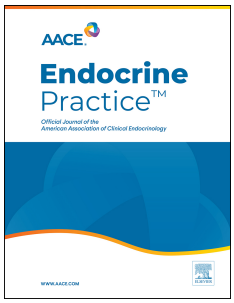
Journal Pre-proof



Association of vitamin D status with hospital morbidity and mortality in adult hospitalized COVID-19 patients

Nipith Charoenngam, MD, Arash Shirvani, MD, PhD, Niyoti Reddy, MBBS, Danica M. Vodopivec, MD, Caroline M. Apovian, MD, Michael F. Holick, MD

PII: S1530-891X(21)00057-4

DOI: https://doi.org/10.1016/j.eprac.2021.02.013

Reference: EPRAC 149

To appear in: *Endocrine Practice*

Received Date: 11 January 2021

Revised Date: 13 February 2021

Accepted Date: 17 February 2021

Please cite this article as: Charoenngam N, Shirvani A, Reddy N, Vodopivec DM, Apovian CM, Holick MF, Association of vitamin D status with hospital morbidity and mortality in adult hospitalized COVID-19 patients, *Endocrine Practice* (2021), doi: https://doi.org/10.1016/j.eprac.2021.02.013.

Association of vitamin D status with hospital morbidity and mortality in adult hospitalized COVID-19 patients

Authors: Nipith Charoenngam, MD[1, 2], Arash Shirvani, MD, PhD[1], Niyoti Reddy, MBBS[1], Danica M. Vodopivec, MD[1], Caroline M. Apovian, MD[3], Michael F. Holick, MD[1]

Affiliation:

[1]Section Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University School of Medicine, Boston, MA, United States

[2]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

[3]Section of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Author of correspondence

Michael F. Holick, PhD, MD
Address: 85 E Newton St., M-1013, Boston, MA 02118
Telephone number: +1-617-358-6139
E-mail address: mfholick@bu.edu

Running Head: Vitamin D and COVID-19

Word count: 2,744 words

Financial support and sponsorship

Nipith Charoenngam receives the institutional research training grant from the Ruth L. Kirchstein National Research Service Award program from the National Institutes of Health (2 T32 DK 7201-42). Caroline M. Apovian is supported by P30 DK046200.

Conflict of Interest

Michael F. Holick is a consultant for Quest Diagnostics Inc., Biogena Inc. and Ontometrics Inc., and on the speaker's Bureau for Abbott Inc. Caroline M. Apovian 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.

Association of vitamin D status with hospital morbidity and mortality in adult hospitalized COVID-19 patients

Authors: Nipith Charoenngam, MD[1, 2], Arash Shirvani, MD, PhD[1], Niyoti Reddy, MBBS[1], Danica M. Vodopivec, MD[1], Caroline M. Apovian, MD[3], Michael F. Holick, MD[1]

Affiliation:

[1]Section Endocrinology, Diabetes, Nutrition and Weight Management, Department of Medicine, Boston University School of Medicine, Boston, MA, United States

[2]Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

[3]Section of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States

Author of correspondence

Michael F. Holick, PhD, MD
Address: 85 E Newton St., M-1013, Boston, MA 02118
Telephone number: +1-617-358-6139
E-mail address: mfholick@bu.edu

Running Head: Vitamin D and COVID-19

Word count: 2,744 words

Financial support and sponsorship

Nipith Charoenngam receives the institutional research training grant from the Ruth L. Kirchstein National Research Service Award program from the National Institutes of Health (2 T32 DK 7201-42). Caroline M. Apovian is supported by P30 DK046200.

Conflict of Interest

Michael F. Holick is a consultant for Quest Diagnostics Inc., Biogena Inc. and Ontometrics Inc., and on the speaker's Bureau for Abbott Inc. Caroline M. Apovian 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.

