DOI: https://doi.org/10.36489/saudecoletiva.2021v11iCOVIDp7033-7044

COVID-19 and serum vitmamine d levels: an integrative review of clinical prognostic correlation in infected patients

Niveles de COVID-19 y vitmamina d en suero: una revisión integrativa de la correlación clínica pronóstica en pacientes infectados

COVID-19 e níveis séricos de vitmamina d: uma revisão integrativa da correlação prognóstica clínca em pacientes infectados

ABSTRACT
Objective: To identify evidence in the medical literature regarding the correlation between serum vitamin D levels and the prognosis of patients infected with Sars-CoV-2 (COVID-19). Method: This study is an integrative review based on the databases: PubMed, MedLine Plus and Google Scholar. Results: A total of 7 articles were analyzed, which presented the necessary results for this review and conclusions about the influence of body levels of Vitamin D and the clinical outcome of patients affected by the new Coronavirus. Conclusion: The researches analyzed describe the prevalence of the association between Vitamin D deficiency and worse symptom evolution in patients affected by COVID-19 in the majority. Satisfactory (not deficient) levels of vitamin D in affected patients are associated with shorter hospital stay and less need for oxygen therapy. However, the use of vitamin D as a treatment still requires confirmation with clinical trials.
DESCRIPTORS: COVID-19; Prognosis; Vitamin D.

RESUMEN
Objetivo: Identificar evidencia en la literatura médica sobre la correlación entre los niveles séricos de vitamina D y el pronóstico de pacientes infectados por Sars-CoV-2 (COVID-19). Método: Este estudio es una revisión integradora basada en las bases de datos: PubMed, MedLine Plus y Google Scholar. Resultados: Se analizaron un total de 7 artículos, los cuales presentaron los resultados necesarios para esta revisión y conclusiones sobre la influencia de los niveles corporales de Vitamina D y la evolución clínica de los pacientes afectados por el nuevo Coronavirus. Conclusión: Las investigaciones analizadas describen la prevalencia de la asociación entre deficiencia de vitamina D y peor evolución de los síntomas en pacientes afectados por COVID-19 en su mayoría. Los niveles satisfactorios (no deficientes) de vitamina D en los pacientes afectados se asocian con una estancia hospitalaria más corta y una menor necesidad de oxigenoterapia. Sin embargo, el uso de vitamina D como tratamiento aún requiere confirmación con ensayos clínicos.
DESCRIPTORES: COVID-19; pronóstico; vitamina D.

RESUMO
Objetivo: Identificar evidências na literatura médica a respeito da correlação entre níveis séricos de Vitamina D e o prognóstico de pacientes infectados por Sars-CoV-2 (COVID-19). Método: Este estudo é uma revisão integrativa baseada nos banco de dados: PubMed, MedLine Plus e Google Acadêmico. Resultados: Foram analisados 7, os quais apresentavam resultados necessários para a realização desta revisão e conclusões a cerca da influência dos níveis corporais de Vitamina D e o desfecho clinico de pacientes acometidos pelo novo Coronavírus. Conclusão: As pesquisas analisadas descrevem a prevalência da associação entre a deficiência de Vitamina D e pior evolução dos sintomas em pacientes acometidos por COVID-19 em sua maioria. Níveis satisfatórios (não deficientes) da vitamina D em pacientes acometidos associa-se a menor tempo de internação e menor necessidade de oxigênioterapia. No entanto, o uso da vitamina D como tratamento ainda requer confirmação com ensaios-clínicos.
DESCRITORES: COVID-19; Prognóstico; Vitamina D.

RECEIVED ON: 01/30/2021 **APPROVED ON:** 02/17/2021

Leonardo Maquiné Hermont
Medical Student, Federal University of Amazonas - Manaus, AM, Brazil.
ORCID: 0000-0002-1727-0264

André Caminha de Figueiredo
Medical Student, Federal University of Amazonas - Manaus, AM, Brazil.
ORCID: 0000-0002-1097-1017

Vitória de Souza Ximenes
Medical Student, Federal University of Amazonas - Manaus, AM, Brazil.
ORCID: 0000-0002-9167-8815

