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.

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Original Article

Association of Vitamin D Status With Hospital Morbidity and Mortality in Adult Hospitalized Patients With COVID-19

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ABSTRACT

Objective: To determine the association between vitamin D status and morbidity and mortality in adult hospitalized coronavirus disease 2019 (COVID-19) patients

Methods: We performed a retrospective chart review study in COVID-19 patients aged ≥18 year hospitalized at Boston University Medical Center between March 1 and August 4, 2020. All studied patients tested positive for COVID-19 and had serum levels of 25-hydroxyvitamin D (25[OH]D) results measured within 1 year prior to the date of positive tests. Medical information was retrieved from the electronic medical record and was analyzed to determine the association between vitamin D status and hospital morbidity and mortality.

Results: Among the 287 patients, 100 (36%) were vitamin D sufficient (25[OH]D >30 ng/mL) and 41 (14%) died during hospitalization. Multivariate analysis in patients aged ≥65 years revealed that vitamin D sufficiency (25[OH]D ≥30 ng/mL) was statistically significantly associated with decreased odds of death (adjusted OR 0.33, 95% CI, 0.12-0.94), acute respiratory distress syndrome (adjusted OR 0.22, 95% CI, 0.05-0.96), and severe sepsis/septic shock (adjusted OR 0.26, 95% CI, 0.08-0.88), after adjustment for potential confounders. Among patients with body mass index <30 kg/m^2, vitamin D sufficiency was statistically significantly associated with a decreased odds of death (adjusted OR 0.18, 95% CI, 0.04-0.84). No significant association was found in the subgroups of patients aged <65 years or with body mass index ≥30 kg/m^2.

Conclusion: We revealed an independent association between vitamin D sufficiency defined by serum 25(OH)D ≥30 ng/mL and decreased risk of mortality from COVID-19 in elderly patients and patients without obesity.

Introduction

Vitamin D is recognized not only for its important functions in calcium and phosphate metabolism but also for its biologic actions on immune modulation. This is due to the presence of the vitamin D receptor in most types of cells including the immune cells and endothelial cells.[1–3] Once synthesized by the skin or ingested, circulating vitamin D is metabolized into 25-hydroxyvitamin D (25[OH]D) by the liver, which is the major circulating metabolite of vitamin D that is clinically measured for determining vitamin D status.[2,4] Circulating 25(OH)D is then further metabolized by the enzyme 1α-hydroxylase (CYP27B1) at the kidneys into the active form 1,25-dihydroxyvitamin D (1,25[OH]$_2$D). In addition, CYP27B1 is expressed by many other tissues, including activated macrophages, parathyroid glands, microglia, breast, colon, and keratinocytes, where 1,25(OH)$_2$D is produced and exerts its tissue-specific autocrine and paracrine functions.[1,2]

Abbreviations: ARDS, acute respiratory distress syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), disproportionately affects the elderly, African Americans, those who are obese, and institutionalized individuals (nursing home residents),[5,6] all of whom are also identified as a high-risk population for vitamin D deficiency.[2–4,7] This association could potentially contribute to higher COVID-19 morbidity and mortality rates appreciated in this population.

Several mechanisms have been proposed to support the potential protective role of vitamin D against morbidity and mortality of COVID-19. First, $1,25(OH)_2D$ induces the macrophage production of the endogenous antimicrobial peptide cathelicidin LL-37, which acts against invading respiratory viruses by disrupting viral envelopes and altering viability of host target cells.[8,9] Second, $1,25(OH)_2D$ alters the expression of angiotensin converting enzyme-2, which serves as the host cell receptor that mediates infection by SARS-CoV-2.[10,11] Third, $1,25(OH)_2D$ alters the activity of different types of lymphocytes. It promotes a shift from T helper 1 and T helper 17 to T helper 2 immune profile and promotes differentiation of regulatory T cells.[12–14] This action is thought to reduce the severity of cytokine storm, thereby alleviating systemic inflammatory response due to viral infection. Finally, experimental studies have shown that vitamin D and its metabolites modulate endothelial function and vascular permeability via multiple genomic and extra-genomic pathways.[15,16] The effects might be of clinical benefit in septic patients with hemodynamic instability.

Although there is evidence for the protective role of vitamin D for other respiratory viral infections or critical illness,[17,18] given the newness of COVID-19, little is known about the direct association between vitamin D status and the severity of COVID-19. Using information from the electronic medical record at the Boston University Medical Center, we aimed to investigate the association between vitamin D status and hospital morbidity and mortality in adult hospitalized patients with COVID-19.

Methods

Study Population

This study was a retrospective chart review cross-sectional study in adult patients with COVID-19 aged ≥18 years who were hospitalized at Boston University Medical Center (latitude 42° 21' N) between March 1 and August 4, 2020. All patients included in this study tested positive for SARS-CoV-2 nucleic acid testing and had serum levels of 25-hydroxyvitamin D results measured within 1 year prior to the date of positive COVID-19 tests. The study protocol was approved by the Boston University Medical Campus institutional review board (H-40341).

Study Measurements

Characteristics of patients were extracted from the Boston University Medical Center hospital database. The following patient baseline characteristics were extracted: age, sex, race, insurance type, latest body mass index (BMI), smoking history, alcohol use, homelessness, receipt of prescription for vitamin D_2 and vitamin D_3 supplementation, in-hospital treatment for COVID-19 (ie, azithromycin, hydroxychloroquine, colchicine, corticosteroids, interleukin-6 antibodies, and interleukin-1 receptor antagonists), and presence of underlying comorbidities, including type 2 diabetes mellitus, hypertension, dyslipidemia, coronary heart disease, heart failure, cerebrovascular disease, asthma, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), end-stage renal disease (ESRD), malignancy, and human immunodeficiency virus (HIV) infection.

