Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

MAYO CLINIC

ORIGINAL ARTICLE

Vitamin D Status Is Associated With In-Hospital Mortality and Mechanical Ventilation: A Cohort of COVID-19 Hospitalized Patients

Angeliki M. Angelidi, MD, PhD; Matthew J. Belanger, MD; Michael K. Lorinsky, MD; Dimitrios Karamanis, PhD; Natalia Chamorro-Pareja, MD; Jennifer Ognibene, BA; Leonidas Palaiodimos, MD, MSc; and Christos S. Mantzoros, MD, DSc

Abstract

Objective: To explore the possible associations of serum 25-hydroxyvitamin D [25(OH)D] concentration with coronavirus disease 2019 (COVID-19) in-hospital mortality and need for invasive mechanical ventilation.

Patients and Methods: A retrospective, observational, cohort study was conducted at 2 tertiary academic medical centers in Boston and New York. Eligible participants were hospitalized adult patients with laboratory-confirmed COVID-19 between February 1, 2020, and May 15, 2020. Demographic and 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; 64 [44.4%] male). Overall mortality was 18%, whereas patients with 25(OH)D levels of 30 ng/mL (to convert to nmol/L, multiply by 2.496) and higher had lower rates of mortality compared with those with 25(OH)D levels below 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 (odds ratio, 0.94; 95% CI, 0.90 to 0.98; P=.007) and need for invasive mechanical ventilation (odds ratio, 0.96; 95% CI, 0.93 to 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 (<30 ng/mL vs ≥30 ng/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 must be conducted to assess the role of vitamin D administration in improving the morbidity and mortality of COVID-19.

 ■ Mayo Clin Proc. 2021;96(4):875-886

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 vitamin D deficiency or insufficiency 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

For editorial comment see page 838

From the Department of Medicine, Beth Israel

Affiliations continued at the end of this article.

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 10 years before diagnosis. More recently, a retrospective observational study including 489 patients reported 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 2 large tertiary academic medical centers with laboratory-confirmed COVID-19.

PATIENTS AND METHODS

Study Design and Patient Population

This retrospective, observational, 2-center cohort study included adult patients from 2 tertiary academic medical centers (Beth Israel Deaconess Medical Center in Boston, Massachusetts, and Montefiore Medical Center in the Bronx, New York). All patients admitted to the hospital who were positive for SARS-CoV-2 on qualitative polymerase chain reaction 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 who 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 3 researchers at each institution and stored in a predefined data extraction sheet that was created for the purpose of this study. The extracted data were cross-validated and included baseline demographic information, clinical characteristics, pertinent home medications, symptoms since disease onset and on presentation, vital signs on presentation, and 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 malignant disease, chronic kidney disease or end-stage renal disease (ESRD), liver cirrhosis, and human immunodeficiency virus infection or acquired immunodeficiency syndrome. The diagnosis of all these disorders and diseases was based on the findings after a manual chart review was conducted of all records for the patients included in the study. In addition, we assessed hemoglobin A_{1c}, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol concentrations (if they were available within 12 months before admission); 25(OH)D concentration during admission or within 6 months before the initiation of the study (if it was not obtained during the hospitalization); mortality; and need for invasive mechanical ventilation (ie, endotracheal intubation). We did not assess the association between 25(OH)D concentration and need for continuous positive airway pressure, bilevel positive airway pressure, or high-flow nasal cannula. At the on-site laboratory of each institution, 25(OH)D was measured by 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 [Abbott Diagnostics] at Montefiore and Elecsys Vitamin D Total II [Roche Diagnostics] 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 with a reference standard and an overall imprecision of less than 10%.[14] The data were processed and analyzed without any personal identifiers to maintain patient confidentiality per the 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 Analyses