Association of vitamin D status with hospital morbidity and mortality in adult hospitalized COVID-19 patients

Abstract (250 words)

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

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

Results: Among the 287 patients, 100 (36%) patients were vitamin D-sufficient [25(OH)D >30 ng/mL] and 41 (14%) patients died during the hospitalization. Multivariate analysis in patients aged ≥65 years old 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 adjustement 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 old or BMI ≥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.

Keywords: Vitamin D, 25-hydroxyvitamin D, COVID-19, Morbidity, Mortality, Acute respiratory distress syndrome

Introduction

Vitamin D is recognized not only for its important functions on 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 [$1,25(OH)_2D$]. In addition, CYP27B1 is expressed by many other tissues, including activated macrophages, parathyroid glands, microglia, breast, colon, and keratinocytes where $1,25(OH)_2D$ is produced and exerts its tissue-specific autocrine and paracrine functions (1, 2).

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), disproportionately affects the elderly, African Americans, those with obesity, and institutionalized individuals (nursing home residents) (5, 6), all of which 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 on 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 COVID-19 patients.

Methods

Study population

This study was a retrospective chart review cross-sectional study in adult COVID-19 patients aged ≥18 years old who were hospitalized at Boston University Medical Center (latitude 42° 21' N) between March 1, 2020 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 one 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 (i.e., 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 the 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 (SD) 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 the analysis of variance (ANOVA), independent sample t-test or Mann Whitney-U test for continuous data, and Chi-square or Fischer's exact test for categorical data. Multivariate logistic regression was used to determine odds ratios (OR) and 95% confidence interval (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.

Since COVID-19 specifically affects older individuals (19) and those with obesity (20) and vitamin D is expected to distribute and modulate immune function differently among those with obesity and lean patients (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 old and patients with BMI <30 and ≥ 30 kg/m^2 were conducted. The cut-off value for age was based on the World Health

Organization's definition of the elderly (23). The cut-off 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 <0.05. SPSS version 23 (SPSS Inc., Chicago, IL) was used to perform all statistical analyses.

Results

We identified 1,478 COVID-19 patients who were hospitalized at the Boston University Medical Center between March 1, 2020 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] and vitamin D-deficient [25(OH)D <20 ng/mL], respectively. Overall, 41 (14%) patients died during the 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 <0.05). Among patients aged ≥65 years old, vitamin D-deficient patients were statistically significantly younger and had lower rate of hypertension (both p <0.05).

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<0.05) 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<0.05). No statistically significant difference among the groups was found among patients aged <65 years old.

Adjusted association 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 (**Figure 1**), vitamin D sufficiency was statistically significantly associated with a decreased odds of severe sepsis/septic shock (adjusted OR

0.43, 95%CI, 0.20 – 0.89). In the subgroup of patients aged ≥65 years old (**Figure 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 were 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 deficient patients (8% vs. 29%, p = 0.011). 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 = 0.029).

Discussion

The present cross-sectional study in 287 COVID-19 patients 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 was

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 with and without obesity.

In fact, there is promising evidence of the connection between vitamin D status and risk of incident COVID-19 infection. For 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 (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 COVID-19 patients 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 CDC 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 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 COVIDAge 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 COVID-19 patients and 197 controls that although serum 25(OH)D levels was significantly lower in COVID-19 patients 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 conducted with the aim to identify 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 supplement in the form of 25-hydroxyvitamin D_3 (calcifediol) or placebo to 76 COVID-19 patients 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 (odds ratio 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 40–60 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 lower in patients with low level of serum 25(OH)D. On the other hand, 15% of 25(OH)D is bound to albumin (34); therefore, low level of albumin at baseline may contribute to 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 gaining 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. Since there is seasonal variation of serum 25(OH)D level (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 ≥ 30 ng/mL and risk of morbidity and mortality from COVID-19 stratified by age group and BMI status. Among aged ≥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 ≥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 deceased 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.