Total serum 25(OH)D ($25[OH]D_2$ and $25[OH]D_3$) levels were measured by in-house chemiluminescent immunoassay (Abbott Architect). The cutoff level of serum total 25(OH)D of 30 ng/mL was used for the definition of vitamin D sufficiency based on the Endocrine Society Clinical Practice Guidelines on Vitamin D that defined vitamin D insufficiency and vitamin D deficiency as a circulating level of 25(OH)D of 20 to 29 ng/mL and less than 20 ng/mL, respectively.[4] Laboratory results measured at the time of hospitalization or as soon thereafter as possible (within 48 hours after admission) were extracted from the hospital database. These included complete blood count, complete metabolic profile, creatinine, blood glucose, C-reactive protein, D-dimer, erythrocyte sedimentation rate, ferritin, and lactate dehydrogenase.

The primary outcome of this study was in-hospital death. Secondary outcomes included intensive care unit (ICU) admission, need for intubation, hospital length of stay, hypoxemia (O_2 saturation <90%) and diagnosis of acute respiratory distress syndrome (ARDS), myocardial infarction, acute kidney injury, severe sepsis/septic shock, deep venous thrombosis, and pulmonary embolism. All outcomes were extracted from the hospital database and validated by manual chart review.

Statistical Analysis

Continuous variables were reported as arithmetic means with standard deviation. Categorical variables were reported as number of patients with percentage. Comparison of baseline characteristics and laboratory measurements among patients with vitamin D sufficiency (25[OH]D ≥30 ng/mL), patients with vitamin D insufficiency (25[OH]D 20-<30 ng/mL), and patients with vitamin D deficiency (25[OH]D <30 ng/mL) was performed using the analysis of variance, independent sample *t* test, or Mann-Whitney *U* test for continuous data and X^2 or Fischer exact test for categorical data. Multivariate logistic regression was used to determine odds ratios (OR) and 95% CI to compare mortality and morbidities between patients with vitamin D sufficiency (25[OH]D ≥30 ng/mL) and patients with vitamin D insufficiency/deficiency (25[OH]D <30 ng/mL). This model was adjusted for potential confounding variables, including age, sex, BMI, insurance, race, smoking, alcohol drinking, type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, cerebrovascular disease, COPD, asthma, CKD, ESRD, malignancy, HIV infection, and heart failure.

Because COVID-19 specifically affects older individuals[19] and those who are obese[20] and vitamin D is expected to distribute and modulate immune function differently among those who are obese and those who are lean,[21,22] we expected that age and BMI may be effect modifiers of the association between vitamin D status and hospital outcomes. Therefore, subgroup analyses in patients aged <65 and ≥65 years and patients with BMI <30 and ≥30 kg/m^2 were conducted. The cutoff value for age was based on the World Health Organization's definition of the elderly.[23] The cutoff value for BMI was based on the Centers for Disease Control and Prevention's definition of obesity.[24] Statistical significance was defined as *P* value of < .05. SPSS version 23 (SPSS Inc) was used to perform all statistical analyses.

Results

We identified 1478 patients with COVID-19 who were hospitalized at the Boston University Medical Center between March 1 and August 4, 2020. A total of 287 (19%) patients had available serum 25(OH)D level within 1 year prior to hospitalization and were included in this study, with 100 (35%), 91 (32%), and 96 (33%) patients being vitamin D sufficient (25[OH]D >30 ng/mL), vitamin D insufficient (25[OH]D 20-<30 ng/mL), or vitamin D deficient

Table 1
Baseline Characteristics of Patients With Serum 25-Hydroxyvitamin D <20, 20 to <30, and ≥30 ng/mL