Patients were classified in 5 quintiles on the basis of age (≤50 years, 51-62 years, 63-68 years, 69-76 years, and ≥77 years) and body mass index (BMI) calculated as the weight in kilograms divided by the height in meters squared (≤24.26 kg/m^2, 24.27-27.71 kg/m^2, 27.72-31.00 kg/m^2, 31.01-34.50 kg/m^2, and ≥34.51 kg/m^2). Moreover, patients were grouped in 2 categories regarding 25(OH)D levels, namely, less than 30 ng/mL and 30 ng/mL or higher (to convert to nmol/L, multiply by 2.496), on the basis of the mean value of the variable and observational and interventional studies that have found a lower incidence of acute respiratory infection and mortality risk in individuals with 25(OH)D levels of 30 ng/mL and higher.[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 a Shapiro-Wilk test. Differences between the groups based on 25(OH)D levels were compared with the Mann-Whitney test or independent-samples *t*-test for the continuous variables and χ^2 test (with Yates continuity correction) or Fisher 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 end points 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 ng/mL, 15.81-23.20 ng/mL, 23.21-31.00 ng/mL, 31.01-45.00 ng/mL, ≥45.01 ng/mL). 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 3 with the addition of angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor, in-hospital drug treatment, and C-reactive protein (CRP) level, which were considered important regressors; model 5 included multivariable analysis model 3 with the addition of significant univariable clinical characteristics: ESRD, COPD, active malignant disease, heart failure, coronary artery disease, diabetes, hypertension, CRP level, and corticosteroids. Models 2 to 5 were adjusted for the hospital of origin in a cross-comparison on 25(OH)D measurement between the 2 centers by inclusion of a binary variable based on the hospital of origin. Data are presented as odds ratio (OR) and 95% CI. Model calibration was assessed by the Hosmer-Lemeshow goodness of fit test. A *P* value greater than .05 indicates a well-calibrated model. A 2-tailed *P* value of less than .05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for the Social Sciences software, version 26.0 (IBM).

RESULTS

Baseline demographic and clinical characteristics are summarized in Table 1. The total

TABLE 1. Baseline Demographic and Clinical Characteristics[a,b,c]

Characteristic	All patients (N=144)	25(OH)D <30 ng/mL (n=79)	25(OH)D ≥30 ng/mL (n=65)	*P* value
Age (y)	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 (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 malignant disease	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 (before 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 the hospital)				
Antivirals	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

Continued on next page

Mayo Clin Proc. ■ April 2021;96(4):875-886 ■ https://doi.org/10.1016/j.mayocp.2021.01.001
www.mayoclinicproceedings.org

TABLE 1. Continued

Characteristic	All patients (N=144)	25(OH)D <30 ng/mL (N=79)	25(OH)D ≥30 ng/mL (N=65)	*P* value
Drugs (in the hospital), continued				
Azithromycin	80 (55.6)	46 (58.2)	34 (52.3)	.59
Antibiotics (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 (d)	10.0 (5.25-18)	10 (6-17)	10 (5-21)	.95

[a]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; 25(OH)D, 25-hydroxyvitamin D; SNF, skilled nursing facility.

[b]SI conversion factor: To convert 25(OH)D values to nmol/L, multiply by 2.496.

[c]Categorical variables are presented as number (%) of patients. Continuous variables are presented as median (interquartile range). *P* values refer to χ^2 test (with Yates continuity correction) or Fisher exact test for categorical independent variables and Mann-Whitney *U* test for continuous variables.

number of patients hospitalized across the 2 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 polymerase chain reaction–confirmed COVID-19 (64 [44.4%] male; median age, 66 years; IQR, 55-74 years). Of the 144 patients, 60 (41.7%) were non-Hispanic Black, 42 (29.2%) non-Hispanic White, and 33 (22.9%) Hispanic/Latino. The mean 25(OH)D level was 30.44 ng/mL (SD, 17.03), and the median was 28.0 ng/mL (IQR, 16.8-39 ng/mL). There were 106 (73.6%) patients who had hypertension, 79 (54.9%) with hyperlipidemia, and 63 (43.8%) with diabetes mellitus type 2, whereas 20 (13.9%) and 19 (13.2%) of the patients had a history of coronary artery disease or cerebrovascular disease, respectively. Asthma, COPD, and obstructive sleep apnea were prevalent in 26 (18.1%), 22 (15.3%), and 18 (12.5%) patients, respectively.

The main presenting symptoms and signs and laboratory findings are summarized in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). Cough, shortness of breath, fever, and malaise were the most prevalent symptoms (88 [61.1%], 87 [60.4%], 86 [59.7%], and 79 [54.9%] patients, respectively). Most of the patients (92 [63.9%]) had increased oxygen requirements, 39 patients (27.1%) required invasive mechanical ventilation, and 56 patients (38.9%) were transferred to the intensive care unit. Moreover, 68 (47.2%) of the patients experienced acute kidney injury and 16 (11.1%) required renal replacement therapy. Overall, in-hospital mortality of the cohort was 18%. Patients with 25(OH)D levels of 30 ng/mL and higher had lower rates of mortality compared with those with levels below 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 (Tables 2 and 3, respectively), 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 ng/mL, 15.81-23.20 ng/mL, 23.21-31.00 ng/mL, 31.01-45.00 ng/mL, ≥45.01 ng/mL). Potential effect modification by timing of 25(OH)D measurements (before 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 of 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).

In this study, each model's calibration power was good according to the Hosmer-Lemeshow test (*P*>.05).

