Evaluation of the usefulness of vitamin D as a predictor of mortality in patients with COVID-19

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Abstract

Introduction: *One of the functions of vitamin D is to regulate respiratory epithelium inflammatory response; therefore, deficiency of this vitamin in the context of COVID-19 could constitute a predictive biomarker of the disease outcome.* **Objective:** *To evaluate the usefulness of vitamin D for predicting mortality in patients with COVID-19.* **Methods:** *Observational, retrospective study in which 154 patients diagnosed with COVID-19 were included, out of whom 111 survived and 43 died. Vitamin D concentration was determined in all of them.* **Results:** *A log-rank p-value < 0.032 was obtained for survival when vitamin D concentration was used as a categorical variable ($\leq$ 20 ng/mL and > 20 ng/mL). On Cox proportional analysis, age and vitamin D concentration were shown to be risk factors associated with mortality in patients with COVID-19 (age: HR = 1.036, 95% CI = 1.016-1.058, p < 0.001; vitamin D: HR ($\leq$ 20 ng/mL and > 20 ng/mL) = 0.478, 95% CI = 0.237-0.966, p < 0.040).* **Conclusion:** *Age and vitamin D concentration were predictive factors for mortality in COVID-19-infected patients.*

KEYWORDS: *Vitamin D. COVID-19. Respiratory epithelium inflammatory response. Predictive factor.*

Evaluación de la utilidad de la vitamina D como predictor de mortalidad en pacientes con COVID-19

Resumen

Introducción: *Una de las funciones de la vitamina D es regular la respuesta inflamatoria del epitelio respiratorio; por ello, la deficiencia de esa vitamina en el contexto de COVID-19 podría constituir un biomarcador preditivo del desenlace de COVID-19.* **Objetivo:** *Evaluar la utilidad de la vitamina D para predecir la mortalidad en pacientes con COVID-19.* **Métodos:** *Estudio observacional y retrospectivo en el que se incluyeron 154 pacientes con diagnóstico de COVID-19, de los cuales 111 sobrevivieron y 43 fallecieron. En todos se determinó la concentración de vitamina D.* **Resultados:** *Se obtuvo un valor log-rank de p < 0.032 para la supervivencia al utilizar la concentración de vitamina D como variable categórica ($\leq$ 20 ng/mL y > 20 ng/mL). Mediante análisis proporcional de Cox se encontró que la edad y concentración de vitamina D mostraron ser factores de riesgo asociados a la mortalidad en pacientes con COVID-19 (edad: HR = 1.036, IC 95 % = 1.016-1.058, p < 0.001; vitamina D: HR $\leq$ 20 ng/mL y > 20 ng/mL = 0.478, IC 95 % = 0.237-0.966, p < 0.040).* **Conclusión:** *La edad y la concentración de vitamina D constituyeron factores predictivos de mortalidad en pacientes infectados por COVID-19.*

PALABRAS CLAVE: *Vitamina D. COVID-19. Respuesta inflamatoria del epitelio respiratorio. Factor predictivo.*

Introduction

Currently, COVID-19 is known to be highly contagious, in addition to being potentially lethal. People older than 60 years of age, and particularly those with comorbidities such as diabetes, hypertension, cardiovascular diseases, cancer and obesity are at higher risk of severity of this disease.[1]

Interestingly, the regions that have been most affected by COVID-19 share similar climatic conditions, and prevalence of the disease could be related to low levels of vitamin D in the populations. Hospitalization rate has also shown a strong correlation with the countries' latitude.[2]

The relevance of vitamin D deficiency or supplementation in this disease has been controversial. Some studies claim that vitamin D supplementation could be a protective factor,[3,4] but others do not recommend its use.[5] On one hand, vitamin D is known to stimulate innate immune response and to modulate acquired immunity, in addition to playing an important role in the outcome of respiratory infections.[6] Vitamin D is also known to be able to attenuate hyper-inflammatory response, reduce the production of pro-inflammatory cytokines and accelerate the repair process of affected epithelia, mainly lung tissue.[7]

On the other hand, vitamin D deficiency has been associated with an increase in thrombotic episodes in patients with COVID-19.[8] Furthermore, a recent study demonstrated that mortality from COVID-19 is higher in patients with vitamin D concentrations lower than 12 ng/mL.[9] However, in another investigation, controlled supplementation of this vitamin in patients with COVID-19 showed no differences in mortality or hospitalization days.[10]

Vitamin D deficiency is also common in dark-skinned people and with few hours of exposure to sunlight. These factors have been studied and associated with a higher risk of COVID-19 severity.[2,11] It should be noted that vitamin D deficiency is more common in institutionalized people, such as prison inmates and older adults confined in geriatric centers.[12]

Gender has also been shown to play an important role in COVID-19 outcome; some studies have proposed that there is higher lethality of the disease in men vs. women.[13] In addition, vitamin D deficiency has shown a significant interaction with age.[14,15] The above variables might predispose to death.[15]

There are several biomarkers for predicting COVID-19 severity, such as C-reactive protein, creatinine, certain comorbidities, etc.;[16] however, vitamin D has not been studied or proposed on any scale as a possible predictive biomarker of mortality in patients with COVID-19. It could constitute a predictor of other causal risk factors, in addition that its measurement would be useful and easily accessible. However, cut-off values are variable and have to be known and studied in the Mexican population.