Characteristics	All patients (N = 287)				Age <65 years old (N = 151)				Age ≥65 years old (N=136)			
	25(OH)D <20 ng/mL (N = 96)	25(OH)D 20 - <30 ng/mL (N = 91)	25(OH)D ≥30 ng/mL (N = 100)	*P* value	25(OH)D <20 ng/mL (N = 62)	25(OH)D 20 - <30 ng/mL (N = 46)	25(OH)D ≥30 ng/mL (N = 43)	*P* value	25(OH)D <20 ng/mL (N = 34)	25(OH)D 20 - <30 ng/mL (N = 45)	25(OH)D ≥30 ng/mL (N = 57)	*P* value
Age (years old)	55.9 ± 15.8	63.7 ± 14.3	66.2 ± 15.7	<0.001*	47.6 ± 12.3	52.5 ± 10.3	52.3 ± 11.6	0.037*	71.9 ± 6.8	74.8 ± 7.2	76.9 ± 8.1	0.012*
Female sex	43 (44.8%)	42 (46.2%)	51 (51.0%)	0.658	31 (50.0%)	20 (43.5%)	19 (44.2%)	0.754	12 (35.3%)	22 (48.9%)	32 (56.1%)	0.157
BMI (kg/m^2)	30.8 ± 8.8	30.2 ± 8.7	29.3 ± 10.1	0.541	32.6 ± 9.5	31.5 ± 10.1	32.5 ± 13.0	0.872	27.3 ± 6.2	28.8 ± 6.9	26.9 ± 6.4	0.337
BMI ≥30 kg/m^2	44 (45.8%)	43 (47.3%)	38 (38.0%)	0.375	33 (53.2%)	26 (56.5%)	20 (46.5%)	0.629	11 (32.4%)	17 (37.8%)	18 (31.6%)	0.788
Race												
White	31 (32.3%)	28 (30.8%)	26 (26.0%)	0.634	23 (37.1%)	18 (39.1%)	15 (34.9%)	0.673	8 (23.5%)	10 (22.2%)	11 (19.3%)	0.823
Black	60 (62.5%)	61 (67.0%)	71 (71.0%)		36 (58.1%)	28 (60.9%)	26 (60.5%)		24 (70.6%)	33 (73.3%)	45 (78.9%)	
Other	5 (5.2%)	2 (2.2%)	3 (3.0%)		3 (4.8%)	0 (0.0%)	2 (4.2%)		2 (5.9%)	2 (4.4%)	1 (1.8%)	
History of smoking	42 (43.8%)	45 (49.5%)	47 (47.0%)	0.735	23 (37.1%)	24 (52.2%)	18 (41.9%)	0.289	19 (55.9%)	21 (46.7%)	29 (50.9%)	0.719
Alcohol use	40 (41.7%)	30 (33.0%)	30 (30.0%)	0.208	23 (37.1%)	18 (39.1%)	16 (37.2%)	0.973	17 (50.0%)	12 (26.7%)	14 (24.6%)	0.028*
Homeless	7 (7.3%)	9 (9.9%)	7 (7.0%)	0.725	4 (6.5%)	8 (17.4%)	5 (11.6%)	0.205	3 (8.8%)	1 (2.2%)	2 (3.5%)	0.334
Underlying diseases												
Type 2 diabetes	53 (55.2%)	47 (51.6%)	61 (61.0%)	0.419	31 (50.0%)	15 (32.6%)	22 (51.2%)	0.126	22 (64.7%)	32 (71.1%)	39 (68.4%)	0.832
Hypertension	64 (66.7%)	75 (82.4%)	90 (90.0%)	<0.001*	35 (56.5%)	34 (73.9%)	36 (83.7%)	0.009*	29 (85.3%)	41 (91.1%)	54 (94.7%)	0.307
Dyslipidemia	45 (46.9%)	55 (60.4%)	67 (67.0%)	0.015*	26 (41.9%)	19 (41.3%)	22 (51.2%)	0.569	19 (55.9%)	36 (80.0%)	45 (78.9%)	0.026*
Coronary heart disease	12 (12.5%)	17 (18.7%)	17 (17.0%)	0.488	4 (6.5%)	6 (13.0%)	6 (14.0%)	0.382	8 (23.5%)	11 (24.4%)	11 (19.3%)	0.801
Heart failure	18 (18.8%)	15 (16.5%)	28 (28.0%)	0.116	7 (11.3%)	3 (6.5%)	8 (18.6%)	0.209	11 (32.4%)	12 (26.7%)	20 (35.1%)	0.658
Cerebrovascular disease	4 (4.2%)	6 (6.6%)	12 (12.0%)	0.107	2 (3.2%)	2 (4.3%)	2 (4.7%)	0.923	2 (5.9%)	4 (8.9%)	10 (17.5%)	0.190
Asthma	21 (21.9%)	19 (20.9%)	19 (19.0%)	0.880	13 (21.0%)	12 (26.1%)	9 (20.9%)	0.785	8 (23.5%)	7 (15.6%)	10 (17.5%)	0.648
COPD	7 (7.3%)	9 (9.9%)	13 (13.0%)	0.414	1 (1.6%)	4 (8.7%)	4 (9.3%)	0.169	6 (17.6%)	5 (11.1%)	9 (15.8%)	0.687
CKD	27 (28.1%)	42 (46.2%)	39 (39.0%)	0.037*	13 (21.0%)	15 (32.6%)	15 (34.9%)	0.227	14 (41.2%)	27 (60.0%)	24 (42.1%)	0.134
ESRD	9 (9.4%)	14 (15.4%)	10 (10.0%)	0.369	6 (9.7%)	9 (17.4%)	7 (16.3%)	0.450	3 (8.8%)	6 (13.3%)	3 (5.3%)	0.361
Malignancy	18 (18.8%)	21 (23.1%)	23 (23.0%)	0.707	8 (12.9%)	7 (15.2%)	8 (18.6%)	0.726	10 (29.4%)	14 (31.1%)	15 (26.3%)	0.863
HIV infection	11 (11.5%)	7 (7.7%)	3 (3.0%)	0.074	10 (16.1%)	4 (8.7%)	2 (4.7%)	0.151	1 (2.9%)	3 (6.7%)	1 (1.8%)	0.410
Receipt of prescription for vitamin D supplementation												
Vitamin D_2 ≥2,000 IUs/d	55 (57.3%)	46 (50.5%)	35 (35.0%)	0.006*	41 (66.1%)	26 (56.5%)	20 (46.5%)	0.133	14 (41.2%)	20 (44.4%)	15 (26.3%)	0.128
Vitamin D_3 ≥2,000 IUs/d	5 (5.2%)	12 (13.2%)	21 (21.0%)	0.005*	2 (3.2%)	8 (17.4%)	10 (23.3%)	0.007*	3 (8.8%)	4 (8.9%)	11 (19.3%)	0.208
In-hospital medical therapy for COVID-19												
Azithromycin	38 (39.6%)	46 (50.5%)	50 (50.0%)	0.231	23 (37.1%)	18 (39.1%)	23 (53.5%)	0.214	15 (44.1%)	28 (62.2%)	27 (47.4%)	0.202
Colchicine	12 (12.5%)	5 (5.5%)	17 (17.0%)	0.047*	9 (14.5%)	4 (8.7%)	8 (18.6%)	0.396	3 (8.8%)	1 (2.2%)	9 (15.8%)	0.068
Hydroxychloroquine	42 (43.8%)	45 (49.5%)	57 (57.0%)	0.177	27 (43.5%)	21 (45.7%)	29 (67.4%)	0.038*	15 (44.1%)	24 (53.3%)	28 (49.1%)	0.719
Corticosteroids	18 (18.8%)	17 (18.7%)	10 (10.0%)	0.154	10 (16.1%)	6 (13.0%)	8 (18.6%)	0.772	1 (2.9%)	2 (4.4%)	0 (0.0%)	0.299
IL-6 antibodies	12 (12.5%)	12 (13.2%)	31 (31.0%)	0.001*	5 (8.1%)	6 (13.0%)	17 (39.5%)	<0.001*	7 (20.6%)	6 (13.3%)	14 (24.6%)	0.366
IL-1 receptor antagonists	3 (3.1%)	4 (4.4%)	7 (7.0%)	0438	1 (1.6%)	2 (4.3%)	5 (11.6%)	0.074	2 (5.9%)	2 (4.4%)	2(3.5%)	0..867
Remdesivir	7 (7.3%)	8 (8.8%)	2 (2.0%)	0.109	3 (4.8%)	5 (10.9%)	1 (2.3%)	0.209	4 (11.8%)	3 (6.7%)	1 (1.8%)	0.140

Abbreviations: BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; IL-1 = interleukin-1; IL-6 = interleukin-6.

* $P < .05$. Data were expressed as mean ± SD or number of patients (%).

