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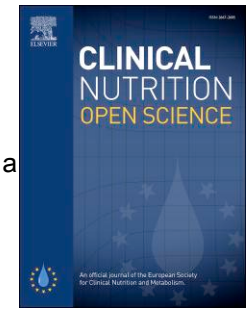

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Exploring the association between vitamin D status and Corona Virus-19 infection in a cohort of adults aged 50 years and older

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Abbreviations:

25-hydroxy-vitamin D: 25(OH)D

1,25-dihydroxy-vitamin D: $1,25(OH)_2D$

Body mass index: BMI

Corona Virus-19 infection: COVID-19 infection

COVID-negative: COVID-Neg

COVID-positive: COVID-Pos

Intensive care unit: ICU

Liquid chromatography-mass spectroscopy/triple quadrupole mass spectroscopy: LC-MS/MS

PCR: polymerase chain reaction

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Vitamin D binding protein: VDBP

Abstract

Objective: Evaluate the association between vitamin D (vitD) status and Corona Virus-19 (COVID-19) infection in adults aged 50 years and older.

Design: Adults ≥50 undergoing COVID-19 testing from July 2020 to December 2021, without prior vaccination, consented to blood analysis. SARS-CoV-2 PCR confirmed current COVID-19 infection. VitD status was assessed via 25(OH)D concentration (LCMS/MS, ZRT Labs, Portland, OR). Sociodemographic data were collected at enrollment. Statistical analyses (SAS 9.4) examined associations between sociodemographics, COVID-19, and vitD status. Multivariate logistic regression analyzed factors linked to COVID-19 or vitD status.

Results: Of 131 participants, 46.6% were ≥65 years old, 71.0% married, 19.9% Black American, 36.6% male, 38.9% Medicaid/Medicare/self-pay, and 42.8% BMI≥30. VitD status and Black American (p=0.0001) significantly associated with COVID-19 infection (p=0.0001). Black American (p=0.0003), males (p=0.003), and BMI (p=0.007) were inversely associated with 25(OH)D concentration. In a multiple logistic regression model predicting COVID-19 infection, only vitamin D status remained significant after controlling for certain sociodemographic and clinical factors (p<0.0001, OR 0.92, 95% CI 0.89-0.95).

Of the 44 COVID-positive participants, 35 (79.6%) were hospitalized and 19 (43.2%) were admitted to the Intensive Care Unit (ICU). Hospitalization due to COVID-19 was associated with age ≥65 years old (p=0.02; OR 12.0, 95% CI 1.34-106.79), male (p=0.02, OR 10.7, 95% CI 1.20-94.73), and 25(OH)D <40 ng/mL (p=0.0006, OR 42.5, 95% CI 3.90-461.01). In multivariate analysis,

the association between vitamin D status and the risk of COVID-related hospitalization remained significant and inversely associated (p=0.03, OR 0.88, 95% CI 0.78-0.99).

In unadjusted analysis, COVID pneumonia was associated with male sex (p=0.049; OR 4.6, 95% CI 1.06-20.16) and 25(OH)D <40 ng/mL (p=0.006, OR 18.8, 95% CI 1.9-184.10). Participants with COVID infection and 25(OH)D <20 ng/mL were 2.1 times more likely to be admitted to ICU/death (p=0.03). In unadjusted analysis, ICU admission and/or death were linked to age ≥65 years (p=0.0002, OR 16.9, 95% CI 3.63-78.56), Medicaid/Medicare/self-pay insurance status (p=0.004, OR 0.1, 0.04-0.56), and 25(OH)D <20 (p=0.03, OR 3.9, 1.09-13.66) and <40 ng/mL (p=0.03); however, only age ≥65 remained significant in multivariate analysis (p=0.04, OR 6.7, CI 1.05-43.0).

Conclusions: Lower 25(OH)D concentration was a significant predictor and/or contributor to COVID-19 infection, suggesting the importance of maintaining adequate vitamin D status in reducing infection risk and mitigating severe outcomes.

Word Count: 347

Introduction

Vitamin D is a fat-soluble secosteroid hormone that is synthesized in the skin upon exposure to sunlight and can also be obtained from certain foods or through supplements. Once ingested, vitamin D is converted into 25-hydroxy-vitamin D (25(OH)D) in the liver and then into the active form, 1,25-dihydroxy-vitamin D ($1,25(OH)_2D$), in the proximal tubules of the kidney and other cells in the body.[1] All forms of vitamin D in circulation are associated with the vitamin D binding protein (DBP) or albumin, with varying affinities.[2,3] While the active form of vitamin D plays a critical role in maintaining calcium homeostasis and bone health by regulating the balance of calcium and phosphorus in the body, vitamin D and its metabolites also influence cell growth and differentiation and affect the function of both the innate and adaptive immune systems.[4] Circulating concentrations of vitamin D as an essential nutrient and preprohormone have also been associated with several health conditions, including cardiovascular disease, preeclampsia, gestational diabetes, autoimmune diseases such as multiple sclerosis and systemic lupus, as well as some cancers (breast, colon and prostate).[5-10] The serum concentration of 25(OH)D is widely used as a marker of vitamin D status, and inadequate levels of vitamin D can lead to vitamin D deficiency. Furthermore, vitamin D has been shown to play a role in racial/ethnic health disparities.[11-13]

Historically, the Endocrine Society defined vitamin D sufficiency as a serum 25(OH)D concentration of greater than 30 ng/mL.[14] Hollis et al[15] and others[16] have suggested optimal vitamin D status occurs when circulating 25(OH)D concentration is at least 40 ng/mL. Studies

have shown that higher concentrations of vitamin D are associated with enhanced immune response and reduced severity of viral respiratory infections, including influenza.[17-23] While most of the studies on this topic have focused on influenza, the same immune response mechanisms are likely to apply to coronaviruses, given the similarities between these diseases in the lower respiratory tract. Vitamin D supplementation has also been shown to be more effective than standard flu vaccines in preventing respiratory infections, especially in those who were deficient prior to supplementation.[20,24] The link between vitamin D deficiency and susceptibility to certain viruses, including swine flu, has been recognized as far back as 1949 in animal studies.[25,26] Critically ill individuals upon admission to the intensive care unit (ICU) have a higher prevalence of vitamin D deficiency, partly attributable to pre-existing malnutrition associated with disease states and lack of sunlight exposure. Conditions such as sepsis, acute respiratory distress syndrome, and acute kidney injury have all been associated with vitamin D deficiency, leading to increased morbidity, mortality, and extended ICU stays.[28]

Vitamin D deficiency exhibits a higher prevalence in certain demographic groups characterized by factors such as darker skin pigmentation, as observed in Black Americans and Hispanic individuals,[27,28] as well as in older adults who encounter limited sun exposure, potentially due to reduced dermal substrate for vitamin D synthesis.[29] This deficiency has been correlated with elevated rates of morbidity and mortality in affected populations.[30] Moreover, individuals belonging to these groups have displayed more severe clinical outcomes following infection with SARS-CoV-2[31,32] (severe acute respiratory syndrome coronavirus 2; a strain of coronavirus that causes COVID-19, the respiratory illness responsible for the COVID-19 pandemic and the

development of COVID-19), providing additional compelling evidence regarding the pivotal role of vitamin D in shaping immune responses and bolstering resistance to infections.

Given the documented prevalence of vitamin D deficiency among high-risk populations and the well-established role of vitamin D in modulating immune function, encompassing both innate and adaptive immunity,[33] this study sought to investigate the relationship between vitamin D status and Corona Virus-19 (COVID-19) infection. Acknowledging the multifaceted nature of COVID-19 infection, which encompasses factors such as prior exposure to coronavirus variants, duration of viral exposure, and individual health conditions—particularly the heightened susceptibility associated with chronic illnesses like diabetes and cardiovascular disease, all of which intricately intersect with immune function and vitamin D status—our study was designed to control for these confounding variables.