Rebeca Patrícia Quereza e Silva Faria
Medical Student, Federal University of Amazonas - Manaus, AM, Brazil.
ORCID: 0000-0002-1588-9709

Daniel Cristian Ferreira de Souza
Medical Student, Federal University of Amazonas - Manaus, AM, Brazil.
ORCID: 0000-0002-9445-7292

Heitor Augusto de Magalhães e Silva
Medical Student, Federal University of Amazonas - Manaus, AM, Brazil.
ORCID: 0000-0003-1025-7275

INTRODUCTION

The new coronavirus pandemic has had a disastrous impact on all countries in the world, affecting the way we live and deal with biosafety today. [1] The rapid evolution of symptoms in affected patients is a cause for concern in hospitals and especially in intensive care units. [2] Among the symptoms, they are manifested as main: Cough, fever, myalgia, headache, nausea and dyspnea. [3] According to a large study carried out in China, the prognosis of infected patients varies according to factors such as obesity, smoking, the presence of cardiovascular diseases, chronic kidney disease and immunodeficiency, [4] showing that factors that worsen the prognosis and that among these, serum vitamin D levels can influence the outcome. [5]

The severe acute respiratory distress syndrome is the most serious complication associated with infections by the virus, being largely responsible for the mortality rate of the virus that varies between 2% and 3%. [6] Support and measures to control symptoms are the main form of medical intervention currently available for the management of the disease. [7] The main form of contamination is through interpersonal respiratory droplets. The average time of exposure and onset of symptoms varies between 5 and 14 days according to a study conducted in Boston. [8] More than 75% of hospitalized patients require supplemental oxygenation and approximately 20% of these have severe symptoms. [9] Different experimental therapies are currently being proposed and put to the test, including immunotherapy, use of convalescent plasma in infected patients, full anticoagulation and viral therapies. [10;11;12] The discovery of new therapies and the determination of new risk factors can contribute to better outcomes in infected patients and those who need nutrition and care during hospitalization, as shown in a study published in the journal Saúde Coletiva. [13] Given this scenario, this study aims to identify evidence in the medical literature regarding the relationship between body levels of Vitamin D with the prognosis of infected patients, as well as their susceptibility to infection.

METHODS

The article is an integrative review, and critically analyzes other studies on the subject. The studies were categorized and interpreted using the PICO method (Problem/ Intervention/ Comparison/ Outcome), to select the studies compatible with the defined choice criteria [14] (P:Covid-19, I: Body vitamin D as an indicator in infected patients, C: Not applicable and O: What the literature has shown regarding the influence of plasma vitamin levels with the outcome of the clinical picture).The guiding question: What are the conclusions of recent studies regarding the relationship between serum Vitamin D levels and prognosis in patients infected with COVID-19?

Articles between 2019 and 2021 were included in the English language. Articles whose approach and theme were incompatible with the proposed theme of this study were excluded from the selection. The search was carried out between the months of December 2020 and February 2021 in the PubMed, MedLine Plus and Google Scholar databases. The PRISMA method was used to prepare the integrative review. This method consists of a series of flowcharts and checklists that help authors to elaborate integrative reviews.[15] The analysis was done through a detailed reading of the selected articles, with their main points shown in a summary table.

RESULTS

To satisfactorily analyze the evidence regarding body Vitamin D levels and the outcome of patients infected with COVID-19, the review covers 7 articles,

5 of which are retrospective (71,5%) and two are retrospective (28,5%). The studies were carried out in different locations, distributed between 2 carried out in the United States (28,5%) and 5 carried out in Europe (71,5%), all published in English and during the year 2020.

DISCUSSION

This review sought to identify whether there is accurate evidence in the

Chart 1: Summary of articles divided according to authors, objectives, type of study and results.

