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An Evaluation of Serum 25-Hydroxy Vitamin D Levels in Patients with COVID-19 in New York City

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ABSTRACT

Aim: Deterioration of patients from COVID-19 is associated with cytokine release syndrome attributed to an elevation in pro-inflammatory cytokines. Vitamin D reduces proinflammatory cytokines, and has the possibility of reducing complications from respiratory tract illnesses.

Method: This was a retrospective, observational, cohort study of patients with COVID-19 disease within a New York City Health System. Adult patients were included if they tested positive for SARS-CoV-2, and had a serum 25-hydroxy vitamin D level (25(OH)D) within the three previous months prior to their detected SARS-CoV-2 test. Patients were compared and evaluated based upon their 25(OH)D levels. The primary endpoints were hospitalization, need for oxygen support, and 90-day mortality.

Results: 437 COVID-19 patients were included [67 (IQR: 56–79) years] within this cohort. Deficient plasma 25(OH)D levels (<20 ng/ml) were associated with an increased likelihood of oxygen support [OR:2.23 (95% CI: 1.46–3.44, $p = 0.0002$)] from COVID-19. Deficient plasma 25(OH)D levels were not independently associated with 90-day mortality or risk of hospitalization. Hospitalization rates (98%), oxygen support (93%), and mortality rates (49%) were highest in patients who had 25(OH)D levels less than 10 ng/ml when compared to other 25(OH)D levels.

Conclusion: Serum 25-hydroxy vitamin D levels may affect the need for oxygen support therapy in patients with COVID-19.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has led to the rapid worldwide spread of COVID-19 disease over the past several months. Clinical manifestations exhibited by COVID-19 patients may be mild and include fever, cough, fatigue, muscle soreness, and headache or more severe which may include acute respiratory distress syndrome (ARDS) (1). Deterioration of patients to ARDS is associated with cytokine release syndrome (CRS) attributed to an elevation in pro-inflammatory cytokines (2). In patients who are vitamin D deficient, supplementation may have the potential to prevent or treat COVID-19 by suppressing the generation of inflammatory cytokines, and therefore CRS (3, 4). Risk factors for vitamin D deficiency include age, race, obesity, kidney disease, winter seasons, higher geographic latitudes, and dietary availability of fortified foods (5–7).

Vitamin D has a broad-spectrum effect in regulating the immune system. Vitamin D reduces proinflammatory cytokines, reduces the survival of viruses by activation of alveolar epithelial cells, and induces differentiation and anti-microbial activity of macrophages to foreign antigens (8, 9). Vitamin D can increase angiotensin-converting enzyme 2 (ACE2) expression, and suppress renin to reduce angiotensin II and reduce lung injury. ACE2 is the receptor responsible for SARS-CoV-2 attachment on the surface of alveolar epithelial cells that causes an increase in angiotensin II formation and pulmonary vasoconstriction in severe COVID-19. By inducing the expression of ACE2, this promotes virus binding, but also results in decreased pulmonary vasoconstriction (10). This is similar to the H7N9 virus in which lung injury was promoted by ACE2 and prevented by expression of ACE2 protein (11). Lastly, vitamin D contains anti-thrombotic properties that may be beneficial in COVID-19 patients to reduce their risk of cardiovascular complications (12). Vitamin D modulates nitric oxide to prevent endothelial dysfunction, and downregulates pro-thrombotic plasminogen activator inhibitor-1 and thrombospondin-1 mRNA expression to decrease the risk of coronary atherosclerosis (13).

Vitamin D has shown the possibility in reducing the risk of respiratory tract infections and influenza-related illness in previous observational reports (14). Protective benefits from vitamin D supplementation were seen in vitamin D deficient patients when they were administered vitamin D daily or weekly (14). Its role in COVID-19 is unknown and limited by a lack of published clinical trials. However, studies have demonstrated that 25(OH)D levels were significantly lower in COVID-19 patients compared to non-COVID-19 patients

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Table 1. Patient Characteristics of Study Population