Based on the above, the severity of COVID-19 infection and its relationship with vitamin D deficiency could be predisposed by dietary, environmental, social and geographic factors. So far, no specific cutoff point has been studied for evaluating vitamin D deficiency in the Mexican population. In this study, we investigate the potential of vitamin D as a prognostic factor of mortality in Mexican patients with COVID-19.

Methods

This was a retrospective, observational study carried out at the National Institute of Nutrition and Medical Sciences "Salvador Zubirán", in Mexico City, which was approved by the ethics committee of the hospital with registration number DMC-3369-20-20-1-1. The study included 154 consecutive patients with COVID-19, 54 women and 100 men, cared for between December 2020 and February 2021, out of whom 111 survived and 43 died. All patients were confirmed with RT-PCR. Vitamin D levels were quantified in the clinical laboratory of the hospital at hospital admission.

Patient data from disease onset to discharge or death were collected from the medical records.

Survival time was considered from the first day of admission at the emergency department to patient death or discharge.

The number of participants was chosen based on feasibility according to the criteria established by Bacchetti.[17,18] Information on 154 patients was collected. For statistical analysis, the SPSS program, version 25, was used. For the bivariate analysis, Student's t-test and the chi-square test were used; study variables were compared between independent groups (survivors vs. deceased). Kaplan-Meier curves were constructed to analyze survival. Multivariate Cox proportional hazards model was used to determine disease predictive factors. For the latter, a categorical variable was designed in which the cutoff point was established by the Endocrine Society:[19] vitamin D concentration $\leq$ 20 ng/mL and > 20 ng/mL.

Statistical difference was accepted in all analyses with a p-value < 0.05.

Results

One-hundred and fifty-four patients with COVID-19 were included; 43 of them died and 111 survived. In the bivariate analysis, mean age was found to be statistically higher in those who died (61.8 ± 13.30 years), in comparison with survivors (51.44 ± 14.59; p < 0.001). Vitamin D concentration was not shown to be statistically significant in surviving patients (18.60 ± 7.65) vs. those who died (17.27 ± 9.60; p = 0.37). No significant differences were found in gender, body mass index and hospitalization days either (Table 1).

Patients were reclassified in two groups according to vitamin D quantification (≤ 20 ng/mL and > 20 ng/mL), based on the criteria established by the Endocrine Society and studies carried out in the Mexican population.[19,20] Kaplan-Meier survival curves showed that patients with vitamin D concentration ≤ 20 ng/mL had a higher probability of death vs. those with a higher concentration (log-rank test, p < 0.032), as it can be observed in figure 1.

Multivariate survival analysis with Cox regression models showed the influence of vitamin D on the outcome of patients with COVID-19. Age (p < 0.001) and vitamin D as a categorical variable (p < 0.040) were factors associated with mortality (age: hazard ratio [HR] = 1.036, 95% confidence interval [CI] = 1.016-1.058, p < 0.000; vitamin D: HR = 0.478, 95% CI = 0.237-0.966, p < 0.04) (Table 2).

Discussion

Given that the cutoff points for vitamin D deficiency and insufficiency in Mexico have been established based on studies conducted in patients with bone and mineral metabolism disorders,[20] using the cutoff point determined by the Endocrine Society was decided in this work.[19] In Mexico, vitamin D deficiency in blood is considered when it is below 30 ng/mL, and insufficiency, when it is below 20 ng/mL.[20]

Our results are consistent with those of previous studies in which age and vitamin D lower concentrations were associated with a higher risk of COVID-19-associated mortality.[9,21,22]

In a study of patients hospitalized for COVID-19, vitamin D insufficiency < 30 ng/mL was present in 75% of the population and in 85% of all patients who required intensive care.[23]

Table 1. Variables studied in patients with COVID-19, who were grouped according to disease outcome

Variable	Deceased	Survivors	p*	χ^2/Z
	Mean ± SD	Mean ± SD		
Age	61.8 ± 13.30	51.44 ± 14.59	0.000	
Body mass index	28.99 ± 6.48	29.81 ± 5.21	NS	
Hospitalization days	18.55 ± 11.90	19.54 ± 17.04	NS	
Vitamin D concentration (ng/mL)	17.27 ± 9.60	18.60 ± 7.65	NS	
	n	%	n	%		
Gender Females Males	16 27	10.38 17.53	38 73	24.67 47.40		NS NS

*Student's t-test, chi-square test or Fisher's exact test.
SD = standard deviation, NS = non-significant.

Table 2. Multivariate survival analysis to determine vitamin D influence on COVID-19 patients outcome

Model	Variable	B	Sig.	Exp (B)	Exp (B) 95% CI	
					Lower	Upper
1	Gender	−0.093	0.765	0.907	0.47	1.724
	Age	0.033	0.002	1.033	1.012	1.055
2	Gender	−0.379	0.265	0.685	0.352	1.332
	Age	0.036	0.001	1.036	1.016	1.058
	Vitamin D	−0.738	0.040	0.478	0.237	0.966

Cox multivariate models.