The primary hypothesis posited that participants at the time of SARS-CoV-2 testing presenting with vitamin D deficiency (25(OH)D <20 ng/mL) or insufficiency (25(OH)D ≥20<40 ng/mL) would exhibit an elevated likelihood of COVID-19 diagnosis compared to individuals with vitamin D sufficiency (25(OH)D ≥40 ng/mL). This hypothesis was formulated irrespective of demographic variables such as race, sex, age, and body mass index (BMI). In addition to the primary hypothesis, a secondary hypothesis was examined, postulating that individuals who had COVID-19 infection would be more likely to experience more severe illness, as defined by hospitalization, pneumonia, ICU admission, and/or death, particularly in the presence of vitamin D deficiency.

Our study focused on a cohort of adults aged 50 years and older, recognizing their increased vulnerability to COVID-19, and encompassed individuals who had recently undergone PCR (polymerase chain reaction) testing for COVID-19. Additionally, participants consented to the analysis of their vitamin D status through blood sample evaluation. Enrollment of participants occurred prior to the availability and/or administration of any COVID-19 vaccine. To gauge infection severity, we utilized objective criteria, including the diagnosis of radiographic pneumonia, hospitalization rates, ICU admission, and mortality rates. The primary objective of this study was to discern the nuanced relationship between COVID-19 status at the time of testing and the severity of infection, while meticulously considering baseline vitamin D status and thoughtfully controlling for other relevant risk factors.

Methods:

Study Design: This study included adults who were 50 years of age or older and had undergone testing for COVID-19. At the time of their enrollment, no participants had received immunization with any COVID-19 vaccines. Participants provided written informed consent (Pro00099939), and the study was registered with ClinicalTrials.gov (Identifier: NCT04482673). Ninety-five participants (87 with negative COVID-19 status at study entrance and 8 with COVID-19 infection at the time of enrollment) voluntarily took part in a randomization process where they were provided either vitamin D supplementation (6000 IU/day) or vs placebo (0 IU/day). The analysis was performed looking at health outcomes based on circulating vitamin D status at the time of study entrance. Treatment had not been enacted at the time of study entry and had not been in place when analyzing vitamin D status (baseline) and hospitalization or pneumonia diagnosis at

the time of presentation. ICU admission was during the participant's admission due to acute COVID infection and was within one month of diagnosis.

Study Setting: All participants were recruited from the Medical University of South Carolina, an urban university hospital in Charleston, SC, USA.

Study Participants: The entry criteria for this study were age of 50 years or greater and a recent COVID-19 test using the methodology described below within 7 days of enrollment into the study with or without notable disease symptoms. The only inclusion criteria were that the participant had to be fluent in English, could not have had a known prior COVID-19 infection, and had the ability to give written informed consent.

Study Data Collection: A standardized questionnaire was utilized to gather information on the sociodemographic and clinical characteristics of the study cohort. This included details such as age, gender, marital status, ethnicity, educational background, history of chronic illnesses, current medications, and vitamin intake.

Polymerase Chain Reaction (PCR) Testing for current SARS-CoV-2 (COVID-19) Infection: Each participant had a nasal swab inserted directly into one of the two nares swirled for 10 seconds per Center for Disease Control guidelines.[34] The nasal swab was immediately placed in buffer, placed in a plastic bag, then sent to MUSC Clinical Chemistry where the sample was tested for the presence or absence of SARS-CoV-2 RNA by PCR, a nucleic acid amplification test. Results were reported in the electronic medical record at MUSC (EPIC) within 48 hours of sample collection.

Vitamin D Status Defined: We defined vitamin D status by combining criteria from the Endocrine Society at the time of study design,[14] our previous research,[15] and findings from others.[16]

Circulating 25(OH)D concentration, expressed in ng/mL, was categorized as follows: a) deficiency: <20 ng/mL; b) insufficiency: ≥20 and <40 ng/mL; and c) sufficiency: ≥40 ng/mL.

Measuring Vitamin D Status through Total Circulating 25(OH)D Concentration: The 25(OH)D concentration was determined using a LCMS/MS method from ZRT Laboratories in Portland, OR. The methodology used was standardized, and the results were cross validated with the Hollis radioimmunoassay method, which was in use at our laboratory (Diasorin, Stillwater, MN). Samples were analyzed by participant identification number and laboratory personnel were blinded to SARS-CoV-2 (COVID-19 infection) status.

Statistical Analysis:

Primary Analysis - Predicting COVID-19 Infection: The primary objective of this study was to assess the relationship between COVID-19 infection and total circulating 25(OH)D concentration. Initially, univariate and bivariate analyses were performed to identify factors associated with COVID-19 status (positive or negative). Sociodemographic and clinical characteristics were assessed for their potential associations with COVID-19 status and baseline 25(OH)D concentration using Chi-square and Student's t-test, respectively.

A logistic regression model was then constructed to predict COVID-19 infection status at the time of testing. This model incorporated variables that were independently associated with COVID-19 status from the univariate and bivariate analyses. The logistic regression aimed to identify predictors of COVID-19 infection, allowing us to understand the factors associated with testing positive for the virus.

Secondary Analysis - Predicting COVID-19 Infection Severity: In a separate analysis focusing exclusively on participants who tested positive for COVID-19, we aimed to predict the severity of COVID-19 illness. Initially, univariate and bivariate analyses were conducted to identify factors associated with infection severity, which was defined by outcomes such as radiographic pneumonia, hospitalization, ICU admission, and mortality.

A second logistic regression model was constructed to predict COVID-19 infection severity among those who tested positive. This model included variables found to be associated with infection severity in the initial analyses. The objective of this secondary analysis was to understand the determinants of illness severity within the COVID-19 positive group.

These two logistic regression models are distinct and address separate research questions. The first model focuses on the likelihood of testing positive for COVID-19 infection, while the second model explores the factors contributing to the severity of COVID-19 illness among those who contracted the viral infection. Both analyses provide valuable insights into the dynamics of COVID-19 infection and its impact on study participants. Statistical analyses were completed with SAS 9.4 and SPSS 28 and examined associations between sociodemographics, COVID-19, and vitamin D status. Multivariate logistic regression analyzed factors linked to COVID-19 or vitamin D status.

Results

Each participant underwent a SARS-CoV-2 PCR test within 7 days prior to enrollment to confirm study inclusion of being either COVID-negative (COVID-Neg) with no prior known history of COVID

infection or COVID-positive (COVID-Pos) with a current COVID infection at the time of study enrollment. Initially, the cohort was comprised of 134 participants; however, after a meticulous review of medical records following consent, it was found that three individuals allocated to the COVID-negative group had a history of remote COVID infection confirmed by prior PCR testing. Consequently, these three participants were excluded from the analysis, resulting in a final sample size of 131 participants, with 87 individuals in the COVID-negative group and 44 in the SARS-CoV-2 positive (COVID-Pos) group at the time of enrollment. Analysis of demographic characteristics (see **Table 1**) revealed no statistically significant difference in mean age, age group distribution (65 vs. ≥ 65 years), sex distribution, marital status, insurance status, or BMI between the two groups. Black American participants exhibited a 2.5-fold higher likelihood of being COVID-Pos compared to Non-Black Americans ($p<0.0001$). In terms of vitamin D status, as measured by total circulating 25(OH)D concentration, a significant disparity was observed between the COVID-Pos and COVID-Neg groups: COVID-pos participants displayed a statistically lower mean level (24.6 ± 16.4 ng/mL) compared to those participants in the COVID-neg group (47.7 ± 17.8 ng/mL; $p<0.0001$).

