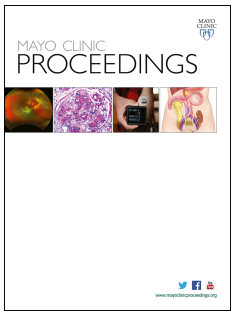


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# Vitamin D Status is Associated With In-hospital Mortality and Mechanical Ventilation: A Cohort of COVID-19 Hospitalized Patients

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**Abbreviations:**

25(OH)D=25-hydroxyvitamin D; ACEi=angiotensin-converting enzyme inhibitor; BMI=body mass index; CKD=chronic kidney disease; COPD=chronic obstructive pulmonary disease; COVID-19=Coronavirus disease 2019; ESRD=end-stage renal disease; IQR=interquartile range; PCR=polymerase chain-reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

**Abstract**

**Objective**

To explore the possible associations of serum 25-hydroxyvitamin D concentration [25(OH)D] with COVID-19 in-hospital mortality and need for invasive mechanical ventilation.

**Patients and Methods**

A retrospective, observational, cohort study was conducted at two tertiary academic medical centers in Boston and New York. Eligible participants were hospitalized adult patients with laboratory-confirmed COVID-19 between 1 February 2020 and 15 May 2020. Demographic, clinical characteristics, comorbidities, medications, and disease-related outcomes were extracted from electronic medical records.

**Results**

The final analysis included 144 patients with confirmed COVID-19 (median age: 66 years, 44.4% male). Overall mortality was 18%, while patients with 25(OH)D levels ≥30 ng/mL had lower rates of mortality compared to those with 25(OH)D levels <30 ng/mL (9.2% vs. 25.3%, *P*=.02). In the adjusted multivariable analyses, 25(OH)D as a continuous variable was independently significantly associated with lower in-hospital mortality (OR, 0.94; 95% CI, 0.90-0.98; *P*=.007) and need for invasive mechanical ventilation (OR, 0.96; 95% CI, 0.93-0.99; *P*=.01). Similar data were obtained when 25(OH)D was studied as a continuous variable after logarithm transformation and as a dichotomous (<30ng/mL vs. ≥30ng/mL) or ordinal variable (quintiles), in the multivariable analyses.

**Conclusion**

Among patients admitted with laboratory-confirmed COVID-19, 25(OH)D levels were inversely associated with in-hospital mortality and the need for invasive mechanical ventilation. Further

observational studies are needed to confirm these findings and randomized clinical trials to assess the role of vitamin D administration in improving the morbidity and mortality of COVID-19.

## Introduction

The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health threat with nearly 27 million confirmed cases and roughly 900,000 deaths as of September 7, 2020.[1] Recently, the relationship between vitamin D status and COVID-19 has been widely discussed.[2] Vitamin D is a potent immunomodulator of the innate and adaptive immune systems with anti-inflammatory properties and has previously been associated with an increased risk of acute respiratory tract infections[3] and worse clinical outcomes in critically ill patients.[4, 5] Moreover, vitamin D deficiency is common and many of the risk factors for severe COVID-19 are associated with low levels of serum 25-hydroxyvitamin D [25(OH)D], including older age, obesity, cardiovascular disease, and chronic kidney disease.[6]

However, whether vitamin D deficiency increases the risk of SARS-CoV-2 infection or more severe clinical outcomes from COVID-19 is not known. Cross-sectional reports have suggested a higher incidence of mortality from COVID-19 in countries at higher latitudes[7] and with lower mean population levels of 25(OH)D.[8] One early small observational study found an inverse association between serum 25(OH)D levels and COVID-19 infection but did not adjust for other predictors or potential confounders.[9] In contrast, two relatively large retrospective case-control studies of UK BioBank participants found no association between vitamin D status and incidence of SARS-CoV-2 infection;[10, 11] however, these studies were limited by analysis of samples that had been collected at least ten years prior to diagnosis. More recently, a retrospective observational study including 489 patients demonstrated an association between likely vitamin D deficiency and increased risk of COVID-19 infection.[12]

Our primary objective with this analysis was to investigate whether vitamin D status is independently associated with worse in-hospital outcomes in patients admitted to two large tertiary academic medical centers with laboratory-confirmed COVID-19.

## Patients and Methods

*Study design and patient population*

This retrospective, observational, two-center cohort study included adult patients from two tertiary academic medical centers (Beth Israel Deaconess Medical Center in Boston, Massachusetts, Montefiore Medical Center in the Bronx, New York). All patients admitted to the hospital that were positive for SARS-CoV-2 on qualitative polymerase chain-reaction (PCR) assays from February 1, 2020, to May 15, 2020, and for whom the necessary information was available, were included in the study. We excluded patients that were discharged home directly from the emergency department. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines (https://www.equator-network.org/reporting-guidelines/strobe/). The study was approved by the institutional review boards at Beth Israel Deaconess Medical Center (#2020P000472) and Albert Einstein College of Medicine (#2020-11296).

*Data Collection*

Clinical data were extracted from the electronic medical record independently by three researchers at each institution and stored in a pre-defined data extraction sheet which was created for the purpose of this study. The extracted data were cross-validated and included: baseline demographic information, clinical characteristics, pertinent home medications, symptomatology

since disease onset and on presentation, vital signs on presentation, laboratory data on the first hospital day.

Among the clinical characteristics we examined the presence of hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), asthma, obstructive sleep apnea, active malignancy, chronic kidney disease (CKD) or end-stage renal disease (ESRD), liver cirrhosis, and human immunodeficiency virus infection or acquired immunodeficiency syndrome. The diagnosis of all the aforementioned disorders and diseases was based on the findings after conducting a manual chart review of all records for the patients included in the study. Additionally, hemoglobin A1c, triglycerides, total cholesterol, low-density and high-density lipoprotein cholesterol (if available within 12 months prior to admission); 25(OH)D concentration during admission or within 6 months prior to the initiation of the study (if not obtained during the hospitalization); mortality and need for invasive mechanical ventilation (i.e. endotracheal intubation). Note, we did not assess the association between 25(OH)D and need for continuous positive airway pressure, bilevel positive airway pressure, or high-flow nasal cannula. 25(OH)D was measured at ~~both~~ the on-site laboratory of each institution~~s~~ using fully automated electrochemiluminescence assays with appropriate controls run by hospital personnel at regular intervals.[13] The vitamin D assay used at each institution (ARCHITECT 25-OH Vitamin D at Montefiore and Elecsys Vitamin D Total II at Beth Israel Deaconess Medical Center) was certified by the Vitamin D Standardization-Certification Program, which requires meeting the performance criterion of +/- 5% mean bias compared to a reference standard and an overall imprecision of < 10%.[14] The data were processed and analyzed without any personal identifiers to maintain patient confidentiality as per Health Insurance Portability and Accountability Act.

*Outcomes*

The primary outcome of the study was in-hospital mortality. The secondary outcome was need for invasive mechanical ventilation.

*Statistical Analysis*

Patients were classified in five quintiles based on age (≤ 50, 51-62, 63-68, 69-76, and ≥77) and body mass index (BMI) (≤24.26, 24.27-27.71, 27.72-31.00, 31.01-34.50, and ≥34.51). Moreover, patients were grouped in two categories regarding 25(OH)D levels, namely <30 ng/mL and ≥30 ng/mL, based on the mean value of the variable and on observational and interventional studies that have demonstrated a lower incidence of acute respiratory infection and mortality risk in individuals with 25(OH)D levels ≥30 ng/Ml.[6] For descriptive statistics, the continuous variables are presented as median with interquartile range (IQR) and categorical variables as absolute numbers and percentage. All data were assessed for the normality assumption by using a Shapiro-Wilk test. Differences between the two groups based on 25(OH)D levels were compared with the Mann-Whitney test or independent-samples t-test for the continuous variables and Chi-square test (with Yates' Continuity Correction, or Fisher's Exact test) for the categorical data.