	Entire cohort, N = 437	Vitamin D deficient, N = 177	Vitamin D sufficient, N = 260	*p*-value
Age, median (IQR)	67 (56–79)	63 (54–76)	69 (58–80)	0.0002
Male, n (%)	210 (48)	97 (55)	113 (43)	0.02
Race, n (%)				
African-American	100 (23)	46 (26)	54 (21)	0.21
White	114 (26)	29 (16)	85 (33)	0.0001
Other	223 (51)	102 (58)	121 (47)	0.02
Ethnicity, n (%)				
Hispanic	115 (26)	46 (26)	69 (27)	0.90
Comorbidities, n (%)				
Asthma	51 (12)	16 (9)	35 (13)	0.16
Chronic obstructive pulmonary disease	31 (7)	10 (6)	21 (8)	0.34
Hypertension	295 (68)	124 (70)	171 (66)	0.35
Coronary artery disease	130 (30)	53 (30)	77 (30)	0.94
Heart failure	74 (17)	28 (16)	46 (18)	0.61
Atrial fibrillation	52 (12)	19 (11)	33 (13)	0.54
Cerebrovascular disease	54 (12)	23 (13)	31 (12)	0.74
Diabetes	195 (45)	79 (45)	116 (45)	0.99
Chronic kidney disease	70 (16)	49 (28)	44 (17)	0.008
End-stage renal disease	50 (11)	24 (14)	25 (10)	0.21
Malignancy	107 (24)	33 (19)	74 (28)	0.02
Transplant	26 (6)	11 (6)	15 (6)	0.84
Obesity	69 (16)	33 (19)	36 (14)	0.18
Clinical outcomes				
Hospitalization, n (%)	372 (85)	154 (87)	218 (84)	0.37
Oxygen support, n (%)	243 (56)	116 (66)	127 (49)	0.0006
Length of hospital stay, median (IQR)	10 (6–20)	11 (6–22)	10 (5–18)	0.25
90-Day mortality, n (%)	132 (30)	52 (29)	80 (31)	0.76
25OHD level, median (IQR)	23 (15–34)	14 (10–17)	31 (25–40)	<0.0001

(15, 16). Likewise, Ilie et al. has described the negative correlation between average vitamin D levels during the COVID-19 pandemic, and the number of COVID-19 cases in European countries (17). A proposed hypothesis of why mortality rates differ in northern latitudes, such as in northern Italy and Spain, is because of the older population, as well as vitamin D deficiency, which may contribute to airway infectious illnesses (18). The aim of this study is to evaluate the association between vitamin D status and COVID-19 clinical outcomes.

Material and methods

Population and study design

This was a retrospective, observational cohort study of patients with COVID-19 disease within the Mount Sinai Health System between March 1, 2020 and May 8, 2020. Adult patients were included if they tested positive for SARS-CoV-2 via nasopharyngeal PCR swab during the timeframe, and had a serum 25-hydroxy vitamin D level (25(OH)D) within the three months prior to their detected SARS-CoV-2 test, or within their admission hospital labs. For cases with more than one 25(OH)D level, we utilized the 25(OH)D level closest to the patient's time of their positive SARS-CoV-2 test. Patients were compared based upon their serum 25(OH)D and defined into two categories: deficient (<20 ng/ml), and sufficient (≥20 ng/ml). The Icahn School of Medicine Institutional Review Board approved this retrospective analysis as minimal-risk research using data collected for routine clinical practice.

Patient characteristics including demographic, comorbidities, and clinical outcomes were obtained from the Mount Sinai Data Warehouse, and confirmed by manual chart review. The primary endpoints were hospital admission, need for oxygen support, and mortality. The mortality endpoint was defined as 90-day mortality documented from the first detected SARS-CoV-2 test. Oxygen support was defined as the need of invasive mechanical ventilation, noninvasive ventilation (i.e. non-rebreather mask, venturi, high flow nasal cannula) or nasal cannula therapy.

Statistical analysis

Differences in baseline characteristics were assessed by a chi-square test for categorical variables or by a Mann-Whitney test or Student's *t*-test for continuous variables. A univariate logistic regression analysis was performed for the association between sufficient 25(OH)D levels and clinical outcomes from COVID-19 infection. Variables yielding a p value ≤0.20 from the univariate analysis were included in a backwards, stepwise, multivariate logistic regression model. The multivariate analysis adjusted for ethnicity, race, sex, age, lung disease, cardiovascular disease, kidney dysfunction, obesity, and malignancy. Statistical significance was measured by a p value <0.05. All statistical analyses were performed using R Studio (Version 1.3.1093).

