Influence of vitamin D status on hospital length of stay and prognosis in hospitalized patients with moderate to severe COVID-19: a multicenter prospective cohort study

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ABSTRACT

Background: Vitamin D acts as a mediator in the immune system regulating antiviral mechanisms and inflammatory processes. Vitamin D insufficiency has been suggested as a potential risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, although its impact on the prognosis of hospitalized patients with coronavirus disease 2019 (COVID-19) remains unclear.

Objective: This multicenter prospective cohort study was designed to investigate whether serum 25-hydroxyvitamin D [25(OH)D] concentration is associated with hospital length of stay and prognosis in hospitalized patients with COVID-19.

Methods: Patients with moderate to severe COVID-19 ($n = 220$) were recruited from 2 hospitals in Sao Paulo, Brazil. Serum 25(OH)D concentrations were categorized as follows: <10 ng/mL, 10 to <20 ng/mL, 20 to <30 ng/mL, and ≥30 ng/mL, and <10 ng/mL and ≥10 ng/mL. The primary outcome was hospital length of stay and the secondary outcomes were the rate of patients who required invasive mechanical ventilation and mortality.

Results: There were no significant differences in hospital length of stay when the 4 25(OH)D categories were compared ($P = 0.120$). Patients exhibiting 25(OH)D <10 ng/mL showed a trend (P = 0.057) for longer hospital length of stay compared with those with 25(OH)D ≥10 ng/mL [9.0 d (95% CI: 6.4, 11.6 d) vs. 7.0 d (95% CI: 6.6, 7.4 d)]. The multivariable Cox proportional hazard models showed no significant associations between 25(OH)D and primary or secondary outcomes.

Conclusions: Among hospitalized patients with moderate to severe COVID-19, those with severe 25(OH)D deficiency (<10 ng/mL) exhibited a trend for longer hospital length of stay compared with patients with higher 25(OH)D concentrations. This association was not significant in the multivariable Cox regression model. Prospective studies should test whether correcting severe 25(OH)D deficiency could improve the prognosis of patients with COVID-19. *Am J Clin Nutr* 2021;00:1–7.

Keywords: SARS-CoV-2 infection, COVID-19, mortality, nutritional status, 25-hydroxyvitamin D

Introduction

As of 30 March 2021, 127 million people have been infected and 2.7 million people have died in the coronavirus disease 2019 (COVID-19) pandemic (1). The predictors of COVID-19 severity remain to be fully clarified.

Subclinical vitamin D deficiency has been shown to negatively affect the function of the immune system and increase the risk of severe infection (2–4), including COVID-19 (3, 4). In this sense, vitamin D emerges in its recognized immunomodulatory role since it is involved in the upregulation of the immune system through effects on both dendritic and T cells (5–7). It can also enhance antiviral mechanisms in epithelial cells by producing antimicrobial peptides and autophagy, as well

as regulating inflammatory responses in the renin-angiotensin system (5). Notwithstanding, insufficient vitamin D status has been suggested as a potential risk factor for noncommunicable (8) and infectious (9) diseases, notably acute respiratory tract infections (2, 10), including viral infections by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (11, 12).

Recent studies have investigated the possible relation between serum 25-hydroxyvitamin D [25(OH)D] and COVID-19 severity (13–17). Although vitamin D deficiency is commonly seen among patients with severe COVID-19, the predictive role of 25(OH)D status on disease prognosis remains inconclusive (12, 18–20). The divergence in the literature could be partially attributed to the use of different definitions of vitamin D insufficiency or sufficiency and the assessment of patients with different disease severity. Concerning the latter, there is a paucity of data investigating the predictive value of 25(OH)D concentrations in hospitalized patients with COVID-19.

This multicenter prospective cohort study aimed to investigate whether different serum 25(OH)D concentrations are associated with hospital length of stay and prognosis (mechanical ventilation requirement and mortality) in hospitalized patients with moderate to severe COVID-19.