Logistic regression models were used to identify potential associations between baseline characteristics and in-hospital mortality and need for invasive mechanical ventilation. We explored the potential associations of vitamin D status with the primary and secondary endpoints by including 25(OH)D as a continuous, logarithmic, categorical (<30 ng/mL and ≥ 30 ng/mL), and ordinal variable (based on quintiles: ≤ 15.80, 15.81-23.20, 23.21-31.00, 31.01-45.00, ≥45.01). We used logarithmic transformation (base 10) for 25(OH)D levels to approximate a normal distribution.

Multivariable logistic regression models were as follows: model(1) consisted of 25(OH)D levels, age (quintiles), and BMI (quintiles); model(2) included multivariable analysis model(1) adjusted for the hospital of origin; model(3) included multivariable analysis model(2) with the addition of sex (male), and smoking as regressors; model(4) included multivariable analysis model(~~1~~3) with the addition of angiotensin II receptor blocker (ARB), or angiotensin-converting-enzyme inhibitor (ACEi), in-hospital drug treatment, and C-reactive protein (CRP), which were considered as important regressors; model(5) included multivariable analysis model(3) with the addition of significant univariable clinical characteristics: ESRD, COPD, active malignancy, heart failure, coronary artery disease, diabetes, hypertension, CRP, and corticosteroids. Models 2 to 5 were adjusted for the hospital of origin including a cross comparison on 25(OH)D measurement between the two centers by including a binary variable based on the hospital of origin. Data are presented as odds ratio (OR) and 95% confidence interval (95% CI). Model calibration was assessed using the Hosmer-Lemeshow goodness of fit test. A $P > 0.05$ indicates a well-calibrated model. A two tailed $P$ value of <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences software, version 26.0 (IBM, Armonk, NY, US).

## Results

Baseline demographic and clinical characteristics are summarized in Table 1. The total number of patients hospitalized across the two centers with COVID-19 was 825. The necessary information was available for 144 patients. Of note, for approximately half of the patients (71 individuals), 25(OH)D levels were measured during their hospitalization.

Therefore, the study population consisted of 144 patients with PCR-confirmed COVID-19 (males: 44.4%; median age: 66 years, IQR: 55–74). Approximately 42% of the patients were non-Hispanic Black, 29% non-Hispanic White, and 23% Hispanic/Latino. The mean 25(OH)D levels were 30.44 ng/mL (SD: 17.03) and the median 28.0 ng/mL (IQR:16.8–39). Approximately 74% of the patients had hypertension, 55% hyperlipidemia, and 43.8% diabetes mellitus type 2 while 14% and 13% of the patients had a history of coronary artery disease or cerebrovascular disease, respectively. Asthma, COPD and obstructive sleep apnea were prevalent in 18.1%, 15.3%, and 12.5% of patients, respectively.

The main presenting symptoms and signs, and laboratory findings are summarized in Supplementary Table 1. Cough, shortness of breath, fever, and malaise were the most prevalent symptoms (61.1%, 60.4%, 59.7%, and 54.9%, respectively). The majority of the patients (63.9%) had increased oxygen requirements, 27.1% required invasive mechanical ventilation, and close to 39% of the patients were transferred to the ICU. Moreover, 47.2% of the patients experienced acute kidney injury and 11.1% required renal replacement therapy. Overall, in-hospital mortality of the cohort was 18%. Patients with 25(OH)D levels ≥30 ng/mL had lower rates of mortality compared to those with <30 ng/mL (9.2% vs. 25.3%, $P$=.02).

*Logistic regression analyses for the primary and secondary outcomes*

For both primary and secondary outcomes, 25(OH)D was assessed as a continuous, logarithmic (base 10, to approximate a normal distribution), dichotomous (<30 ng/mL and ≥ 30 ng/mL) and ordinal variable (based on quintiles: ≤ 15.80, 15.81-23.20, 23.21-31.00, 31.01-45.00, ≥45.01) (Tables 2 and 3, respectively). Potential effect modification by timing of 25(OH)D measurements (prior or during hospitalization) was tested and no significant interaction was detected. Moreover, the timing of 25(OH)D measurement was examined as a potential covariate.

However, no significant association between the timing of 25(OH)D measurement with mortality and the need for invasive mechanical ventilation was observed in the univariable and multivariable analyses (data not shown herein).

In the current study, each model's calibration power was good, according to the Hosmer-Lemeshow test ($P > 0.05$).

*Primary Outcome: In-hospital mortality*

Univariable analyses were performed for all the available variables to determine which variables were associated with in-hospital mortality. 25(OH)D assessed as either a continuous, logarithmic, dichotomous, or ordinal variable was significantly inversely associated with mortality (OR, 0.96; 95% CI, 0.93-0.996; *P*=.03, OR, 0.12; 95% CI, 0.02-0.77; *P*=.03, OR, 0.30; 95% CI, 0.11-0.80; *P*=.02, OR, 0.72; 95% CI, 0.52-0.98; *P*=.04, respectively). Moreover, ESRD (OR, 2.98; 95% CI, 1.05-8.43; *P*=.04), COPD (OR, 5.52; 95% CI, 2.05-14.86; *P*=.001), active malignancy (OR, 6.41; 95% CI, 2.23-18.43; *P*=.001), and azithromycin (OR, 3.22; 95% CI, 1.21-8.60; *P*=.02) were found to have significant associations.

In the multivariable analysis (model ~~3~~ 5, Table 2), vitamin D status as a continuous variable, (OR, 0.91; 95% CI, 0.85-0.97; *P*=.003), age (OR, 1.81; 95% CI, 1.05-3.13; *P*=.03), COPD (OR, 6.69; 95% CI, 1.10-40.89; *P*=.04), and active malignancy (OR, 16.31; 95% CI, 2.25-118.4; *P*=.01), were found to be significantly associated with in-hospital mortality risk. Likewise, in the multivariable analysis (model 5, Supplementary Table 2), including the logarithmic transformation of 25(OH)D, 25(OH)D (OR, 0.004; 95% CI, 0.00-0.10; *P*=.001), age (OR, 1.98; 95% CI, 1.12-3.51; *P*=.02), COPD (OR, 6.12; 95% CI, 0.99-37.96; *P*=.05), and active malignancy (OR, 18.09; 95% CI, 2.36-138.7; *P*=.01), were also significantly associated with in-hospital mortality risk. Similar results were obtained by including 25(OH)D as a

dichotomous and ordinal variable (Supplementary Table 2). In total, significant and consistent associations were observed between in-hospital mortality risk and 25(OH)D levels (inverse), age (positive), COPD (positive), and active malignancy (positive). Moreover, no significant association of CRP or corticosteroid administration with mortality was observed. Of note, the association of 25(OH)D levels remained significant and robust among the multivariable analyses.

Similar findings were obtained by including 25(OH)D as a dichotomous variable with a threshold of 20 (<20 ng/mL and ≥ 20 ng/mL, data not shown herein). Additional sensitivity analyses excluding the COPD variable resulted in similar findings (data not shown herein). Similar results were obtained when the race variable was added in all multivariable analyses (data not shown herein).

*Secondary Outcome: Need for invasive mechanical ventilation*

25(OH)D as a continuous variable showed a borderline association with the need for invasive mechanical ventilation, while as a logarithmic variable this association was significant (OR, 0.98; 95% CI, 0.96-1.00; *P*=.09, and OR, 0.20; 95% CI, 0.04-0.93; *P*=.04, respectively). Moreover, azithromycin (OR, 3.07; 95% CI, 1.36-6.93; *P*=.007), antibiotic administration other than azithromycin (OR, 5.17; 95% CI, 1.15-23.36; *P*=.03), corticosteroids administration (OR, 4.00; 95% CI, 1.76-9.07; P=.001), CRP levels (OR, 1.01; 95% CI, 1.01-1.02; P<.001) were found to have a significant association with the need for invasive mechanical ventilation.