Results

During March 1, 2020 until May 8, 2020, there were 437 COVID-19 patients who had serum 25(OH)D levels drawn within the three preceding months of their COVID-19 diagnosis. Baseline characteristics are depicted within Table 1. The overall cohort population was of older age [67 (IQR: 56–79) years] with their main comorbidities being

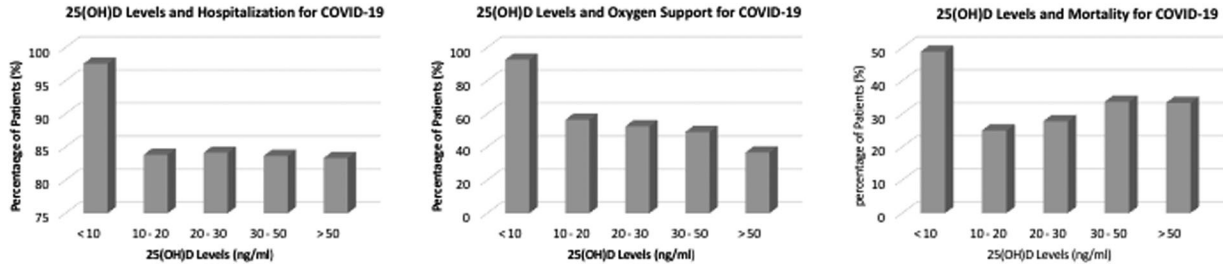

Figure 1. 25(OH)D levels and outcomes associated with COVID-19 infection.

Table 2. Association between Vitamin D and Outcomes from COVID-19 Infection

Predictor variable	Odds ratio (OR)	95% Confidence interval (CI)	*p*-value
Association between vitamin D and oxygen support			
Age	1.03	1.01–1.04	0.0002
Diabetes	1.61	1.07–2.42	0.02
Hispanic ethnicity	1.85	1.16–2.99	0.01
Male sex	1.50	1.00–2.26	0.049
Vitamin D deficient	2.23	1.46–3.44	0.0002
Association between vitamin D and hospitalization for COVID-19 infection			
Age	1.08	1.06–1.11	<0.0001
Kidney disease	3.29	1.24–10.58	0.03
Malignancy	0.20	0.10–0.39	<0.0001
Diabetes	3.20	1.52–7.29	0.003
Association between vitamin D and 90-day mortality			
Age	1.05	1.03–1.06	<0.0001
Obesity	2.08	1.14–3.78	0.02
Male sex	1.59	1.03–2.48	0.04

Multivariate analysis adjusted for ethnicity, race, sex, age, lung disease, cardiovascular disease, kidney dysfunction, obesity, and malignancy.

hypertension (68%), diabetes (45%), coronary artery disease (30%), and malignancy (24%). There were 177 patients classified as vitamin D deficient compared to 260 patients who were vitamin D sufficient. In comparison, there were more males who were vitamin D deficient compared to vitamin D sufficient (n = 97, 55% vs n = 113, 43%, $p = 0.02$) and patients who had chronic kidney disease (n = 49, 28% vs n = 44, 17%, $p = 0.008$). Conversely, there were significantly less patients of the white race (n = 29, 16% vs n = 85, 33%, $p = 0.0001$), and those who had active malignancy (n = 33, 19% vs n = 74, 28%, $p = 0.02$) within the vitamin D deficient group compared to the vitamin D sufficient group, respectively.

Figure 1 displays 25(OH)D levels and outcomes associated with COVID-19 infection. Hospitalization rates (98%), oxygen support (93%), and mortality rates (49%) were highest in patients who had 25(OH)D levels less than 10 ng/ml (n = 30) when compared to other 25(OH)D levels. Oxygen support had a trend of decreasing as 25(OH)D levels increased: <10 ng/ml (93%), 10–20 ng/ml (56%), 20–30 ng/ml (52%), 30–50 ng/ml (49%), and >50 ng/ml (37%). There was no significant difference in clinical outcomes in vitamin D deficient patients compared to vitamin D sufficient regarding hospitalization rates (n = 154, 87% vs n = 218, 84%, $p = 0.37$), length of hospitalization stay in survivors [11 (IQR:6–22) vs 10 (IQR: 5–18), $p = 0.25$), and 90-day mortality rates (n = 52, 29% vs n = 80, 31%, $p = 0.76$). Conversely, patients who were vitamin D deficient required significantly more oxygen support compared to patients within the vitamin D sufficient cohort (n = 116, 66% vs n = 127, 49%, $p = 0.0006$) (Table 1).

