

Interacción entre la edad y el déficit de vitamina D en la COVID-19 grave

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ABSTRACT

Background: coronavirus disease 2019 (COVID-19) can induce an exaggerated inflammatory response. Vitamin D is a key modulator of the immune system. We hypothesized that vitamin D deficiency (VDD) could increase the risk of developing severe COVID-19 infection.

Methods: patients with confirmed COVID-19 seen at the emergency department of our hospital with recent measurements of 25(OH)D were recruited. We explored the association of vitamin D deficiency (VDD), defined as 25-hydroxyvitamin D < 20 ng/mL, with a composite of adverse clinical outcomes.

Results: we included 80 patients, of which 31 (39 %) presented the endpoint. VDD tended to predict an increased risk of developing severe COVID-19 after adjusting for age, gender, obesity, cardiac disease, and kidney disease [OR 3.2 (95 % CI: 0.9-11.4), $p = 0.07$]. Age had a negative interaction with the effect of VDD on the composite outcome ($p = 0.03$), indicating that the effect was more noticeable at younger ages. Furthermore, male gender was associated with VDD and with severe COVID-19 at younger ages.

Conclusions: in this retrospective study, vitamin D deficiency showed a signal of association with severe COVID-19 infection. A

significant interaction with age was noted, suggesting VDD may have a greater impact in younger patients. These findings should be confirmed in larger, prospective, adequately powered studies.

Keywords: Coronavirus disease 2019. Severe acute respiratory syndrome. Vitamin D deficiency. Angiotensin converting enzyme 2.

RESUMEN

Antecedentes: la enfermedad por coronavirus 2019 (COVID-19) puede inducir una respuesta inflamatoria exagerada. La vitamina D es un modulador clave del sistema inmune. Planteamos que la deficiencia de vitamina D (VDD) podría aumentar el riesgo de desarrollar infección grave por COVID-19.

Métodos: se reclutaron pacientes consecutivos que acudieron al servicio de urgencias de nuestro centro con diagnóstico de COVID-19 confirmado (PCR-COVID-19 positiva) y mediciones recientes de 25(OH)D. Exploramos la asociación de la deficiencia de vitamina D (VDD), definida como una 25-hidroxivitamina D < 20 ng/ml, con un compuesto de resultados clínicos adversos.

Resultados: se incluyeron 80 pacientes, de los cuales 31 (39 %) presentaron el criterio de valoración primario. El VDD tendió a predecir un mayor riesgo de desarrollar COVID-19 grave después de ajustar edad, sexo, obesidad, enfermedad cardíaca y enfermedad renal [OR: 3,2 (IC 95 %: 0,9-11,4), $p = 0,07$]. La edad tuvo una interacción negativa con el efecto de la VDD en el resultado compuesto ($p = 0,03$), lo que indica que el efecto fue más notable a edades más tempranas. Además, el género masculino se asoció con la VDD y con la COVID-19 grave en las edades más jóvenes.

Conclusiones: en este estudio retrospectivo, la deficiencia de vitamina D mostró una tendencia de asociación con la infección grave por COVID-19. Se observó una interacción significativa con la edad, lo que sugiere que la VDD puede tener un mayor impacto en los

pacientes más jóvenes. Estos hallazgos deben confirmarse en estudios más grandes, prospectivos y con potencia adecuada.

Palabras clave: COVID-19. Síndrome de distrés respiratorio grave. Déficit de vitamina D. Enzima convertidora de angiotensina 2.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19) pandemic poses a major challenge for the scientific community. Given its novelty, and our dearth of knowledge regarding its characteristics, the identification of prognostic factors that could mediate disease severity/lethality is a priority. Vitamin D plays a key role in host response against infections, including the boosting of antimicrobial actions and modulation of the inflammatory response (1). The latter is mediated through several pathways directly involving the immune system, but also by regulation of the renin-angiotensin system and of angiotensin-converting enzyme 2 (ACE2) (2,3).

Vitamin D deficiency (VDD) is highly prevalent worldwide (4). Southern Europe and Spain are known to have a high prevalence of VDD, particularly during winter months, coincidentally with respiratory virus outbreaks (5,6). VDD increases the risk of respiratory tract infections and the development of SARS (1,7). In fact, some patients with COVID-19 develop an inflammatory response that can lead to SARS (8). The aim of this study was to explore the association between VDD and the development of severe COVID-19.