Methods

This multicenter prospective cohort study was performed between 2 June 2020 and 21 July 2020 at the Clinical Hospital of the School of Medicine of the University of Sao Paulo (a quaternary referral teaching hospital) and from 22 July 2020 to 25 September 2020 at the Ibirapuera Field Hospital. The screening assumed the same criteria for both centers and the end of follow-up occurred on 7 October 2020.

The study was approved by the ethics committee of both centers. All the procedures were conducted in accordance with the Declaration of Helsinki. The participants provided written informed consent before being enrolled in the study (Ethics Committee Approval Number 38,237,320.3.0000.0068).

Eligibility criteria

Inclusion criteria were as follows: *1*) age ≥ 18 y; *2*) diagnosis of COVID-19 by polymerase chain reaction testing for SARS-CoV-2 from nasopharyngeal swabs or computed tomography scan findings compatible with the disease (bilateral multifocal ground-glass opacities $\geq 50\%$), and subsequent COVID-19 confirmation; and *3*) diagnosis of flu syndrome with hospitalization criteria on hospital admission, presenting with respiratory rate >24 breaths/min, saturation $<93\%$ on room air, or risk factors for complications (e.g., heart disease, diabetes, systemic arterial hypertension, neoplasms, immunosuppression, pulmonary tuberculosis, obesity), followed by COVID-19 confirmation. Patients who met these criteria were considered to have moderate to severe COVID-19 according to the NIH (21).

The exclusion criteria were as follows: *1*) patient unable to sign the written informed consent, *2*) patient previously receiving invasive mechanical ventilation during hospitalization, *3*) creatinine ≥ 2.0 mg/dL or requiring dialysis, *4*) total calcium ≥ 10.5 mg/dL, *5*) prior vitamin D_3 supplementation (>1000 IU/), and *6*) pregnant or lactating women.

Patients immediately admitted to hospitals and who met the eligibility criteria were enrolled and followed up until the day of discharge or death. Anthropometric characteristics (self-reported weight and height), acute COVID-19 symptoms, coexisting chronic diseases, patients' concomitant medications during hospitalization, oxygen supplementation requirement, imaging features, and serum 25(OH)D were assessed upon hospital admission. The investigation of coexisting chronic diseases was self-reported and, subsequently, all of them were checked according to the medical records of each patient, including previous medications. Obesity was classified according to the WHO criteria for BMI (22). To provide comprehensive demographic characterization, self-reported race data were also collected based on the following fixed categories: White, Black, Asian, and Pardo (the latter refers to people of mixed race/ethnicities, according to the Brazilian Institute of Geography and Statistics).

Outcome measures

The primary outcome was hospital length of stay, defined as the total number of days that patients remained hospitalized from the date of study inclusion until the date of hospital discharge. For the Cox proportional hazard models, this outcome was labeled as hospital discharge, aiming to facilitate the interpretation of the HR for discharge.

The criteria used for patient discharge were as follows: *1*) no need for supplemental oxygen in the last 48 h, *2*) no fever in the last 72 h (i.e., temperature $\leq 37.2^\circ$C), and *3*) oxygen saturation $\geq 93\%$ in room air without respiratory distress (such as difficulty breathing, shortness of breath, pain or pressure in the chest). The secondary outcomes were *1*) the rate of patients who required invasive mechanical ventilation and *2*) mortality, defined as the rate of death during hospitalization.

Vitamin D status was initially planned as a primary independent variable; therefore, blood samples for serum 25(OH)D were collected on the day of patients' study inclusion. Serum 25(OH)D was quantified by chemiluminescent immunoassay (ARCHITECT 25-OH Vitamin D 5P02; Abbott Diagnostics). All samples were analyzed at the same time in the same laboratory (Laboratory of the Clinical Hospital of the School of Medicine of the University of Sao Paulo).

The results were categorized as follows: severely deficient (<10 ng/mL), moderately deficient (10 to <20 ng/mL), insufficient (20 to <30 ng/mL), and sufficient (≥ 30 ng/mL) (23).

