract

Aim. Assess the association of plasma vitamin D levels or vitamin D supplementation in the outcomes of COVID- 19. Methods. PubMed, EMBASE, and Cochrane Library databases were searched. Studies with COVID-19 patients that reported an association between plasma vitamin D levels or vitamin D supplementation and mortality, need of hospitalization, ICU admission, or ventilation requirement published until December 8, 2020, were included. The risk ratio (RR) and confidence interval (CI) were pooled using a fixed-effects model. Results. A total of 16 studies were included in the meta-analysis, eleven cohorts, one case-control, one randomized clinical trial, and two quasi-experimental studies. Low plasma vitamin D levels in patients with COVID-19 were associated with mortality (RR=1.42, 95%CI 1.14 – 1.71), need for ICU admission (RR=1.76, 95%CI 1.03-2.49), and need for ventilation (RR=3.58, 95%CI 1.45-5.70). Regular supplementation showed a decreased risk of death, and vitamin D supplementation in patients with COVID-19 showed a decrease in the need for ICU admission. Conclusion. Sufficient vitamin D level is associated with better outcomes in patients with COVID-19. Vitamin D supplementation in patients with COVID-19 appears to reduce the risk of ICU admission and regular supplementation reduces mortality.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interests.

ABSTRACT

Aim . Assess the association of plasma vitamin D levels or vitamin D supplementation with the outcomes of COVID- 19.**Methods** . PubMed, EMBASE, and Cochrane Library databases were searched. Studies with COVID-19 patients that reported an association between plasma vitamin D levels or vitamin D supplementation and mortality, need of hospitalization, ICU admission, or ventilation requirement published until December 8, 2020, were included. The risk ratio (RR) and confidence interval (CI) were pooled using a fixed-effects model. **Results** . A total of 16 studies were included in the meta-analysis, eleven cohorts, one case-control, one randomized clinical trial, and two quasi-experimental studies. Low plasma vitamin D levels in patients with COVID-19 were associated with mortality (RR=1.42, 95%CI 1.14 – 1.71), need for ICU admission (RR=1.76, 95%CI 1.03-2.49), and need for ventilation (RR=3.58, 95%CI 1.45-5.70). Regular vitamin D supplementation showed a decreased risk of death, and vitamin D treatment in patients with

COVID-19 showed a decrease in the need for ICU admission. **Conclusion** . Sufficient vitamin D level is associated with better outcomes in patients with COVID-19. Vitamin D supplementation in patients with COVID-19 appears to reduce the risk of ICU admission and regular supplementation reduces mortality.

Keywords : 25-hydroxyvitamin D; Cholecalciferol; Ergocalciferols; Meta-analysis. SARS-Cov2.

INTROducTion

Since the first case registered in December 2019 in the city of Wuhan, Hubei Province, China, COVID-19 has spread rapidly throughout the world for presenting strong contagious and infectious characteristics[1–3], which have caused 1,663,474 deaths until December 19th, 2020 in 198 countries[4].

Worldwide data from the pandemic demonstrate a mortality rate of 0.9% in patients without comorbidities, which increases progressively based on the number of comorbidities and the age of the patients[5]. The existence of studies relating vitamin D levels to Acute respiratory infections[6], led to the carrying out an ecological study wich showed that countries, where the plasma mean vitamin D population is low, had higher rates of infection and mortality from SARS-CoV2[7].

Isaia et al[8] found a correlation between regions with higher levels of solar ultraviolet (UV) radiation and lower rates of morbidity and mortality related to COVID-19, the hypothesis discussed by the authors is that it may be related to vitamin D levels. Exposure to UV radiation determines the photo-conversion of the pro-vitamin D3 (7-dehydrocholesterol) in the skin to pre-vitamin D3[9].

In addition, many observational studies relating vitamin D level to COVID-19 outcomes have emerged with divergent results[10–14] and in the absence of randomized clinical trials, we proposed conducting a systematic review to assess the association of plasma vitamin D levels or vitamin D supplementation in the mortality, and severity of COVID- 19.

