Exploring the link between Vitamin D and clinical outcomes in COVID-19.

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Abstract

Background

The immunomodulating role of vitamin D might play a role in COVID-19 disease.

Objective

To study the association between vitamin D and clinical outcomes in COVID-19 patients.

Methods

Retrospective cohort study on COVID-19 patients with documented vitamin D levels within the last year. Vitamin D levels were grouped as ≥ 20 ng/mL or <20 ng/mL. Main outcomes were mortality, need for mechanical ventilation, new DVT or pulmonary embolism, and ICU admission.

Results

A total of 270 patients (mean (SD) age, 63.81 (14.69) years); 117 (43.3%) males; 216 (80%) African Americans; 139 (51.5%) in 65 and older age group were included. Vitamin D levels were less than 20 ng/ml in 95 (35.2%) patients. During admission, 72 patients (26.7%) died, 59 (21.9%) needed mechanical ventilation, and 87 (32.2%) required ICU**.** Vitamin D levels showed no significant association with mortality (OR=0.69; 95% CI, 0.39 - 1.24; p=0.21), need for mechanical ventilation (OR=1.23; 95% CI, 0.68 – 2.24; p=0.49), new DVT or PE(OR= 0.92; 95% CI, 0.16- 5.11; p=1.00) or ICU admission (OR=1.38; 95% CI, 0.81 – 2.34; p=0.23).

Conclusion

We did not find any significant association of vitamin D levels with mortality, the need for mechanical ventilation, ICU admission and the development of thromboembolism in COVID-19 patients.

Key words

Vitamin D, Mortality, Critical care, Mechanical Ventilation, Thromboembolism

New and Noteworthy

Low vitamin D has been associated with increased frequency and severity of respiratory tract infections in the past. Current literature linking clinical outcomes in COVID-19 with low vitamin D is debatable. This study evaluated the role of vitamin D in severe disease outcomes among COVID-19 patients and found no association of vitamin D levels with mortality, the need for mechanical ventilation, ICU admission and thromboembolism in COVID-19.

Introduction

Coronavirus disease (COVID-19) originated in Wuhan, China, and has now become a pandemic resulting in 926,000 deaths worldwide as of mid-September 2020. The lack of evidence-based information and highly variable clinical presentation of individuals infected with this novel virus has perplexed clinicians worldwide. Elderly patients, especially those with underlying comorbidities, are at a higher risk for severe infection and worse clinical outcomes(53, 58). Prior studies point that 25-hydroxyvitamin D plays a role in immune regulation and induction of antimicrobial peptides to both viral and bacterial infections(18, 19, 33, 41). Review of literature points towards the association of low levels of vitamin D and increased frequency and susceptibility to acute respiratory tract infections including COPD exacerbation(7, 16, 22, 24). Many reports also suggest that vitamin D supplementation reduces the risk of respiratory tract infections, decreases symptom duration, and length of stay in hospitalized patients(10, 35, 50, 63).

Vitamin D has immunomodulating properties(18) and acts at various levels i.e. maintains cellular junctions(45), enhances innate immunity(59), induces antimicrobial peptides (cathelicidins and defensins)(1, 33), which lowers viral replication, decreases proinflammatory Th1 cytokines(8, 31, 61), increases anti-inflammatory cytokines(23) and modulates adaptive immunity(55). Cytokine release syndrome has been reported in some of the critically ill COVID-19 patients(39, 60), and given its immunomodulating properties, one can hypothesize that vitamin D levels might have a role in this syndrome. Vitamin D has been documented to have antioxidant(30) and antifibrotic properties(47), and modulate renin-angiotensin-aldosterone-system (RAAS) and angiotensin converting enzyme-2 (ACE2) expression(57). A leading cause of mortality in COVID-19 patients has been reported to be acute respiratory distress syndrome (ARDS)(37). Vitamin D has been shown to reduce lung permeability in ARDS and regenerate lung lining(13). This led us to explore a possible correlation between vitamin D levels and clinical outcomes in COVID-19 patients. Interestingly, vitamin D deficiency is very prevalent in the United States and about 41% of the adult US population has inadequate vitamin D levels(15).

A high incidence of thrombotic complications has been reported in COVID-19 patients who need intensive care(26). There have been conflicting results reported by studies on the role of vitamin D and venous thromboembolism. Some studies have documented that 25-hydroxyvitamin D plays a critical role in the pathogenesis of deep vein thrombosis (DVT)(56) and reported an association between decreased vitamin D levels and increased risk of venous thromboembolism(6). However other studies have refuted any such correlation(5).

The immunomodulating role of vitamin D may play a role in COVID-19 disease progression and there is a paucity of literature on the role of vitamin D in COVID-19. The main objective of this study is to understand the association between vitamin D levels and mortality among COVID-19 patients. Our study also explores if vitamin D levels have any association with other clinical outcomes such as the need for mechanical ventilation, development of new DVT or pulmonary embolism (PE), and intensive care unit (ICU) requirement in COVID-19 patients.

Methods

Study Design

We conducted a retrospective cohort study on 2001 adult patients with a confirmed COVID-19 diagnosis. The study was exempt by the Detroit Medical Center (DMC) and Wayne State University Institutional Review Board (IRB application # 20-06-2422). No external funding was received for conducting the study.

Study Site and Patient Population

Adult patients (≥18 years of age) with a confirmed COVID-19 diagnosis (either via nasopharyngeal or oropharyngeal swab) were included. Testing for COVID-19 was done at DMC, one of the largest academic medical centers and healthcare providers in southeast Michigan. DMC comprises four distinct hospitals in Michigan and all four hospital locations were included in the study. These hospitals primarily serve the Detroit metropolitan area.