(25[OH]D <20 ng/mL), respectively. Overall, 41 (14%) patients died during hospitalization. Baseline characteristics of patients are shown in Table 1. Vitamin D sufficient patients were significantly older than vitamin D insufficient/deficient patients and had higher rates of hypertension, dyslipidemia, heart failure, and cerebrovascular disease (all $P < .05$). Among patients aged ≥65 years old, vitamin D deficient patients were statistically significantly younger and had lower rates of hypertension (both $P < .05$).

Comparison of laboratory results among vitamin D sufficient, vitamin D insufficient, and vitamin D deficient patients is demonstrated in Table 2. Serum albumin was statistically significantly higher in vitamin D sufficient patients (both $P < .05$) than the rest of the patients in both age groups of <65 years old and ≥65 years old. Among patients aged ≥65 years old, in addition, vitamin D sufficient patients had statistically significantly lower plasma ferritin and higher oxygen saturation than vitamin D deficient/insufficient patients.

Hospital outcomes stratified by age and vitamin D status are shown in Table 3. Among patients aged ≥65 years old, vitamin D sufficient patients had statistically significantly lower rates of death (12% vs 32%), ICU admission (21% vs 38%), intubation (11% vs 28%), ARDS (5% vs 19%), and severe sepsis/septic shock (9% vs 30%) compared with vitamin D deficient/insufficient patients (all $P < .05$). No statistically significant difference among the groups was found among patients aged <65 years old.

Adjusted associations between vitamin D sufficiency and hospital outcomes in all patients, patients aged ≥65 years old, and patients with BMI <30 kg/m^2 are shown in Figures 1, 2, and 3, respectively. Among all patients (Fig. 1), vitamin D sufficiency was statistically significantly associated with decreased odds of severe

Table 2
Inflammatory markers and biochemical profile of patients with serum 25-hydroxyvitamin D <20, 20 to <30, and ≥30 ng/mL

Inflammatory markers and biochemical profile	Age <65 years old (N = 151)					Age ≥65 years old (N = 136)				
	25(OH)D <20 ng/mL (N = 62)	25(OH)D 20 -<30 ng/mL (N = 46)	25(OH)D ≥30 ng/mL (N = 43)	*P* value[a]	*P* value[b]	25(OH)D <20 ng/mL (N = 34)	25(OH)D 20 -<30 ng/mL (N = 45)	25(OH)D ≥30 ng/mL (N = 57)	*P* value[a]	*P* value[b]
Albumin (g/dL)	3.5 ± 0.6	3.7 ± 0.5	3.8 ± 0.4	0.007*	0.014*	3.4 ± 0.4	3.5 ± 0.6	3.7 ± 0.4	0.009*	0.004*
Bicarbonate (mmol/L)	22.7 ± 3.4	22.4 ± 5.2	24.0 ± 4.9	0.625	0.192	22.6 ± 5.3	23.6 ± 5.3	22.8 ± 4.0	0.188	0.772
Corrected Calcium (mg/dL)	9.2 ± 0.7	9.1 ± 0.9	9.3 ± 0.5	0.103	0.271	9.3 ± 0.5	9.6 ± 0.7	9.6 ± 1.0	0.513	0.186
Creatinine (mg/dL)	1.9 ± 1.7	2.8 ± 5.1	1.6 ± 1.2	0.337	0.418	2.7 ± 2.3	2.6 ± 2.6	2.1 ± 2.0	0.187	0.058
C-reactive protein (mg/L)	81.1 ± 111	60.2 ± 53.0	72.5 ± 62.6	0.889	0.295	110 ± 89.1	117 ± 89.1	118 ± 95.0	0.480	0.861
D-dimer (ng/mL FEU)	1424 ± 6350	3136 ± 10232	612 ± 1118	0.669	0.103	1084 ± 1319	777 ± 860	957 ± 1155	0.261	0.618
Erythrocyte Sedimentation Rate (mm/h)	73.9 ± 35.9	66.9 ± 30.4	72.5 ± 62.7	0.825	0.295	82.4 ± 31.2	85.2 ± 37.5	118 ± 95.0	0.641	0.865
Ferritin (ng/mL)	939 ± 2663	755 ± 1059	924 ± 1272	0.090	0.285	1611 ± 2128	1765 ± 3564	803 ± 1040	0.884	0.022*
Lactate dehydrogenase (U/L)	357 ± 196	340 ± 147	332 ± 152	0.779	0.636	382 ± 149	402 ± 250	413 ± 241	0.770	0.862
Glucose (mg/dL)	171 ± 116	131 ± 70.8	173 ± 202	0.784	0.509	205 ± 206	188 ± 115	183 ± 142	0.256	0.337
Oxygen saturation (%)	96.6 ± 3.9	96.9 ± 3.1	96.2 ± 4.1	0.005*	0.613	92.9 ± 5.6	95.5 ± 3.5	95.8 ± 4.2	0.690	0.009*
Hemoglobin (g/dL)	11.7 ± 2.2	12.1 ± 2.1	12.5 ± 1.8	0.581	0.054	11.7 ± 2.1	11.7 ± 2.6	12.1 ± 2.0	0.117	0.297
WBC (10^9/fL)	8.3 ± 5.8	7.2 ± 3.1	7.0 ± 4.0	0.467	0.244	8.1 ± 6.8	7.1 ± 3.2	8.4 ± 4.4	0.303	0.271
Absolute neutrophil count (10^9/fL)	5.9 ± 5.5	5.0 ± 3.1	5.1 ± 3.5	0.361	0.771	6.7 ± 6.5	5.2 ± 3.1	6.6 ± 4.1	0.462	0.207
Absolute lymphocyte count (10^9/fL)	1.4 ± 0.8	1.3 ± 0.7	1.2 ± 0.8	0.642	0.155	1.1 ± 0.6	1.2 ± 0.8	1.1 ± 0.6	0.414	0.801
Platelet count (10^9/fL)	254 ± 130	227 ± 157	214 ± 87	0.331	0.331	210 ± 110	240 ± 151	244 ± 109	0.267	0.126

Abbreviation: FEU = Fibrinogen equivalent unit.
Data were expressed as mean ± SD.
* *P* < .05.
[a] *P* value was determined by the analysis variance of overall between-group difference.
[b] *P* value was determined by the analysis of comparison between patients with 25-hydroxyvitamin D levels of ≥30 versus patients with 25-hydroxyvitamin D levels <30 ng/mL.