TITLE	STUDY OBJECTIVE	TYPE	RESULTS
Article 1 H. Lau. et al[16]. 2020. EUA	To determine the prevalence of patients with insufficient levels of Vitamin D in inpatients due to COVID-19 infection in an Intensive Care Unit.	Retrospective	The prevalence of patients with insufficient vitamin D levels among severe cases of COVID-19 infection is high. Among the associations also found are arterial hypertension, obesity, male gender, previous coagulopathies and immunodeficiency.
Article 2 E. Hastie. et al[17]. 2020. United Kingdom	Determine whether the concentration of 25-hydroxyvitamin D (25 (OH) D) was associated with the risk of COVID-19 and explained the higher incidence of COVID-19 in blacks and South Asians.	Retrospective	The results do not support a potential link between vitamin D concentrations and the risk of COVID-19 infection, nor that the vitamin D concentration can explain ethnic differences in COVID-19 infection.
Article 3 Cédric Annweiler. et al[18]. 2020. France	To determine by means of an experimental study whether the administration of Vitamin D boluses (Supplementation) to patients infected with COVID-19 or about to be infected is effective in increasing survival.	Experimental	The administration of a bolus of Vitamin D to patients infected or about to be infected with COVID-19 resulted in less severe cases. Elderly patients had a better survival rate. Larger scale randomized and controlled tests are needed to firmly conclude the association between Vitamin D levels and increased patient survival.
Article 4 O. Meltzer. et al[19]. 2020. USA	Examine whether the pre-infection status of body Vitamin D levels correlates with test results for COVID-19.	Retrospective	Vitamin D deficiency was associated with an increased risk of COVID-19 infection. All participants had their Vitamin D levels measured one year before they became infected. The authors point out that randomized clinical studies are needed to determine whether interventions in patients' Vitamin D levels can decrease the incidence of COVID-19 infection in them.
Article 5 A, Radujkovic. et al[20]. 2020. Germany	Determine if there is an association between the status of Vitamin D in the body and the severity of manifestations by COVID-19.	Retrospective	The study demonstrated an association between vitamin D deficiency and symptom severity in patients with COVID-19. Patients with low levels of Vitamin D had a higher rate of hospitalization and needed more intense oxygenation. Disability was associated with increased risk of severe symptoms and death.
Article 6 Castillo et al[21]. 2020. Spain	Demonstrate the function of vitamin D on cells and tissues involved in the progression of COVID-19.	Experimental	The administration of calcifediol can improve serum vitamin D levels. In addition, it was seen in the study that among the 50 patients treated with calcifediol, only 1 had to be admitted to the ICU, while of the 26 who were not treated, 13 required admission to the ICU.

Article 7 Ilie et al[22]. 2020. United Kingdom	Demonstrate the anti-inflammatory and immunomodulatory action of vitamin D, with positive results in a study with influenza, coronavirus and other respiratory infections.	Experimental	In this study, the function of vitamin D as an immunomodulatory and anti-infectious hormone was demonstrated. It helps to inhibit the synthesis of pro-inflammatory cytokines, such as TNF-α and INF-αas well as the development of chronic diseases. Low levels of vitamin D favor the production of Th1 cytokines by the coronavirus, easily altering the respiratory epithelium. Whereas, high levels repress the recruitment of eosinophils and lymphocytes into the airway, attenuating the inflammatory response.

medical literature regarding the relationship between body levels of Vitamin D and the prognosis of patients infected with COVID-19. Among the articles analyzed, the relationship between insufficient levels of body Vitamin D and the presence of more severe symptoms among those infected is predominant. Among the 7 articles analyzed, a total of 6 (including experimental ones) demonstrated a positive correlation between adequate levels of Vitamin D and a better prognosis in patients. Other risk factors were also found among patients, including obesity, male gender, high blood pressure, coagulopathies and immunodeficiency as also demonstrated in a study conducted in Wuhan, China. [23] In study 1, conducted in the United States, twenty patients with COVID-19 had their serum levels of 25-hydroxyvitamin D assessed. Vitamin D deficiency was present in 84,6% of patients who required ICU admission. Among the less severe patients, without the need for ICU admission, Vitamin D deficiency was present in 57,1%. Surprisingly, 100% of patients under the age of 75 who required ICU admission had vitamin deficiency.

The results of the aforementioned study show a suspicion regarding the relevance of serum Vitamin D levels with the evolution of the disease, including the need for admission to the ICU or not. In study 2, carried out in England, the complete data were available for 348.598 participants from the "UK Biobank", the database in which the research was carried out. Of these, 449 had confirmed infection by COVID-19. The object of study was the serum concentration of Vitamin D among the participants, exploring the possible association between plasma levels and a greater chance of infection.