In the multivariable analyses (model 4), including 25(OH)D as either a continuous (Table 3) or logarithmic variable (Supplementary Table 3), 25(OH)D levels (OR, 0.93; 95% CI, 0.90-0.98; *P*=.002 and OR, 0.01; 95% CI, 0.001-0.17; *P*=.001, respectively), antibiotic administration other than azithromycin (OR, 7.87; 95% CI, 1.12-55.48; *P*=.04 and OR, 8.30; 95% CI, 1.10-62.91; *P*=.04, respectively), corticosteroid administration (OR, 4.05; 95% CI, 1.18-13.91; *P*=.03

and OR, 3.86; 95% CI, 1.13-13.13; *P*=.03, respectively) and CRP levels (OR,1.01; 95% CI, 1.00-1.02; *P*=.01 and OR, 1.01; 95% CI, 1.00-1.02; *P*=.01, respectively) were significantly associated with the need for invasive mechanical ventilation. The inverse association between 25(OH)D levels and risk of invasive mechanical ventilation remained significant even when 25(OH)D was assessed as a dichotomous or ordinal variable in multivariable logistic regression analysis (model 3) (Table 3 and Supplementary Table 3). However, in some of the multivariable models a borderline association was observed between 25(OH)D levels and the need for invasive mechanical ventilation (Table 3 and Supplementary Table 3).

Similar findings were obtained by including 25(OH)D as a dichotomous variable with a threshold of 20 (<20 ng/mL and ≥ 20 ng/mL, data not shown herein). Additional sensitivity analyses excluding the COPD variable resulted in similar findings (data not shown herein). Similar results were obtained when the race variable was added in all multivariable analyses (data not shown herein).



## Discussion

In this retrospective, two-center, cohort study of adults admitted to the hospital with laboratory-confirmed COVID-19, 25(OH)D levels were independently associated with in-hospital mortality and need for invasive mechanical ventilation. Increasing age, COPD, and active malignancy were also independently associated with in-hospital mortality. Moreover, an association was observed between ESRD, CRP and corticosteroid usage with invasive mechanical ventilation. It seems that corticosteroids were more often administered in critically ill patients needing invasive mechanical ventilation, while no causal association can be made based

on our study's design. Our study expands upon a recent observational cohort study that found a substantially higher risk of COVID-19 infection in patients with likely vitamin D deficiency.[12]

Vitamin D deficiency or insufficiency affects an estimated 1 billion people globally and is more prevalent in individuals of lower socioeconomic strata and in Black, Asian, and Hispanic/Latino populations.[6, 15, 16] Additionally, many of the risk factors that are associated with worse clinical outcomes from COVID-19, such as older age, obesity, cardiovascular disease, and chronic kidney disease are associated with lower levels of 25(OH)D.[6] Thus, we performed multivariable logistic regression analyses and found that 25(OH)D was strongly and independently associated with in-hospital mortality. 25(OH)D was also independently associated with need for invasive mechanical ventilation, although the association was less robust. Both associations remained significant after adjustment for several clinical conditions, including ESRD, COPD, congestive heart failure, coronary artery disease, and diabetes, CRP, and administration of corticosteroids.

Vitamin D sufficiency is generally defined as a serum 25(OH)D concentration greater than 20 ng/mL, while insufficiency and deficiency are defined as 25(OH)D concentrations of 12 to 20 ng/mL and less than 12 ng/mL, respectively.[17] Moreover, observational and interventional studies have demonstrated that individuals with 25(OH)D levels <30 ng/mL had a 58% higher risk of acute respiratory infection and a 10-fold increased mortality risk.[6]

Vitamin D deficiency has previously been associated with an increased risk of acute viral respiratory tract infections,[3] acute respiratory distress syndrome (ARDS), prolonged mechanical ventilation, and increased mortality in critically ill patients.[5, 18] While vitamin D status has emerged as a potential risk factor for COVID-19 infection,[9, 12] our study suggests an independent association between vitamin D status and in-hospital mortality. These data support the need for

future studies to validate these findings and randomized controlled trials (RCTs) to causally prove any role of vitamin D in the treatment of patients with COVID-19.

The clinical presentation of COVID-19 ranges from asymptomatic infection to life-threatening multi-organ dysfunction and death. The most severe cases are characterized by a massive pro-inflammatory release of cytokines (i.e., "cytokine storm") which may mediate the diffuse lung inflammation and severe outcomes in some patients with COVID-19.[19] Vitamin D is a steroid hormone that exists in two forms (vitamin D2 and vitamin D3), and exerts its biological effects on various cells and tissues through interaction with the nuclear vitamin D receptor.[20] At higher levels, 25(OH)D may also display physiological effects similar to those of glucocorticoids due to interactions with other steroid hormone receptors.[21] While the mechanisms by which vitamin D may protect against severe presentations of COVID-19 are unclear, vitamin D is known to suppresses T helper type 1 cell potentiated pro-inflammatory cytokines, including interleukin-6, tumor necrosis factor-α, and interferon-β while enhancing the anti-inflammatory responses of T helper type 2 cells and T regulatory cells.[22, 23, 24, 25] In vitro experiments have also elucidated possible immunomodulatory responses against several viral respiratory pathogens, including rhinovirus, respiratory syncytial virus, and influenza.[26] Moreover, vitamin D enhances the activity of the innate immune system by inducing the expression of antimicrobial peptides, such as cathelicidin and defensins,[25, 27, 28, 29, 30] and may have antioxidative effects against COVID-19.[31] Furthermore, evidence supports a potential role of vitamin D in protecting against acute lung injury (ALI) or ARDS in COVID-19 by targeting the unbalanced renin-angiotensin system (RAS), including both the expression and concentration of angiotensin-converting enzymes (ACE and ACE2).[31, 32, 33]

Our study also found that increasing age, COPD, ESRD, and advanced malignancy are strongly associated with in-hospital mortality. These findings are not unexpected given the numerous observational studies and reports with similar findings.[34, 35, 36] In contrast with other observational studies, there was no association between male sex, congestive heart failure, coronary artery disease, obesity, diabetes, or hypertension and in-hospital outcomes in our cohort. We suspect that the relatively small sample size of our population limited our ability to elucidate all associations between underlying comorbidities and more severe outcomes from COVID-19.

Our study was strengthened by its two-center design, which allowed the inclusion of a diverse patient population in both Boston and New York, including primarily Black and Hispanic/Latino patients. This increases generalizability and provides important clinical information regarding outcomes in underrepresented groups. Splitting the sample on separate analysis according to the center of origin revealed similar results.

Our study has limitations. First, our sample size was relatively small; however, it was sufficient to show significant results that were robust in several models tested herein. Since CKD/ESRD may result in less conversion of 25(OH)D to the more active form 1-25(OH)D, we added sensitivity analysis with and without these patients and the results were similar and robust. Second, approximately half of the patients (51%) did not have 25(OH)D measurements available during their hospitalization (instead within 6 months prior to the initiation of the study), which raises the possibility that some of the participants might have received vitamin D supplementation prior to hospitalization that was not recorded in the electronic medical record. Any potential misclassification due to the above is random and could only have suppressed the effect estimates and the corresponding *P* values and would not have led to the statistically

significant results reported herein. Third, seasonal variability may affect 25(OH)D concentration, and the results may be lower in winter months. However, 25(OH)D measurements both on admission and prior to admission were associated with the outcomes of interest, which provides reassurance that reverse causality is not confounding the results reported herein. Moreover, all analyses have been adjusted for center to eliminate potential confounding by any systematic differences between sites. Finally, the ability to draw causal inferences is limited by the retrospective design of our study. In critically ill patients, vitamin D supplementation has been an active area of investigation with mixed results in randomized clinical trials.[37, 38, 39] Given the lack of consistent benefit of vitamin D supplementation in the critically ill in randomized trials, observational trials regarding vitamin D status and COVID-19 outcomes should be interpreted with caution.[37, 39] The association of 25(OH)D status with COVID-19 severity in observational trials may be the result of residual confounding or reverse causality. However, these results can form the basis on which power calculations can be performed to design future prospective observational cohort studies and RCTs to examine the causal hypotheses raised by our study.

