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ORIGINAL ARTICLE

Very Low Vitamin D Levels are a Strong Independent Predictor of Mortality in Hospitalized Patients with Severe COVID-19

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Background. There is controversy regarding the association between hypovitaminosis D and COVID-19 outcomes.

Aim of the study. We assessed the association between 25-hydroxyvitamin D levels and COVID-19 outcomes in hospitalized subjects with severe SARS-CoV-2 infection.

Methods. Retrospective cohort study. Serum 25-hydroxyvitamin D levels of subjects with severe COVID-19 pneumonia were measured at hospital admission, between March 17th, 2020, and March 1st, 2021.

Results. Out of 2,908 patients, 571 (19.6%) had vitamin D deficiency (defined as a serum 25-hydroxyvitamin D level <12.5 ng/mL [<31.25 nmol/L]), and 1069 (36.7%) had levels between 12.5 ng/mL (31.25 nmol/L) and 20 ng/mL 850 nmol/L). Compared to subjects without vitamin D deficiency, those with 25-hydroxyvitamin D level <12.5 ng/mL had higher rates of in-hospital mortality at 30 d (28.0 vs. 17.3%; p <0.001), global mortality (31.9 vs. 20.8%; p <0.001), mechanical ventilation requirement (23.8 vs. 17.2%; p <0.001), and significantly longer hospital stay (median [interquartile range] of 9 [6–17 d] vs. 7 [5–12 d], p <0.001). In the unadjusted analysis, the risk of in-hospital death was greater for patients with vitamin D deficiency (HR 1.43; 95% CI, 1.20–1.70; p <0.001). After adjusting for confounders, the risk of in-hospital death within 30 d remained significantly greater in patients with vitamin D deficiency (HR 1.46; 95% CI, 1.21–1.76; p <0.001). The risk was reduced but remained significant with 25-hydroxyvitamin D levels between 12.5 ng/mL and 20 ng/mL (HR 1.31; 95% CI 1.10–1.55, p = 0.02). In comparison with other clinical biomarkers, vitamin D deficiency was an independent predictive marker of in-hospital mortality after adjusting for confounders.

Conclusion. Very low 25-hydroxyvitamin D levels measured at hospital admission were significantly associated with in-hospital mortality and are a useful prognostic biomarker in severe COVID-19 patients.

Key Words: SARS-CoV-2, COVID-19, Vitamin D, 25-hydroxyvitamin D, Mortality, Length of hospital stay.

Introduction

Low levels of 25-hydroxyvitamin D (vitamin D) have been suggested to be a risk factor for COVID-19 infection and the severity of the disease caused by SARS-CoV-2 virus (1–3). Vitamin D deficiency is a potential modifiable risk

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factor for worse outcomes in patients with acute respiratory infections, including viral infections (4). Vitamin D has crucial regulatory roles in the immune response to viral infections established by its anti-inflammatory, antioxidant, and antiviral effects (5), and thus could be employed as an adjuvant treatment to improve COVID-19 outcomes.

Nevertheless, there is controversy regarding the association between hypovitaminosis D and risk of COVID-19 infection and mortality; particularly, since a large part of the evidence is derived from observational cohort studies with mixed results (2,6) and underpowered clinical trials (7,8). Many health professionals have not only recommended to avoid supplementation of vitamin D, but also are against measuring 25-hydroxyvitamin D at hospital admission of COVID-19 patients (9,10).

Recent observational studies have concluded that hypovitaminosis D is not associated with adverse outcomes in hospitalized COVID-19 patients (11,12); however, most of these studies lack sufficient statistical power since the sample size was relatively small (6,12–14) or were carried out in subjects with a low mortality risk (15). Few other observational studies have assessed 25-hydroxyvitamin D many weeks or years before hospitalization and not on the admission day (12,15). In a few studies the principal outcome was observed in surrogate endpoints such as D-dimer levels, or C-reactive protein (CRP), yet the association between hypovitaminosis D and clinically important outcomes such as mortality or requirement of respiratory support is commonly inconclusive (2,16,17).