References

1. Charoenngam N, Holick MF. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients. 2020;12(7).
2. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81.
3. Charoenngam N, Shirvani A, Holick MF. Vitamin D for skeletal and non-skeletal health: What we should know. J Clin Orthop Trauma. 2019;10(6):1082-93.
4. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911-30.
5. Snowden LR, Graaf G. COVID-19, Social Determinants Past, Present, and Future, and African Americans' Health. J Racial Ethn Health Disparities. 2020:1-9.
6. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? BMJ. 2020;369:m1548.
7. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health. Dermatoendocrinol. 2013;5(1):51-108.
8. Shahmiri M, Enciso M, Adda CG, Smith BJ, Perugini MA, Mechler A. Membrane Core-Specific Antimicrobial Action of Cathelicidin LL-37 Peptide Switches Between Pore and Nanofibre Formation. Scientific Reports. 2016;6(1):38184.
9. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006;311(5768):1770-3.
10. Aygun H. Vitamin D can prevent COVID-19 infection-induced multiple organ damage. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(7):1157-60.
11. Ortega JT, Serrano ML, Pujol FH, Rangel HR. Role of changes in SARS-CoV-2 spike protein in the interaction with the human ACE2 receptor: An in silico analysis. EXCLI J. 2020;19:410-7.
12. Lemire JM, Archer DC, Beck L, Spiegelberg HL. Immunosuppressive actions of 1,25-dihydroxyvitamin D3: preferential inhibition of Th1 functions. J Nutr. 1995;125(6 Suppl):1704S-8S.
13. Tang J, Zhou R, Luger D, Zhu W, Silver PB, Grajewski RS, et al. Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. J Immunol. 2009;182(8):4624-32.
14. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HFJ, O'Garra A. 1α,25-Dihydroxyvitamin D3 Has a Direct Effect on Naive CD4⁺ T Cells to Enhance the Development of Th2 Cells. The Journal of Immunology. 2001;167(9):4974.
15. Gibson CC, Davis CT, Zhu W, Bowman-Kirigin JA, Walker AE, Tai Z, et al. Dietary Vitamin D and Its Metabolites Non-Genomically Stabilize the Endothelium. PLoS One. 2015;10(10):e0140370.
16. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and Endothelial Function. Nutrients. 2020;12(2).
17. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017;356:i6583.
18. de Haan K, Groeneveld ABJ, de Geus HRH, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Critical Care. 2014;18(6):660.

19. Romero Starke K, Petereit-Haack G, Schubert M, Kämpf D, Schliebner A, Hegewald J, et al. The Age-Related Risk of Severe Outcomes Due to COVID-19 Infection: A Rapid Review, Meta-Analysis, and Meta-Regression. Int J Environ Res Public Health. 2020;17(16):5974.
20. Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S. Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract. 2020;14(4):295-300.
21. Migliaccio S, Di Nisio A, Mele C, Scappaticcio L, Savastano S, Colao A, et al. Obesity and hypovitaminosis D: causality or casualty? Int J Obes Suppl. 2019;9(1):20-31.
22. Vanlint S. Vitamin D and obesity. Nutrients. 2013;5(3):949-56.
23. Rudnicka E, Napierała P, Podfigurna A, Męczekalski B, Smolarczyk R, Grymowicz M. The World Health Organization (WHO) approach to healthy ageing. Maturitas. 2020;139:6-11.
24. Defining Adult Overweight and Obesity: Centers for Disease Control and Prevention; [Available from: https://www.cdc.gov/obesity/adult/defining.html.
25. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLOS ONE. 2020;15(9):e0239252.
26. 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 Network Open. 2020;3(9):e2019722-e.
27. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PLOS ONE. 2020;15(9):e0239799.
28. Radujkovic A, Hippchen T, Tiwari-Heckler S, Dreher S, Boxberger M, Merle U. Vitamin D Deficiency and Outcome of COVID-19 Patients. Nutrients. 2020;12(9).
29. Hars M, Mendes A, Serratrice C, Herrmann FR, Gold G, Graf C, et al. Sex-specific association between vitamin D deficiency and COVID-19 mortality in older patients. Osteoporos Int. 2020;31(12):2495-6.
30. Hernández JL, Nan D, Fernandez-Ayala M, García-Unzueta M, Hernández-Hernández MA, López-Hoyos M, et al. Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection. The Journal of Clinical Endocrinology & Metabolism. 2020.
31. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, Bouillon R, et al. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". J Steroid Biochem Mol Biol. 2020;203:105751-.
32. Amrein K, Schnedl C, Holl A, Riedl R, Christopher KB, Pachler C, et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA. 2014;312(15):1520-30.
33. Jain S, Gautam V, Naseem S. Acute-phase proteins: As diagnostic tool. J Pharm Bioallied Sci. 2011;3(1):118-27.
34. Bikle DD, Schwartz J. Vitamin D Binding Protein, Total and Free Vitamin D Levels in Different Physiological and Pathophysiological Conditions. Frontiers in Endocrinology. 2019;10:317.
35. Kroll MH, Bi C, Garber CC, Kaufman HW, Liu D, Caston-Balderrama A, et al. Temporal Relationship between Vitamin D Status and Parathyroid Hormone in the United States. PLOS ONE. 2015;10(3):e0118108.