Our study has clinical implications. 25(OH)D supplementation has previously been evaluated for the prevention and treatment of acute viral respiratory tract infections and as a potentially beneficial therapy for critically ill patients.[37, 38, 39] A recent meta-analysis showed that supplementation with 25(OH)D reduces the risk of acute respiratory infections by 12% in all participants.[40] While a benefit of vitamin D supplementation in the critically has not been demonstrated, there is biologically plausible evidence to suggest that vitamin D may dampen inflammatory cascades that mediate severe outcomes from COVID-19. Given the rather safe profile and low cost, further investigation of vitamin D supplementation as a preventive and therapeutic strategy for COVID-19 with randomized trials are warranted.

## Conclusion

In conclusion, in this two-center observational cohort study of adults admitted to the hospital with COVID-19, 25(OH)D levels were independently associated with in-hospital mortality and need for invasive mechanical ventilation. Given our findings, larger observational studies to evaluate the relationship between vitamin D status and COVID-19 clinical outcomes are needed. Furthermore, pilot studies and randomized trials evaluating the effects of vitamin D supplementation for the prevention and treatment of COVID-19 are warranted.



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Table 1. Baseline demographic and clinical characteristics

| Characteristic | All patients (N=144) | 25(OH)D <30 ng/mL (N=79) | 25(OH)D ≥30 ng/mL (N=65) | *P* value |
|---|---|---|---|---|
| **Age**, median (IQR), years | 66 (55-74) | 60 (48-72) | 68 (63.5-76.0) | < .001 |
| **Male sex** | 64 (44.4) | 41 (51.9) | 23 (35.4) | .69 |
| **Residence status** | | | | .51 |
| SNF resident | 35 (24.3) | 17 (21.5) | 18 (27.7) | |
| Community-based | 109 (75.7) | 62 (78.5) | 47 (72.3) | |
| **Race/Ethnicity** | | | | .13 |
| Non-Hispanic Black | 60 (41.7) | 30 (38.0) | 30 (46.2) | |
| Non-Hispanic White | 42 (29.2) | 23 (29.1) | 19 (29.2) | |
| Non-Hispanic Asian | 4 (2.8) | 2 (2.5) | 2 (3.1) | |
| Hispanic/Latino | 33 (22.9) | 23 (29.1) | 10 (15.4) | |
| Other/multiracial | 3 (2.1) | 0 (0.0) | 3 (4.6) | |
| Unknown | 2 (1.4) | 1 (1.3) | 1 (1.5) | |
| **BMI**, median (IQR), kg/m$^2$ | 29 (25.2-33.3) | 30 (26.3-34.7) | 28 (24.6-32.3) | .05 |
| **Smoking** | 23 (16.0) | 13 (16.5) | 10 (15.4) | > .99 |
| **Alcohol** | 22 (15.3) | 14 (17.7) | 8 (12.3) | .51 |
| **Coexisting disorder** | | | | |
| Any | 131 (91.0) | 69 (52.7) | 62 (47.3) | .17 |
| Hypertension | 106 (73.6) | 58 (73.4) | 48 (73.8) | > .99 |
| Diabetes | 63 (43.8) | 37 (46.8) | 26 (40.0) | .51 |

| | | | | |
|---|---|---|---|---|
| Hyperlipidemia | 79 (54.9) | 37 (46.8) | 42 (64.6) | .06 |
| Coronary artery disease | 20 (13.9) | 8 (10.1) | 12 (18.5) | .23 |
| Characteristic | All patients (N=144) | 25(OH)D <30 ng/mL (N=79) | 25(OH)D ≥30 ng/mL (N=65) | *P* value |
| Cerebrovascular disease | 19 (13.2) | 10 (12.7) | 9 (13.8) | > .99 |
| Heart failure | 26 (18.1) | 14 (17.7) | 12 (18.5) | > .99 |
| Asthma | 26 (18.1) | 11 (13.9) | 15 (23.1) | .23 |
| COPD | 22 (15.3) | 13 (16.5) | 9 (13.8) | .84 |
| Obstructive Sleep Apnea | 18 (12.5) | 11 (13.9) | 7 (10.8) | .75 |
| CKD | 51 (35.4) | 29 (36.7) | 22 (33.8) | .53 |
| ESRD | 20 (13.9) | 12 (15.2) | 8 (12.3) | .80 |
| Active malignancy | 18 (12.5) | 11 (13.9) | 7 (10.8) | .75 |
| Liver cirrhosis | 7 (4.9) | 4 (5.1) | 3 (4.6) | > .99 |
| HIV/AIDS | 4 (2.8) | 1 (1.3) | 3 (4.6) | .33 |
| **Drugs (pre-admission)** | | | | |
| ACEi or ARB | 42 (29.2) | 24 (30.4) | 18 (27.7) | .87 |
| ACEi | 22 (15.3) | 15 (19.0) | 7 (10.8) | .26 |
| ARB | 20 (13.9) | 9 (11.4) | 11 (16.9) | .48 |
| Immunosuppressive | 22 (15.3) | 9 (11.4) | 13 (20.0) | .23 |
| **Drugs (in-hospital)** | | | | |
| Antiviral(s) | 15 (10.4) | 8 (10.1) | 7 (10.8) | > .99 |
| Lopinavir/Ritonavir | 7 (4.9) | 5 (6.3) | 2 (3.1) | .458 |
| Remdesivir | 9 (6.3) | 4 (5.1) | 5 (7.7) | .732 |

| | | | | |
|---|---|---|---|---|
| Corticosteroids | 34 (23.6) | 14 (17.7) | 20 (30.8) | .102 |
| Azithromycin | 80 (55.6) | 46 (58.2) | 34 (52.3) | .59 |
| Antibiotic(s) (except azithromycin) | 103 (71.5) | 57 (72.2) | 46 (70.8) | .80 |
| Hydroxychloroquine | 64 (44.4) | 34 (43.0) | 30 (46.2) | .89 |
| Length of hospital stay (days) | 10.0 (5.25-18) | 10 (6-17) | 10 (5-21) | .95 |

Data are presented as absolute numbers and percentages [No. (%)] of patients unless otherwise indicated; *P* values refer to Chi-square test (with Yates' Continuity Correction) or Fisher's Exact Test for categorical independent variables, and Mann-Whitney U Test for continuous variables.

Abbreviations and symbols: ACEi, angiotensin-converting enzyme inhibitor; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; IQR, interquartile range; kg, kilogram; m, meter; No and N, number; SNF, skilled nursing facility; 25(OH)D, 25-hydroxyvitamin D.