Factors that influence vitamin D status historically were analyzed for this cohort and are listed in **Table 2**. Being male was associated with lower mean 25(OH)D concentration than females (32.5 v 44.2 ng/mL; p=0.0006). Black Americans had significantly lower mean 25(OH)D compared to Non-Black Americans (26.4 v 43.3 ng/mL; p=0.0001). BMI was significantly associated with vitamin D status (≥30: 34.2 v <30: 44.2 ng/mL; p=0.004). Age ≥ 65 years, marital status and insurance status were not significantly associated with vitamin D status.

248

249 **Table 3** presents bivariate analyses comparing sociodemographic and clinical characteristics
250 between participants who tested positive for COVID and those who tested negative. The main
251 differences between the groups were race/ethnicity and baseline 25(OH)D concentration and
252 threshold levels: COVID-pos participants were more likely Black American ($p<0.0001$) and had
253 significantly lower 25(OH)D concentrations ($p<0.0001$). Black American were 2.5 times more
254 likely than non-Black Americans to be COVID-pos at presentation. Those who were vitamin D
255 deficient with 25(OH)D concentration of <20 ng/mL (deficiency) were 4.2 times as likely to be
256 COVID-pos than those with a level of ≥20 ng/mL. Those with a 25(OH)D concentration of <40
257 ng/mL (deficiency or insufficiency) were 5.2 times more likely to be COVID-pos than those with a
258 level of ≥40 ng/mL.

259

260 Factors significant in bivariate analyses or previously associated with either COVID infection or
261 vitamin D status were included in a multivariate logistic regression model in identifying
262 independent predictors of COVID infection (age ≥ 65 years, sex, race/ethnicity, marital status,
263 insurance status, BMI ≥ 30, and baseline 25(OH)D concentration). The only factor that remained
264 statistically significant in the model was 25(OH)D concentration ($p <0.0001$, 95% CI 0.90.95; OR
265 0.92) (**Table 4a**), which was inversely related to COVID positive status: those with lower 25(OH)D
266 were more likely to be COVID positive. When the model was changed to include 25(OH)D at the
267 threshold of <20 ng/mL (**Table 4b**), with the other factors remaining the same, those with
268 25(OH)D <20 ng/mL were 24.9 times more likely to be COVID pos than those with 25(OH)D ≥20
269 ng/mL ($p<0.0001$, 95% CI 6.14-100.82). When vitamin D status was dichotomized, there was a

trend where being Black American also was an independent predictor of COVID-pos status (p=0.05, OR 3.37, 95% CI 1.009-11.26).

A summary of illness severity of those who were COVID-pos in this cohort is found in **Table 5a-5e**. Of the 44 COVID-pos participants, 35 (79.6%) were hospitalized and 19 (43.2%) were admitted to the Intensive Care Unit (ICU). Thirty-one (70.5%) were diagnosed with pneumonia confirmed by chest radiograph at the time of diagnosis. Of the 19 admitted to the ICU, 11 (57.9%) died due to acute COVID infection and its complications.

As shown in **Table 5**a, those who required hospitalization due to their acute COVID infection compared to those who were not differed significantly by age (those hospitalized were more likely older, p=0.02), sex (males were more likely than females to be hospitalized, p=0.02), and by 25(OH)D concentration at presentation <40 ng/mL (p=0.0006). Those with 25(OH)D <40 ng/mL were 5.4 times more likely to be hospitalized than those with a level ≥40 ng/mL. In a multivariate logistic regression analysis performed to assess factors associated with hospitalization, including age ≥65, sex, race/ethnicity, marital status, insurance, BMI, and 25(OH)D concentration, only 25(OH)D concentration remained a significant independent predictor of hospitalization (estimate: -0.14, p-value=0.008, odds ratio: 0.9, 95% CI: 0.78-0.99).

Those participants who were diagnosed with COVID pneumonia confirmed by radiograph (**Table 5b**) did not differ from those without pneumonia on the basis of age, marital status, insurance status, BMI, race/ethnicity, or 25(OH)D <20 ng/mL but did differ on the basis of sex (males were

1.5 times more likely than females to have radiographic-confirmed pneumonia at presentation than females, p=0.049) and 25(OH)D concentration <40 ng/mL (p=0.006). Those with a 25(OH)D concentration <40 ng/mL were 4.7 times as likely to be diagnosed with COVID pneumonia (p=0.006) than those with a level of ≥40 ng/mL. In the bivariate logistic regression, 25(OH)D concentration was significantly associated with COVID pneumonia; however, in the multivariate logistic regression analysis, after controlling for other independent factors, 25(OH)D concentration was no longer significant (estimate: -0.08, p-value=0.05, odds ratio: 0.9, 95% confidence interval: 0.86-1.002).

Intensive Care (ICU) admission (**Table 5c**) was associated with age (those who were 65 years or older were 5.3 times more likely to be admitted to the ICU (p=0.0002), have Medicaid/Medicare/self-pay (p=0.004), and vitamin D deficiency and/or insufficiency (p=0.03). In a multivariate logistic regression analysis for ICU admission, there were no independent factors identified that were associated with ICU admission. Death attributed to COVID infection in this cohort (see **Table 5d**) was associated with age ≥65 years and insurance status but were no longer significant in the multivariate regression model. While no deaths were observed among the 6 participants with a 25(OH)D level ≥40 ng/mL at presentation, this association did not reach statistical significance. ICU admission and/or death attributed to COVID infection (see **Table 5e**) were associated with age (those ≥65 years were 5.3 times more likely to have an ICU admission and/or death), Medicaid/Medicare/self-pay insurance status, and 25(OH)D levels categorized at cutpoints of 20 and 40 ng/mL. In multivariate logistic regression, however, none of these factors exhibited a statistically significant association with ICU admission and/or death due to COVID.

Discussion

This pilot study aimed to explore the potential correlation between vitamin D status and COVID-19 infection among adults aged 50 years and older, while considering various factors that might impact both vitamin D status and the likelihood of contracting COVID-19. Building on previous research by Hollis et al. regarding optimal vitamin D status,[15] our main hypothesis proposed that older adults with vitamin D deficiency (25(OH)D <20 ng/mL) or insufficiency (25(OH)D ≥20 to <40 ng/mL) would have a higher risk of being diagnosed with COVID-19 compared to those with sufficient vitamin D levels, defined as 25(OH)D concentrations ≥40 ng/mL. Additionally, we hypothesized that individuals with both COVID-19 infection and vitamin D deficiency would experience more severe illness.

Within this cohort of adults aged 50 years and older, the analysis revealed various factors that independently were associated with positive COVID-19 status at the time of testing. These factors included sex, insurance status, race/ethnicity, and vitamin D status. Specifically, males, individuals with Medicaid/Medicare or self-pay without insurance, those of Black-American ethnicity, and those with lower circulating 25(OH)D concentrations exhibited a heightened likelihood of testing positive for COVID-19. Additionally, among those who tested positive for COVID-19, a relationship emerged between lower 25(OH)D concentrations and the occurrence of hospitalization and pneumonia.

To ascertain the independent influence of vitamin D status on testing positive for COVID-19 infection, a bivariate logistic regression model was employed. The results indicated that vitamin D status remained the sole factor that exhibited a statistically significant association with COVID-19 infection. Similarly, in the multivariate logistic regression model showed that vitamin D status was inversely related to testing positive for COVID-19 infection at the time of presentation, with lower 25(OH)D concentration more likely associated with COVID-19 infection. When vitamin D status was dichotomized in the multivariate logistic regression, 25(OH)D <20 ng/mL as well as being Black American were independently associated with COVID-pos status.

Further examination of COVID-positive individuals revealed a significant association between vitamin D deficiency, defined by 25(OH)D concentrations below 20 ng/mL, and insufficiency, defined by 25(OH)D concentrations below 40 ng/mL, and increased rates of hospitalization, pneumonia, ICU admission, and/or death. Specifically, in bivariate logistic regression, individuals who were deficient or insufficient in vitamin D were 4.7 times more likely to have radiographic evidence of pneumonia and 5.4 times more likely to require hospitalization. However, in this small subgroup, the significance was attenuated when other factors were included in a multivariate logistic regression. Despite this attenuation, these findings highlight the significant impact of vitamin D deficiency on the morbidity associated with COVID infection within this specific cohort.