Table 3
Hospital outcomes of patients with serum 25-hydroxyvitamin D <20, 20 to <30, and ≥30 ng/mL

Hospital outcomes	Age <65 years old (N = 151)					Age ≥65 years old (N = 136)				
	25(OH)D <20 ng/mL (N = 62)	25(OH)D 20-<30 ng/mL (N = 46)	25(OH)D ≥30 ng/mL (N = 43)	*P* value[a]	*P* value[b]	25(OH)D <20 ng/mL (N = 34)	25(OH)D 20-<30 ng/mL (N = 45)	25(OH)D ≥30 ng/mL (N = 57)	*P* value[a]	*P* value[b]
Death	3 (4.8%)	1 (2.2%)	5 (11.6%)	0.151	0.119	11 (32.4%)	14 (31.1%)	7 (12.3%)	0.031*	0.009*
ICU admission	14 (22.6%)	12 (26.1%)	13 (31.0%)	0.634	0.389	12 (35.3%)	18 (40.0%)	12 (21.1%)	0.098	0.035*
Intubation	7 (11.3%)	5 (10.9%)	8 (18.6%)	0.471	0.220	11 (32.4%)	11 (24.4%)	6 (10.5%)	0.033*	0.014*
Hospital length of stay (days)	10.4 ± 16.2	8.5 ± 8.8	10.4 ± 12.6	0.738	0.303	10.2 ± 13.0	15.5 ± 17.3	9.6 ± 10.0	0.145	0.392
Hypoxemia (O_2 saturation <90%)	3 (4.9%)	1 (2.2%)	3 (7.0%)	0.558	0.409	2 (5.9%)	9 (20.0%)	5 (8.8%)	0.102	0.357
ARDS	3 (4.8%)	5 (10.9%)	7 (16.3%)	0.151	0.100	7 (20.6%)	8 (17.8%)	3 (5.3%)	0.062	0.022*
Myocardial infarction	4 (6.5%)	5 (10.9%)	3 (7.0%)	0.676	1.000	3 (8.8%)	8 (17.8%)	5 (8.8%)	0.310	0.427
Acute kidney injury	26 (41.9%)	18 (39.1%)	21 (48.8%)	0.635	0.364	19 (55.9%)	29 (64.4%)	32 (56.1%)	0.645	0.589
Severe sepsis/Septic shock	6 (9.7%)	9 (19.6%)	8 (18.6%)	0.282	0.467	8 (23.5%)	16 (35.6%)	5 (8.8%)	0.004*	0.002*
Deep venous thrombosis	6 (9.7%)	1 (2.2%)	2 (4.7%)	0.242	1.000	3 (8.8%)	2 (4.4%)	3 (5.3%)	0.691	1.000
Pulmonary embolism	4 (6.5%)	1 (2.2%)	0 (0.0%)	0.168	0.322	2 (5.9%)	2 (4.4%)	2 (3.5%)	0.867	1.000

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; ARDS = acute respiratory distress syndrome; ICU = intensive care unit.
Data were expressed as mean ± SD. Deceased patients were excluded in the analysis for hospital length of stay.
* *P* < .05.
[a] *P* value was determined by the analysis of overall between-group difference.
[b] *P* value was determined by the analysis of comparison between patients with 25-hydroxyvitamin D levels of ≥30 versus patients with 25-hydroxyvitamin D levels <30 ng/mL.

sepsis/septic shock (adjusted OR, 0.43; 95% CI, 0.20-0.89). In the subgroup of patients aged ≥65 years old (Fig. 2), vitamin D sufficiency was statistically significantly associated with decreased odds of death (adjusted OR, 0.33; 95% CI, 0.12-0.94), ARDS (adjusted OR, 0.22; 95% CI, 0.05-0.96), and severe sepsis/septic shock (adjusted OR, 0.26; 95% CI, 0.08-0.88). In the subgroup of patients with BMI <30 kg/m^2, vitamin D sufficiency was statistically significantly associated with a decreased odds of death (adjusted OR, 0.18; 95% CI, 0.04-0.84). No statistically significant association between vitamin D sufficiency and any hospital outcomes was found among patients aged <65 years old and among patients with BMI ≥30 kg/m^2. All effect estimates were adjusted for age, sex, BMI, insurance, race, smoking, alcohol drinking, type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, cerebrovascular disease, COPD, asthma, CKD, ESRD, malignancy, HIV infection, and heart failure.

Given the significant results in patients age ≥65 years old, we performed additional univariate subgroup analyses in patients aged ≥65 years old with BMI <30 kg/m^2 and ≥30 kg/m^2, which are shown in Table 4. Among the patients aged ≥65 years old with BMI <30 kg/m^2, vitamin D sufficient patients had a statistically significantly lower rate of death compared with vitamin D insufficient or