The study authors suggest that Vitamin D is unlikely to be the underlying risk factor seen in blacks and ethnic minorities seen in UK patients. They assess the effectiveness of Vitamin D supplementation as unlikely as an interventionist measure in patients infected with COVID-19. Study 3, carried out in Europe, analyzed 66 residents of a French nursing home, all infected with COVID-19. The intervention group was defined as the one containing participants who received vitamin D supplementation during infection or in recent pre-infection moments. The control group was formed by the remaining participants. The secondary results were the mortality rate and the Ordinal Scale of Clinical Improvement (OSCI) in the acute phase of the infection.

The study concludes that elderly participants who received vitamin D supplementation during or just before COVID-19 infection had lower rates of complications and lower mortality rates. Vitamin supplementation proved to be an effective, accessible and tolerated treatment for cases of COVID-19. In a future perspective, preferably in stricter interventionist studies, more studies are needed to confirm the true effectiveness of vitamin supplementation as a treatment for the disease, as well as its effectiveness in prevention.

Conducted in the USA, study 4 proposed to examine whether the vitamin D status of patients analyzed 1 year before the COVID-19 tests would be associated with the results of these tests for COVID-19. In this cohort study, 489 patients were analyzed. Overall, 71 participants (15%) tested positive for COVID-19. In the multivariate analysis, the risk of the test being positive was associated with advanced age (up to 50 years), non-white race, and "probably deficient" vitamin D levels. Positive results were prevalent in 21.6% of participants with a "probably deficient" level, and in contrast to the prevalence of 12,2% in the group with a "probably sufficient" level. The relative risk of a positive test is 1,77 times higher in patients with a "probably deficient" level when compared to the "probably sufficient" group, an increase in relative risk that is significantly statically relevant.

The results appear to support the hypothesis of the influential role of Vitamin D in risk of infection by COVID-19, a conclusion also suggested in a study conducted in the United States that associates vitamin supplementation with shorter hospital stay. [24] Article 5 studied 185 patients diagnosed with COVID-19 and analyzed the status of vitamin D in each one to demonstrate the relationship of low levels of it with a higher rate of hospitalization and evolution with severe forms. A total of 41 (22%) patients were deficient (<12 ng/mL) and 118 (64%) patients had VitD levels <20 ng/mL. Thus, the highest proportion of hospitalized patients was deficient in Vitamin D (<12 ng/mL). The follow-up was 66 days. A total of 16 patients died and 23 patients required invasive mechanical ventilation.

The relationship between the presence of IL-6 (pro-inflammatory) and vitamin D deficiency was also noted, being one of the factors responsible for the worsening of COVID-19. Finally, the study concluded the association between VitD deficiency and COVID-19 severity. Patients with Vitamin D deficiency had a higher rate of hospitalization and required more oxygen therapy.

Article 6 evaluated the relationship between vitamin D and the evolution to the Acute Respiratory Suffering Syndrome in patients infected with COVID-19. The study involved the participation of 76 patients admitted by COVID-19, of which 50 were treated with vitamin D and 26 were not treated. Of the 50, only 1 needed to be admitted to the ICU, while of the 26, 13 required hospitalization. All patients treated with vitamin D were discharged without complications, the 13 who were hospitalized, 2 died and the others were discharged. Article 7 shows the anti-inflammatory and immunomodulatory role of vitamin D in the body, being responsible for decreasing the amount of pro-inflammatory cytokines, such as TNF-α, INF-γ, IL-6 and increasing anti-inflammatory cytokines, such as IL-10. In addition, it showed the relationship of high levels of vitamin D with less development of chronic diseases, such as multiple sclerosis, gastrointestinal inflammatory disorders and type 1 diabetes. Finally, the article shows evidence that high doses of vitamin D are associated with a reduction of sepsis and acute respiratory distress syndrome.

Finally, the study concluded the association between VitD deficiency and COVID-19 severity. Patients with Vitamin D deficiency had a higher rate of hospitalization and required more oxygen therapy.

CONCLUSION

Given the mapped studies, there is a demonstration of the relationship involving the deficiency of this vitamin and susceptibility to acute respiratory tract infections, since calcitriol (One of the active forms of Vitamin D) receives stimuli from antimicrobial peptides in response to viral and bacterial infections.