Emerging evidence suggests that low vitamin D levels could potentially exacerbate COVID-19 infection, particularly when the viral infection reaches the lower respiratory tract. The virus

targets alveolar type II epithelial cells (ATII), which are pivotal in producing pulmonary surfactant and facilitating lung repair. These cells are susceptible to infection due to their high expression of the angiotensin-converting enzyme 2 (ACE2) receptor, the primary cellular attachment point for SARS-CoV-2. [35-37] Previous research has indicated that innate and adaptive immune cells in the lungs, as well as ATII cells themselves, have the capability to synthesize the active form of vitamin D and are strongly regulated by this hormone.[38,39] Disruption of ATII cell functions resulting from SARS-CoV-2 infection could lead to pulmonary surfactant deficiency, dysregulation of the local renin-angiotensin system, impaired lung fluid clearance and repair mechanisms. These processes, coupled with the subsequent inflammatory cytokine storm, contribute to the development of acute respiratory distress syndrome, which is a defining feature of severe COVID-19 infection and pneumonia. Notably, these adverse outcomes disproportionately affect racial and ethnic minorities in the United States. Adequate vitamin D levels may enhance the pulmonary immune response against the virus, mitigate the harmful cytokine storm, and alleviate surfactant dysregulation, potentially preventing or ameliorating the acute syndrome.

Furthermore, a recent meta-analysis conducted by Meng et al.[40] involving 8,128 participants across 8 clinical trials revealed valuable insights. While the meta-analysis did not find a significant reduction in the rate of SARS-CoV-2 infection with vitamin D supplementation, it did indicate improved clinical outcomes, including a reduced need for ICU admissions (RR 0.63; 95% CI 0.44 to 0.89) and decreased reliance on mechanical ventilation (RR 0.58; 95% CI 0.39 to 0.84), albeit without a statistically significant effect on mortality. Subgroup analyses within this meta-analysis, focused on patients with specific conditions, did, however, reveal a significant reduction in

mortality among individuals with preexisting vitamin D deficiency (RR 0.76; 95% CI 0.58 to 0.98). These findings suggest that vitamin D may play a role in mitigating illness severity, particularly in cases where vitamin D deficiency is known or exists. Notably, our findings align with the observation that vitamin D deficiency was more prevalent among individuals who tested positive for SARS-CoV-2 infection.

This pilot study exhibits several strengths that enhance its value. Firstly, it is notable for its diverse participant demographics, encompassing individuals from various racial and ethnic backgrounds. Additionally, the study includes participants with a wide range of health statuses and varying body mass indices (BMI), adding to the robustness and generalizability of the findings. Moreover, the analysis is enriched by the inclusion of detailed socioeconomic and clinical characteristics, which allows for a comprehensive exploration of potential associations.

This study has some limitations that should be acknowledged. Firstly, the reliance solely on PCR testing for COVID-19 diagnosis, without subsequent antibody confirmation, represents a potential limitation. While PCR testing is highly sensitive for detecting active infections, there is a possibility that participants with previous COVID infections may have been included, leading to a potential underestimation of COVID-19 cases. However, it is important to note that the study meticulously collected data on signs and symptoms of infection from both COVID-negative and COVID-positive participants, which helped mitigate some of the potential limitations associated with PCR-based diagnosis. Additionally, all participants received care through the same medical center system, utilizing a centralized electronic medical record (EMR). Each participant's EMR

was thoroughly screened for prior SARS-CoV-2 testing to minimize the inclusion of individuals with previous COVID infections.

Another limitation of this study is the relatively small sample size of participants, which was influenced by the challenges of recruiting unvaccinated individuals once COVID-19 vaccines became widely available. Additionally, only six COVID-positive patients had serum 25(OH)D concentrations ≥40 ng/mL. Given this very small number, severity endpoints related to this threshold should be interpreted with caution. While the ≥40 ng/mL threshold may represent a better benchmark for defining vitamin D adequacy compared to the 20 ng/mL threshold, the sample size was insufficient to perform robust comparisons of outcomes between 25(OH)D levels of 20–40 ng/mL and those ≥40 ng/mL. Consequently, caution is warranted in interpreting the findings related to severe outcomes when comparing 25(OH)D levels <40 ng/mL with those ≥40 ng/mL, due to the small number of participants in the latter group.

Furthermore, the small sample size of participants receiving vitamin D supplementation is another limitation in assessing its potential effect on ICU admission and/or death. Of the 44 participants randomized to the longitudinal treatment arm of the study, only eight were supplemented with vitamin D, 4 in the treatment group and 4 in the placebo group, with one hospitalized at study entry with COVID-19 pneumonia. It remains unclear, then, whether vitamin D supplementation mitigated disease severity, as the study lacked sufficient statistical power to draw definitive conclusions. Despite these limitations, the findings underscore the potential

423 importance of maintaining adequate vitamin D status during a viral epidemic, particularly in the
424 early stages of a novel virus outbreak when vaccines are not yet available.
425
426 In summary, in this small cohort, vitamin D status was associated with COVID-19 infection after
427 controlling for other independent factors. In addition, those hospitalized due to COVID infection
428 were more likely to be vitamin D insufficient or deficient. This exploratory study highlights the
429 importance of vitamin D status in relation to COVID-19 risk, with lower 25(OH)D concentration
430 found to be a significant predictor of COVID-19 infection and severity of illness. These findings
431 have implications for mitigating the risk of acute viral infections such as COVID-19 and suggest
432 that maintaining adequate vitamin D levels may be important in reducing the risk of COVID-19
433 infection in older adults. Further research is needed to assess the impact of achieving optimal
434 vitamin D status of at least 40 ng/mL on the longitudinal risk of COVID infection in older adults.
435
436
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438
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Dedication

The authors dedicate this manuscript to the memory of Carole A. Baggerly, MS, co-author, whose unwavering passion and dedication to advancing the understanding of vitamin D deficiency inspired this work and countless others in the field. Carole was instrumental in the conception, design, and successful completion of this study. Her tireless efforts to educate the world about the importance of vitamin D have left an indelible mark on public health and scientific research. She will be deeply missed, but her legacy will continue to guide and inspire future endeavors in this field.

Presentations

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Bruce W. Hollis, PhD: conceptualization, study design/methodology, revision of manuscript, critical review of manuscript

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Table 1. Sociodemographics and Clinical Characteristics of Cohort by COVID-19 Status at Baseline[ς]

Characteristic	All N=131	COVID-19 Positive N=44 (33.6%)	COVID-19 Negative N=87 (66.4%)	p-value *p<0.05
Age in Years, Mean ± SD	64.3 ± 9.3	65.9 ± 11.3	63.5 ± 7.9	0.2
(range)	(50.6-96.0)	(52.0-96.0)	(50.6-80.0)	
Ages				0.6
≥ 65 years, N (%)	61 (46.6%)	22 (36.1%)	39 (63.9%)	
< 65 years, N (%)	70 (53.4%)	22 (31.4%)	48 (68.6%)	
Sex				0.06
Males, N (%)	48 (36.6%)	21 (43.8%)	27 (56.3%)	
Females, N (%)	83 (63.4%)	23 (27.7%)	60 (72.3%)	
Marital Status				0.9
Married, N (%)	93 (71.0%)	31 (33.3%)	62 (66.7%)	
Not Married, N (%)	38 (29.0%)	13 (34.2%)	25 (65.8%)	
Insurance Status				0.9
Private, N (%)	80 (60.9%)	27 (33.8%)	53 (66.3%)	
Medicaid/Medicare/Self-Pay, N (%)	51 (38.9%)	17 (33.3%)	34 (66.7%)	
Body Mass Index (BMI)				0.05
≥ 30, N (%)	56 (42.8%)	24 (42.9%)	32 (57.1%)	
BMI <30, N (%)	75 (57.3%)	20 (26.7%)	55 (73.3%)	
Race/Ethnicity				**<0.0001***
Black, N (%)	26 (19.9%)	17 (65.4%)	9 (34.6%)	
Non-Black, N (%)	105 (80.2%)	27 (25.7%)	78 (74.3%)	
Baseline 25(OH)D, ng/mL	39.9 ± 20.5	24.6 ± 16.4	47.7 ± 17.8	**<0.0001***
(range)	(4.0-105.0)	(4.0-89.0)	(9.0-105.0)	

[ς] Within the ALL column, percentages are the % of the total within that column. For the COVID-19 Positive and Negative Columns, percentages are read across the columns comparing COVID-19 Positive and Negative Participants for each attribute or characteristic.