Figure legend

Figure 1. Adjusted association between serum 25-hydroxyvitamin D ≥30 ng/mL and hospital outcomes in all COVID-19 patients

Note: 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.

Figure 2. Adjusted association between serum 25-hydroxyvitamin D ≥30 ng/mL and hospital outcomes in COVID-19 patients aged ≥65 years old

Note: 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.

Figure 3. Adjusted association between serum 25-hydroxyvitamin D ≥30 ng/mL and hospital outcomes in COVID-19 patients with body mass index <30 kg/m^2

Note: 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.

Table 1. Baseline characteristics of patients with serum 25-hydroxyvitamin D <20, 20 – <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

Note: "*" denotes p <0.05. Data were expressed as mean ± SD or number of patients (%). Abbreviations: BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; HIV: Human Immunodeficiency Virus; IL-1: Interleukin-1; IL-6: Interleukin-6

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/hr)	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

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

"*" denotes p <0.05.

p-value[a] was determined by the analysis variance of overall between-group difference.

p-value[b] was determined by the analysis of comparison between patients with 25-hydroxyvitamin D levels of ≥30 *vs.* patients with 25-hydroxyvitamin D levels <30 ng/mL.

Data were expressed as mean ± SD.

Abbreviation: FEU: Fibrinogen Equivalent Unit

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

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

"*" denotes p <0.05.

p-value[a] was determined by the analysis of overall between-group difference.

p-value[b] was determined by the analysis of comparison between patients with 25-hydroxyvitamin D levels of ≥30 *vs.* patients with 25-hydroxyvitamin D levels <30 ng/mL.

Data were expressed as mean ± SD. Deceased patients were excluded in the analysis for hospital length of stay.

Abbreviation: 25(OH)D: 25-hydroxyvitamin D; ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit

Table 4. Hospital outcomes of patients aged ≥65 years old with serum 25-hydroxyvitamin D <20, 20 – <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