Table 2. Univariable and multivariable logistic regression analyses for in-hospital mortality

| **Variable** | **Univariable** | **Multivariable** | | | | |
|---|---|---|---|---|---|---|
| | | (1) | (2) | (3) | (4) | (5) |
| | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value |
| 25(OH)D (continuous) | 0.96 (0.93-0.996) *P*=.03 | 0.95 (0.92-0.99) *P*=.01 | 0.953 (0.92 -0.99) *P*=.01 | 0.96 (0.92-0.99) *P*=.01 | 0.94 (0.90-0.98) *P*=.01 | 0.91 (0.85-0.97) *P*=.003 |
| Age (quintiles) | 1.24 (0.91-1.69) *P*=.18 | 1.41 (1.01-1.97) *P*=.04 | 1.42 (1.01-1.98) *P*=.04 | 1.43 (1.01-2.02) *P*=.04 | 1.72 (1.10-2.68) *P*=.02 | 1.81 (1.05-3.13) *P*=.03 |
| BMI (quintiles) | 1.04 (0.77-1.41) *P*=.79 | 1.02 (0.74-1.40) *P*=.92 | 1.02 (0.74-1.41) *P*=.91 | 1.02 (0.72-1.43) *P*=.92 | 1.05 (0.65-1.71) *P*=.84 | 1.16 (0.68-1.99) *P*=.58 |
| Male sex | 1.09 (0.46-2.55) *P*=.85 | | | 1.04 (0.40-2.74) *P*=.93 | 1.07 (0.28-4.12) *P*=.92 | 2.00 (0.47-8.63) *P*=.35 |
| Smoking | 1.77 (0.62-5.03) *P*=.29 | | | 2.24 (0.68-7.35) *P*=.18 | 3.19 (0.76-13.46) *P*=.11 | 1.26 (0.23-7.02) *P*=.79 |
| Heart failure | 1.47 (0.52-4.12) *P*=.46 | | | | | 2.47 (0.43-14.39) *P*=.31 |
| Coronary artery disease | 1.16 (0.35-3.81) *P*=.81 | | | | | 0.29 (0.02-3.64) *P*=.34 |
| ESRD | 2.98 (1.05-8.43) *P*=.04 | | | | | 5.49 (0.79-38.05) *P*=.09 |
| COPD | 5.52 (2.05-14.86) *P*=.001 | | | | | 6.69 (1.10-40.89) *P*=.04 |
| Diabetes | 1.36 (0.58-3.19) *P*=.48 | | | | | 0.49 (0.11-2.09) *P*=.33 |
| Active malignancy | 6.41 (2.23-18.43) *P*=.001 | | | | | 16.31 (2.25-118.4) *P*=.01 |
| Hypertension | 1.63 (0.57-4.68) *P*=.36 | | | | | 0.84 (0.15-4.73) *P*=.84 |
| ACEI or ARB use prior to admission | 0.68 (0.25-1.84) *P*=.45 | | | | 0.69 (0.18-2.56) *P*=.57 | |
| Antiviral | 12.6 (0.80-8.29) *P*=0.11 | | | | 2.42 (0.35-16.54) *P*=.37 | |

| | | | | |
|---|---|---|---|---|
| Azithromycin | 3.22 (1.21-8.60) *P*=.02 | | 1.34 (0.30-6.10) *P*=.70 | |
| Antibiotic (except azithromycin) | 1.71 (0.46-6.29) *P*=.42 | | 0.91 (0.14-6.12) *P*=.93 | |
| Hydroxychloroquine | 0.73 (0.31-1.74) *P*=.48 | | 0.79 (0.18-3.49) *P*=.76 | |
| Corticosteroids | 1.97 (0.78-4.95) *P*=.15 | | 3.25 (0.88-12.06) *P*=.08 | 4.00 (0.80-19.98) *P*=.09 |
| C-reactive protein | 1.00 (0.995-1.01) *P*=.98 | | 1.00 (0.99-1.01) *P*=.68 | 1.00 (0.99-1.01) *P*=.83 |

Model(1): Multivariable analysis with 25(OH)D (as a continuous), age (analyzed in quintiles), BMI (analyzed in quintiles); Model(2): Multivariable analysis model(1) adjusted for the hospital of origin; Model(3): Multivariable analysis model(2) with addition of male, smoking as regressors; Model(4): Multivariable analysis model(3) with addition of ARB or ACEi, in-hospital drug treatment and C-reactive protein; Model(5): Multivariable analysis model(3) with addition of statistically significant variables of the univariable analysis and heart failure, coronary artery disease, diabetes, hypertension, C-reactive protein, and corticosteroids. Age in years, BMI in kg/m$^2$, 25(OH)D levels in ng/mL, C-reactive protein in mg/dL.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D.

Table 3. Univariable and multivariable logistic regression analyses for receiving invasive mechanical ventilation

| Variable | Univariable | Multivariable | | | | |
|---|---|---|---|---|---|---|
| | | (1) | (2) | (3) | (4) | (5) |
| | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value |
| 25(OH)D (continuous) | 0.98 (0.96-1.00) *P*=.09 | 0.98 (0.95-1.00) *P*=.10 | 0.97 (0.95-0.999) *P*=.05 | 0.97 (0.95-1.00) *P*=.05 | 0.93 (0.90-0.98) *P*=.002 | 0.94 (0.91-0.98) *P*=.004 |
| Age (quintiles) | 1.03 (0.79-1.34) *P*=.85 | 1.11 (0.84-1.47) *P*=.45 | 1.10 (0.82-1.47) *P*=.52 | 1.11 (0.83-1.49) *P*=.48 | 1.10 (0.71-1.69) *P*=.67 | 1.29 (0.84-1.98) *P*=.25 |
| BMI (quintiles) | 1.14 (0.87-1.48) *P*=.35 | 1.11 (0.84-1.47) *P*=.48 | 1.10 (0.83-1.46) *P*=.53 | 1.12 (0.83-1.51) *P*=.45 | 1.10 (0.69-1.76) *P*=.68 | 1.19 (0.78-1.80) *P*=.42 |
| Male sex | 1.10 (0.53-2.30) *P*=.80 | | | 1.26 (0.55-2.92) *P*=.59 | 1.45 (0.38-5.55) *P*=.58 | 0.90 (0.27-2.97) *P*=.86 |
| Smoking | 1.53 (0.59-3.96) *P*=.38 | | | 1.10 (0.39-3.10) *P*=.85 | 0.89 (0.21-3.86) *P*=.88 | 1.50 (0.36-6.38) *P*=.58 |
| Heart failure | 0.77 (0.29-2.09) *P*=.61 | | | | | 2.14 (0.42-10.87) *P*=.36 |
| Coronary artery disease | 0.43 (0.12-1.56) *P*=.20 | | | | | 0.23 (0.03-2.04) *P*=.19 |
| ESRD | 1.55 (0.57-4.22) *P*=.39 | | | | | 8.38 (1.31-53.48) *P*=.025 |
| COPD | 0.76 (0.26-2.23) *P*=.62 | | | | | 1.01 (0.20-5.11) *P*>.99 |
| Diabetes | 1.52 (0.73-3.18) *P*=.27 | | | | | 0.62 (0.19-2.02) *P*=.42 |
| Active malignancy | 0.74 (0.23-2.41) *P*=.62 | | | | | 0.18 (0.02-1.39) *P*=.10 |
| Hypertension | 1.06 (0.46-2.44) *P*=.90 | | | | | 0.67 (0.18-2.49) *P*=.55 |
| ACEI or ARB use prior to admission | 1.11 (0.50-2.48) *P*=.80 | | | | 1.16 (0.31-4.26) *P*=.83 | |
| Antiviral | 1.94 (0.64-5.86) *P*=.24 | | | | 5.20 (0.67-40.41) *P*=.12 | |

| | | | | |
|---|---|---|---|---|
| Azithromycin | 3.07 (1.36-6.93) *P*=.01 | | 1.84 (0.49-6.87) *P*=.37 | |
| Antibiotic (except azithromycin) | 5.17 (1.15-23.36) *P*=.03 | | 7.87 (1.12-55.48) *P*=.04 | |
| Hydroxychloroquine | 0.81 (0.39-1.71) *P*=.58 | | 2.23 (0.54-9.26) *P*=.27 | |
| Corticosteroids | 4.00 (1.76-9.07) *P*=.001 | | 4.05 (1.18-13.91) *P*=.03 | 4.24 (1.22-14.67) *P*=.02 |
| C-reactive protein | 1.01 (1.01-1.02) *P*<.001 | | 1.01 (1.00-1.02) *P*=.01 | 1.02 (1.01-1.02) *P*<0.01 |

Model(1): Multivariable analysis with 25(OH)D (as a continuous), age (analyzed in quintiles), BMI (analyzed in quintiles); Model(2): Multivariable analysis model(1) adjusted for the hospital of origin; Model(3): Multivariable analysis model(2) with addition of male, smoking as regressors; Model(4): Multivariable analysis model(3) with addition of C-reactive protein, ARB or ACEi and in-hospital drug treatment; Model(5): Multivariable analysis model(3) with addition of statistically significant variables of the univariable analysis and heart failure, coronary artery disease, diabetes, hypertension, C-reactive protein, and corticosteroids. Age in years, BMI in kg/m$^2$, vitamin levels in ng/mL, C-reactive protein in mg/dL.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D.