In our multivariate analysis, that controlled for demographic variables and comorbidities, low plasma 25(OH)D levels were associated with an increased likelihood of oxygen support from COVID-19 [OR: 2.23 (95% CI:1.46–3.44, $p = 0.0002$)]. The risk of hospitalization was independently associated with age [OR: 1.08 (95% CI:1.06–1.11, $p < 0.0001$)], kidney disease [OR: 3.29 (95% CI: 1.24–10.58, $p = 0.03$)], and diabetes [OR: 3.20 (95% CI: 1.52–7.29, $p = 0.003$)]. An independent negative association was observed between the risk of hospitalization from COVID-19 infection and having a diagnosis of malignancy [OR: 0.20 (95% CI: 0.10–0.39, $p < 0.0001$)]. The risk of oxygen support was independently associated with age [OR: 1.03 (95% CI: 1.01–1.04, $p = 0.0002$)], male sex [OR: 1.50 (95% CI: 1.00–2.26, $p = 0.049$)], Hispanic ethnicity [OR: 1.85 (95% CI: 1.16–2.99, $p = 0.01$)], and diabetes [OR: 1.61 (95% CI: 1.07–2.42, $p = 0.02$)]. The risk of 90-day mortality from COVID-19 infection was not associated with 25(OH)D levels, and was independently associated with older age [OR: 1.05 (95% CI: 1.03–1.06, p < 0.0001)], obesity [OR: 2.08 (95% CI: 1.14–3.78, $p = 0.02$)], and male sex [OR: 1.59 (95% CI: 1.03–2.48, $p = 0.04$)] (Table 2). When 25(OH)D levels were analyzed as a continuous variable, multivariate analysis results were similar depicted in Appendix A.

Discussion

The cohort described in this study is comparable to other COVID-19 studies in which older patients, and patients with chronic comorbidities, may have an increased rate of contracting COVID-19 disease and be hospitalized for COVID related complications (19). Male patients of a non-white race, and patients who have kidney dysfunction were more likely to be vitamin D deficient within this cohort. Previous studies have found that elderly females are at a higher risk than males for vitamin D deficiency, however, with the increased utilization of screening and prevention, males have now become more likely to be deficient in vitamin D. This may be due to the lack of use of vitamin D supplements, consumption of cola drinks, and central obesity (20). Vitamin D deficiency is also more prevalent in people of color. This is from their increased skin pigmentation that reduces the ability of the skin to produce vitamin D from sun exposure, and due to the possibility of lower cellular glutathione (GSH) levels that impairs the vitamin D biosynthesis pathway (9). The prevalence of vitamin D

deficiency within the chronic kidney disease (CKD) population is common, with sufficient 25(OH)D levels being reported in only 17–33% in stage 3 and 4 CKD patients (21). In CKD, FGF-23 increases to inhibit renal 1α-hydroxylase expression leading to degradation of 1,25-(OH_2)D and impaired uptake of 25(OH)D by the kidneys (22).

This retrospective analysis demonstrates that there were clinical differences in outcomes based upon serum 25(OH)D levels and the need for oxygen support therapy. After adjusting for confounding variables, multivariate analysis also demonstrated an independent and significant association between low 25(OH)D levels and the increased likelihood of oxygen support. Lower 25(OH)D levels have been documented to be associated with a greater extent of lung involvement, as documented on chest computed tomography (CT) and poor outcomes in COVID-19 infection ($p < 0.01$) (23). A small case series of four COVID-19 patients showed the benefit of high dose vitamin D (ergocalciferol 50,000 IU daily) supplementation in normalizing serum vitamin D levels, and improving clinical outcomes such as oxygen requirements (24). In a univariate analysis by Merzon et al. low plasma 25(OH)D levels, defined as less than 30 ng/mL, were associated with an increased risk of hospitalization from COVID-19 infection (OR: 2.09, 95% CI: 1.01–4.31, $p < 0.05$). However, this was not preserved within their multivariate analysis (OR: 1.95, 95% CI 0.98–4.84, $p = 0.06$) (16). Rastogi et al. discovered a greater proportion of asymptomatic or mild symptomatic patients with COVID-19 disease, who received cholecalciferol, to have the ability to become SARS-CoV-2 negative compared to patients who did not receive supplementation (25). Similarly, Annweiler et al. reported that vitamin D3 supplementation was associated with better survival and less severe COVID-19 in the elderly. Yet, there was no improvement in outcomes if vitamin D supplements were initiated after a diagnosis of COVID-19 (26). Patients may still benefit from vitamin D supplementation by preventing the need of oxygen assistance during their COVID-19 disease. Such clinical outcomes were not assessed in previous studies.