To our knowledge, there are no published cohort studies with a sufficient sample size to allow adjustment of different confounding variables, including exposure to treatments. In this sense, we report the association between 25-hydroxyvitamin D levels and COVID-19 outcome in a large cohort of 2,908 hospitalized, severe patients attending a COVID-19 reference center in Mexico.

Methods

This study included COVID-19 patients who required supplemental oxygen, consecutively hospitalized at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (March 17th, 2020–March 1st, 2021), a third-level healthcare center in Mexico City designated to treat COVID-19 patients. COVID-19 was confirmed in all patients by RT-qPCR test from nasopharyngeal swabs and/or computerized tomography. All patients had severe COVID-19 as defined by the National Institute of Health criteria of a SpO_2 of less than 94%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of (PaO_2/FiO_2) <300 mmHg, respiratory frequency of >30 breaths/min, or lung infiltrates >50% (18). Patients underwent a chest computerized tomography (CT), and a radiologist determined the degree of pulmonary parenchymal disease. We excluded patients who remained hospitalized after April 1st, 2021, because the follow-up period of 90 d was incomplete at the moment of the analysis. For readmitted patients the analysis only included the data of the first hospitalization to avoid duplication of patients. Other subjects excluded were those who requested voluntary discharge or were transferred to another institution where full clinical data was not available.

Blood samples were obtained at the time of initial evaluation. Serum 25-hydroxyvitamin D levels were measured at hospital admission in all subjects by chemiluminescence assay using the Abbott Architect I2000 equipment (Santa Clara, USA). Deficiency of vitamin D was defined as a very low level of <12.5 ng/mL (<31.25 nmol/L, to convert to nmol/L, multiply by 2.496). The 12.5 ng/mL cut-off baseline was selected according to the National Health and Nutrition Examination Survey (NHANES) criteria (19), and considering is the threshold concentration upon which participants in clinical trials have experienced the most consistent benefits of vitamin D supplementation (20). We also performed an exploratory analysis to investigate COVID-19 outcomes in subgroups defined by a 20 ng/mL and 30 ng/mL cut-off level of vitamin D at hospital admission, since many experts consider that less than 30 ng/mL may also be independently associated with an increased risk of adverse outcomes(21).

The primary outcome was in-hospital mortality within 30 d. Secondary outcomes included global mortality (mortality during all follow-up, from 0–102 d, including in-hospital mortality within 30 d), requirement for mechanical ventilation, and length of hospital stay (LOS). For time-to-event analyses, we estimated the time from hospital admission until last follow-up (censoring) or death, whichever occurred first. Clinical variables and laboratory measurements were obtained from electronic files. Charlson Comorbidity Index, an index which predicts 10 year survival in patients with multiple comorbidities, was calculated (22). The study was approved by the local Human Research and Ethics Boards (reference NMM-3646).

Endpoints (in-hospital mortality, global mortality, and requirement of mechanical ventilation) and differences in LOS were compared between subjects with and without vitamin D deficiency using Pearson's χ^2 test and the U Mann-Whitney test respectively. Kaplan-Meier analysis was conducted to compare survival rates using log-rank test. Univariate and multivariate Cox regression analyses were constructed to assess the unadjusted and multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). In model 1, age (per 10 year increment), sex, obesity (≥35 kg/m^2), diabetes, community acute kidney injury, medical treatments (including dexamethasone), hypertension, and presence of one or more comorbidities (cardiovascular or cerebrovascular disease, lung diseases, cancer, chronic kidney disease, solid organ or hematopoietic

stem cell transplantation, smoking) were used as covariates for adjustment. Model 2 was adjusted for covariates in model 1 plus other laboratory measurements performed at hospital admission (CRP, D-dimer, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), high-sensitive cardiac troponin I (Hs-cTnI), serum creatinine, PaO_2 at room air, PaO_2/FiO_2 ratio, and others). Analyses were carried out using SPSS 24.0 (IBM, Armonk, New York, USA) and GraphPad Prism 8.4.3 (GraphPad Software, San Diego, USA). A 2-sided significance threshold was set at $p < 0.05$.