Patients with COVID-19 had a higher prevalence of insufficient vitamin D levels, related to increased ferritin and D-dimer (inflammatory status), especially hypertensive and cardiac patients, obese, men and diabetics; which has led some studies to correlate disability with greater chances of complications, more severe symptoms and longer hospital stay. The correlation alone does not define with complete certainty that Vitamin D deficiency can be used as a treatment, requiring more randomized clinical trials for this. ■

REFERENCES

1. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). Indian J Pediatr [Internet]. 2020 Mar 13 [cited 2021 Jan 4];87:281-286. DOI 10.1007/s12098-020-03263-6. Available from: https://pubmed.ncbi.nlm.nih.gov/32166607/.

2. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Nature Public Health Emergency Collection [Internet]. 2020 Apr 02 [cited 2021 Jan 4];:1–10. DOI 10.1007/s11684-020-0767-8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7115348/.

3. Rogers G, Swift S. The world is upside down; how coronavirus changes the way we care for our patients. Int Urogynecol J [Internet]. 2020 May 31 [cited 2021 Jan 5];:1-2. DOI 10.1007/s00192-020-04292-7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7110290/.

4. Yang Z, Chen X, Huang R, et al. Atypical presentations of coronavirus disease 2019 (COVID-19) from onset to readmission. BMC Infectious Diseases [Internet]. 2021 Jan 29 [cited 2021 Jan 5];(21) DOI 10.1186/s12879-020-05751-8. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05751-8#citeas

5. Vyas N, Kurian J, Bagchi D, Manu M, Saravu K, Unnikrishnan M. Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects. Journal of the American College of Nutrition [Internet]. 2020 Sep 01 [cited 2021 Jan 6]; DOI 10.1080/07315724.2020.1806758. Available from: https://www.tandfonline.com/doi/full/10.1080/07315724.2020.1806758

6. Krishnan A, Hamilton J, Alqahtani S, Woreta T. A narrative review of coronavirus disease 2019 (COVID-19): clinical, epidemiological characteristics, and systemic manifestations. Internal and Emergency Medicine [Internet]. 2021 Jan 16 [cited 2021 Jan 6];(2021) DOI 0.1007/s11739-020-02616-5. Available from: https://link.springer.com/article/10.1007/s11739-020-02616-5#citeas

REFERENCES

7. Zhang W, Hou W, Jin W, Liang L, Xu B, Hu Z. Clinical characteristics and outcomes in elderly with coronavirus disease 2019 in Beijing, China: a retrospective cohort study. Internal and Emergency Medicine [Internet]. 2020 Oct 10 [cited 2021 Jan 8]; DOI 10.1007/s11739-020-02517-7. Available from: https://link.springer.com/article/10.1007/s11739-020-02517-7

8. Jawahri E, Bohossian A, Paasche-Orlow M, et al. Clinical Outcomes of Patients Hospitalized with Coronavirus Disease 2019 (COVID-19) in Boston. Journal of General Internal Medicine [Internet]. 2021 Feb 24 [cited 2021 Jan 8];(2021) DOI 10.1007/s11606-021-06622-x. Available from: https://link.springer.com/article/10.1007/s11606-021-06622-x#citeas

9. Omrani A, Almaslamani M, Daghfal J, et al. The First Consecutive 5000 Patients with COVID-19 in Qatar; a Nation-wide Cohort Study. BMC Infectious Diseases [Internet]. 2020 Jun 16 [cited 2021 Jan 8]; DOI 10.1186/s12879-020-05511-8. Available from: https://www.medrxiv.org/content/10.1101/2020.07.15.20154690v2.article-info

10. Gharebaghi N, Nejadrahim R, Mousavi S, Sadat-Ebrahimi S, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infectious Diseases [Internet]. 2020 Oct 21 [cited 2021 Jan 9];(10) DOI 10.1186/s12879-020-05507-4. Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05507-4#citeas

11. Lin H, Cho S, Aravamudan V, et al. Remdesivir in Coronavirus Disease 2019 (COVID-19) treatment: a review of evidence. Nature Public Health Emergency Collection [Internet]. 2021 Jan 02 [cited 2021 Jan 6]; DOI 10.1007/s15010-020-01557-7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7778417/.