Limitations of this study deserve acknowledgment. Several demographic variables were not assessed and therefore not evaluated between vitamin D groups. Patients were not assessed if they were nursing home residents or bed bound as this can influence their sun exposure for vitamin D resources. Likewise, socioeconomic status was also not assessed as this has the potential to influence the diet of patients and the availability of fortified foods. Genotypes or conditions that can impair vitamin D metabolism such as medication therapy, malnutrition, or bariatric surgery were not assessed. This study was retrospective in nature, and therefore serum 25(OH)D levels were analyzed over vitamin D medications as it was unknown if patients were taking supplements over the counter or adherent to their medications. There was no comparison to healthy patients who did not have COVID-19 disease, but also had serum 25(OH)D levels. Therefore, it is unknown the protective benefits vitamin D has on obtaining the disease. We included all patients within the ambulatory care and inpatient setting, and therefore a sample size calculation was not performed. It is unknown if vitamin D therapy may be beneficial in the subgroup of intensive care patients. Previous reports have demonstrated that high dose vitamin D (2,50,000–5,00,000 IU) were associated with reduced hospital stays in mechanically ventilated patients (27, 28). We did not evaluate intensive care unit (ICU) admission, as this data point was difficult to gather as many of our medicine wards became ICUs during the pandemic. The authors did not set mortality at 15-day mortality or 30-day mortality due to our small sample size, and the extended hospital stays the patients were experiencing at our institution. Prospective studies may not confirm these results, as odds ratios less than 3 may be due to uncontrollable bias (29). Lastly, there is no consensus on the cutoff of vitamin D sufficiency. The Institute of Medicine (IOM) defines vitamin D deficiency as serum 25(OH)D < 20 ng/ml (50 nmol/l), yet many studies have utilized different cutoffs (30).

Conclusion

To the knowledge of the authors, this is the first study to demonstrate that serum 25-hydroxy vitamin D levels may influence the need for oxygen support therapy. This association was preserved after adjusting for confounding variables. By preventing the need for oxygen support, such as mechanical ventilation, vitamin D supplementation may help to decrease healthcare costs and healthcare bed availability associated with COVID-19 infection. Further prospective studies are underway to provide answers on the role of serum 25-hydroxy vitamin D levels and vitamin D supplementation in COVID-19 infection (31).

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Disclosure statement

The authors declare that they do not have a conflict of interest.

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Appendix A. Multivariate analysis between 25(OH)D levels and outcomes from COVID-19 infection

Table 1a. Association between 25(OH)D Levels and Oxygen Support.

Predictor variable	Odds ratio (OR)	95% Confidence interval (CI)	*p*-value
Age	1.02	1.01–1.04	0.002
Hispanic ethnicity	1.80	1.13–2.90	0.02
Male sex	1.52	1.01–2.29	0.045
25(OH)D levels	0.97	0.96–0.99	0.0003

Table 1b. Association between 25(OH)D Levels and Hospitalization for COVID-19 Infection.

Predictor variable	Odds ratio (OR)	95% Confidence interval (CI)	*p*-value
Age	1.08	1.06–1.11	<0.0001
Kidney disease	3.40	1.28–10.97	0.02
Malignancy	0.19	0.10–0.38	<0.0001
Diabetes	3.06	1.46–6.93	0.005

Table 1c. Association between 25(OH)D Levels and 90-Day Mortality.

Predictor variable	Odds ratio (OR)	95% Confidence interval (CI)	*p*-value
Age	1.05	1.03–1.06	<0.0001
Obesity	2.08	1.14–3.78	0.02
Male Sex	1.59	1.03–2.48	0.04

Multivariate analysis adjusted for ethnicity, race, sex, age, lung disease, cardiovascular disease, kidney dysfunction, obesity, and malignancy.