 

Supplementary Table 1. Symptoms and signs on presentation and main laboratory results.

| Characteristics | All patients (N=144) | 25(OH)D <30 ng/mL (N=79) | 25(OH)D ≥30 ng/mL (N=65) | *P* value |
|---|---|---|---|---|
| **Symptoms, No. (%)** | | | | |
| Fever | 86 (59.7) | 52 (65.8) | 34 (52.3) | .25 |
| Cough | 88 (61.1) | 50 (63.3) | 38 (58.5) | .68 |
| Shortness of breath | 87 (60.4) | 44 (55.7) | 43 (66.2) | .27 |
| Malaise | 79 (54.9) | 45 (57.0) | 34 (52.3) | .63 |
| Diarrhea | 32 (22.2) | 21 (26.6) | 11 (16.9) | .26 |
| Myalgia | 36 (25.0) | 24 (30.4) | 12 (18.5) | .15 |
| Sputum production | 29 (20.1) | 18 (22.8) | 11 (16.9) | .51 |
| Headache | 23 (16.0) | 19 (24.1) | 4 (6.2) | .007 |
| Nasal congestion or rhinorrhea | 8 (5.6) | 3 (3.8) | 5 (7.7) | |
| Nausea or vomiting | 28 (19.4) | 19 (24.1) | 9 (13.8) | .18 |
| Sore throat | 11 (7.6) | 7 (8.9) | 4 (6.2) | .75 |
| **Signs** | | | | |
| $SpO_2$ on room air median(IQR),% | 95 (91-97) | 95 (91-97) | 94.5 (91-98) | .96 |
| Temperature, mean (SD), °C | 37.6 (1.9) | 37.6 (1.9) | 37.6 (1.9) | .95 |
| HR, mean (SD), beats/min | 94.0 (17.5) | 94.3 (16.8) | 93.7 (18.5) | .86 |
| SBP, mean (SD), mmHg | 124 (22.3) | 123 (22.9) | 125 (22.0) | .75 |
| DBP, mean (SD), mmHg | 72 (60-81) | 72 (61-82) | 71.5 (60-80) | .67 |
| **Laboratory results, median (IQR)** | | | | |

| | | | | |
|---|---|---|---|---|
| White-cell count, per $10^3$/uL | 6.7 (4.6-9.5) | 6.7 (4.2-9.5) | 6.7 (5.1-9.8) | .62 |
| Lymphocyte count, per $10^3$/uL | 0.90 (0.7-1.3) | 0.90 (0.7-1.3) | 0.90 (0.7-1.3) | .93 |
| Hemoglobin, g/dL | 12.2 (10.3-14) | 12.5 (10.3-14.2) | 11.8 (10.4-13.3) | .13 |
| Platelets, per 10/uL | 197 (153-260) | 195 (148-259) | 201 (160-265) | .27 |
| Creatinine, mg/dL | 1.2 (0.8-1.9) | 1.1 (0.9-2.1) | 1.2 (0.8-1.8) | .70 |
| AST, U/L | 33 (23-60) | 38 (25-72) | 31 (23-51) | .16 |
| ALT, U/L | 23.5 (16-38) | 29 (16-45) | 21 (15-29) | .02 |
| CK, U/L | 161 (74-341) | 148 (70-424) | 169 (75-299) | .86 |
| Troponin T, ng/mL | 0.01 (0.01-0.04) | 0.01 (0.01-0.04) | 0.01 (0.01-0.04) | .64 |
| LDH, U/L | 340 (248-468) | 377 (281-491) | 305 (238-448) | .85 |
| CRP, mg/dL | 55 (9.8-151) | 25 (7.2-100) | 76 (12.3-197) | .03 |
| D-dimer, ug/mL | 1077 (553-2240) | 1191 (611-2769) | 1018 (532-2048) | .67 |
| Ferritin, ng/mL | 619 (283-1300) | 754 (381-1552) | 591 (197-1030) | .14 |
| IL-6, ng/mL | 79.4 (46.9-168) | 82.5 (55-149) | 79.4 (43.6-314) | .98 |
| Glu, mg/dL | 122 (97-163) | 125 (98-148) | 122 (95-170) | .78 |
| HbA1c, % | 6.3 (5.6-8.1) | 6.4 (5.7-7.8) | 6.2 (5.4-8.1) | .63 |
| Cholesterol, mg/dL | 154 (122-186) | 152 (118-195) | 154 (135-183) | .60 |
| LDL, mg/dL | 79 (61-99) | 79 (58-116) | 79 (62-98) | .88 |
| HDL, mg/dL | 48 (37-55) | 46 (36-59.5) | 49 (39-54) | .62 |
| Triglycerides, mg/dL | 125 (85-193) | 125 (86.5-186) | 122 (81.3-197) | .97 |

Note: For the descriptive statistics, the normally distributed continuous variables are presented as mean (standard deviation), while the non-normally distributed continuous variables as median with interquartile range (IQR); categorical variables are described as absolute numbers and

percentages [No. (%)]; *P* values refer to Chi-square test (with Yates' Continuity Correction) or Fisher's Exact Test for categorical independent variables, and Mann-Whitney U Test or independent-samples t-test for continuous variables.

SI conversion factors: To convert total cholesterol, HDL-C, and LDL-C levels to mmol/L, multiply values by 0.0259; triglyceride values to mmol/L, multiply by 0.0113; D-dimer values to nmol/L, multiply values by 5.476; CRP values to mg/L, multiply by 10, Creatine levels to µmol/L, multiply values by 76.25.

Abbreviations and symbols: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; DBP, diastolic blood pressure; Glu, glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein cholesterol; HR, heart rate; IL-6, interleukin-6; LDH, lactate dehydrogenase; LDL, low-density lipoprotein cholesterol; No and N, number; SBP, systolic blood pressure; $SpO_2$, oxygen saturation; 25(OH)D, 25-hydroxyvitamin D.

Supplementary Table 2. Multivariable logistic regression analyses for in-hospital mortality

| Variable | Multivariable | | | | |
|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) |
| | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value |
| 25(OH)D (log10) | 0.06 (0.01-0.47) *P*=.01 | 0.06 (0.01-0.48) *P*=.01 | 0.07 (0.01-0.52) *P*=.01 | 0.02 (0.002-0.32) *P*=.01 | 0.004 (0.00-0.10) *P*=.001 |
| Age (quintiles) | 1.44 (1.03-2.03) *P*=.04 | 1.45 (1.03-2.05) *P*=.03 | 1.46 (1.03-2.08) *P*=.03 | 1.79 (1.14-2.82) *P*=.01 | 1.98 (1.12-3.51) *P*=.02 |
| BMI (quintiles) | 1.03 (0.74-1.41) *P*=.88 | 1.03 (0.74-1.41) *P*=.88 | 1.03 (0.73-1.45) *P*=.89 | 1.06 (0.66-1.73) *P*=.80 | 1.14 (0.67-1.94) *P*=.64 |
| Male sex | | | 1.03 (0.39-2.70) *P*=.96 | 1.01 (0.26-3.93) *P*=.99 | 1.78 (0.42-7.67) *P*=.44 |
| Smoking | | | 2.12 (0.65-6.95) *P*=.22 | 2.89 (0.70-12.02) *P*=.14 | 1.47 (0.27-8.05) *P*=.66 |
| Heart failure | | | | | 2.30 (0.40-13.30) *P*=.35 |
| Coronary artery disease | | | | | 0.28 (0.02-3.41) *P*=.32 |
| ESRD | | | | | 4.84 (0.68-34.62) *P*=.12 |
| COPD | | | | | 6.12 (0.99-37.96) *P*=.05 |
| Diabetes | | | | | 0.56 (0.13-2.34) *P*=.42 |
| Active malignancy | | | | | 18.09 (2.36-138.7) *P*=.01 |
| Hypertension | | | | | 0.73 (0.13-4.18) *P*=.72 |
| ACEI or ARB use prior to admission | | | | 0.62 (0.16-2.38) *P*=.48 | |
| Antiviral | | | | 1.99 (0.30-13.23) *P*=.48 | |
| Azithromycin | | | | 1.29 (0.28-5.84) *P*=.75 | |