Statistical analysis

Kaplan-Meier estimate curves for serum 25(OH)D categories (independent variables; model 1: <10 ng/mL, 10 to <20 ng/mL, 20 to <30 ng/mL, and ≥ 30 ng/mL; model 2: <10 ng/mL and ≥ 10 ng/mL) were compared using the log-rank test for hospital length of stay (deaths were considered censored events). Cox regression models were used to estimate unadjusted and adjusted HRs, with corresponding 2-sided 95% CIs, between independent variables and outcomes: hospital discharge, mechanical ventilation requirement, and rate of death by COVID-19. Multivariable Cox proportional hazard models were adjusted for possible confounders (age, sex, race, and BMI) and for

variables found to be associated with vitamin D deficiency in bivariate analyses at the $P < 0.20$ level (cardiovascular disease and chronic obstructive pulmonary disease). All analyses were stratified by the center to avoid possible effect modification. The proportionality assumption for Cox regression models was confirmed by assessing Schoenfeld residuals.

A post hoc power analysis with the present sample size and obtained Pearson's correlation between length of hospital stay and vitamin D concentrations yielded a power of 100%, assuming 2-sided $\alpha = 0.05$ Statistical analyses were performed with IBM-SPSS software (version 20.0). Data are expressed as means $\pm$ SDs or medians and IQRs, as appropriate, and 95% CIs. The significance level was set at $P = 0.05$.

Results

Patients

A total of 220 confirmed cases of COVID-19 were included in this study (**Supplemental Figure 1**). Overall, the mean $\pm$ SD age, BMI (in kg/m^2), and median (IQR) time from hospital admission to study inclusion were 55.1 $\pm$ 14.6 y, 30.6 $\pm$ 6.5, and 1.6 (1.0) d, respectively. **Table 1** presents baseline demographic and clinical characteristics in patients with COVID-19 according to 25(OH)D categories (<10 or $\geq$10 ng/mL). Both groups were similar with regard to demographic characteristics. There were significant differences between groups for chronic obstructive pulmonary disease, use of concomitant medications, oxygen supplementation, and imaging features. Twenty-two patients required invasive mechanical ventilation, 8 patients died, and 6 patients were transferred to other hospitals (dropouts) (Supplemental Figure 1).

Primary outcome

We assessed the hospital length of stay among 25(OH)D categories. Model 1 did not show a significant difference in hospital length of stay among categories (**Table 2** and **Figure 1**A). There was a trend for longer hospital length of stay for patients with 25(OH)D <10 ng/mL (9.0 d; 95% CI: 6.4, 11.6 d) compared with $\geq$10 ng/mL (7.0 d; 95% CI: 6.6, 7.4 d; $P = 0.057$; Table 2, model 2; Figure 1B).

The unadjusted and adjusted HR for hospital discharge according to the 25(OH)D categories did not show a significant difference for either model 1 or model 2 (**Table 3**).

Secondary outcomes

The rate of patients who required mechanical ventilation was not significantly different between the 25(OH)D categories (model 1 and model 2) in both unadjusted and adjusted Cox regression models (Table 3). Mortality was compared among the 25(OH)D categories (model 1 and model 2) only in the unadjusted Cox regression models (Table 3), with no significant difference between them. Considering the stratification by center and the adjustment for possible confounders, there were not enough cases to estimate the adjusted HR (Table 3).

Discussion

This is the first multicenter, prospective cohort study evaluating the association of serum 25(OH)D concentrations on hospital length of stay and other clinical outcomes in hospitalized patients with moderate to severe COVID-19. To date, only 1 multicenter prospective cohort study evaluated vitamin D status on COVID-19 severity [19], although the authors did not assess the relation between different concentrations of vitamin D and the hospital length of stay, the number of patients who required mechanical ventilation, and mortality. The present study demonstrated that severe vitamin D deficiency [defined as 25(OH)D <10 ng/mL] is associated with a trend ($P = 0.057$) for longer hospital length of stay in the aforementioned patients, while the association of 25(OH)D $\geq$10 ng/mL with an increased HR for discharge did not reach statistical significance in the multivariable Cox regression model, indicating that this association may be due to other factors and not to vitamin D deficiency.