Table 2. Sociodemographic and Clinical Characteristics of Cohort in Relation to Vitamin D Status as Measured by Total Circulating 25(OH)D Concentration (ng/mL)

Sociodemographic and Clinical Characteristic	25(OH)D (ng/mL), Mean ± SD (range)	p-value *p<0.05
Age		0.1
≥65 years (N=61)	36.9 ± 18.8 (4.0-82.0)	
<65 years (N=70)	42.6 ± 21.6 (8.0-105.0)	
Sex		**0.002***
Males (N=48)	32.6 ± 15.8 (4.0-64.0)	
Females (N=83)	44.2 ± 21.7 (8.9-105.0)	
Race/Ethnicity		**0.0001***
Black American (N=26)	26.4 ± 19.0 (4.0-70.0)	
Non-Black American (N=108)	43.3 ± 19.5 (10.9-105.0)	
Marital Status		0.4
Married (N=93)	40.4 ± 20.3 (8.9-105.0)	
Non-Married (N=38)	38.2 ± 19.9 (4.0-89.0)	
Insurance Status)		0.32
Private Insurance (N=80)	41.0 ± 20.9 (4.0-105.0)	
Medicaid/Medicare/Self Paying (N=52	37.7 ± 20.7 (8.0-82.0)	
Body Mass Index		**0.004***
BMI ≥30 (n=56)	34.2 ±16.8 (4.0-70.0)	
BMI <30 (N=75)	44.2 ± 22.0 (8.9-105.0)	

Table 3. COVID-19 Positive vs. COVID-19 Negative Participants by Sociodemographic and Clinical Characteristics with Odds Ratios and Relative Risk

Characteristic	All N=131	COVID-19 Positive N=44 (33.6%)	COVID-19 Negative N=87 (66.4%)	p-value (*p<0.05) Odds Ratio (95% CI)[1] or Relative Risk (95% CI)
Age in Years, Mean ± SD (range)	64.3 ± 9.3 (50.6-96.0)	65.9 ± 11.3 (52.0-96.0)	63.5 ± 7.9 (50.6-80.0)	0.2 OR (95% CI) 1.0 (0.99-1.07)
Ages				0.6
≥ 65 years, N (%)	61 (46.6%)	22 (36.1%)	39 (63.9%)	RR (95% CI)
< 65 years, N (%)	70 (53.4%)	22 (31.4%)	48 (68.6%)	1.1 (0.70-1.86)
Sex				0.06
Males, N (%)	48 (36.6%)	21 (43.8%)	27 (56.3%)	RR (95% CI)
Females, N (%)	83 (63.4%)	23 (27.7%)	60 (72.3%)	1.6 (0.98-2.53)
Marital Status				0.9
Married, N (%)	93 (71.0%)	31 (33.3%)	62 (66.7%)	RR (95% CI)
Not Married, N (%)	38 (29.0%)	13 (34.2%)	25 (65.8%)	0.9 (0.58-1.95)
Insurance Status				0.9
Private, N (%)	80 (60.9%)	27 (33.8%)	53 (66.3%)	RR (95% CI)
Medicaid/Medicare/Self-Pay, N (%)	51 (38.9%)	17 (33.3%)	34 (66.7%)	1.0 (0.62-1.66)
Body Mass Index (BMI)				0.05
≥ 30, N (%)	56 (42.8%)	24 (42.9%)	32 (57.1%)	RR (95% CI)
<30, N (%)	75 (57.3%)	20 (26.7%)	55 (73.3%)	1.6 (0.99-2.60)
Race/Ethnicity				**<0.0001***
Black, N (%)	26 (19.9%)	17 (65.4%)	9 (34.6%)	**RR (95% CI)**
Non-Black, N (%)	105 (80.2%)	27 (25.7%)	78 (74.3%)	**2.5 (1.66-3.90)**
Baseline 25(OH)D, ng/mL (range)	39.9 ± 20.5 (4.0-105.0)	24.6 ± 16.4 (4.0-89.0)	47.7 ± 17.8 (9.0-105.0)	**<0.0001*** **OR (95% CI)** **0.9 (0.88-0.94)**
25(OH)D Concentration (ng/mL)				**<0.0001***
<20, N (%)	25 (19.1%)	22 (88.0%)	3 (12.0%)	**RR (95% CI)**
≥20, N (%)	106 (80.9%)	22 (20.8%)	84 (79.3%)	**4.2 (2.84-6.32)**
25(OH)D Concentration (ng/mL)				**<0.0001***
< 40, N (%)	72 (55.0%)	38 (52.8%)	34 (47.2%)	**RR (95% CI)**
≥40, N (%)	59 (45.0%)	6 (10.2%)	53 (89.8%)	**5.2 (2.36-11.43)**

[1]OR = Odds Ratio for continuous variables
RR = Relative Risk for categorical variables

Chi-square analysis was used for categorical variables to assess associations and calculate relative risk for being Covid-Positive. Bivariate logistic regression was used for the continuous independent variable of 25(OH)D concentration to assess association with Covid-Positive and to calculate odds ratios.

Table 4a. Logistic Regression Model in Predicting COVID-Positive Status with 25(OH)D Concentration

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	0.35	0.60	0.34	1.42	0.44-4.57	0.56
Male	0.24	0.49	0.24	1.28	0.49-3.36	0.62
Black American	0.92	0.61	2.27	2.52	0.76-8.39	0.13
Unmarried	-0.13	0.54	0.06	0.87	0.30-2.53	0.80
Medicaid/Medicare/Self-Pay	-0.59	0.62	0.94	0.56	0.17-1.84	0.33
BMI ≥ 30	0.35	0.50	0.50	1.42	0.54-3.75	0.48
25(OH)D Concentration	-0.08	0.018	20.95	0.92	0.89-0.95	**<0.0001***

SE = standard error

OR = odds ratio

95% CI = 95% Wald Confidence Limits

Table 4b. Logistic Regression Model in Predicting COVID-Positive Status with 25(OH)D <20 ng/mL

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	0.62	0.59	1.12	1.86	0.587-5.912	0.29
Male	0.61	0.50	1.49	1.84	0.691-4.886	0.22
Black American	1.22	0.62	3.90	3.37	1.009-11.261	0.05
Unmarried	-0.11	0.56	0.04	0.89	0.30-2.69	0.84
Medicaid/Medicare/Self	-1.20	0.64	3.57	0.30	0.09-1.05	0.06
BMI ≥ 30	0.55	0.50	1.24	1.74	0.657-4.598	0.27
25(OH)D <20 ng/mL	3.21	0.71	20.26	24.87	6.137-100.821	**<.0001***