TABLE 2. Univariable and Multivariable Logistic Regression Analyses for In-hospital Mortality[a]

	Univariable	Multivariable[b]				
		Model 1	Model 2	Model 3	Model 4	Model 5
Variable	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 malignant disease	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 before 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

[a]ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

[b]Model 1: multivariable analysis with 25(OH)D (as a continuous variable), age (analyzed in quintiles), and 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 sex and smoking as regressors. Model 4: multivariable analysis model 3 with addition of ARB or ACEi, in-hospital drug treatment, and C-reactive protein level. 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 level, and corticosteroids.

TABLE 3. Univariable and Multivariable Logistic Regression Analyses for Receiving Invasive Mechanical Ventilation[a]

	Univariable	Multivariable[b]				
		Model 1	Model 2	Model 3	Model 4	Model 5
Variable	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 malignant disease	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 before 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

[a]ACEi, angiotensin-converting enzyme inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

[b]Model 1: multivariable analysis with 25(OH)D (as a continuous variable), age (analyzed in quintiles), and 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 sex and smoking as regressors. Model 4: multivariable analysis model 3 with addition of C-reactive protein level, 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 level, and corticosteroids.

Primary Outcome: In-Hospital Mortality

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

In the multivariable analysis (model 5, Table 2), vitamin D status as a continuous variable (OR, 0.91; 95% CI, 0.85 to 0.97; *P*=.003), age (OR, 1.81; 95% CI, 1.05 to 3.13; *P*=.03), COPD (OR, 6.69; 95% CI, 1.10 to 40.89; *P*=.04), and active malignant disease (OR, 16.31; 95% CI, 2.25 to 118.4; *P*=.01) were found to be significantly associated with in-hospital mortality risk. Likewise, in the multivariable analysis (model 5; Supplemental Table 2, available online at http://www.mayoclinicproceedings.org), including the logarithmic transformation of 25(OH)D, 25(OH)D (OR, 0.004; 95% CI, 0.00 to 0.10; *P*=.001), age (OR, 1.98; 95% CI, 1.12 to 3.51; *P*=.02), COPD (OR, 6.12; 95% CI, 0.99 to 37.96; *P*=.05), and active malignant disease (OR, 18.09; 95% CI, 2.36 to 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 (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). 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 malignant disease (positive). Moreover, no significant association of CRP level 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). Additional sensitivity analyses excluding the COPD variable resulted in similar findings (data not shown). Similar results were obtained when the race variable was added in all multivariable analyses (data not shown).

Secondary Outcome: Need for Invasive Mechanical Ventilation

As a continuous variable, 25(OH)D showed a borderline association with the need for invasive mechanical ventilation (OR, 0.98; 95% CI, 0.96 to 1.00; *P*=.09); as a logarithmic variable, this association was significant (OR, 0.20; 95% CI, 0.04 to 0.93; *P*=.04). Moreover, azithromycin (OR, 3.07; 95% CI, 1.36 to 6.93; *P*=.007), antibiotic administration other than azithromycin (OR, 5.17; 95% CI, 1.15 to 23.36; *P*=.03), corticosteroid administration (OR, 4.00; 95% CI, 1.76 to 9.07; *P*=.001), and CRP levels (OR, 1.01; 95% CI, 1.01 to 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 (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org), 25(OH)D levels (OR, 0.93 [95% CI, 0.90 to 0.98; *P*=.002] and OR, 0.01 [95% CI, 0.001 to 0.17; *P*=.001], respectively), antibiotic administration other than azithromycin (OR, 7.87 [95% CI, 1.12 to 55.48; *P*=.04] and OR, 8.30 [95% CI, 1.10 to 62.91; *P*=.04], respectively), corticosteroid administration (OR, 4.05 [95% CI, 1.18 to 13.91; *P*=.03] and OR, 3.86 [95% CI, 1.13 to 13.13; *P*=.03], respectively), and CRP levels (OR, 1.01 [95% CI, 1.00 to 1.02; *P*=.01] and OR, 1.01 [95% CI, 1.00 to 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 Supplemental Table 3, available online at http://www.mayoclinicproceedings.org). 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 Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

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). Additional sensitivity analyses excluding the COPD variable resulted in similar findings (data not shown). Similar results were obtained when the race variable was added in all multivariable analyses (data not shown herein).

DISCUSSION

In this retrospective, 2-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 malignant disease were also independently associated with in-hospital mortality. Moreover, an association with invasive mechanical ventilation was observed for ESRD, CRP level, and corticosteroid use. It seems that corticosteroids were more often administered in critically ill patients needing invasive mechanical ventilation, whereas no causal association can be made on the basis of our study's design. Our study expands on 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] In addition, 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, diabetes, CRP level, and administration of corticosteroids.