METHODS

Data Search

Two investigators searched MEDLINE, EMBASE, and Cochrane Library. Studies published until December 8, 2020 were included. The following search strategy was used: (coronavirus OR "coronavirus infections" OR COVID-19 OR "severe acute respiratory syndrome coronavirus 2") AND ("vitamin D" OR "ergocalciferol" OR "cholecalciferol" OR "vitamin D deficiency" OR calcitriol OR calcifediol OR alfacalcidol OR paricalcitol OR doxercalciferol). The language of the searches was limited to English, Spanish and Portuguese.

Study selection

The studies were screened by two independent authors. Disagreements were resolved through discussion among all authors. Summaries of retrieved articles were reviewed to exclude irrelevant studies, followed by reading full text for screening.

Studies were included if they met the following inclusion criteria: (1) enrolled COVID-19 patients with plasma vitamin D level (25-hydroxyvitamin D) or COVID-19 patients in vitamin D or analogs use. All studies used throat swab SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR) nucleic acid to confirm COVID-19; (2) examined the association between vitamin D use or plasma vitamin D level with mortality or disease severity (death, hospitalization, intensive care unit - ICU admission and ventilation requirement); (3) observational or interventional studies. Ecological, cross-sectional, and studies that plasma vitamin D level was measured more than a year ago were excluded.

Data Extraction

Eligible studies included assessment of death or disease severity in individuals with plasma vitamin D or vitamin D non-use. They should provide odds ratio (OR), risk ratio (RR), or hazard ratio (HR) with 95% confidence intervals (CI). Inclusion was not restricted by study size.

Data extraction was performed by two independent investigators. Data extracted included authors, study design, country of origin, demographic characteristics (age, sex, and sample size), COVID-19 diagnosis, outcomes relevant studies on the study question. Disagreements were resolved through discussion among all authors.

Results evaluation

The primary analysis focused on the outcomes: Mortality in patients with COVID-19 in the low plasma vitamin D levels group compared with plasma sufficient vitamin D levels group or supplement vitamin D group compared with non-supplement vitamin D group. The secondary analysis focused on need for hospitalization, ICU admission, and need for mechanical ventilation.

We performed a stratified analysis by plasma vitamin D level and hospitalized patients. Besides, a sensitivity analysis was performed when necessary omitting each study to detect the influence on the estimate of the overall effect.

Quality assessment and statistical analysis

This systematic review was conducted in accordance with the Preferred Items guidelines for Reporting for Systematic Reviews and Meta-Analysis (PRISMA), and this study has not been registered.

The New-Castle-Ottawa quality scale[15] was used to evaluate the quality of the observational studies. The Cochrane risk of bias tool was used for randomized controlled trials[16]. In the case of non-randomized interventional studies, the ROBINS - I tool was used[17].

Studies included in the meta-analysis reported OR, HR, or RR. For studies that did not report these measures of effects, the RR calculation was based on the Cochrane Handbook for Systematic Reviews[18].

Effect estimates with the greatest degree of adjustment for potential confounding factors were extracted. HR was considered comparable to RR. For studies that reported OR, a corrected RR was computed as already described[19]. Pooled RR and 95% confidence interval (CI) were calculated using a fixed or random-effects model according to the homogeneity of the studies. The Cochran Q test and the I^2 statistic were used to evaluate the statistical significance and degree of heterogeneity between the studies, respectively. The statistic I^2[?]50% reveals substantial heterogeneity. Finally, the publication bias was examined by the Egger test. All analyses were performed with Stata/SE v.14.1 software (StataCorpLP, USA).

RESULTS

Characteristics of the selection studies

Four-hundred and six (406) studies were identified through database research. Of these, 353 studies are duplicate articles or were excluded based on predetermined eligibility criteria during title/abstract review. Excluded criteria were ecological studies, case reports, cross-sectional, not human, not on vitamin D level or not vitamin D supplementation at COVID-19. We identified 17 studies[13,20,29–35,21–28] (total 3,108 participants) that were eligible for this review (Figure 1), of which 16 were involved in the meta-analysis. Eleven of them was cohort[20,21,35,24,26,28–31,33,34], one case-control[27], one randomized clinical trial[25], and two quasi-experimental studies[22,23]. It was not possible to extract data from Pizzini et al[32] for analysis. The characteristics of selected studies and participants are summarized in Table 1.