Vitamin D has an important role in the immune system, acting as a regulator of both innate and adaptative immune response [5, 6]. From a mechanistic point of view, antigen-presenting cells can synthesize 1,25-dihydroxyvitamin D (the active form of vitamin D) from 25(OH)D, a reaction that is mediated by 1α-hydroxylase (CYP27B1) [5, 7, 24]. Vitamin D could also participate in antiviral responses in epithelial cells (which also express CYP27B1) by producing antimicrobial peptides and inducing autophagy, as well as by regulating inflammatory responses through the renin-angiotensin system, whose overactivation is related to poor prognosis in COVID-19 [5, 14, 24, 25]. This biological plausibility underlies the speculation that vitamin D sufficiency can elicit immunomodulatory and anti-inflammatory effects that could ultimately improve the recovery of COVID-19 patients [26, 27].

A few retrospective studies observed that lower 25(OH)D concentrations were associated with a worse prognosis in COVID-19 (hospital length of stay, lung involvement, or mortality) [15, 28, 29]. In contrast, some studies found no significant association between serum 25(OH)D and clinical outcomes in patients with COVID-19 (admission to the intensive care unit, requirements for mechanical ventilation, or mortality) [18, 19, 30]. The use of different cutoff values for defining 25(OH)D insufficiency and sufficiency may partially explain the divergence. In the current study, the differences between the 4 25(OH)D categories did not reach statistical significance for hospital length of stay, whereas severe 25(OH)D deficiency (<10 ng/mL) was associated with longer stays as compared with all other higher 25(OH)D concentrations. Altogether, these findings appear to suggest that, at least for hospitalized patients with severe COVID-19, only severe 25(OH)D deficiency could be associated with a poor prognosis.

The other reason for the contrasting findings could be related to the observational design of the studies, which hampers causation inferences. Decreases in serum 25(OH)D are expected in severely hospitalized patients. This could be explained by decreased vitamin D carrier proteins, increased conversion of 25(OH)D to 1,25-dihydroxyvitamin D, and hemodilution [31]. Therefore, caution is needed when interpreting 25(OH)D values among hospitalized patients, since the deficiency may be secondary to hospitalization and the severity of the disease. Furthermore, a recent study involving COVID-19 patients admitted to an Italian referral hospital found a significant positive association between

TABLE 1 Baseline demographic and clinical characteristics in patients with moderate to severe COVID-19 according to 25(OH)D categories[1]