Results

From March 17th, 2020–March 1st, 2021, a total of 3,581 patients with COVID-19 symptoms were evaluated at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Of these, 2,908 patients fulfilled inclusion criteria and were included in the study. We excluded 673 subjects for several reasons: 29 (4.3%) remained hospitalized after April 1st, 2021, 32 (4.7%) requested voluntary discharge, 18 (2.6%) were readmitted following discharge, and 594 (88.2%) were transferred to another institution. All subjects included had COVID-19 associated pneumonia requiring oxygen supplementation. The median (interquartile range [IQR]) age was 57 (46–67 years), 1,750 (60.2%) were men, 895 (30.8%) had diabetes, 1,141 (39.2%) had obesity, and the median time between symptom onset and hospitalization was 8 (5–11 d). In all patients, including subjects with and without vitamin D deficiency, in-hospital mortality within 30 d was 21.4% ($n = 624$) and global mortality was 22.9% ($n = 667$). Invasive mechanical ventilation was required in 29.2% ($n = 848$) cases, and the median LOS was 7 (IQR 5–14, range 4–102) d.

At the moment of hospital admission, 19.6% ($n = 571$) of the patients had vitamin D deficiency (<12.5 mg/dL [<31.25 nmol/L]) and 36.0% ($n = 1069$) had levels between 12.5 ng/mL (31.25 nmol/L) and 20 ng/mL (50 nmol/L).

In comparison with patients without vitamin D deficiency, patients with vitamin D deficiency were older, had a higher proportion of previous diagnosis of hypertension, diabetes, and chronic kidney disease, their duration from symptom onset to hospital admission was lower, and the proportion of males and previously healthy subjects were lower (Table 1). Laboratory abnormalities were more common in subjects with vitamin D deficiency such as higher concentrations of D-dimer, LDH, CPK, or Hs-cTnI, as well as lower levels of calcium, hemoglobin, and total lymphocyte count. All patients had high levels of inflammatory biomarkers such as CRP (median 14.1 mg/dL [IQR 7.1–21.3]), ferritin (median 520 mg/dL [IQR 112–520]), and fibrinogen (median 640 mg/dL [IQR 472–770]). Ferritin and fibrinogen levels at admission were marginally higher in subjects with vitamin D deficiency compared to subjects without deficiency, (464 mg/dL [IQR 215–846] vs. 541 mg/dL [IQR 273–976] and 604 mg/dL [IQR 442–760] vs. 645 mg/dL [481–774], respectively). As it is shown in Table 1, other parameters showed significant differences between the groups due to the large sample size, but of little clinical significance.

Vitamin D deficient subjects had higher rates of in-hospital mortality within 30 d (28.0 vs. 17.3%; P <0.001, Figure 1), global mortality (31.9 vs. 20.8%, $p < 0.001$), requirement of mechanical ventilation (23.8 vs. 17.2%; $p < 0.001$), pulmonary involvement higher than 50% (62 vs. 58%, $p < 0.001$), and longer LOS (9 [6–17 d] vs. 7 [5–12 d], $p < 0.001$, Figure 2). Dexamethasone treatment was prescribed more frequently in vitamin D deficient subjects (57 vs. 50%, $p < 0.001$). Likewise, such patients also had higher rates of in-hospital mortality within 30 d (29.3 vs. 19.1%, $p < 0.001$), and global mortality (31.1 vs. 20.9%, $p < 0.001$), compared to those who received dexamethasone but had 25-hydroxyvitamin D levels ≥12.5 ng/mL (≥31.25 nmol/L).