Plasma vitamin D level and mortality in patients with COVID-19

The mortality outcome was extracted from 10 studies, but the adjusted analysis used 9. As shown in figure 2, the mortality in patients with deficient plasma vitamin D levels was significantly high when compared to patients with sufficient plasma vitamin D levels (Adjusted analysis, removing Carpagnano et al, RR=1.41, 95%CI 1.13 – 1.69, I^2=0.0%). The analysis included Carpagnano et al[13] showed no has significant statically (RR=7.41, 95%CI -2.27 – 17.09) with high heterogeneity (I^2=99.9%).

In subgroup analysis, hospitalized patients with deficient plasma vitamin D levels also have an increased risk of mortality (RR=1.42, 95%CI 1.14 – 1.71, I^2=0.0%). The plasma vitamin D levels adopted in studies was <10 ng / ml by one study, <12 ng / ml in four studies, <20 ng / ml in five studies and <25 ng / ml in one study.

Vitamin D supplementation and risk of deaths in patients with COVID-19

The pooled RR of deaths in COVID-19 patients in vitamin D supplementation versus non-vitamin D supplementation was 0.10 (95%CI 0.07 – 0.28), without significant heterogeneity (I^2=0.0%) (Figure 3). Subgroup analysis showed RR = 0.10 (95% CI 0.08 - 0.28) for regular vitamin D supplementation.

Plasma vitamin D level and hospitalization in patients with COVID-19 The data were extracted from two studies[30,31] that showed that there was no increase in the risk of hospitalization in patients with COVID-19 when the serum vitamin D is low (OR=1.80, 95%CI 0.97-2.64, I^2=0.0%) (Figure 4). Mendy et al[30] analyzed patients with plasma vitamin D levels lass 12 ng/ml and Merzon et al[31] analyzed levels lass 30 ng/ml.**Plasma vitamin D level, vitamin D supplementation and ICU admission in patients with COVID-19**The data was extracted from three studies[21,27,30](Figure 5), two cohorts, and one case-control. The analysis showed that patients with low vitamin D level have was increased risk of ICU admission (RR=1.76, 95%CI 1.03-2.49, I^2=0.0%). In the analysis of vitamin D supplementation, the data was extracted from two studies, one randomized clinical trial[25] with calcifediol treatment and one cohort[35] that analyzed at the use of cholecalciferol (Figure S1). The analysis showed that the treatment group has was a decreased risk of ICU admission (RR=0.04, CI95% 0.07-0.16, I^2=0.0%).**Plasma vitamin D level and ventilation requirement in patients with COVID-19**The data was extracted and pooled from three cohorts (Figure 6). Alguwaihes et al[21] analyzed patients with plasma vitamin D level lass 5 ng/ml, Baktash et al[24] analyze level lass 12 ng/ml, and Radujkovic et al[33] analyzed patients with plasma vitamin D level lass 12 ng/ml and lass 20 mg/ml separately. Comparing the deficient plasma vitamin D level with the control group, the results suggested that there is an increased risk of ventilation requirement (RR=3.58, 95%CI 1.45-5.70, I^2=0.0%).**Plasma vitamin D level and COVID-19 severity** The data COVID-19 severity (Outcomes combined analysis: Death, ICU, and Mechanical Ventilation) was extracted and pooled from three cohort[21,29,30] and one case-control[27]. The analysis showed that patients with low vitamin D level have was increased risk of deaths, ICU admission, or mechanical ventilation (RR=1.77, 95%CI 1.13-2.42, I^2=0.0%) (Figure 7).**Sensitivity analyses, assessment of heterogeneity**

For sensitivity analyses were performed by excluding one study at a time for the mortality outcome. The inclusion of Carpagnano et al[13] in any scenario raised the $I^2$from 0.0% to 99.9%, which led us to carry out the adjusted analysis (Figure 2). Carpagnano et al[13], despite showing an effect measure for mortality with low vitamin D level (<10 ng / ml), had only 3 deaths in their study (two in the group with vitamin D deficiency). As the others analysis did not show heterogeneity (I^2=0.0% to I^2=6.2%), a sensitivity analysis was not performed.