Demographic and clinical characteristics	25(OH)D		P
	<10 ng/mL ($n = 16$)	≥10 ng/mL ($n = 204$)	
Age, mean ± SD, y	61.3 ± 14.4	54.7 ± 14.5	0.08
BMI, mean ± SD, kg/m²	29.8 ± 8.0 ($n = 15$)	31.0 ± 6.4 ($n = 188$)	0.48
Time from hospital admission to study inclusion, median (IQR), d	1.5 (1.0–2.0)	1.0 (1.0–2.0)	0.56
Time between the onset of symptoms and hospital admission, median (IQR), d	7.0 (3.5–9.5)	8.0 (6.0–11.0)	0.08
Sex, n (% within stratum)			
Male	6 (37.5)	111 (54.4)	0.21
Female	10 (62.5)	93 (45.6)	
Race, n (% within stratum)			
White	10 (62.4)	96 (47.1)	0.31
Pardo[2]	3 (18.8)	79 (38.7)	
Black	3 (18.8)	29 (14.2)	
Acute COVID-19 symptoms, n (% within stratum)			
Fatigue	11 (68.8)	183 (89.7)	0.03
Cough	11 (68.8)	175 (85.8)	0.08
Nasal congestion/coryza	10 (62.5)	121 (59.3)	1.00
Joint pain/myalgia	9 (56.3)	142 (69.6)	0.40
Fever	8 (50.0)	150 (73.5)	0.08
Diarrhea	5 (31.3)	92 (45.1)	0.31
Sore throat	0 (0.0)	70 (34.3)	<0.01[3]
Coexisting diseases, n (% within stratum)			
Hypertension	8 (50.0)	97 (47.5)	1.00
Diabetes	7 (43.8)	55 (27.0)	0.25
Obesity	4 (26.7) ($n = 15$)	104 (55.3) ($n = 188$)	0.06
Cardiovascular disease	4 (25.0)	21 (10.3)	0.09
Chronic obstructive pulmonary disease	3 (18.8)	4 (2.0)	0.01
Asthma	1 (6.3)	9 (4.4)	1.00
Rheumatic disease	0 (0.0)	18 (8.8)	0.37[3]
Concomitant medications, n (% within stratum)			
Antibiotic	13 (81.3) ($n = 16$)	187 (93.0) ($n = 201$)	0.12
Anticoagulant	9 (56.3) ($n = 16$)	189 (94.0) ($n = 201$)	<0.001
Corticosteroids	7 (43.8) ($n = 16$)	160 (79.6) ($n = 201$)	<0.01
Antihypertensive	7 (43.8) ($n = 16$)	99 (49.3) ($n = 201$)	0.80
Analgesic	5 (31.3) ($n = 16$)	143 (71.1) ($n = 201$)	<0.01
Hypolipidemic	3 (18.8) ($n = 16$)	27 (13.4) ($n = 201$)	0.70
Hypoglycemic	2 (12.5) ($n = 16$)	46 (22.9) ($n = 201$)	0.38
Antiviral	0 (0.0) ($n = 16$)	4 (2.0) ($n = 201$)	1.00[3]
Oxygen supplementation, n (% within stratum)			
No oxygen therapy	0 (0.0)	57 (27.9)	0.01[3]
Oxygen therapy	15 (93.8)	125 (61.3)	0.01
Noninvasive ventilation	1 (6.3)	22 (10.8)	0.71
Imaging features, n (% within stratum)			
Ground-glass opacity ≥50%	5 (31.3)	129 (63.2)	<0.01
Ground-glass opacity <50%	6 (37.4)	64 (31.4)	
Not available	5 (31.3)	11 (5.4)	

[1]Continuous variables used independent t test. Categorical variables used chi-square test. COVID-19, coronavirus disease 2019; 25(OH)D, 25-hydroxyvitamin D.

[2]Pardo is the exact term used in Brazilian Portuguese, meaning "mixed race/ethnicity," according to the Brazilian Institute of Geography and Statistics.

[3]Fisher's exact test.

serum 25(OH)D concentration and in-hospital mortality (OR: 1.73; $P = 0.02$) (20). The authors argue that reverse causality could explain their data since serum 25(OH)D can be considered a negative acute-phase reactant (31).

Studies assessing 25(OH)D concentrations at the time of hospitalization may differ from those using prehospitalization

25(OH)D concentrations in several ways. In this sense, Szeto et al. (32) examined relations between retrospectively available prehospitalization serum vitamin D concentrations and COVID-19 clinical outcomes. The authors did not find a relation between prehospitalization vitamin D status and clinical outcomes, indicating that critical illness can interfere with vitamin

TABLE 2 Estimate for hospital length of stay according to 25-hydroxyvitamin D (ng/mL) categories in patients with moderate to severe COVID-19[1]

Hospital length of stay	n/Total n[2]	Estimated days, median (95% CI)	P[3]
Model 1			0.120
<10 ng/mL	15/16	9.0 (6.4, 11.6)	
10 to <20 ng/mL	96/97	7.0 (6.4, 7.6)	
20 to <30 ng/mL	67/71	7.0 (6.3, 7.7)	
≥ 30	28/30	7.0 (6.3, 7.7)	
Model 2			0.057
<10 ng/mL	15/16	9.0 (6.4, 11.6)	
≥10 ng/mL	191/198	7.0 (6.6, 7.4)	

[1]COVID-19, coronavirus disease 2019.