METHODS

A retrospective study was performed on a cohort of consecutive patients attending the emergency department of a tertiary hospital in Madrid, Spain. Inclusion criteria were: 1) a positive reverse-transcriptase polymerase chain reaction for SARS-CoV-2, and 2) an available measurement of serum 25-hydroxyvitamin D (25(OH)D)

(chemiluminescent immunoassay, Abbott Diagnostics) at admission or within the 3 previous months. Electronic medical records were reviewed to retrieve blood tests and clinical information, which was then entered in a dedicated database. VDD was considered as a $[25(\text{OH})\text{D}] < 20 \text{ ng/mL}$ (50 nmol/L). The main composite outcome defining severity of COVID-19 included death, admission to the intensive care unit, and/or need for higher oxygen flow than that provided by a nasal cannula. Follow-up was completed at discharge or upon death. A univariate analysis was performed with the t-test or rank-sum test for continuous variables, and chi-squared test or Fisher's exact test for categorical ones. The primary association was measured with multivariable logistic regression. Results were initially adjusted for obesity [body mass index (BMI) $\geq 30 \text{ kg/m}^2$], cardiac disease and age, since these are associated simultaneously with worse outcomes in COVID-19 and VDD (4,9), as well as for inter-group imbalanced variables such as gender and advanced chronic kidney disease (CKD). Age group (defined by percentile 50)-specific analyses were conducted owing to a significant interaction between VDD and age. All analyses were performed using the Stata 13 software (StataCorp LP, College Station, TX, USA).

RESULTS

Of the 1,011 patients attending our emergency department between March 5th and March 31st who tested positive for SARS-CoV-2, 91 (9 %) had available 25(OH)D levels. Of these, 80 had completed their clinical follow-up at the time of the statistical analysis. Demographics are presented in table I. A total of 31 patients (39 %) presented the adverse composite outcome. These patients were older, more often male, and showed a non-significant trend towards higher advanced CKD. There were no differences in the prevalence of VDD or in the median levels of 25(OH)D between patients with and without the composite outcome, nor were there in the proportion of patients

taking vitamin D supplements (numerically higher in those with the composite outcome).

Patients with VDD (n = 45, 56 %) tended to be admitted to hospital more often (84 % vs. 66 %, p = 0.051) and had a higher incidence of bacterial co-infection (33 % vs. 11 %, p = 0.022), but the difference in composite outcome was not significant overall (44 % vs. 31 %, p = 0.236). Nevertheless, after adjusting for age, gender, obesity, and severe CKD, the OR for VDD was 3.2 (95 % CI: 0.9-11.4), p = 0.070. In this multivariate model, age over 75 years (3rd tertile) and male gender were significantly associated with the composite outcome [OR 10.4 (95 % CI: 2.0-54.8) vs. the first tertile, p = 0.006; OR 6.2 (95 % CI: 2.0-19.5), p = 0.002, respectively].

The association of VDD with the composite outcome was significantly modified by patient age ($p_{\text{interaction}} = 0.03$). Figure 1 depicts the plotting of age, gender, and [25(OH)D] against the composite outcome. Lack of statistical power prevented from conducting adjusted subgroup analyses; however, the characteristics of patients below the median age (percentile 50: 67 years) can be seen in table I. Of note, patients with adverse outcomes were more often male (80 % vs. 20 %, p = 0.001) and had more frequently VDD (100 % vs. 43 %, p = 0.002). Patients with VDD below 67 years of age (n = 23, 57 % of this age subgroup) were more often male (48 % vs. 18 %, p = 0.048) and had more often adverse events such as the composite outcome (43 % vs. 6 %, p = 0.008), hospital admission (74 % vs. 29 %, p = 0.005) and bacterial co-infection (35 % vs. 0 %, p = 0.013). These worse outcomes were accompanied by greater alterations in biomarkers: lower median nadir lymphocyte count (0.7 vs 1.5 x 10⁶/mL) and higher peaks of D-dimer (1,359 vs. 596 ng/mL), C-reactive protein (13 vs. 2 mg/dL), and lactate dehydrogenase (669 vs. 410 U/L), with all p values < 0.01. On the other hand, patients over 67 years with VDD did not show significant differences in any adverse event.