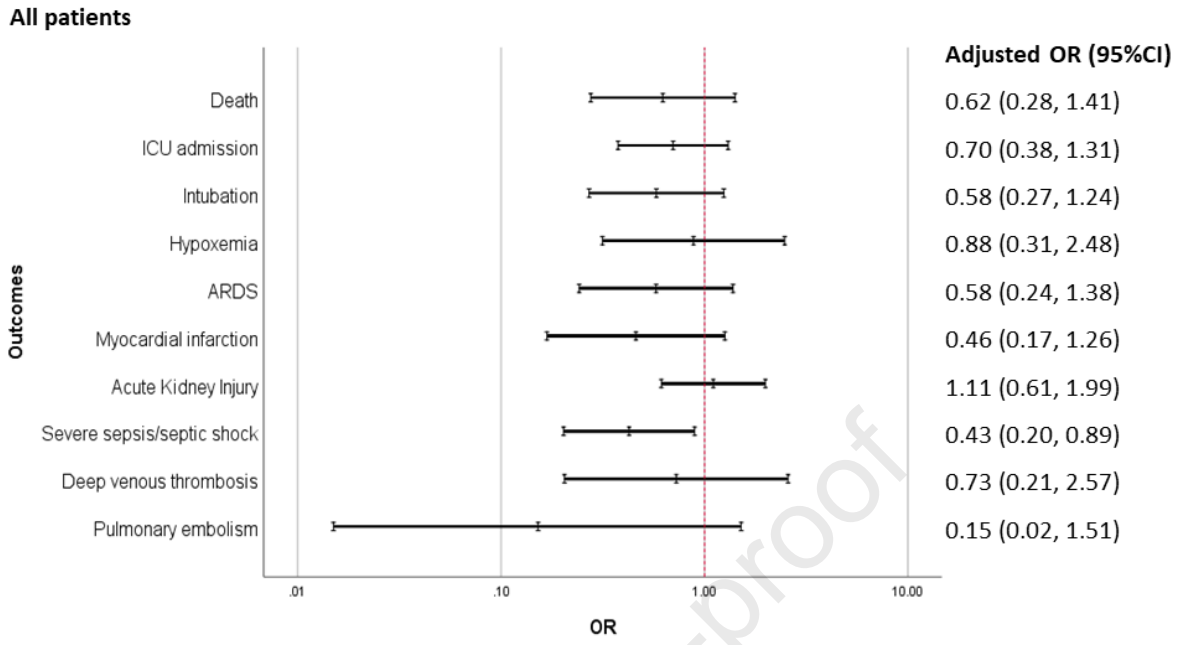
"*" denotes p <0.05.

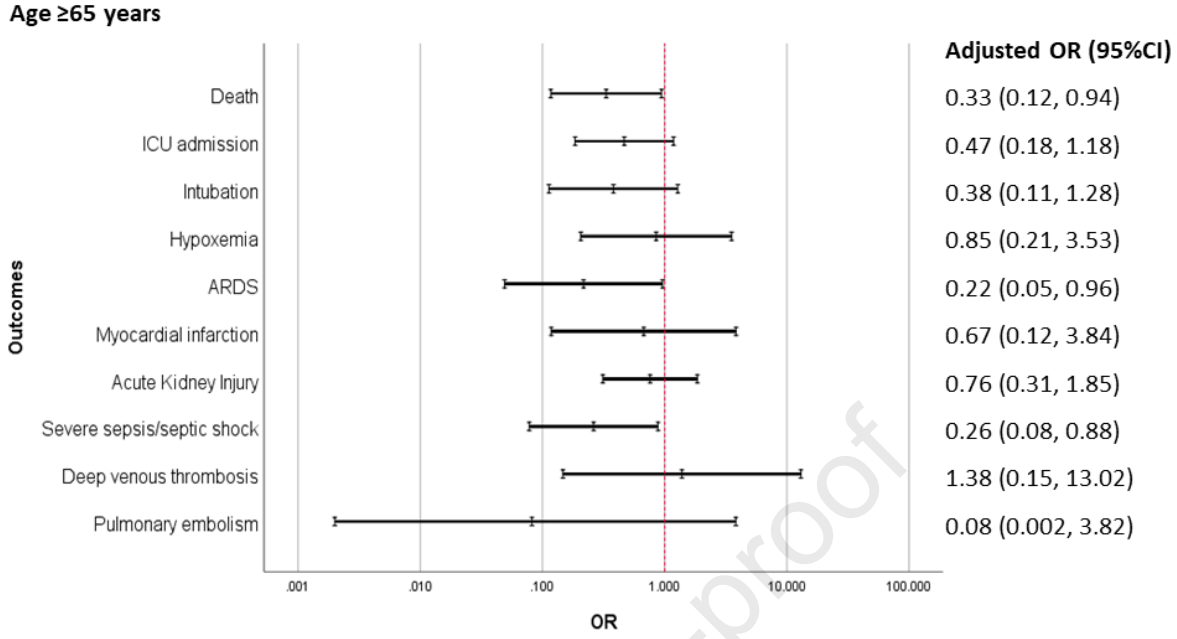
p-value[a] was determined by the analysis of overall between-group difference.