[2]Number of surviving patients (censored events, death, $n = 8$)/total patients with available information (excluding dropouts, $n = 6$).

[3]Log-rank test for categorical variables.

D concentrations and bias the results of studies evaluating 25(OH)D at hospitalization (32). This highlights the limitations of observational studies and the need for further randomized clinical trials to clarify the role of vitamin D on COVID-19.

Recently, our research group conducted a double-blind, randomized clinical trial to investigate the effect of a single dose of 200,000 IU vitamin D_3 in patients with moderate to severe COVID-19. Serum 25(OH)D concentrations significantly increased after a single high dose of vitamin D_3 but did not significantly reduce hospital length of stay or any other relevant outcomes compared with placebo (33). However, the study was underpowered to make conclusions about the effect of vitamin D_3 in patients with 25(OH)D deficiency. Further longitudinal, controlled studies are necessary to examine whether correcting insufficient 25(OH)D concentration translates into clinical benefits among COVID-19 patients.

The strengths of this study were the longitudinal follow-up of the patients, the assessment of hospitalized patients with COVID-19, and the multiple comparisons between different 25(OH)D categories. The main limitations of this study involve its observational design, which hampers causative relations; the relatively small sample size (determined according to feasibility, including patients' availability, and hospital and staff resources) that could increase the chances of type 2 error, particularly concerning the low incidence of the secondary outcomes; and the small number in the 25(OH)D category of <10 ng/mL. Furthermore, the results could have been affected by sample heterogeneity given the severity of coexisting diseases. However, we adjusted for potential confounders, including age, sex, race, BMI, cardiovascular disease, and chronic obstructive pulmonary disease, to strengthen the results.
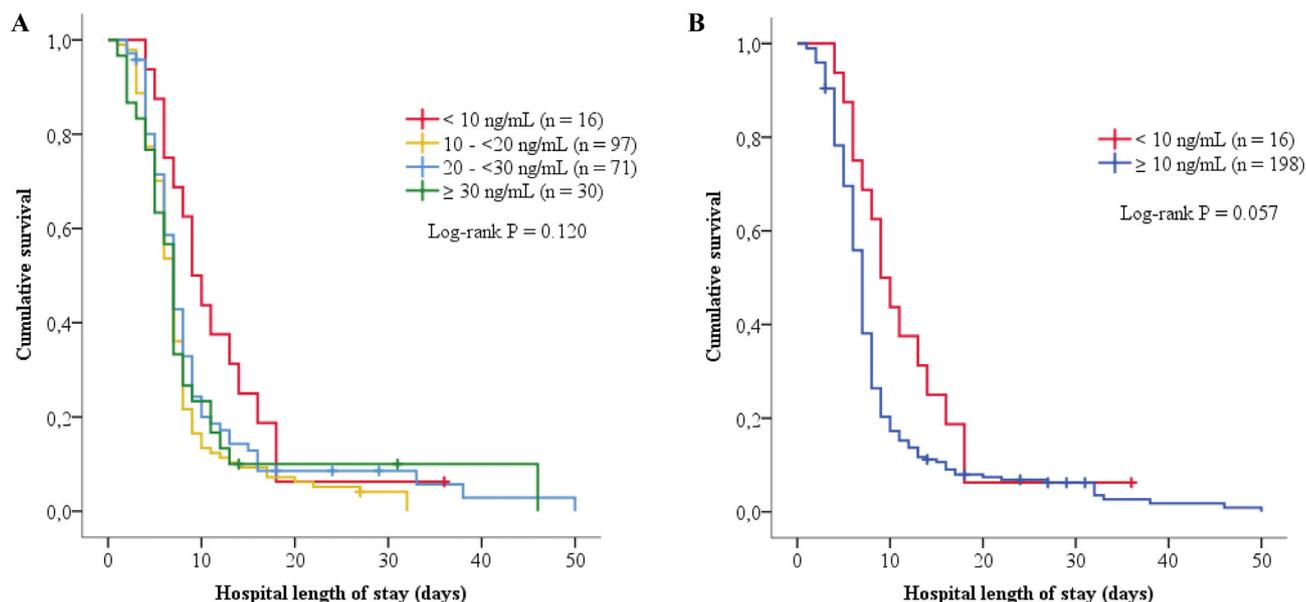
FIGURE 1 Kaplan-Meier curves for hospital length of stay according to 25-hydroxyvitamin D categories in patients with moderate to severe COVID-19. (A) Model 1: <10 ng/mL, 10 to <20 ng/mL, 20 to <30 ng/mL, and ≥30 ng/mL. (B) Model 2: <10 ng/mL and ≥10 ng/mL. Vertical bars represent single censored events (deaths). Both analyses represent 214 total patients (excluding dropouts). COVID-19, coronavirus disease 2019.