SE = standard error

OR = odds ratio

95% CI = 95% Wald Confidence Limits

Table 5a. COVID Positive – Hospitalization at Time of Study Entry

Characteristic	All N=44	Hospitalized N=35 (79.6%)	Not Hospitalized N=9 (20.5%)	p-value (*p<0.05) Relative Risk (RR) Odds Ratio (OR) (95% CI)
Ages				**0.02* Fisher's Exact**
≥ 65 years, N (%)	22 (50.0%)	21 (95.5%)	1 (4.6%)	1.5 (1.08-2.08) **RR**
< 65 years, N (%)	22 (50.0%)	14 (63.6%)	8 (36.4%)	12.0 (1.34-106.79) **OR**
Gender				**0.02* Fisher's Exact**
Males, N (%)	21 (47.7%)	20 (95.2%)	1 (4.8%)	1.5 (1.07-2.00) **RR**
Females, N	23 (52.3%)	15 (65.2%)	8 (34.8%)	10.7 (1.20-94.73) **OR**
Marital Status				1.0 **Fisher's Exact**
Married, N (%)	31 (70.5%)	25 (80.7%)	6 (19.4%)	1.0 (0.74-1.48) **RR**
Not Married, N (%)	13 (29.5%)	10 (76.9%)	3 (23.1%)	1.3 (0.26- 6.00) **OR**
Insurance Status				0.1 **Fisher's Exact**
Private, N (%)	27 (61.4%)	19 (70.4%)	8 (29.6%)	0.7 (0.57-0.98) **RR**
Medicaid/Medicare/self-pay, N (%)	17 (38.6%)	16 (94.1%)	1 (5.9%)	0.1 (0.02-1.32) **OR**
Body Mass Index (BMI)				1.0 **Fisher's Exact**
BMI ≥ 30, N (%)	24 (54.6%)	19 (79.2%)	5 (20.8%)	0.9 (0.73-1.34) **RR**
BMI <30, N (%)	20 (45.4%)	16 (80.0%)	4 (20.0%)	0.9 (0.22-4.15) **OR**
Race/Ethnicity				1.0 **Fisher's Exact**
Black, N (%)	17 (38.6%)	14 (82.4%)	3 (17.6%)	1.1 (0.79-1.43) **RR**
Non-Black, N (%)	27 (61.4%)	21 (77.8%)	6 (22.2%)	1.3 (0.29-6.23) **OR**
25(OH)D < 20 ng/mL				0.1 **Fisher's Exact**
<20, N (%)	22 (50.0%)	20 (90.9%)	2 (9.1%)	1.3 (0.97-1.83) **RR**
≥20, N (%)	22 (50.0%)	15 (68.2%)	7 (31.8%)	4.7 (0.80-25.75) **OR**
25(OH)D < 40 ng/mL				**0.0006* Fisher's Exact**
< 40, N (%)	38 (86.4%)	34 (89.5%)	4 (10.5%)	5.4 (0.89-32.23) **RR**
≥40, N (%)	6 (13.6%)	1 (16.7%)	5 (83.3%)	42.5 (3.90-461.01) **OR**
	N Mean ± STD range	**N Mean ± STD range**	**N Mean ± STD range**	**p-value (*p<0.05) Odds Ratio (OR) (95% CI)**
25(OH)D concentration (ng/mL)	44 24.6 ± 16.4 4.0-89.0	35 20.2 ± 9.5 4.0-41.4	9 41.7 ± 25.5 10.9-89.0	**0.03* Student's T-test** **0.008* regression** 0.9 (0.86-0.98) **OR**

Multivariate Logistic Regression

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	0.96	1.71	0.31	2.61	0.09-74.74	0.58
Male	2.62	1.41	3.46	13.68	0.87-215.71	0.06
Black American	-1.57	1.44	1.19	0.21	0.01-3.49	0.28
Unmarried	-1.94	1.66	1.36	0.14	0.01-3.75	0.24
Medicaid/Medicare/Self	4.09	2.56	2.55	59.54	0.12-80.59	0.11
BMI ≥ 30	1.13	1.66	0.46	3.10	0.12-80.59	0.50
25(OH)D Concentration	-0.13	0.06	4.72	0.88	0.78-0.99	**0.03***

In chi square analysis, factors independently associated with hospitalization at time of study entry included age ≥65 years, male sex, and 25(OH)D concentrations categorized at cutpoints of 20 and 40 ng/mL. Additionally, based on Student's t-test, 25(OH)D concentration was found to be associated with hospitalization. In bivariate logistic regression, a significant association was observed between hospitalization and 25(OH)D concentration (p=0.008, 95% CI 0.86-0.98). Subsequently, a multivariate logistic regression analysis was performed to assess factors associated with hospitalization, including age ≥65, sex, race/ethnicity, marital status, insurance status, BMI, and 25(OH)D concentration. The results demonstrated that only 25(OH)D concentration remained a significant independent predictor of hospitalization (estimate: 0.9, p-value=0.03, odds ratio: 0.9, 95% CI: 0.78-0.99).

Table 5b. COVID Positive – Pneumonia at time of Study Entry

Characteristic	All N=44	Pneumonia N=31 (70.5%)	No Pneumonia N=13 (29.6%)	p-value (*p<0.05) Relative Risk (RR) Odds Ratio (OR) (95% CI)
Ages				0.2 **Fisher's Exact**
≥ 65 years, N (%)	22 (50.0%)	18 (81.8%)	4 (18.2%)	1.4 (0.93-2.06) **RR**
< 65 years, N (%)	22 (50.0%)	13 (59.1%)	9 (40.9%)	3.1(0.79-12.3) **OR**
Gender				**0.049* Fisher's Exact**
Males, N (%)	21 (47.7%)	18 (85.7%)	3 (14.3%)	1.5 (1.02-2.26) **RR**
Females, N	23 (52.3%)	13 (56.5%)	10 (43.5%)	4.6 (1.06-20.16) **OR**
Marital Status				0.4 **Student's T-test**
Married, N (%)	31 (70.4%)	23 (74.2%)	8 (25.8%)	1.2 (0.70-1.94) **RR**
Not Married, N (%)	13 (29.6%)	8 (61.5%)	5 (38.5%)	1.8 (0.40-7.12) **OR**
Insurance Status				0.7 **Fisher's Exact**
Private, N (%)	27 (61.4%)	18 (66.7%)	9 (33.3%)	0.9 (0.60-1.27) **RR**
Medicaid/Medicare/self-pay, N (%)	17 (38.6%)	13 (76.5%)	4 (23.5%)	0.6 (0.16-2.44) **OR**
Body Mass Index (BMI)				0.9 **Chi-Square**
BMI ≥ 30, N (%)	24 (54.6%)	17 (70.8%)	7 (29.2%)	1.0 (0.69-1.49) **RR**
BMI <30	20 (45.4%)	14 (70.0%)	6 (30.0%)	1.0 (0.28-3.82) **OR**
Race/Ethnicity				0.9 **Chi-Square**
Black, N (%)	17 (38.6%)	12 (70.6%)	5 (29.4%)	1.0 (0.68-1.49) **RR**
Non-Black, N (%)	27 (61.4%)	19 (70.4%)	8 (29.6%)	1.0 (0.27-3.82) **OR**
25(OH)D < 20 ng/mL				0.3 **Chi-Square**
<20, N (%)	22 (50.0%)	17 (77.3%)	5 (22.73%)	1.2 (0.82-1.79) **RR**
≥20, N (%)	22 (50.0%)	14 (63.6%)	8 (36.4%)	1.9 (0.52-7.29) **OR**
25(OH)D < 40 ng/mL				**0.006* Fisher's Exact**
< 40, N (%)	38 (86.4%)	30 (78.9%)	8 (21.1%)	4.7 (0.79-28.56) **RR**
≥40, N (%)	6 (13.6%)	1 (16.7%)	5 (83.3%)	18.8 (1.91-184.10) **OR**
	N Mean ± STD range	**N Mean ± STD range**	**N Mean ± STD range**	**p-value (*p<0.05) Odds Ratio (OR) (95% CI)**
25(OH)D concentration (ng/mL)	44 24.6 ± 16.4 4.0-89.0	31 20.5 ± 9.7 4.0-41.4	13 34.3 ± 24.2 10.9-89.0	0.07 **Student's T-test** **0.03* regression[1]** 0.9 (0.90-0.99) **OR**