In the unadjusted analysis, the risk of in-hospital death was greater for those subjects with vitamin D deficiency (HR, 1.43; 95% CI, 1.20–1.70; $p < 0.001$). After adjusting for confounders, two Cox proportional hazard models were plotted (model 1 depicted in Figure 1 and model 2 in Figure 2). In model 1, the time to in-hospital death within 30 d was defined as the time variable and the following as independent variables: age per 10 year increment, sex, body mass index ≥35 kg/m^2, diabetes, acute kidney injury, and dexamethasone treatment after admission. Body mass index between 30 kg/m^2 and 35 kg/m^2, and previous diagnosis of high blood pressure had a HR of 1.20 (95% CI, 1.01–1.25) and 1.31 (95% CI, 1.01–1.51) respectively. However, the P value for interaction between age and both variables was <0.01. In the multivariate model, diagnosis of high blood pressure and body mass index between 30 and 35 kg/m^2 were not associated to the dependent variable and were excluded in the final model. The risk of in-hospital death within 30 d remained significantly greater among patients with vitamin D deficiency (HR, 1.46; 95% CI, 1.21–1.76; $p < 0.001$, Figure 3). The risk was reduced in patients with vitamin D levels between 12.5 ng/mL (31.25 nmol/L) and 20 ng/mL 850 nmol/L) (HR, 1.31; 95% CI 1.10–1.55, $p = 0.02$). There were no differences in the LOS, in-hospital mortality within 30 d, or requirement of mechanical ventilation in patients with levels between 20 ng/mL (50 nmol/L) and 30 ng/mL (75 nmol/L) and those with more than 30 ng/mL (Supplementary Figure 1). In model 2, the independent variables were age per 10 years increment, sex, and laboratory parameters assessed now of hospital admission. In comparison with other clinical biomarkers, vitamin D deficiency was an independent predictive marker of in-hospital mortality

Table 1. Study Population Baseline Characteristics.

Parameter	25-hydroxyvitamin D ≤12.5 ng/mL (≤31.25 nmol/L), *n* = 571	25-hydroxyvitamin D >12.5 ng/mL (>31.25 nmol/L), *n* = 2337	*p*
Age, years	60 (48–70)	56 (46–66)	<0.001
Female sex, *n* (%)	313, 55%	845, 36%	<0.001
BMI, mg/kg^2	28.1 (24.4–32.9)	28.1 (25.8–32.2)	0.039
Obesity, *n* (%)	225, 40%	916, 40%	1.00
Current smoker, *n* (%)	87, 15%	417, 18%	0.32
HTN, *n* (%)	248, 44%	768, 33%	<0.001
DM, *n* (%)	238, 42%	657, 28%	<0.001
CKD, *n* (%)	61, 11%	110, 5%	<0.001
None comorbidities, *n* (%)	75, 13%	563, 24%	<0.001
Charlson Comorbidity Index, points	1 (1–3)	1 (0–2)	<0.001
Time since symptom onset, days	7 (4–11)	8 (6–11)	0.002
Respiratory rate at admission, rpm	28 (24–32)	28 (23–32)	0.41
Systolic Blood Pressure, mmHg	123 (110–142)	126 (112–139)	0.29
Diastolic Blood Pressure, mmHg	72 (62–82)	75 (69–83)	<0.001
PaO_2 at room air, mmHg	68.8(55.6–88.4)	68.9(56.8–85.4)	0.74
Arterial pH	7.45 (7.40–7.48)	7.46 (7.42–7.48)	<0.001
Hemoglobin, g/dL	14.5 (12.3–15.9)	15.2 (13.9–16.4)	<0.001
Total lymphocytes, cells/mcL	69 (47–108)	76 (52–107)	0.005
Serum glucose, mg/dL	132 (106–206)	127 (107–180)	0.055
Serum creatinine, mg/dL	0.9 (0.8–1.6)	1.0 (0.7–1.2)	0.041
Calcium, mg/dL	8.4 (8.0–8.8)	8.6 (8.3–9.0)	<0.001
Phosphate, mg/dL	3.3 (2.7–4.1)	3.2 (2.8–4.1)	0.074
C-reactive protein, mg/dL	14.3 (6.7–21.4)	14.1 (7.1–21.3)	0.689
C-reactive protein >15 mg/dL, *n* (%)	262, 47%	1039, 45%	0.51
Ferritin, mg/dL	464 (215–846)	541 (273–976)	<0.001
D-Dimer, ng/mL	1104 (644–2270)	821 (506–1391)	<0.001
D-Dimer >500 ng/mL	469, 85%	1737, 76%	<0.001
Fibrinogen, mg/dL	604 (442–760)	645 (481–774)	<0.001
AST, U/L	35 (24–53)	37 (26–57)	0.019
ALT, U/L	27 (16–41)	33 (21–51)	<0.001
LDH, U/L	352 (243–468)	332 (259–453)	0.03
LDH >271 U/L, *n* (%)	375, 67%	1426, 61%	<0.001
Albumin, g/dL	3.4 (3.0–3.8)	3.7 (3.4–4.0)	<0.001
CPK, U/L	88 (43–189)	87 (50–184)	0.12
CPK >223 U/L, *n* (%)	111, 20%	476, 21%	0.72
Hs-cTnI, pg/mL	10.0 (4.5–37.7)	6 (3.6–24.5)	<0.001
Hs-cTnI >15 pg/mL, *n* (%)	222, 39%	558, 24%	<0.001
Lung involvement >50%, *n* (%)	339, 62%	1336, 58%	<0.001
ARB use, *n* (%)	140, 25%	408, 17%	<0.001
ACEi use, *n* (%)	58, 10%	194, 8%	0.16
Vitamin D treatment after covid diagnosis, *n* (%)	12, 2.1%	35, 1.5%	0.35