TABLE 3 Cox regression models for primary and secondary outcomes according to 25(OH)D categories in patients with moderate to severe COVID-19[1]

25(OH)D (ng/mL)	Number of events	Unadjusted			Adjusted[2]		
		HR	(95% CI)	P	HR	(95% CI)	P
Hospital discharge[3]							
Model 1							
<10	15	Ref			Ref		
10 to <20	96	1.64	(0.92, 2.91)	0.092	1.58	(0.86, 2.91)	0.142
20 to <30	67	1.35	(0.76, 2.41)	0.312	1.45	(0.78, 2.71)	0.242
≥30	28	1.45	(0.76, 2.80)	0.263	1.33	(0.66, 2.67)	0.433
Model 2							
<10	15	Ref			Ref		
≥10	191	1.48	(0.85, 2.57)	0.162	1.50	(0.83, 2.70)	0.181
Mechanical ventilation							
Model 1							
<10	1	Ref			Ref		
10 to <20	7	0.72	(0.06, 8.26)	0.790	0.36	(0.02, 6.33)	0.482
20 to <30	11	1.96	(0.20, 19.24)	0.564	2.56	(0.19, 34.39)	0.480
≥30	3	2.49	(0.21, 28.99)	0.467	3.40	(0.21, 55.65)	0.391
Model 2							
<10	1	Ref			Ref		
≥10	21	1.60	(0.17, 15.24)	0.684	1.45	(0.12, 17.51)	0.768
Mortality							
Model 1							
<10	1	Ref			Ref		
10 to <20	1	0.27	(0.02, 4.93)	0.378	*		
20 to <30	4	0.99	(0.10, 9.70)	0.990	*		
≥30	2	1.47	(0.11, 19.04)	0.775	*		
Model 2							
<10	1	Ref			Ref		
≥10	7	0.77	(0.08, 7.38)	0.824	*		

*There were not enough cases to estimate after stratification by center and adjustment for possible confounders.
[1]All analyses were stratified by center. COVID-19, coronavirus disease 2019; Ref, reference; 25(OH)D, 25-hydroxyvitamin D.
[2]Multivariable Cox regression adjusted for age, sex, race, BMI, cardiovascular disease, and chronic obstructive pulmonary disease.
[3]Hospital discharge refers to the number of surviving patients (death censored).

In conclusion, among hospitalized patients with moderate to severe COVID-19, severe 25(OH)D deficiency was associated with a trend for longer hospital length of stay. This association was not significant in the multivariable Cox regression model. The prognostic value of severe 25(OH)D deficiency and the efficacy of its correction on COVID-19 outcomes warrant further investigations.

Data Availability

Data described in the manuscript, codebook, and analytic code will be made available upon request pending application and approval.

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