12. Moradi S, Masoumi M, Mohammadi, S, et al. Prevalence of coronavirus disease 2019 in rheumatic patients and evaluation of the effect of disease-modifying anti-rheumatic drugs. Intern Emerg Med [Internet]. 2020 Oct 31 [cited 2021 Jan 7]; DOI 10.1007/s11739-020-02535-5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7599976/.

13. Ferreira D, Santos D, Vieira M, et al. Manejo nutricional para pacientes hospitalizados com COVID-19: Uma revisão integrativa. Revista Saúde Coletiva [Internet]. 2020 Sep 12 [cited 2021 Jan 13];(10):4140-4151. DOI https://doi.org/10.36489/saudecoletiva.2020v10i59p4140-4151. Available from: http://www.revistas.mpmcomunicacao.com.br/index.php/saudecoletiva/article/view/1056

14. Galvão T, Pereira M. Revisões sistemáticas da literatura: passos para sua elaboração. Epidemiol. Serv. Saúde [Internet]. 2014 Mar 03 [cited 2021 Jan 14];23 DOI 10.5123/S1679-49742014000100018. Available from: http://scielo.iec.gov.br/scielo.php?script=sci_arttext&pid=S1679-49742014000100018

15. Moher D, Liberati A, Tetzlaff L, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Epidemiol. Serv. Saúde [Internet]. 2015 Jun 01 [cited 2021 Jan 15];24 DOI 10.5123/S1679-49742015000200017. Available from: http://scielo.iec.gov.br/scielo.php?script=sci_arttext&pid=S1679-49742015000200017

16. Lau F, Majumder R, Torabi R, et al. Vitamin D insufficiency is prevalent in severe COVID-19. Medrxiv [Internet]. 2020 Apr 08 [cited 2021 Jan 13]; DOI 10.1101/2020.04.24.20075838. Available from: https://www.medrxiv.org/content/10.1101/2020.04.24.20075838v1

17. Hastie C, Mackay D, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr [Internet]. 2020 May 07 [cited 2021 Jan 21];14:561-565. DOI 10.1016/j.dsx.2020.04.050. Available from: https://pubmed.ncbi.nlm.nih.gov/32413819/.

18. Murai I, Fernandes A, Sales L, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19 A Randomized Clinical Trial. JAMA [Internet]. 2021 Feb 17 [cited 2021 Jan 11]; DOI 10.1001/jama.2020.26848. Available from: https://jamanetwork.com/journals/jama/fullarticle/2776738

19. Meltzer D, Best T, Zhang H, et al. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. JAMA Netw Open [Internet]. 2020 Sep 03 [cited 2021 Jan 13];3 DOI 10.1001/jamanetworkopen.2020.19722. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770157

20. Radujkovic A, Hippchen T, Tiwari-Heckler S, et al. Vitamin D Deficiency and Outcome of COVID-19 Patients. Nutrients [Internet]. 2020 Sep 10 [cited 2021 Jan 15];12 DOI 10.3390/nu12092757. Available from: https://pubmed.ncbi.nlm.nih.gov/32927735/.

21. Castillo M, Costa L, Barrios J, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. J Steroid Biochem Mol Biol [Internet]. 2020 Aug 29 [cited 2021 Jan 22]; DOI 10.1016/j.jsbmb.2020.105751. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456194/.

22. Ilie P, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res [Internet]. 2020 Jul 01 [cited 2021 Jan 27];32 DOI 10.1007/s40520-020-01570-8. Available from: https://pubmed.ncbi.nlm.nih.gov/32377965/.

23. Li X, Xu S, Yu M, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. Journal of Allergy and Clinical Immunology [Internet]. 2020 Apr 12 [cited 2021 Jan 29];46:110-118. DOI 10.1016/j.jaci.2020.04.006. Available from: https://www.sciencedirect.com/science/article/pii/S0091674920304954

24. Ohaegbulam K, Swalih M, Patel P, et al. Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. Am J Ther [Internet]. 2020 Aug 13 [cited 2021 Jan 30]; DOI 10.1097/MJT.0000000000001222. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7473790/.