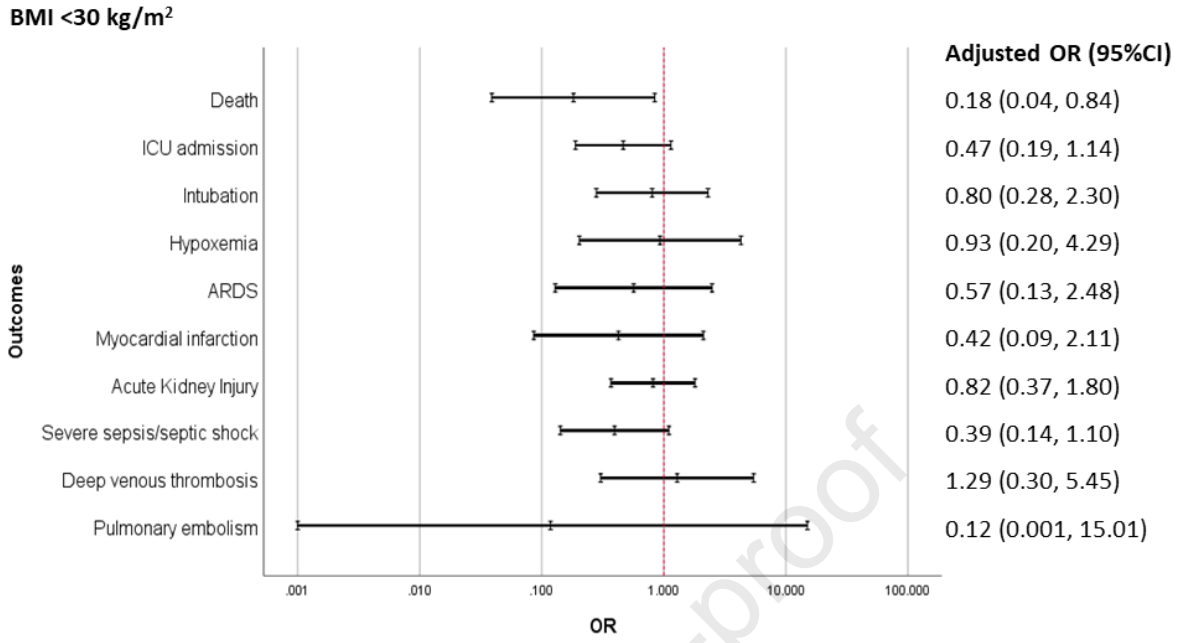
p-value[b] was determined by the analysis of comparison between patients with 25-hydroxyvitamin D levels of ≥30 *vs.* patients with 25-hydroxyvitamin D levels <30 ng/mL.

Data were expressed as mean ± SD. Deceased patients were excluded in the analysis for hospital length of stay.

Abbreviation: 25(OH)D: 25-hydroxyvitamin D; ARDS: Acute Respiratory Distress Syndrome; BMI: Body Mass Index; ICU: Intensive Care Unit







Highlights

- It has been proposed that vitamin D is an immunomodulatory agent that is protective against severity of COVID-19.
- We found an independent association between serum 25-hydroxyvitamin D ≥30 ng/mL and decreased risk of mortality from COVID-19 in elderly patients and patients without obesity.
- It is advisable to maintain serum 25-hydroxyvitamin D at least 30 ng/mL to reduce the risk of developing severe COVID-19.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Michael F. Holick is a consultant for Quest Diagnostics Inc., Biogena Inc. and Ontometrics Inc, and on the speaker's Bureau for Abbott Inc. Caroline M. Apovian 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.