Vitamin D sufficiency is generally defined as a serum 25(OH)D concentration greater than 20 ng/mL, whereas 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 reported that individuals with 25(OH)D levels below 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, prolonged mechanical ventilation, and increased mortality in critically ill patients.[5,18] Whereas 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 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 multiorgan dysfunction and death. The most severe cases are characterized by a massive proinflammatory release of cytokines (ie, cytokine storm) that 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 2 forms (vitamin D_2 and vitamin D_3) and exerts its biologic effects on various cells and tissues through interaction with the nuclear vitamin D receptor.[20] At higher levels, 25(OH)D may also display physiologic effects similar to those of glucocorticoids because of interactions with other steroid hormone receptors.[21] Whereas 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 proinflammatory 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.[22-25] 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,[25,27-30] and may have antioxidative effects against COVID-19.[31] Furthermore, evidence supports a potential role of vitamin D in protecting against acute lung injury or acute respiratory distress syndrome in COVID-19 by targeting the unbalanced renin-angiotensin system, including both the expression and concentration of angiotensin-converting enzymes (ACE and ACE2).[31-33]

Our study also found that increasing age, COPD, ESRD, and advanced malignant disease are strongly associated with in-hospital mortality. These findings are not unexpected, given the numerous observational studies and reports with similar findings.[34-36] 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 2-center design, which allowed the inclusion of a diverse population of patients in both Boston and New York, including primarily Black and Hispanic/Latino patients. This increases generalizability and provides important clinical information about 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. Because chronic kidney disease or 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 (73 [51%]) did not have 25(OH)D measurements available during their hospitalization (instead within 6 months before the initiation of the study), which raises the possibility that some of the participants might have received vitamin D supplementation before hospitalization that was not recorded in the electronic medical record. Any potential misclassification because of this 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 before admission were associated with the outcomes of interest, which provides reassurance that reverse causality is not confounding the results reported. 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.[37-39] Given the lack of consistent benefit of vitamin D

Mayo Clin Proc. ■ April 2021;96(4):875-886 ■ https://doi.org/10.1016/j.mayocp.2021.01.001
www.mayoclinicproceedings.org

supplementation in the critically ill in randomized trials, observational trials of 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 randomized controlled trials to examine the causal hypotheses raised by our study.

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

CONCLUSION

In this 2-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.

ACKNOWLEDGMENTS

Drs Angeliki M. Angelidi and Matthew J. Belanger share first authorship.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **COPD** = chronic obstructive pulmonary disease; **COVID-19** = coronavirus disease 2019; **ESRD** = end-stage renal disease; **IQR** = interquartile range; **25(OH)D** = 25-hydroxyvitamin D; **OR** = odds ratio; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2

Affiliations (Continued from the first page of this article.): Deaconess Medical Center/Harvard Medical School, Boston, MA (A.M.A., M.J.B., M.K.L., C.S.M.); the Department of Economics, University of Piraeus, Greece (D.K.); Albert Einstein College of Medicine, Bronx, NY (N.C.-P., J.O., L.P.); the Department of Medicine, Jacobi Medical Center (N.C.-P., L.P.), and Division of Hospital Medicine, Montefiore Medical Center (L.P.), Albert Einstein College of Medicine, Bronx, NY; and the Section of Endocrinology, VA Boston Healthcare System, Harvard Medical School, Boston, MA (C.S.M.).

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Christos S. Mantzoros, MD, DSc, Professor of Medicine, Harvard Medical School, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02215 (mbelang1@bidmc.harvard.edu; Twitter: @MatthewBelang1).

ORCID

Angeliki M. Angelidi: https://orcid.org/0000-0001-9886-7785

REFERENCES

1. World Health Organization. Coronavirus disease 2019 (COVID-19): weekly epidemiological update. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200620-covid-19-sitrep-152.pdf?sfvrsn=83aff8ee_4. Accessed September 8, 2020.
2. Chakhtoura M, Napoli N, El Hajj Fuleihan G. Commentary: myths and facts on vitamin D amidst the COVID-19 pandemic. *Metabolism*. 2020;109:154276.
3. Pham H, Rahman A, Majidi A, Waterhouse M, Neale RE. Acute respiratory tract infection and 25-hydroxyvitamin D concentration: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2019;16(17):3020.
4. Ginde AA, Camargo CA Jr, Shapiro NI. Vitamin D insufficiency and sepsis severity in emergency department patients with suspected infection. *Acad Emerg Med*. 2011;18(5):551-554.