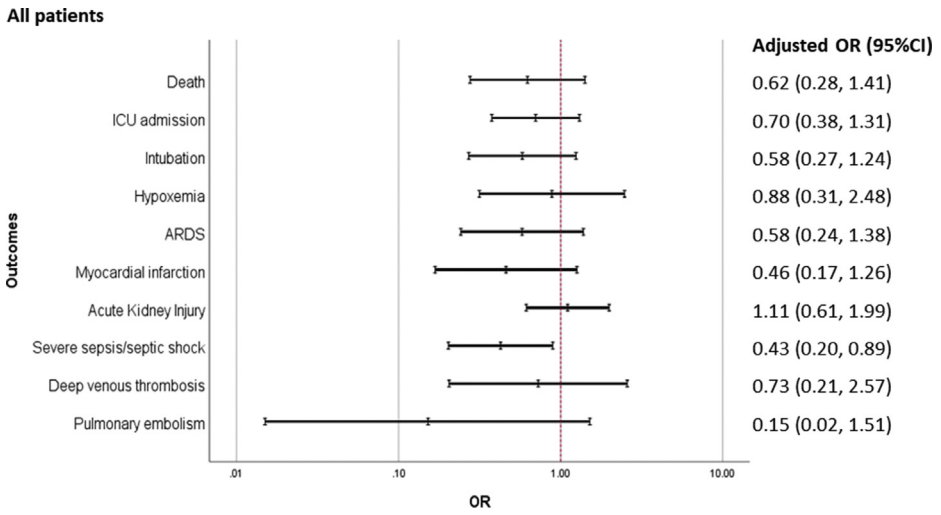

Fig. 1. Adjusted association between serum 25-hydroxyvitamin D ≥30 ng/mL and hospital outcomes in all patients with COVID-19. Effect estimates were adjusted for age, sex, body mass index, insurance, race, smoking, alcohol drinking, type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, cerebrovascular disease, COPD, asthma, CKD, ESRD, malignancy, HIV infection, and heart failure. *CKD* = chronic kidney disease; *COPD* = chronic obstructive pulmonary disease; *COVID-19* = coronavirus disease 2019; *ESRD* = end-stage renal disease; *HIV* = human immunodeficiency virus.

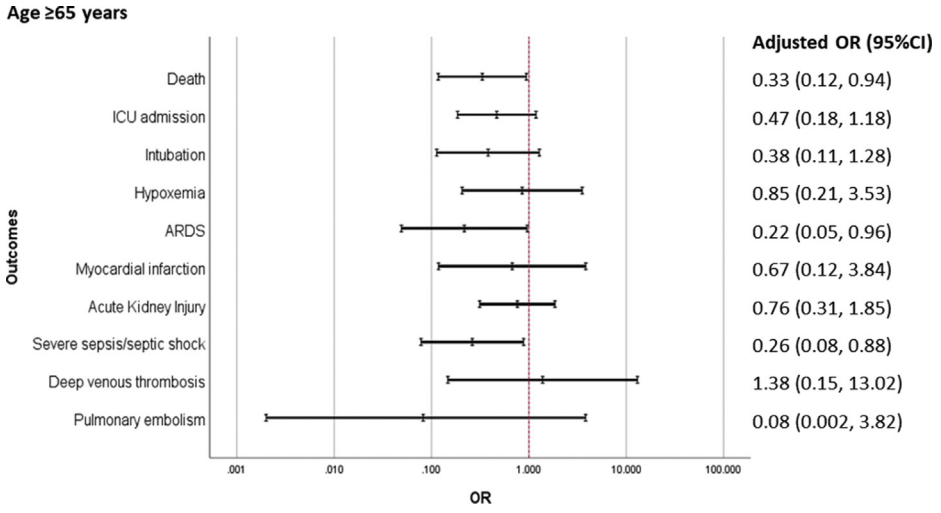

Fig. 2. Adjusted association between serum 25-hydroxyvitamin D ≥30 ng/mL and hospital outcomes in patients with COVID-19 aged ≥65 years. Effect estimates were adjusted for age, sex, body mass index, insurance, race, smoking, alcohol drinking, type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, cerebrovascular disease, COPD, asthma, CKD, ESRD, malignancy, HIV infection, and heart failure. *CKD* = chronic kidney disease; *COPD* = chronic obstructive pulmonary disease; *COVID-19* = coronavirus disease 2019; *ESRD* = end-stage renal disease; *HIV* = human immunodeficiency virus.

deficient patients (8% vs 29%, $P = .011$). Among patients aged ≥65 years old with BMI ≥30 kg/m^2, although with limited sample size, vitamin D sufficient patients had a statistically significantly lower rate of severe sepsis/septic shock compared with vitamin D insufficient or deficient patients (0% vs 29%, $P = .029$).

Discussion

The present cross-sectional study in 287 patients with COVID-19 hospitalized at the Boston University Medical Center found that, among 136 patients aged ≥65 years old, vitamin D sufficiency (25 [OH]D >30 ng/mL) was associated with statistically significantly decreased rates of death, ICU admission, intubation, ARDS, and severe sepsis/septic shock. After adjustment for potential confounders, the association between vitamin D sufficiency and death, ARDS, and severe sepsis/septic shock remained statistically significant, while none of the associations were observed among the younger patients. This is likely because of the higher inflammatory burden of COVID-19 in older patients, thereby amplifying the immunological effects of vitamin D observed in the study. This observation is supported by the observed significantly lower levels of the inflammatory marker ferritin and higher oxygen saturation on admission in vitamin D sufficient patients among older patients but not younger patients. Moreover, the absolute rates of morbidity and mortality in the younger patients were relatively low, which most likely compromised the statistical power to determine the association. Interestingly, there was a statistically significantly deceased odds of death in vitamin D sufficient patients among those with BMI <30 kg/m^2, but not those with BMI ≥30 kg/m^2. This reinforces that vitamin D is distributed differently and may influence immune function differently among those who are and those who are not obese.

In fact, there is promising evidence of the connection between vitamin D status and risk of incident COVID-19 infection. For