Multivariate Logistic Regression

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	0.29	1.04	0.08	1.33	0.17-10.24	0.78
Male	1.42	0.89	2.56	4.12	0.73-23.40	0.11
Black American	-0.84	0.93	0.82	0.43	0.07-2.67	0.37
Unmarried	-1.53	1.09	1.95	0.22	0.03-1.85	0.16
Medicaid/Medicare/Self	0.24	1.04	0.05	1.27	0.17-9.80	0.82
BMI ≥ 30	1.19	1.04	1.30	3.27	0.43-25.02	0.25
25(OH)D Concentration	-0.08	0.04	3.69	0.93	0.86-1.002	0.05

In chi-square analysis, male sex and 25(OH)D concentration below 40 ng/mL were identified as independent factors associated with COVID pneumonia. Furthermore, bivariate logistic regression revealed a significant association between pneumonia and 25(OH)D concentration (p=0.03; 95% CI: 0.90-0.99). Upon conducting multivariate logistic regression analysis adjusting for age ≥65, sex, race, marital status, insurance, BMI, and 25(OH)D concentration, the significance of 25(OH)D concentration was attenuated (estimate: -0.08, p-value=0.05, odds ratio: 0.9, 95% confidence interval: 0.86-1.002).

Table 5c. COVID Positive – Intensive Care Unit (ICU) Admission during Hospitalization

Characteristic	All N=44	ICU N=19 (43.2%)	No ICU N=25 (56.8%)	p-value (*p<0.05) Relative Risk (RR) Odds Ratio (OR) (95% CI)
Ages				**0.0002* Fisher's Exact**
≥ 65 years, N (%)	22 (50.0%)	16 (72.7%)	6 (27.3%)	5.3 (1.81-15.74) **RR**
< 65 years, N (%)	22 (50.0%)	3 (13.6%)	19 (86.4%)	16.9 (3.63-78.56) **OR**
Gender				0.07 **Chi-Square**
Males, N (%)	21 (47.7%)	12 (57.1%)	9 (42.9%)	1.9 (0.91-3.86) **RR**
Females, N	23 (52.3%)	7 (30.4%)	16 (69.6%)	3.0 (0.88-10.52) **OR**
Marital Status				0.3 **Fisher's Exact**
Married, N (%)	31 (70.4%)	15 (48.4%)	16 (51.6%)	1.5 (0.64-3.84) **RR**
Not Married, N (%)	13 (29.6%)	4 (30.8%)	9 (69.2%)	2.1 (0.54-8.32) **OR**
Insurance Status				**0.004* Chi-Square**
Private, N (%)	27 (61.4%)	7 (25.9%)	20 (74.1%)	0.4 (0.18-0.75) **RR**
Medicaid/Medicare/self-pay, N (%)	17 (38.6%)	12 (70.6%)	5 (29.4%)	0.1 (0.04-0.56) **OR**
Body Mass Index (BMI)				0.1 **Chi-Square**
BMI ≥ 30, N (%)	24 (54.6%)	8 (33.3%)	16 (66.7%)	0.6 (0.30-1.21) **RR**
BMI <30	20 (45.4%)	11 (55.0%)	9 (45.0%)	0.4 (0.12-1.39) **OR**
Race/Ethnicity				0.7 **Chi-Square**
Black	17 (38.6%)	8 (47.1%)	9 (52.9%)	1.2 (0.59-2.28) **RR**
Non-Black	27 (61.4%)	11 (40.7%)	16 (59.36%)	1.3 (0.38-4.39) **OR**
25(OH)D < 20 ng/mL				**0.03* Chi-Square**
<20, N (%)	22 (50.0%)	13 (59.1%)	9 (40.9%)	2.1 (1.00-4.66) **RR**
≥20, N (%)	22 (50.0%)	6 (27.3%)	16 (72.7%)	3.9 (1.09-13.66) **OR**
25(OH)D < 40 ng/mL				**0.03* Fisher's Exact**
< 40, N (%)	38 (86.4%)	19 (50.0%)	19 (50.0%)	N/A **RR**
≥40, N (%)	6 (13.6%)	0 (0.0%)	6 (100.0%)	N/A **OR**
	N Mean ± STD range	**N Mean ± STD range**	**N Mean ± STD range**	**p-value (*p<0.05) Odds Ratio (OR) (95% CI)**
25(OH)D concentration (ng/mL)	44 24.6 ± 16.4 4.0-89.0	19 19.3 ± 8.6 8.9-35.0	25 28.6 ± 19.7 4.0-89.0	**0.04* Student's T-test** 0.08 **regression[1]** 0.9 (0.91-1.01) **OR**

Multivariate Logistic Regression

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	1.91	0.95	4.05	6.73	1.05-43.00	**0.04***
Male	1.34	0.93	2.05	3.80	0.61-23.65	0.15
Black American	-0.68	0.98	0.48	0.51	0.08-3.45	0.49
Unmarried	- 0.57	1.06	0.29	0.56	0.07-4.52	0.59
Medicaid/Medicare/Self	1.89	1.05	3.23	6.63	0.84-52.24	0.07
BMI ≥ 30	-0.21	1.00	0.05	0.81	0.11-5.73	0.83
25(OH)D Concentration	-0.02	0.04	0.35	0.98	0.91-1.06	0.55

In chi-square analysis, factors independently associated with ICU admission included age ≥65 years, Medicaid/Medicare/self-pay, and 25(OH)D concentrations categorized at cutpoints of 20 and 40 ng/mL. Additionally, based on Student's t-test, 25(OH)D concentration was found to be associated with ICU admission. Subsequently, a multivariate logistic regression analysis was conducted to evaluate factors associated with ICU admission, encompassing age ≥65 years, sex, race/ethnicity, marital status, insurance, BMI, and 25(OH)D concentration. Only age ≥65 years and not 25(OH)D concentration (estimate: -0.0232, p-value: 0.08, odds ratio: 0.9, 95% CI: 0.91-1.06), exhibited a statistically significant, independent association with ICU admission during hospitalization.