DISCUSSION

In this retrospective series of patients with confirmed COVID-19, vitamin D deficiency showed a statistically borderline association with severe illness. Furthermore, we found a significant interaction with age, indicating that vitamin D deficiency was more clearly associated with negative outcomes in younger patients. Male gender was associated with vitamin D deficiency and with adverse outcomes in this younger subset of patients. All these findings merit further research in larger-scale, prospective cohorts.

Patients with severe COVID-19 develop an exaggerated inflammatory response that ultimately jeopardizes their own integrity (8). Vitamin D promotes movement and phagocytic ability in macrophages, and induces the synthesis of bactericidal chemicals such as cathelicidin and beta-defensin (1). But vitamin D also modulates inflammatory response by reducing the expression of pro-inflammatory cytokines through the induction of macrophage M2 differentiation and promotion of T-helper type 2 and T-reg cells (1,2,10). Furthermore, vitamin D has been shown to regulate the renin-angiotensin system and ACE2 expression in animal models (11). ACE2 is the host receptor for SARS-CoV-2, and is downregulated by it (12). Dysregulation of the renin-angiotensin system increases lung permeability and may lead to the development of severe acute respiratory syndrome (3,13). Moreover, observational clinical data indicate that VDD confers a greater risk of respiratory infections, and supplementation with this vitamin reduces this risk (1). Taken together, all these data provide a rationale to consider vitamin D as an important factor implicated in the pathophysiology of SARS in COVID-19. D'Avolio et al. recently found that patients with a positive COVID-19 test had lower 25(OH)D levels than those with a negative test (14). Also interesting, an ecological study has shown a significant inverse correlation between published levels of vitamin D and COVID-19 mortality per country (15).

We have found that male gender and age are independently associated with worse outcomes of patients with COVID-19, which is

not novel but consistent with current knowledge of the disease (8,16). The impact of male gender in outcomes is not fully understood, but it has been suggested that sex hormones may influence the expression and/or function of angiotensin-converting enzyme 2, and this could be enhanced in the setting of VDD (17). On the other hand, the potential interaction of age with VDD is an interesting finding that merits further investigation. Waldhoer et al. found a similar interaction of age in the association between VDD and mortality during the follow-up of a cohort of 78,581 patients (18). The effects of aging and its associated increased comorbidity translate into a complex interplay of causative mechanisms of morbidity and mortality in the older subset of patients with COVID-19 that is difficult to interpret. In addition, aging entails a dysfunction of normal immune responses and a profound dysregulation of inflammatory pathways (19). All this may explain why we could not find an association of VDD with adverse outcomes in the elderly whereas we did find it in the younger patients.

Our study findings are limited by a reduced sample size, but to date represent the only data available regarding this important topic. In our country, vitamin D is routinely measured in the elderly and in patients with comorbidities, renal disease, and obesity (20). This has obviously led to patient selection in our sample. Also, as a consequence of the retrospective nature of the study, the effect of vitamin D supplements in our population is uncertain. Despite the fact that no significant differences were noted between groups, the measurements of 25(OH)D could have potentially led to a prescription of supplements before the patient contracted COVID-19, which may add a degree of confusion to the primary association. Larger, all-comer, prospective studies are required to elucidate the impact of vitamin D deficiency in COVID-19 outcomes.

CONCLUSIONS

In this retrospective study, vitamin D deficiency showed a signal of association with severe COVID-19 infection. This association was significantly modified by age, indicating that vitamin D deficiency may have a greater impact in the younger subset of patients. Moreover, male gender was associated with VDD and with adverse outcomes in the younger patients. These findings should be confirmed in larger, prospective, adequately powered studies.