D'Avolio et al. evaluated vitamin D concentration in 107 volunteers; they found that vitamin D mean concentration was 22.2 ng/mL in subjects without COVID-19, while the mean in 27 individuals with PCR-confirmed SARS-CoV-2 infection was 11.1 ng/mL.[24] It should be noted that, in both groups (deceased subjects vs. survivors) of the research herein presented, vitamin D mean concentration was within values of insufficiency; however, concentrations ≤ 20 ng/mL were associated with higher mortality in patients with COVID-19, which has also been observed in similar studies, where levels < 30 ng/mL and age ≥ 65 years were found to be associated with higher COVID-19 mortality.[25,26]

Some investigations have shown that vitamin D levels do not determine COVID-19 outcome and that vitamin D is not a prognostic factor for mortality.[27] The
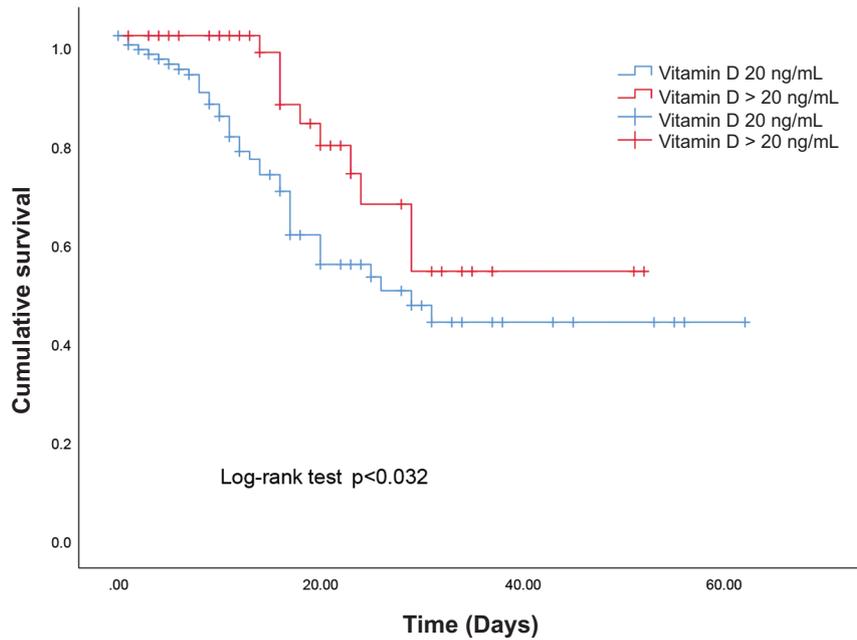
Figure 1. *Kaplan-Meier survival analysis according to vitamin D levels. Vitamin D deficiency was associated with survival reduction (log-rank test, p = 0.032).*

variables included in the different mathematical models, the cutoff points used or the measures before or after supplementation can determine the differences in the results.[10]

In the Cox proportional models adjusted for age, gender and vitamin D, our results showed that age and vitamin D were statistically significant factors for COVID-19 mortality. In model 2, age and vitamin D showed a higher statistically significant association than in model 1, in which vitamin D was not considered. In neither model was an association with gender identified (Table 2).

Peruzzu et al. did not find significant differences in vitamin D between genders either, which suggests that the presence of biological or hormonal factors, particularly estrogens and testosterone, could underlie these differences.[28]

It is possible that vitamin D concentration in this work constituted a risk factor for disease severity. It would be tempting to hypothesize that vitamin D and estrogen affect gender differences in COVID-19 patients outcomes.[29] It is important adding that age and vitamin D concentrations point at a potential effect on COVID-19 patients outcome. Both surviving and deceased patients showed vitamin D insufficiency, which could suggest various research questions associated

with diet, metabolism, and even geographic factors (latitude).[30,31]

Lanham et al. analyzed COVID-19 severity associated with vitamin D levels in a European population. They concluded that, in countries with high vitamin D deficiency, it was associated with high rates of infection and death.[32]

In a recent study in Mexico, in which variables such as temperature, humidity and ultraviolet radiation were evaluated, as well as their association with the incidence of transmission and death from COVID-19, ultraviolet radiation was shown to have a physiological effect that impacts on the reduction of COVID-19 mortality, which was explained by vitamin D deficiency.[33]

It is also possible that some metabolic pathways, or immune or social factors are relevant and determinant in the SARS-CoV-2 infection process and consequent mortality.[34] However, if well-controlled clinical studies with vitamin D supplementation failed to show statistical differences in COVID-19 outcome, then vitamin D concentration could be, at least, a good predictor of severity that no validated predictive model for this disease includes so far.

Conclusion

In this study, age and vitamin D concentration were shown to be possible predictive factors of mortality in

COVID-19 patients, and thus could be considered as independent factors for the risk of mortality from this disease. However, complementary studies are required to evaluate the interaction of other variables associated with vitamin D regulation.

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Conflict of interests

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this research.

Confidentiality of data. The authors declare that they followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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