Table 5d. COVID Positive – Death during Hospitalization

Characteristic	All N=44	Death N=11 (25.0%)	No Death N=33 (75.0%)	p-value (*p<0.05) Relative Risk (RR) Odds Ratio (OR) (95% CI)
Ages				**0.0002* Fisher's Exact**
≥ 65 years, N (%)	22 (50.0%)	11 (50.0%)	11 (50.0%)	N/A **RR**
< 65 years, N (%)	22 (50.0%)	0 (0.0%)	22 (100.0%)	N/A **OR**
Gender				0.3 **Fisher's Exact**
Males, N (%)	21 (47.7%)	7 (33.3%)	14 (66.7%)	1.9 (0.65-5.63) **RR**
Females, N	23 (52.3%)	4 (17.4%)	19 (82.6%)	2.4 (0.58-9.72) **OR**
Marital Status				1.0 **Fisher's Exact**
Married, N (%)	31 (70.4%)	8 (25.8%)	23 (74.2%)	1.1 (0.35-3.56) **RR**
Not Married, N (%)	13 (29.6%)	3 (23.1%)	10 (76.9%)	1.2 (0.25-5.30) **OR**
Insurance Status				**0.01* Fisher's Exact**
Private, N (%)	27 (61.4%)	3 (11.1%)	24 (88.9%)	0.2 (0.07-0.77) **RR**
Medicaid/Medicare/self-pay, N (%)	17 (38.6%)	8 (47.1%)	9 (52.9%)	0.1 (0.03-0.65) **OR**
Body Mass Index (BMI)				1.0 **Chi-Square**
BMI ≥ 30, N (%)	24 (54.6%)	6 (25.0%)	18 (75.0%)	1.0 (0.36-2.79) **RR**
BMI <30, N (%)	20 (45.5%)	5 (25.0%)	15 (75.0%)	1.0 (0.25-3.94) **OR**
Race/Ethnicity				0.2 **Chi-Square**
Black	17 (38.6%)	6 (35.3%)	11 (64.7%)	1.9 (0.69-5.29) **RR**
Non-Black	27 (61.4%)	5 (18.5%)	22 (81.5%)	2.4 (0.60-9.64) **OR**
25(OH)D < 20 ng/mL				0.2 **Fisher's Exact**
<20, N (%)	22 (50.0%)	8 (36.4%)	14 (63.6%)	2.7 (0.81-8.75) **RR**
≥20, N (%)	22 (50.0%)	3 (13.6%)	19 (86.4%)	3.6 (0.81-16.15) **OR**
25(OH)D < 40 ng/mL				0.3 **Fisher's Exact**
< 40, N (%)	38 (86.4%)	11 (28.9%)	27 (71.1%)	N/A **RR**
≥40, N (%)	6 (13.6%)	0 (0.0%)	6 (100.0%)	N/A **OR**
	N Mean ± STD range	**N Mean ± STD range**	**N Mean ± STD range**	**p-value (*p<0.05) Odds Ratio (OR) (95% CI)**
25(OH)D concentration (ng/mL)	44 24.6 ± 16.4 4.0-89.0	11 18.6 ± 8.3 8.9-34.7	33 26.6 ± 18.2 4.0-89.0	0.05 **Student's T-test** 0.2 **Regression** 0.9 (0.90-1.02) **OR**

Multivariate Logistic Regression

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	14.91	163.10	0.01	>999.99	<0.001-999.99	0.93
Male	0.19	1.28	0.02	1.21	0.10-14.84	0.88
Black American	1.16	1.29	0.82	3.20	0.26-39.89	0.37
Unmarried	1.63	2.01	0.65	5.08	0.10-261.91	0.42
Medicaid/Medicare/Self	1.49	1.42	1.11	4.46	0.28-71.95	0.29
BMI ≥ 30	0.87	1.34	0.40	2.40	0.16-35.49	0.52
25(OH)D Concentration	0.04	0.08	0.23	1.04	0.89-1.21	0.63

In the chi-square analysis, age ≥65 years and Medicaid/self-pay were identified as factors independently associated with death due to COVID. While no deaths were observed among the 6 participants with a 25(OH)D concentration ≥40 ng/mL, this association did not reach statistical significance (p=0.3). Subsequently, a multivariate logistic regression analysis was conducted to further evaluate factors associated with death due to COVID, including age ≥65, sex, race/ethnicity, marital status, insurance, BMI, and 25(OH)D concentration. None of these factors, including 25(OH)D concentration (estimate +0.04, p-value=0.6, OR 1.04, CI 0.89-1.21), showed a statistically significant association.

Table 5e. COVID Positive – ICU Admission and/or Death during Hospitalization

Characteristic	All N=44	ICU and/or Death N=19 (43.2%)	No ICU or Death N=25 (56.8%)	p-value (*p<0.05) Odds Ratio (OR) / Relative Risk (RR) (95% CI)
Ages				**0.0002* Fisher's Exact**
≥ 65 years, N (%)	22 (50.0%)	16 (72.7%)	6 (27.3%)	5.3 (1.81-15.74) **RR**
< 65 years, N (%)	22 (50.0%)	3 (13.64%)	19 (86.4%)	16.9 (3.63-78.56) **OR**
Gender				0.07 **Chi-Square**
Males, N (%)	21 (47.7%)	12 (57.1%)	9 (42.9%)	1.9 (0.91-3.86) **RR**
Females, N	23 (52.3%)	7 (30.43%)	16 (69.6%)	3.0 (0.88-10.52) **OR**
Marital Status				0.3 **Fisher's Exact**
Married, N (%)	31 (70.4%)	15 (48.4%)	16 (51.6%)	1.6 (0.64-3.84) **RR**
Not Married, N (%)	13 (29.6%)	4 (30.8%)	9 (69.2%)	2.1 (0.54-8.32) **OR**
Insurance Status				**0.004* Chi-Square**
Private, N (%)	27 (61.4%)	7 (25.9%)	20 (74.1%)	0.4 (0.18-0.75) **RR**
Medicaid/Medicare/self-pay, N (%)	17 (38.6%)	12 (70.6%)	5 (29.4%)	0.1 (0.04-0.56) **OR**
Body Mass Index (BMI)				0.1 **Chi-Square**
BMI ≥ 30, N (%)	24 (54.6%)	8 (33.3%)	16 (66.7%)	0.6 (0.30-1.21) **RR**
BMI <30, N (%)	20 (45.4%)	11 (55.0%)	9 (45.0%)	0.4 (0.12-1.39) **OR**
Race/Ethnicity				0.7 **Chi-Square**
Black	17 (38.6%)	8 (47.1%)	9 (52.9%)	1.2 (0.59-2.28) **RR**
Non-Black	27 (61.4%)	11 (40.7%)	16 (59.3%)	1.3 (0.38-4.39) **OR**
25(OH)D <20 ng/mL				**0.03* Chi-Square**
<20, N (%)	22 (50.0%)	13 (59.1%)	9 (40.9%)	2.2 (1.01-4.66) **RR**
≥20, N (%)	22 (50.0%)	6 (27.3%)	16 (72.7%)	3.9 (1.09-13.66) **OR**
25(OH)D < 40 ng/mL				**0.03* Fisher's Exact**
< 40, N (%)	38 (86.4%)	19 (50.0%)	19 (50.0%)	N/A **RR**
≥40, N (%)	6 (13.6%)	0 (0.0%)	6 (100.0%)	N/A **OR**
	N Mean ± STD range	**N Mean ± STD range**	**N Mean ± STD range**	**p-value (*p<0.05) Odds Ratio (OR) (95% CI)**
25(OH)D concentration (ng/mL)	44 24.6 ± 16.4 4.0-89.0	19 19.3 ± 8.6 8.9-35.0	25 28.6 ± 19.7 4.0-89.0	**0.04* Student's T-test** 0.08 regression 0.9 (0.91-1.01) **OR**

Multivariate Logistic Regression

Independent Variable	Estimate	Standard Error (SE)	Wald Chi Square	Odds Ratio Estimates (OR)	95% Confidence Interval (CI)	p-value *p<0.05
Age ≥ 65 years	1.91	0.95	4.05	6.73	1.05-43.00	0.04
Male	1.34	0.93	2.05	3.80	0.61-23.65	0.15
Black American	-0.68	0.98	0.48	0.51	0.08-3.45	0.49
Unmarried	- 0.57	1.06	0.29	0.56	0.07-4.52	0.59
Medicaid/Medicare/Self	-1.89	1.05	3.23	6.63	0.84-52.24	0.07
BMI ≥ 30	-0.21	1.00	0.05	0.81	0.11-5.70	0.83
25(OH)D Concentration	-0.02	0.04	0.35	0.98	0.91-1.06	0.55

In chi-square analysis, factors independently associated with ICU admission and/or death due to COVID included age ≥65 years, insurance status, and 25(OH)D concentrations categorized at cutpoints of 20 and 40 ng/mL. Additionally, based on Student's t-test, 25(OH)D concentration was found to be associated with ICU admission and/or death. In multivariate logistic regression, however, modeling age ≥65, sex, race, marital status, insurance, BMI, only age ≥65 years exhibited a statistically significant, independent association with ICU admission and/or death due to COVID.