Risk of bias of the included studies in the meta-analysis

The Cochrane risk of bias tool for RCTs for evaluation of the risk of bias in Castillo et al[25]. Data showed in Figure S2. The risk of bias assessment of the two non-randomized interventional studies is shown in Table S1. The risk of bias in observational studies is detailed in Table S2.

Results of the estimated bias coefficient were from 0.014 to 0.141, giving a P-value > 0.05 for all analyses. Therefore, the tests provide weak evidence for the presence of publication bias.

DISCUSSION

This is the first systematic review with meta-analysis to show an association between low plasma vitamin D level and increased risk of death in inpatients with COVID-19 (1.41-fold). The results of this study also show an association between low plasma vitamin D levels in COVID-19 patients and increase ICU admission risk (1.76-fold) and ventilation requirement (3.50-fold).

Vitamin D deficiency is associated with an increased risk of developing viral and bacterial infections[36]. Several studies have linked the reduction of plasma vitamin D levels with increase respiratory infections[37,38], as influenza infection, and vitamin D supplementation with the decrease of risk of these infections[39–41]. Others studies revealed a higher risk of ICU admission, sepsis, and death in hospitalized patients who had low levels of vitamin D in pre-admission[42,43].

Vitamin D has a role in regulating mineral metabolism, an important role in the modulation of the immune response, and control the exacerbation of the cellular immune response[36,44,45]. Studies report that critically ill patients with COVID-19 have elevated in inflammatory cytokines such as IL-1 and IL-6, and chemokines associated with a Th1 response, corroborating the hypothesis of a cytokine storm in this disease[46,47].Vitamin D regulates feedback control pathways that serve to decrease potential inflammatory damage from disproportionate activation of the immune response[48]

Others authors question the role of the cytokine storm in COVID-19, and that severity of the disease occurs due to direct viral injury, endovasculitis, and or viral-induced immunosuppression[49]. There is some evidence to support this question. The less pronounced cytokine elevations in COVID-19 could reflect a regulated, or inadequate, inflammatory response to infection from SARS-Cov2. In addition, non-cytokine biomarkers, such D-dimer, C-reactive protein, and ferritin, are elevated to a similar in patients with COVID-19 when comparing with patients of another disorders[49,50].

Vitamin D has other roles in regulating the immune system. LL37 peptide, a component of the innate immune system that acts in the lungs against SARS-CoV-2, requires sufficient levels of vitamin D to be effective, which could indicate the preventive effect of vitamin D levels for the development of respiratory viruses[51].

T lymphocytes are directly susceptible to SARS-CoV-2 infection and are depleted in clinical COVID-19[52]. Vitamin D modulates the function of immune cells, such as T and B cells, monocytes, and dendritic cells, in an interaction between the innate and adaptive immune systems[53]. Lachmann et al[54]conducted an RCT that showed that vitamin D deficiency is associated with an absolute lower $CD4^+$ T cell count in HIV patients, however, that vitamin D supplementation increased the absolute recovery of $CD4^+$ T cell count in these patients.

It has also been previously shown that vitamin D affects on blood coagulation parameters[55]. Hejazi et al[56] where the treatment of the deficiency of vitamin D in patients with thromboembolism resulted in control of events with the lowest doses of warfarin. Although COVID-19 is a respiratory disease, many data have pointed to coagulopathy as a marker of mortality from this disease[57]. Thus, anticoagulant therapy seems to be associated with a better prognosis in critically ill patients with COVID-19 [57]. Therefore, it is possible to assume that the sufficient levels of vitamin D may be useful in the anticoagulant treatment of critically ill patients with COVID-19 or may prevent mild cases from becoming severe.

SARS- CoV-2 uses the angiotensin-converting enzyme receptor 2 to enter alveolar epithelial cells, which would lead to the deregulation of the Renin-Angiotensin System (RAS), accumulating the toxic product angiotensin II in alveolar cells and causing an acute lung injury[58,59]. Vitamin D regulates the balance between the expression of members of the RAS and their deficiency pointed to excessive activation of this system[60]. Therefore, vitamin D deficiency may exacerbate pulmonary RAS dysregulation induced by SARS-CoV-2 infection.