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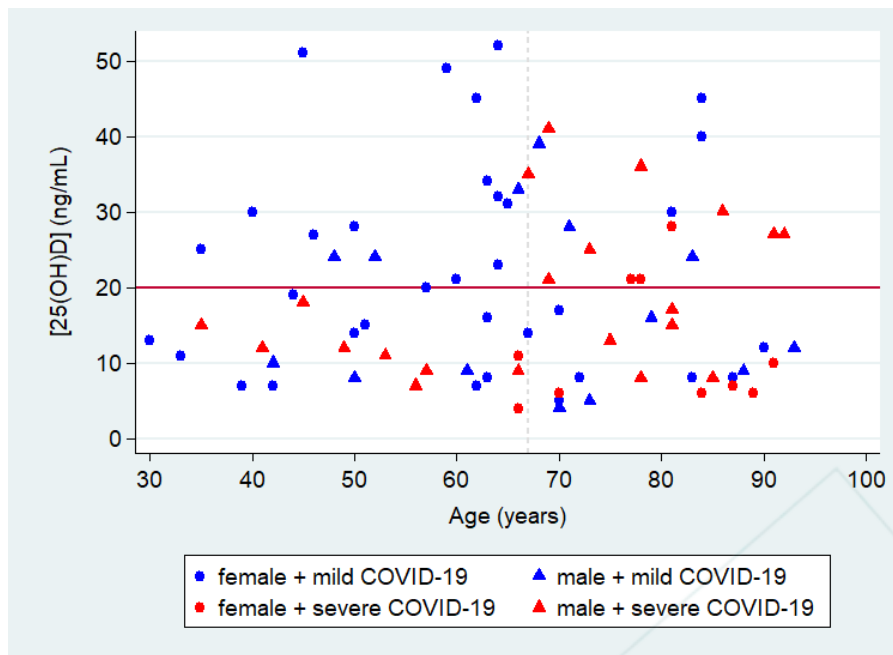


Fig. 1. Scatterplot of age, gender, and levels of 25(OH)D (25-hydroxyvitamin D) against the composite outcome. Triangles represent male patients and circles female patients. The horizontal maroon thick line defines the threshold for vitamin D deficiency (20 ng/dL). The vertical grey dashed line is the median age for this population (67 years).

Table I. Patient characteristics and outcomes according to the composite endpoint

	All (n = 80)			Under 67 years (n = 40)		
	non-severe COVID-19 (n = 49)	severe COVID-19* (n = 31)	<i>p</i>	non-severe COVID-19 (n = 30)	severe COVID-19* (n = 10)	<i>p</i>
Baseline characteristics						
Age	63 (50-72)	75 (66-84)	0.014	51.5 (44-63)	54.5 (45-66)	0.662
Male gender	14 (29 %)	21 (68 %)	0.001	6 (20 %)	8 (80 %)	0.001
Smoking history	6 (12 %)	7 (23 %)	0.222	4 (13 %)	1 (10 %)	1.000
Hypertension	20 (57 %)	30 (67 %)	0.383	9 (30 %)	5 (50 %)	0.278
Diabetes mellitus	20 (41 %)	12 (39 %)	0.851	8 (27 %)	2 (20 %)	1.000
Cardiac disease	11 (22 %)	8 (26 %)	0.731	2 (7 %)	1 (10 %)	1.000
Advanced chronic kidney disease (CKD-EPI < 30 mL/min/m ²)	12 (24 %)	14 (45 %)	0.054	5 (17 %)	5 (50 %)	0.085
Chronic respiratory disease	8 (16 %)	5 (16 %)	0.981	1 (3 %)	0	1.000
Obesity (BMI ≥ 30 kg/m ²)	13 (27 %)	10 (32 %)	0.581	6 (20 %)	4 (40 %)	0.232
BMI (kg/m ²)	27.0 (24.5-30.8)	26.9 (24.3-32.1)	0.983	26.8 (24.1-29.5)	32.2 (23.3-34.0)	0.465
Vitamin D supplements	24 (49 %)	20 (65 %)	0.174	15 (50 %)	6 (60 %)	0.721
[25(OH)D] (ng/mL)	19 (9-30)	13 (8-25)	0.145	22 (11-31)	11 (9-12)	0.009
Vitamin D deficiency ([25(OH)D] < 20 ng/mL)	25 (51 %)	20 (65 %)	0.236	13 (43 %)	10 (100 %)	0.002

*Defined by the composite endpoint: death, ICU admission or requirement of high flow oxygen (greater than nasal cannula). BMI: body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration equation.