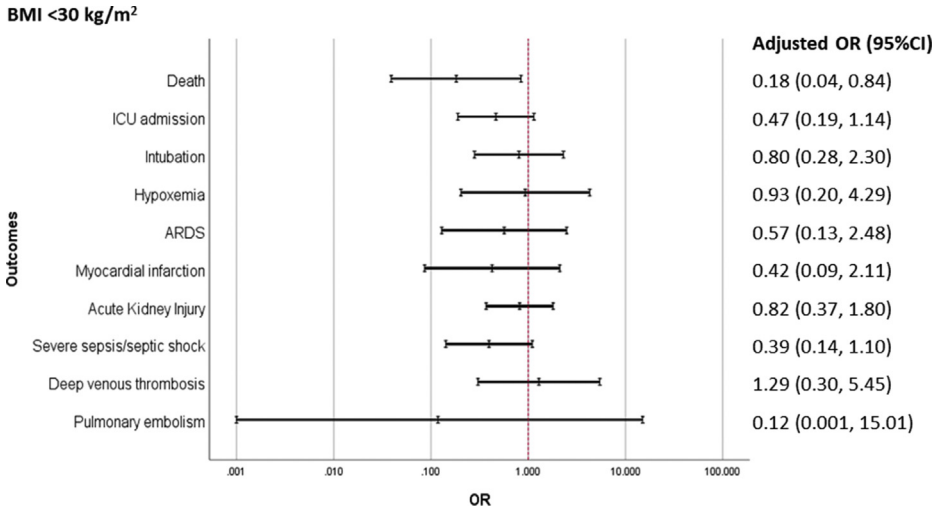

Fig. 3. Adjusted association between serum 25-hydroxyvitamin D ≥30 ng/mL and hospital outcomes in patients with COVID-19 with body mass index <30 kg/m^2. Effect estimates were adjusted for age, sex, body mass index, insurance, race, smoking, alcohol drinking, type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, cerebrovascular disease, COPD, asthma, CKD, ESRD, malignancy, HIV infection, and heart failure. *CKD* = chronic kidney disease; *COPD* = chronic obstructive pulmonary disease; *COVID-19* = coronavirus disease 2019; *ESRD* = end-stage renal disease; *HIV* = human immunodeficiency virus.

Table 4
Hospital outcomes of patients aged ≥65 years with serum 25-hydroxyvitamin D <20, 20 to <30, and ≥30 ng/mL stratified by body mass index

Hospital outcomes	Age ≥65 years old, BMI <30 kg/m^2 (N = 90)					Age ≥65 years old, BMI ≥30 kg/m^2 (N = 41)				
	25(OH)D <20 ng/mL (N = 23)	25(OH)D 20-<30 ng/mL (N = 28)	25(OH)D ≥30 ng/mL (N = 39)	*P* value[a]	*P* value[b]	25(OH)D <20 ng/mL (N = 9)	25(OH)D 20-<30 ng/mL (N = 15)	25(OH)D ≥30 ng/mL (N = 17)	*P* value[a]	*P* value[b]
Death	7 (30.4%)	8 (28.6%)	3 (7.7%)	0.038	0.011*	4 (44.4%)	6 (40.0%)	4 (23.5%)	0.471	0.321
ICU admission	9 (39.1%)	12 (42.9%)	9 (23.1%)	0.189	0.071	3 (33.3%)	5 (33.3%)	3 (17.6%)	0.536	0.309
Intubation	8 (34.8%)	6 (21.4%)	5 (12.8%)	0.123	0.120	3 (33.3%)	5 (33.3%)	1 (5.9%)	0.112	0.056
Hospital length of stay (days)										
Hypoxemia (O_2 saturation <90%)	1 (4.3%)	4 (14.3%)	4 (10.3%)	0.499	1.000	1 (11.1%)	5 (33.3%)	1 (5.9%)	0.104	0.207
ARDS	5 (21.7%)	4 (14.3%)	2 (5.1%)	0.144	0.105	2 (22.2%)	4 (26.7%)	1 (5.9%)	0.266	0.207
Myocardial infarction	2 (8.7%)	4 (14.3%)	3 (7.7%)	0.655	0.726	1 (11.1%)	4 (26.7%)	1 (5.9%)	0.238	0.373
Acute kidney injury	12 (52.2%)	19 (67.9%)	21 (53.8%)	0.425	0.527	6 (66.7%)	9 (60.0%)	10 (58.8%)	0.922	1.000
Severe sepsis/Septic shock	3 (13.0%)	7 (25.0%)	3 (7.7%)	0.135	0.138	3 (33.3%)	4 (26.7%)	0 (0.0%)	0.046*	0.029*
Deep venous thrombosis	2 (8.7%)	1 (3.6%)	3 (7.7%)	0.723	1.000	1 (11.1%)	1 (6.7%)	0 (0.0%)	0.421	0.502
Pulmonary embolism	1 (4.3%)	2 (7.1%)	2 (5.1%)	0.899	1.000	1 (11.1%)	0 (0.0%)	0 (0.0%)	0.162	1.000

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; ARDS = acute respiratory distress syndrome; BMI = body mass index; ICU = intensive care unit.
Data were expressed as mean ± SD. Deceased patients were excluded in the analysis for hospital length of stay.
* $P < .05$.
[a] *P* value was determined by the analysis of overall between-group difference.
[b] *P* value was determined by the analysis of comparison between patients with 25-hydroxyvitamin D levels of ≥30 versus patients with 25-hydroxyvitamin D levels <30 ng/mL.

example, Kaufman et al[25] investigated the likelihood of a positive test for COVID-19 in a national clinical laboratory database of 191 779 patients and found that SARS-CoV-2 positivity is strongly and inversely associated with circulating 25(OH)D levels, a relationship that persists across latitudes, races/ethnicities, both sexes, and age ranges. The result was in line with that of a single-center, retrospective cohort study by Meltzer et al[26] showing that deficient vitamin D status was associated with an increased risk of testing positive for COVID-19 (relative risk [RR], 1.77; 95% CI, 1.12-2.81) after adjustment in a multivariate analysis compared with likely sufficient vitamin D status.

Nevertheless, the relationship between vitamin D status and morbidity and mortality outcomes seems to be relatively unclear. Maghbooli et al[27] reported in a cross-sectional study of 235 hospitalized patients with COVID-19 that 9.7% of 206 patients older than 40 years who were vitamin D sufficient succumbed to the infection compared to 20% who were vitamin D insufficient or deficient (25[OH]D <30 ng/mL). In addition, vitamin D sufficiency was found to be independently associated with decreased disease severity according to the Centers for Disease Control criteria, after adjusting for potential confounders. Radujkovic et al[28] demonstrated in a retrospective cohort study of 185 patients that serum 25(OH)D level of <12 ng/mL was associated with higher risk of invasive mechanical ventilation (adjusted hazard ratio [HR], 6.12; 95% CI, 2.79-13.42) and death (adjusted HR, 14.73; 95% CI, 4.16-52.19), after adjusting for age, sex, and comorbidities. Hars et al[29] used data of 160 elderly inpatients from the COVID Age study and showed that vitamin D was independently associated with in-hospital mortality risk in men (adjusted HR, 2.47; 95% CI, 1.02-5.97) but not in women after adjustment for age, comorbidities, C-reactive protein level, and frailty status. On the other hand, Hernández et al[30] reported in a case-control study of 216 patients with COVID-19 and 197 controls that although serum 25(OH)D levels were significantly lower in patients with COVID-19 versus controls, the authors suggested that there was causal relationship between vitamin D deficiency and COVID-19 severity.