This study also showed that regular vitamin D supplementation was associated with a lower risk of death and vitamin D treatment of patients with COVID-19 was associated with a lower risk of ICU admission. Castilho

et al and Tan et al showed that administration of calcifediol and cholecalciferol, respectively, reduced the need for ICU admission of patients with COVID-19 that requiring hospitalization. However, treatment with vitamin D in patients already diagnosed with COVID-19 needs to be further studied.

This study has several strengths. To our knowledge, this is the first meta-analysis using interventional studies associating vitamin D with COVID-19 patients, and that included analyzing the risk of mortality in hospitalized patients. This study informs physicians and patients regarding the importance of monitoring vitamin D levels. Some limitations of our study were the small number of interventional studies, the analysis that used different treatments for vitamin D supplementation, different cut-off plasma vitamin D levels, observational design of the selected studies, and sample size.

CONCLUSION

These results suggest that COVID-19 patients with sufficient plasma vitamin D levels is decreased risks of death, ICU admission, and ventilation requirement. However, randomized clinical trials are needed to confirm the benefits of vitamin D treatment in patients with COVID-19.

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Table 1. Characteristics of studies selected.

Author	Country	Study Design	Follow-up	Population	Age (years)	Outcomes	Sample Size	Exposure or Intervention (n/cut-off or dose)	Co ad jus
Abrishami et al	Iran	retrospective Cohort	February 28, 2020 and April 19, 2020	Hospitalized patients with COVID-19	55.18±14.98	Death and hospitalization	73	Vitamin D [?]25ng/mL	Ag BM cor
Alguwaihes et al	Saudi Arabia	retrospective Cohort	May to July 2020	Hospitalized adults with COVID-19	55 (19–101)*	Mortality, ICU admission and NVI	150	112 (Vitamin D [?]12ng/mL)	Ag BM sm cor tie ser vit D, me tio Hb Ne cou Cr an

Annweiler, C et al	France	Quasi-experimental study	March-April 2020	Frail elderly nursing-home residents with COVID-1	87.7 ± 9.0	Mortality of COVID-19 and clinical improvement	66	57	80,000 IU vitamin D3 either in the week following the suspicion or diagnosis of COVID-19, or during the previous month	Ag ge nu dr da ta fu ab nu st CC tr wi co an hy ch qu an de an ot ho iz CC

Annweiler, G et al	France	Quasi-experimental study	March–May 2020	Patients hospitalized with COVID-19 in geriatric acute care unit	88 (85–92)*	14-Day COVID-19 Mortality and clinical improvement	77	Group 1 (n=29): Regular Vitamin D Supplementation Group 2 (n=16): Vitamin D Supplementation After COVID-19 Diagnosis	Ag ge fu ab se un tri his ca hy sio ca op gly he nu ac he iss ad ho us tib us sy co te an ph log tre me res to dis

Baktash et al	UK	Prospective cohort	1 March to 30 April 2020	Hospitalized patients aged [?]65 years with COVID-19		Mortality secondary to COVID-19; NIV support and admission to HDU, COVID-19 radio-graphic changes on chest X-ray	70	39 (Vitamin D [?]12ng/mL)	Vi D; D- fer hig ser tro T, an ph cou Ag we hei eth sm sta cor
Carpagnano et al	Italy	retrospective cohort	11 March to 30 April, 2020	COVID-19 hospital-ized patients	65±13	Survival	42	10 (Vitamin D [?] [?]10ng/mL)	De cha ist me his un cor tie syr tor lab fin res tor pa ter fra ins oxy (F an art pa pre oxy Pa rat pir an ph log tre