| | | | | | |
|---|---|---|---|---|---|
| Antibiotic (except azithromycin) | | | | 0.87 (0.13-5.96) *P*=.88 | |
| Hydroxychloroquine | | | | 0.71 (0.16-3.12) *P*=.65 | |
| Corticosteroids | | | | 3.16 (0.85-11.68) *P*=.09 | 3.62 (0.71-18.55) *P*=.12 |
| C-reactive protein | | | | 1.00 (0.99-1.01) *P*=.63 | 1.00 (0.99-1.01) *P*=.92 |
| | | | | | |
| 25(OH)D (≥30ng/mL) | 0.22 (0.08-0.63) *P*=.01 | 0.23 (0.08-0.64) *P*=.01 | 0.23 (0.08-0.66) *P*=.01 | 0.14 (0.03-0.59) *P*=.01 | 0.12 (0.02-0.60) *P*=.01 |
| Age (quintiles) | 1.45 (1.03-2.03) *P*=0.03 | 1.45 (1.03-2.03) *P*=.03 | 1.46 (1.03-2.06) *P*=.03 | 1.73 (1.12-2.67) *P*=.01 | 1.80 (1.06-3.07) *P*=.03 |
| BMI (quintiles) | 1.07 (0.77-1.48) *P*=.69 | 1.07 (0.77-1.48) *P*=.69 | 1.07 (0.76-1.50) *P*=.71 | 1.16 (0.72-1.87) *P*=.55 | 1.22 (0.72-2.07) *P*=.46 |
| Male sex | | | 1.08 (0.41-2.79) *P*=.88 | 1.16 (0.32-4.18) *P*=.83 | 1.70 (0.42-6.80) *P*=.45 |
| Smoking | | | 1.94 (0.60-6.27) *P*=.27 | | 1.20 (0.23-6.31) *P*=.83 |
| Heart failure | | | | | 1.90 (0.35-10.40) *P*=.46 |
| Coronary artery disease | | | | | 0.25 (0.02-2.66) *P*=.25 |
| ESRD | | | | | 4.31 (0.70-26.40) *P*=.11 |
| COPD | | | | | 5.08 (0.996-25.88) *P*=.05 |
| Diabetes | | | | | 0.54 (0.14-2.16) *P*=.38 |
| Active malignancy | | | | | 10.28 (1.77-59.72) *P*=.01 |
| Hypertension | | | | | 0.79 (0.15-4.33) *P*=.79 |
| ACEI or ARB use prior to admission | | | | 0.56 (0.15-2.04) *P*=.38 | |

| | | | | | |
|---|---|---|---|---|---|
| Antiviral | | | | 2.87 (0.44-18.61) *P*=.27 | |
| Azithromycin | | | | 1.72 (0.39-7.62) *P*=.48 | |
| Antibiotic (except azithromycin) | | | | 0.92 (0.14-5.91) *P*=.93 | |
| Hydroxychloroquine | | | | 0.66 (0.15-2.79) *P*=.57 | |
| Corticosteroids | | | | 3.27 (0.90-11.86) *P*=.07 | 3.52 (0.78-15.88) *P*=.10 |
| C-reactive protein | | | | 1.00 (0.995-1.01) *P*=.45 | 1.00 (0.99-1.01) *P*=.57 |
| | | | | | |
| 25(OH)D (quintiles) | 0.65 (0.46-0.92) *P*=.02 | 0.65 (0.46-0.93) *P*=.02 | 0.66 (0.47-0.94) *P*=0.02 | 0.53 (0.34-0.84) *P*=.01 | 0.39 (0.22-0.71) *P*=.002 |
| Age (quintiles) | 1.39 (0.996-1.93) *P*=.05 | 1.39 (1.00-1.95) *P*=.05 | 1.41 (1.00-1.99) *P*=0.05 | 1.71 (1.10-2.67) *P*=.02 | 1.79 (1.04-3.09) *P*=.04 |
| BMI (quintiles) | 1.02 (0.74-1.41) *P*=.89 | 1.03 (0.74-1.41) *P*=.88 | 1.03 (0.73-1.45) *P*=0.87 | 1.03 (0.63-1.68) *P*=.91 | 1.09 (0.64-1.85) *P*=.76 |
| Male sex | | | 1.08 (0.41-2.81) *P*=0.88 | 1.038 (0.27-4.05) *P*=.96 | 1.81 (0.42-7.83) *P*=.43 |
| Smoking | | | 2.13 (0.66-6.91) *P*=0.21 | 2.95 (0.71-12.23) *P*=.14 | 1.64 (0.31-8.75) *P*=.56 |
| Heart failure | | | | | 1.96 (0.35-11.03) *P*=.44 |
| Coronary artery disease | | | | | 0.30 (0.03-3.27) *P*=.32 |
| ESRD | | | | | 4.36 (0.64-29.59) *P*=.13 |
| COPD | | | | | 6.44 (1.07-38.66) *P*=.04 |
| Diabetes | | | | | 0.58 (0.14-2.38) *P*=.45 |
| Active malignancy | | | | | 16.47 (2.33-116.6) *P*=.01 |
| Hypertension | | | | | 0.86 (0.16-4.77) *P*=.86 |

| | | | |
|---|---|---|---|
| ACEI or ARB use prior to admission | | 0.70 (0.18-2.63) *P*=.59 | |
| Antiviral | | 2.15 (0.33-14.02) *P*=.42 | |
| Azithromycin | | 1.25 (0.28-5.58) *P*=.78 | |
| Antibiotic (except azithromycin) | | 0.96 (0.14-6.62) *P*=.97 | |
| Hydroxychloroquine | | 0.69 (0.16-2.98) *P*=.62 | |
| Corticosteroids | | 3.21 (0.88-11.71) *P*=.08 | 3.74 (0.77-18.21) *P*=.10 |
| C-reactive protein | | 1.00 (0.99-1.01) *P*=.63 | 1.00 (0.99-1.01) *P*=.82 |

Model(1): Multivariable analysis with 25(OH)D (as a continuous), age (analyzed in quintiles), BMI (analyzed in quintiles); Model(2): Multivariable analysis model(1) adjusted for the hospital of origin; Model(3): Multivariable analysis model(2) with addition of male, smoking as regressors; Model(4): Multivariable analysis model(3) with addition of ARB or ACEi, in-hospital drug treatment and C-reactive protein; Model(5): Multivariable analysis model(3) with addition of statistically significant variables of the univariable analysis and heart failure, coronary artery disease, diabetes, hypertension, C-reactive protein, and corticosteroids. Age in years, BMI in kg/m2, 25(OH)D levels in ng/mL, C-reactive protein in mg/dL.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D.