Given the potential benefit of vitamin D in prevention of COVID-19 and reduction of its severity, multiple ongoing clinical trials are being conducted with the aim of identifying the impact of different forms of vitamin D supplements on risk and severity of COVID-19. A pilot randomized clinical trial that gave vitamin D supplements in the form of 25-hydroxyvitamin D_3 (calcifediol) or placebo to 76 patients with COVID-19 showed that the treatment group had a reduced rate of ICU admission.[31]

Despite the limited evidence on the potential benefit of vitamin D supplementation for this specific disease, it is reasonable to believe that vitamin D could lessen the risk of acquiring respiratory viral infection and alleviate systemic inflammation according to the evidence from previous clinical trials conducted in other diseases with similar pathogenesis. For instance, a meta-analysis of 25 randomized controlled trials showed that supplementation of vitamin D_2 or D_3 protects against the development of acute respiratory tract infection compared with placebo (OR, 0.88; 95% CI, 0.81-0.96).[17] In addition, a randomized controlled trial giving enteral 540 000 IUs of vitamin D_3 followed by monthly 90 000 IU for 5 months or placebo to 475 vitamin D deficient (25[OH])D <20 ng/mL) critically ill patients observed a significant decrease in-hospital mortality in a subgroup of 200 patients with severe vitamin D deficiency defined by serum 25(OH)D <12 ng/mL (HR, 0.56; 95% CI, 0.35-0.90).[32] Based on the results of this study along with others, it is therefore advisable to have sensible sunlight exposure and/or increase vitamin D intake to maintain serum 25(OH)D at least 30 ng/mL and preferably at 40 to 60 ng/mL to achieve the optimal overall health benefits of vitamin D and to reduce the risk of developing severe COVID-19.

It is of particular interest that vitamin D sufficient patients had statistically significantly higher levels of serum albumin on admission than vitamin D insufficient and vitamin D deficient patients. The association between vitamin D status and serum albumin is likely bidirectional. On one hand, low serum 25(OH)D level may be causative for more severe systemic inflammation and therefore albumin, as a negative acute phase reactant and an indicator for vascular leakage,[33] is expected to be lower in patients with a low level of serum 25(OH)D. On the other hand, 15% of 25(OH)D is bound to albumin[34]; therefore, a low level of albumin at baseline may contribute to a low level of total serum 25(OH)D.

The present study carries a number of strengths, including (1) inclusion of multiple hospital morbidities, (2) extensive adjustment for possible confounders in multivariate analysis, and (3) subgroup analysis by age and BMI, which helps to gain more insight into the influence of these factors on the effect estimation. Nevertheless, there are certain limitations that should be acknowledged. First, this study is cross-sectional by design; therefore, causal relationship could not be determined with certainty. Second, patients who had serum 25(OH)D levels measured were selectively included into this study. Serum 25(OH)D measurement is not routine and is primarily indicated for patients with susceptibility to low level of serum 25-hydroxyvitamin D. These patients might have had different characteristics from the rest of the population, and therefore the results may have limited generalizability. Third, we used data of serum 25(OH)D level measured up to 1 year prior to hospitalization. Because there is seasonal variation of serum 25(OH)D levels,[35] discrepancies between the month of the year for each 25(OH)D measurement in patients may compromise the accuracy of ascertainment of vitamin D status in our study. Furthermore, it is probable that patients who were found to have vitamin D deficiency prior to the infection would have been treated for vitamin D deficiency and became vitamin D repleted by the time they were infected. This may indicate that there might be the legacy effect of being vitamin D sufficient and that raising serum 25(OH)D concentrations over a short period of time might not be as beneficial as maintaining serum 25(OH)D concentrations in a preferred range over the long term. Further studies are required to investigate the short-term and long-term effects of raising serum 25(OH)D level. It should also be noted that we used data of patients who were hospitalized between March and August 2020. Therefore, as shown in Table 1, the treatment strategy in our study may not be representative of the most updated standard treatment for COVID-19. Finally, the number of patients in this study is relatively low. Further studies with a larger sample size should be conducted to confirm our findings.

Conclusion

We demonstrated an independent association between vitamin D sufficiency defined by serum 25(OH)D $\geq$ 30 ng/mL and risk of morbidity and mortality from COVID-19 stratified by age group and BMI status. Among aged $\geq$65 years old, vitamin D sufficiency was associated with statistically significantly decreased rates of death, ICU admission, intubation, ARDS, and severe sepsis/septic shock. After adjustment for potential confounders, the association between vitamin D sufficiency and death, ARDS, and severe sepsis/septic shock remained statistically significant. We also found among patients aged $\geq$65 years old significantly lower levels of the inflammatory marker ferritin and higher oxygen saturation on admission in vitamin D sufficient patients compared with vitamin D insufficient or deficient patients. In addition, we found a statistically significantly decreased odds of death in vitamin D sufficient patients among those with BMI <30 kg/m^2. The results support the potential benefit of raising serum level of serum 25(OH)D to at least 30 ng/mL to reduce the risk of morbidity and mortality of COVID-19. Further clinical trials are required to determine the benefit of vitamin D supplementation for this purpose.

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Disclosure

M.F.H. is a consultant for Quest Diagnostics, Inc, Biogena, Inc, and Ontometrics, Inc, and on the speaker's bureau for Abbott, Inc. C.M.A. reports receiving personal fees from Nutrisystem, Zafgen, Sanofi-Aventis, Orexigen, EnteroMedics, GI Dynamics, Scientific Intake, Gelesis, Novo Nordisk, SetPoint Health, Xeno Biosciences, Rhythm Pharmaceuticals, Eisai, and Takeda outside of the funded work, reports receiving grant funding from Aspire Bariatrics, GI Dynamics, Orexigen, Takeda, the Vela Foundation, Gelesis, Energesis, Coherence Lab, and Novo Nordisk outside of the funded work, and reports past equity interest in ScienceSmart, LLC. The remaining authors have no conflicts of interest.

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