Quantitative data are presented as median (interquartile range). ARB: antagonist II receptors blockers, ACEi: angiotensin-converting enzyme inhibitors, BMI: Body Mass Index, HTN: hypertension, CVD: cardiovascular disease, CKD: chronic kidney disease, CPK: creatine phosphokinase, Hs-cTnI: high-sensitive cardiac troponin I, LDH: lactate dehydrogenase, DM: diabetes mellitus. Obesity was defined as a BMI ≥30 kg/m^2.

after adjusting for confounders (HR, 1.43; 95% CI 1.29–1.45, p <0.001, Figure 4).

Discussion

This large cohort study appraises the importance of 25-hydroxyvitamin D level measurement upon hospital admission in a Mexican cohort of patients with severe SARS-CoV-2 infection. Two main results emerged. First, baseline vitamin D levels <12.5 ng/mL (<31.25 nmol/L) had a strong independent association with mortality and morbidity, including longer LOS and requirement of mechanical ventilation. Second, very low levels of vitamin D were a strong biomarker of worse prognosis compared to other laboratory parameters evaluated now of hospital admission. To the best of our knowledge, this is the largest cohort of severely COVID-19 infected patients with sufficient power to detect a mortality difference adjusted for multiple confounders related to vitamin D status assessed at the time of hospitalization.

Previous reports in similar populations, including one in our center (23), have shown a higher mortality risk as-

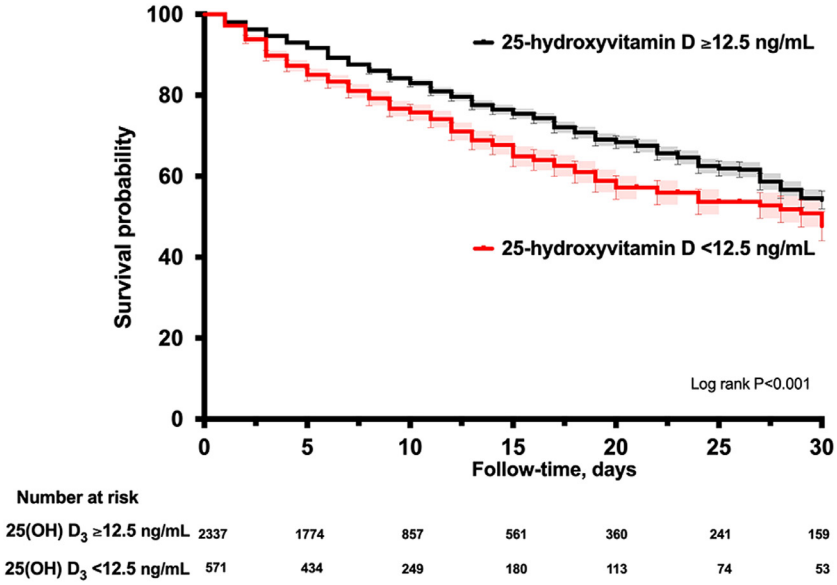

Figure 1. Kaplan-Meier Curves for in-hospital mortality during a 30 d period among subjects with COVID-19 and 25-hydroxyvitamin D deficiency vs. patients without deficiency.