5. Nair P, Venkatesh B, Center JR. Vitamin D deficiency and supplementation in critical illness—the known knowns and known unknowns. *Crit Care*. 2018;22(1):276.
6. Manson JE, Bassuk SS. Commentary. Eliminating vitamin D deficiency during the COVID-19 pandemic: a call to action. *Metabolism*. 2020;112:154322.
7. Rhodes JM, Subramanian S, Laird E, Kenny RA. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. *Aliment Pharmacol Ther*. 2020;51(12):1434-1437.
8. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res*. 2020;32(7):1195-1198.
9. D'Avolio A, Avataneo V, Manca A, et al. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. *Nutrients*. 2020;12(5):1359.
10. Hastie CE, Mackay DF, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr*. 2020;14(4):561-565.
11. Raisi-Estabragh Z, McCracken C, Bethell MS, et al. Greater risk of severe COVID-19 in Black, Asian and minority ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. *J Public Health (Oxf)*. 2020;42(3):451-460.
12. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D status and other clinical characteristics with COVID-19 test results. *JAMA Netw Open*. 2020;3(9):e2019722.
13. Freeman J, Wilson K, Spears R, Shalhoub V, Sibley P. Performance evaluation of four 25-hydroxyvitamin D assays to measure 25-hydroxyvitamin D2. *Clin Biochem*. 2015;48(16-17):1097-1104.
14. Centers for Disease Control and Prevention. Vitamin D standardization-certification program. https://www.cdc.gov/labstandards/vdscp_participants.html. Accessed November 23, 2020.
15. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008;87(4):1080S-1086S.
16. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? *J Steroid Biochem Mol Biol*. 2014;144(pt A):138-145.
17. Giustina A, Adler RA, Binkley N, et al. Controversies in vitamin D: summary statement from an international conference. *J Clin Endocrinol Metab*. 2019;104(2):234-240.
18. Dancer RC, Parekh D, Lax S, et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax*. 2015;70(7):617-624.
19. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. 2020;20(6):363-374.
20. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930.
21. Demer LL, Hsu JJ, Tintut Y. Steroid hormone vitamin D: Implications for cardiovascular disease. *Circ Res*. 2018;122(11):1576-1585.
22. Lemire JM, Adams JS, Kermani-Arab V, Bakke AC, Sakai R, Jordan SC. 1,25-Dihydroxyvitamin D_3 suppresses human T helper/inducer lymphocyte activity in vitro. *J Immunol*. 1985;134(5):3032-3035.
23. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D and 1, 25(OH)2D regulation of T cells. *Nutrients*. 2015;7(4):3011-3021.
24. Jeffery LE, Burke F, Mura M, et al. 1,25-Dihydroxyvitamin D_3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol*. 2009;183(9):5458-5467.
25. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation Could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12(4):988.
26. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients*. 2015;7(6):4240-4270.
27. Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D—mediated human antimicrobial response. *Science*. 2006;311(5768):1770-1773.
28. Adams JS, Ren S, Liu PT, et al. Vitamin D—directed rheostatic regulation of monocyte antibacterial responses. *J Immunol*. 2009;182(7):4289-4295.
29. Laaksi I. Vitamin D and respiratory infection in adults. *Proc Nutr Soc*. 2012;71(1):90-97.
30. Herr C, Shaykhiev R, Bals R. The role of cathelicidin and defensins in pulmonary inflammatory diseases. *Expert Opin Biol Ther*. 2007;7(9):1449-1461.
31. Martín Giménez VM, Inserra F, Tajer CD, et al. Lungs as target of COVID-19 infection: protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. *Life Sci*. 2020;254:117808.
32. Malek Mahdavi A. A brief review of interplay between vitamin D and angiotensin-converting enzyme 2: implications for a potential treatment for COVID-19. *Rev Med Virol*. 2020;30(5):e2119.
33. Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity—plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2, and thrombosis. *J Intern Med*. 2020;289(1):97-115.
34. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242.
35. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985.
36. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism*. 2020;108:154262.
37. Langlois PL, Szwec C, D'Aragon F, Heyland DK, Manzanares W. Vitamin D supplementation in the critically ill: a systematic review and meta-analysis. *Clin Nutr*. 2018;37(4):1238-1246.
38. Putzu A, Belletti A, Cassina T, et al. Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials. *J Crit Care*. 2017;38:109-114.
39. Ginde AA, Brower RG, Caterino JM, et al. Early high-dose vitamin D_3 for critically ill, vitamin D—deficient patients. *N Engl J Med*. 2019;381(26):2529-2540.
40. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. 2017;356:i6583.