Supplementary Table 3. Multivariable logistic regression analyses for receiving invasive mechanical ventilation

| Variable | Multivariable | | | | |
|---|---|---|---|---|---|
| | (1) | (2) | (3) | (4) | (5) |
| | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value | OR (95% CI) *P* value |
| 25(OH)D (log10) | 0.17 (0.03-0.91) P=.04 | 0.12 (0.02-0.69) P=.02 | 0.13 (0.02-0.76) P=.02 | 0.01 (0.001-0.17) P=.001 | 0.01 (0.001-0.19) P=.002 |
| Age (quintiles) | 1.15 (0.86-1.53) P=.34 | 1.13 (0.84-1.52) P=.41 | 1.14 (0.84-1.54) P=.39 | 1.17 (0.75-1.82) P=.49 | 1.40 (0.89-2.20) P=.15 |
| BMI (quintiles) | 1.10 (0.83-1.45) P=.50 | 1.10 (0.82-1.46) P=.53 | 1.12 (0.83-1.51) P=.47 | 1.11 (0.68-1.79) P=.68 | 1.18 (0.77-1.80) P=.46 |
| Male sex | | | 1.22 (0.53-2.85) P=.64 | 1.41 (0.36-5.47) P=.62 | 0.88 (0.261-2.93) P=.83 |
| Smoking | | | 1.04 (0.37-2.95) P=.94 | 0.83 (0.19-3.68) P=.81 | 1.38 (0.32-5.94) P=.67 |
| Heart failure | | | | | 1.89 (0.36-9.94) P=.45 |
| Coronary artery disease | | | | | 0.24 (0.03-2.07) P=.20 |
| ESRD | | | | | 9.61 (1.40-66.18) P=.02 |
| COPD | | | | | 1.00 (0.18-5.5) P>.99 |
| Diabetes | | | | | 0.599 (0.177-2.03) P=.41 |
| Active malignancy | | | | | 0.18 (0.02-1.43) P=.10 |
| Hypertension | | | | | 0.60 (0.15-2.33) P=.46 |
| ACEI or ARB use prior to admission | | | | 1.05 (0.27-4.05) P=.95 | |
| Antiviral | | | | 4.39 (0.53-36.39) P=.17 | |
| Azithromycin | | | | 1.63 (0.43-6.22) P=.48 | |

| | | | | | |
|---|---|---|---|---|---|
| Antibiotic (except azithromycin) | | | | 8.30 (1.10-62.91) P=.04 | |
| Hydroxychloroquine | | | | 2.11 (0.52-8.61) P=.30 | |
| Corticosteroids | | | | 3.86 (1.13-13.13) P=.03 | 4.17 (1.19-14.66) P=.03 |
| C-reactive protein | | | | 1.01 (1.00-1.02) P=.01 | 1.02 (1.01-1.02) P<.001 |
| | | | | | |
| 25(OH)D (≥30ng/mL) | 0.78 (0.36-1.71) P=.54 | 0.64 (0.28-1.44) P=.28 | 0.65 (0.28-1.48) P=.30 | 0.15 (0.04-0.60) P=.01 | 0.22 (0.06-0.78) P=.02 |
| Age (quintiles) | 1.09 (0.82-1.44) P=.57 | 1.08 (0.81-1.45) P=.60 | 1.10 (0.82-1.47) P=.55 | 1.16 (0.77-1.8) P=.48 | 1.37 (0.89-2.10) P=.15 |
| BMI (quintiles) | 1.14 (0.87-1.50) P=.34 | 1.13 (0.86-1.49) P=.39 | 1.16 (0.87-1.55) P=.32 | 1.18 (0.76-1.85) P=.46 | 1.22 (0.81-1.83) P=.35 |
| Male sex | | | 1.32 (0.58-3.04) P=.51 | 1.48 (0.43-5.15) P=.53 | 0.91 (0.29-2.88) P=.87 |
| Smoking | | | 1.02 (0.37-2.79) P=.98 | 0.83 (0.21-3.28) P=.79 | 1.51 (0.36-6.29) P=0.57 |
| Heart failure | | | | | 2.30 (0.46-11.53) P=.31 |
| Coronary artery disease | | | | | 0.18 (0.02-1.48) P=.11 |
| ESRD | | | | | 7.55 (1.27-44.78) P=.03 |
| COPD | | | | | 0.75 (0.15-3.65) P=.72 |
| Diabetes | | | | | 0.70 (0.22-2.22) P=.55 |
| Active malignancy | | | | | 0.20 (0.03-1.44) P=.11 |
| Hypertension | | | | | 0.62 (0.17-2.32) P=.48 |
| ACEI or ARB use prior to admission | | | | 1.27 (0.36-4.42) P=.71 | |

| | | | | | |
|---|---|---|---|---|---|
| Antiviral | | | | 4.49 (0.61-32.84) P=.14 | |
| Azithromycin | | | | 2.09 (0.58-7.54) P=.26 | |
| Antibiotic (except azithromycin) | | | | 7.00 (1.06-46.41) P=.04 | |
| Hydroxychloroquine | | | | 2.33 (0.57-9.55) P=.24 | |
| Corticosteroids | | | | 3.76 (1.13-12.57) P=.03 | 3.49 (1.06-11.49) P=.04 |
| C-reactive protein | | | | 1.01 (1.00-1.02) P=.01 | 1.02 (1.01-1.02) P<.001 |
| | | | | | |
| 25(OH)D (quintiles) | 0.81 (0.61-1.07) P=.14 | 0.77 (0.58-1.02) P=.07 | 0.78 (0.58-1.04) P=.09 | 0.50 (0.32-0.79) P=.003 | 0.54 (0.35-0.84) P=.01 |
| Age (quintiles) | 1.11 (0.84-1.47) P=.46 | 1.09 (0.82-1.46) P=.55 | 1.11 (0.82-1.48) P=.51 | 1.12 (0.73-1.72) P=.60 | 1.32 (0.85-2.03) P=.21 |
| BMI (quintiles) | 1.11 (0.84-1.46) P=.47 | 1.10 (0.83-.45) P=.52 | 1.12 (0.84-1.51) P=.44 | 1.09 (0.68-1.73) P=.73 | 1.14 (0.75-1.72) P=.55 |
| Male sex | | | 1.28 (0.55-2.95) P=.57 | 1.49 (0.40-5.54) P=.55 | 0.91 (0.28-2.98) P=.88 |
| Smoking | | | 1.06 (0.38-2.94) P=.92 | 0.91 (0.21-3.86) P=.89 | 1.63 (0.38-6.89) P=.51 |
| Heart failure | | | | | 1.93 (0.38-9.73) P=.42 |
| Coronary artery disease | | | | | 0.21 (0.03-1.72) P=.15 |
| ESRD | | | | | 7.63 (1.23-47.50) P=.03 |
| COPD | | | | | 0.96 (0.19-4.88) P=.96 |
| Diabetes | | | | | 0.71 (0.22-2.28) P=.57 |
| Active malignancy | | | | | 0.21 (0.03-1.50) P=.12 |
| Hypertension | | | | | 0.65 (0.18-2.44) P=.53 |

| | | | |
|---|---|---|---|
| ACEI or ARB use prior to admission | | 1.21 (0.33-4.42) P=.77 | |
| Antiviral | | 4.24 (0.52-34.38) P=.18 | |
| Azithromycin | | 1.61 (0.44-5.94) P=.48 | |
| Antibiotic (except azithromycin) | | 8.42 (1.17-60.58) P=.03 | |
| Hydroxychloroquine | | 1.93 (0.48-7.73) P=.36 | |
| Corticosteroids | | 3.83 (1.15-12.80) P=.03 | 3.75 (1.12-12.58) P=.03 |
| C-reactive protein | | 1.01 (1.00-1.02) P=.01 | 1.02 (1.01-1.02) P<0.001 |



Model(1): Multivariable analysis with 25(OH)D (as a continuous), age (analyzed in quintiles), BMI (analyzed in quintiles); Model(2): Multivariable analysis model(1) adjusted for the hospital of origin; Model(3): Multivariable analysis model(2) with addition of male, smoking as regressors; Model(4): Multivariable analysis model(3) with addition of C-reactive protein, ARB or ACEi and in-hospital drug treatment; Model(5): Multivariable analysis model(3) with addition of statistically significant variables of the univariable analysis and heart failure, coronary artery disease, diabetes, hypertension, C-reactive protein, and corticosteroids. Age in years, BMI in kg/m2, vitamin levels in ng/mL, C-reactive protein in mg/dL.

Abbreviations: ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D.