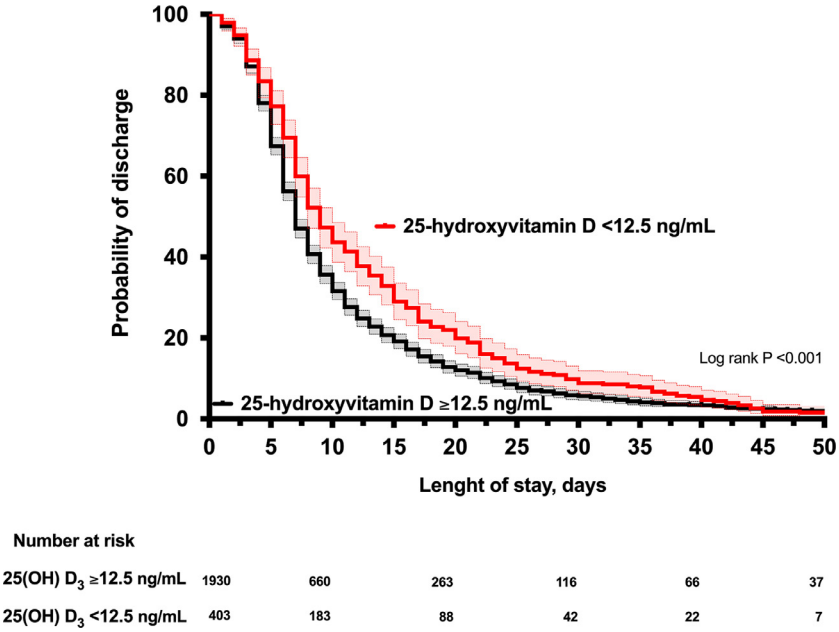

Figure 2. Kaplan-Meier Curves for total length of stay until discharge among subjects with COVID-19 and 25-hydroxyvitamin D deficiency vs. patients without deficiency.

sociated to vitamin D deficiency (16,17,24). Nevertheless, recent publications did not find an association between vitamin D levels and mortality or other important outcomes. For example, Al-Jarallah M, et al. found that overall mortality was not significantly associated to vitamin D levels in 231 hospitalized subjects with severe COVID-19 (13), and Bianconi V, et al. reported that vitamin D levels were not prospectively associated to the composite endpoint of intensive care unit admission/in-hospital death in 200 patients (14). In both studies, we believe that the sample size was relatively small, affecting the adjustment for multiple confounders. In another recent publication, Güven M, et al. found that 25-hydroxyvitamin D levels were not associated to in-hospital mortality after adjustment for confounders in 520 patients. However, vitamin D levels were measured one month before the PCR test for COVID-19 (12). In a similar way, an analysis conducted using UK biobank data found no association between mortality and vitamin D levels obtained around a decade prior to COVID-19 diagnosis (15). The knowledge about