Castillo et al	Spain	Parallel pilot randomized open label, double-masked clinical trial	calcifediol,	Hospitalized patients with COVID-19 i	53 ± 10	ICU admission and deaths	76	50 Treatment group 20000-IU in admission (10000-IU on days 3 and 7)
Cereda et al	Italy	cohort	March - April 2020	Hospitalized patients with COVID-19 i	77 (65.0-85.0)*	Mortality	129	99 (Vitamin D <20 ng/mL)
Hernández et al	Spain	case-control		hospitalized patients aged [?]18 years with confirmed COVID-19	61.0 (47.5-70.0)*	COVID-19 severity (death and ICU admission)	197	162 (Vitamin D [?] [?]20ng/mL)

Jain et al	India	Prospective cohort	6 weeks	Patients with COVID-19		Serum IL-6, serum TNF-α, serum ferritin and serum level of vitamin D	154	90 (Vitamin D <20 ng/mL)	Ag ge co ity mo as to pa an cri pa
Macaya et al	Spain	retrospective cohort	March 5 to March 31, 2020	COVID-19 hospital-ized patients	Non-severe COVID-19: 63 (50-72)* Severe COVID-19: 75 (66-84)*	COVID-19 severity (death, admission to ICU, and/or NVI)	80	45 (Vitamin D [?] [?]20ng/mL)	Ag ge ob ca dis kid dis an vit
Mendy et al (preprint)	USA	retrospective cohort	March 13, 2020 to May 31, 2020	Patients with COVID-19	49.5 (35.2-67.5)*	Hospitalization and disease severity (ICU and/or death)	689	89 (Vitamin D <12 ng/mL)	Ag ra sm co
Merzon et al	Israel	retrospective Cohort	February 1 to April 30, 2020	Patients tested for COVID-19	COVID-19 group: 35.58 (34.49-36.67)** Non-COVID-19 group: 47.35 (46.87–47.85)**	Risk of COVID-19 and hospitalization	782 COVID-19 group	703 (Vitamin D [?]30ng/mL)	Ag BM sm an co

Pizzini et al	Austria	Prospective cohort	8 weeks	COVID-19 hospitalized patients and outpatients with persistent symptoms	58 ± 14	Severity and persistent cardiopulmonary damage of COVID-19 patients	109	41 (Vitamin D <12 ng/mL)	Ag ge co ity vit su me e a se lev vit D, ca ph ph cre ur CF int 6, fe an D-
Radujkovic et al	Germany	Prospective cohort	18 Marchto 18 June 2020	Inpatients and Outpatients diagnosed with COVID-19		NVI and survival	185	41 (Vitamin D <12 ng/mL)	Ag ge co ity vit su me e a se lev vit
Smet et al	Belgium	retrospective cohort	March 1, 2020, to April 7, 2020	Hospitalized patients with COVID-19 i		COVID-19 severity (stage disease and death)	186	109 (Vitamin D <20 ng/mL)	Ag an co

Tan et al	China	retrospective cohort	January 15 and April 15, 2020	hospitalized patients [?]50 y of age with COVID-19	Treatmente group:58.4 ±7 Control group: 64.1 ±7.9	Requiring oxygen therapy or ICU	43	17 1000-IU dose of vitamin D3 (cholecalciferol)	Ag cli fea an co d), of siu oxi vit B1 (m

25OHD: 25-hydroyvitamin D, ALT: alanine transaminase, AST: aspartate aminotransferase, BMI: body-mass index, CK: creatine kinase, CRP: C reactive protein, GFR: glomerular filtration rate, HDU: High dependency unit, IL-6: interleukin-6; ICU: Intensive Care Unit, LDH: lactate dehydrogenase, NVI: Non-invasive ventilation, PCT: procalcitonin, PTH: parathy-

Figure 1. Flow chart of study selection.

Figure 2. Association of plasma vitamin D level with mortality in patients with COVID-19.

Figure 3. Effect of vitamin D supplementation on the risk of death in patients with COVID-19.

Figure 4. Association of plasma vitamin D level with need for hospitalization in patients with COVID-19.

Figure 5. Association of plasma vitamin D level with ICU admission in patients with COVID-19.

Figure 6. Association of plasma vitamin D level with ventilation requirement in patients with COVID-19.

Figure 7. Association of plasma vitamin D level with COVID-19 severity (Death, ICU and need for ventilation).