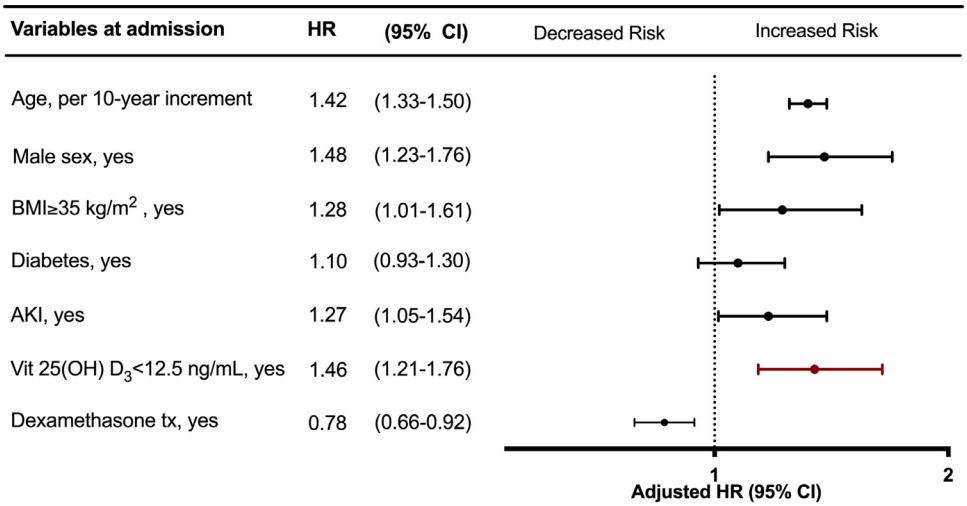

Figure 3. Forest plot demonstrating the hazard ratios and 95% confidence interval (CI) for in-hospital mortality during a 30 d period after multivariate logistic regression for clinical data in the cohort.

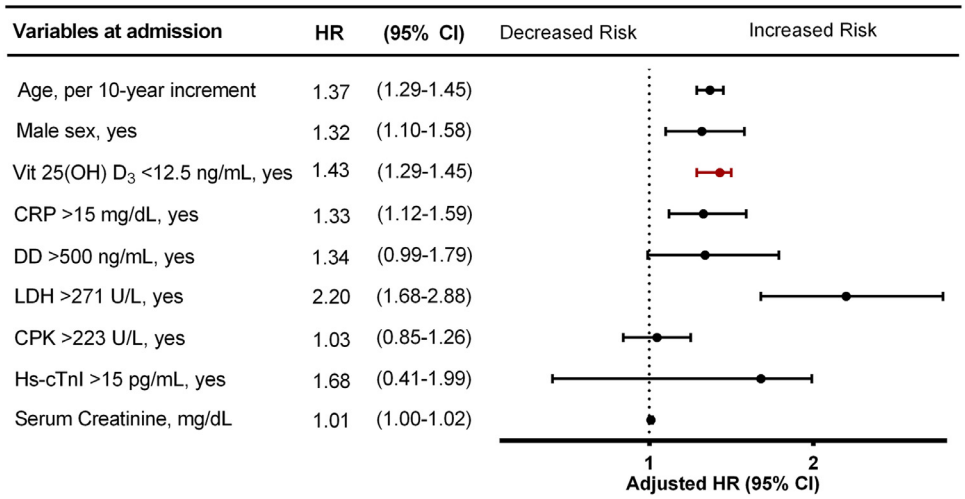

Figure 4. Forest plot demonstrating the hazard ratios and 95% confidence interval (CI) for in-hospital mortality during a 30 d period after multivariate logistic regression for laboratory measurements performed at the moment of hospital admission in the cohort.

the time interval between vitamin D levels and COVID-19 diagnosis is critical to understand the discrepancies among clinical studies. Our data strongly supports that very low levels of vitamin D are associated to worse prognosis in patients with severe COVID-19 only if the status of vitamin D is assessed now of hospital admission.

Vitamin D measurement could be a powerful prognostic biomarker in COVID-19 subjects, even in the presence of multiple confounders, including exposure to effective treatments. In our center, dexamethasone treatment was not commonly prescribed until the first days of July 2020, when the preliminary results of The Recovery trial were released (25). After dexamethasone introduction, mortality was reduced 22% (95% CI 8–34%). Nevertheless, in patients who received dexamethasone, mortality and other adverse outcomes remained significantly associated to 25-hydroxyvitamin D levels <12.5 ng/mL (<31.25 nmol/L). The subjects included in this study had an exacerbated inflammatory response represented by high concentrations of ferritin, CRP, or Dimer-D, but the association strength of these biomarkers with mortality was minor when multiple confounders were adjusted. Only LDH and vitamin D had an independent association with in-hospital mortality compared to other acute phase reactants.

The complex interplay between vitamin D and the immune response to viral infections impedes any conclusion about vitamin D deficiency as a causal factor of mortality in COVID-19. Although very low levels vitamin D could decrease ACE-2 expression, increase vascular permeability, and magnify acute lung injury (26), reverse causation could be an alternative hypothesis which could explain our results.

It is possible that severe SARS-CoV-2 infection could decrease vitamin D concentrations in early phases. In the traditional dogma, 25-hydroxyvitamin D production was considered stable given the constant expression of hepatic 25-hydroxylases, yet recent studies have challenged this concept (21). New evidence suggests that non-traditional factors decrease vitamin D production such as aging, body fat percentage, or ethnicity (27). We hypothesize that COVID-19 patients with severe inflammation might have an early decrease in serum vitamin D levels due to down-regulation of CYP2R1, one of the six cytochromes that catalyzes hydroxylation at C-25 of both forms of vitamin D (vitamin D2 and D3) (28), similar to the metabolic signals induced by fasting, diabetes, or glucocorticoids (29,30).

Other plausible mechanism of this "reverse causation" hypothesis includes a decrease in vitamin D binding protein (DBP) levels, the major transport protein of vitamin D. It has been shown that DBP binds to actin and other protein complexes released by lung inflammation; subsequently, the decrease of DBP induces a decrease in total levels of vitamin D (31).

At the time of writing, there are very limited data of clinical trials. A randomized clinical trial published by Murai IH, et al. (7) found that a single high dose of vitamin D3, compared with a placebo, did not reduce hospital length of stay in 240 hospitalized patients with moderate to severe COVID-19. As the authors point out, the trial had a relatively low number of patients with 25-hydroxyvitamin D levels <20 ng/mL (<31.25 nmol/L) ($n = 108$) and was unable to identify differences in rates of in-hospital mortality. The trial joins other small observational studies with a high risk of bias (11). We believe that a randomized clinical trial in COVID-19 patients with vitamin D levels <12.5 ng/mL (31.25 nmol/L) would be the best approach to determine whether vitamin D supplementation improves the prognosis of COVID-19 or if hypovitaminosis D is an epiphenomenon due to severe inflammation. Unfortunately, there are no ongoing clinical trials in COVID-19 in which the design includes patients with a cut-off level of <12.5 ng/mL (31.25 nmol/L) (32).

The present observational study has limitations. In our analysis, we adjusted for many confounders, including age, sex, obesity, diabetes, acute kidney injury, hypertension, baseline vital signs, and inflammatory markers of the severity of COVID-19. Despite this extensive adjustment, it is still possible that some amount of unmeasured confounding variables remains. Another limitation is that a chemiluminescence immunoassay was employed to measure vitamin D levels, which may lead to inconsistent results compared to other techniques, including competitive binding protein, radioimmunoassay, or liquid chromatography mass spectrometry. This could be an important issue, especially when values of vitamin D are between 20 ng/mL (50 nmol/L) and 40 ng/mL (100 nmol/L). However, in our study we selected a cut-off value of 12.5 ng/mL (a very low level) which is associated with less variation (33). The trajectory of vitamin D concentrations before hospitalization and during the disease course were not available. This data could be important to test the hypothesis that inflammation may drive an inverse acute phase response in vitamin D levels. Treatment data of many experimental drugs were not included in the analyses, as most patients were included in randomized blinded clinical trials. Finally, the single-center design may limit the generalizability of these findings.

In conclusion, this analysis, which constitutes a large patient cohort, confirms that in hospitalized COVID-19 patients a serum vitamin D concentration lower than 12.5 ng/mL (31.25 nmol/L) is significantly associated with in-hospital mortality and other adverse outcomes. This suggests that the measurement of vitamin D concentrations now of hospital admission may be a useful prognostic biomarker. Clinical trials exploring whether reversing vitamin D deficiency improves survival need to be carried out.

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Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2021.09.006.

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