Data Collection

A list of 2001 patients who visited DMC between March 10, 2020, and June 30, 2020, with a laboratory-confirmed COVID-19 PCR diagnosis was collected in collaboration with institutional information technology services. Patients under the age of 18, any readmission during the time frame, and pregnant patients were excluded from the study. A total of 67 patients were excluded initially as they met the above criteria. We reviewed 1,944 electronic medical records to screen if these patients had a previously documented vitamin D, 25-OH level within the past 12 months. After the initial screen, there were a total of 277 patients with a documented vitamin D level within the past 12 months. However, 7 of these patients were excluded from the study as they presented only for ambulatory surgery leaving a total of 270 patients, who were included in the study (Figure 1). We then classified the patients based on their vitamin D levels into 2 groups as ≥ 20 ng/mL (patients with normal vitamin D levels) and < 20 ng/mL (patients with low vitamin D levels). Data points were manually collected and coded for each patient. Data regarding the prescription of vitamin D supplements (weekly/daily) were also collected. For additional analysis based upon stratified vitamin D levels, patients with normal vitamin D levels were further divided into two subgroups, patients with vitamin D level 20-30 ng/mL and patients with vitamin D level >30ng/mL.

Outcomes

The main outcomes for this study were mortality, the need for mechanical ventilation, new DVT or PE during hospitalization, and ICU admission among COVID-19 patients. All of the patients included in the study had a documented outcome (mortality/discharged status) at the time of data collection. Additionally, the number of prior comorbidities, BMI, disposition upon emergency department (ED) visit (discharge home, inpatient admission, and direct ICU admission), and maximum oxygen requirement during admission were collected. Charts were screened to determine if the patient required transfer to ICU from inpatient floors. Demographic data collected included age, sex, and race.

Statistical Analysis

Categorical variables have been described as frequency and percentages. We categorized age into two groups (18-64 years, and 65 and older). A crude relative association measure (odds ratio, OR) was calculated for each correlation using the Pearson chi-square and Fisher test. An adjusted odds ratio was calculated using binary logistic regression. We adjusted for age, sex, BMI, and presence of comorbidities. Age and BMI were taken as continuous variables and the presence of comorbidities as a categorical variable for the adjusted model. Subgroup analyses were done based on sex and age groups as defined earlier. Subgroup analysis based on race was limited to African Americans and Caucasians due to the limited sample size of other races. The 95% confidence intervals (CI) were estimated using a binomial distribution. A p-value of less than 0.05 was determined to be significant. Bonferroni correction was used in order to protect from the inflated type 1 error while performing multiple analyses. Additional analyses were performed on the stratified vitamin D levels (<20 ng/mL, 20-30 ng/mL and > 30 ng/mL). Among the patients with low vitamin D levels, further comparison was made between the patients who were prescribed vitamin D supplements and those who were not prescribed any vitamin D supplements. Statistical analyses were completed using IBM SPSS Statistics software (version 26).

Results

Baseline Characteristics

There were 2001 patient records with positive COVID-19 test at the 4 DMC hospitals with a nasopharyngeal/oropharyngeal PCR swab between March 10, 2020, and June 30, 2020. Based on the exclusion criteria, only 270 patients were included in the study. In the cohort analysis, there were 117 males (43.3%) and 153 females (56.7%). The mean age of patients was 63.81 years (Standard deviation (SD) 14.69). More than half of the patients (n=139, 51.5%) were in the 65 and older age group, with African Americans being the predominant race (n= 216, 80%).

Distribution of vitamin D levels showed that more than a third of the patients had levels less than 20 ng/ml (n=95, 35.2%). Among the patients with low vitamin D levels, only 27.4% (n=26) were prescribed vitamin D supplements. About 70% of patients had three or more comorbid diseases (n= 187, 69.3%). The mean BMI of patients was 32.09 (standard deviation (SD) 9.12), and more than 50% of patients (n=139) were in the obese category as per the World Health Organization criteria. The baseline characteristics of the population included are detailed in Table 1.

Clinical Course

The total mortality in this cohort was 26.7% (n = 72). About 14.8% (n = 40) patients were admitted straight to ICU from the ED. An additional 47 patients were later transferred to ICU from the inpatient service. Approximately one in every three patients in this study (n=87, 32.2%) who came to ED ended up requiring ICU. Around 3.7% of the total patients were sent home from ED (n= 10), while 81.5% (n=220) were admitted to the inpatient service. Close to 81% (n=219) of patients required supplemental oxygen during their admission stay and 21.9% (n=59) required mechanical ventilation. About 2.2% of the patients (n=6) developed new DVT or PE during their hospitalization. The clinical course of the patient population is further detailed in Table 2.

Vitamin D and Mortality

In the cohort analysis vitamin D levels showed no significant association with mortality (OR=0.69; 95% CI, 0.39 - 1.24; p=0.21). No correlation between mortality and vitamin D levels was seen in either males (OR=1.10; 95% CI, 0.46 - 2.63; p=0.83) or females (OR=0.49; 95% CI, 0.22 - 1.09; p=0.08). With sub group analysis based on age groups and race, no significant association was found between vitamin D levels and mortality in patients less than 65 years old (OR=0.90; 95% CI, 0.37 – 2.18; p=0.81), or in patients 65 years and older (OR=0.83; 95% CI, 0.35 - 1.92; p=0.66), African Americans (OR=0.78; 95% CI, 0.41 - 1.48; p=0.44) or Caucasians (OR=0.51; 95% CI, 0.12 - 2.19; p=0.36). Similarly, no correlation between vitamin D and mortality was noted in the total cohort when adjustment was made for age, sex, BMI and presence of comorbidities (adjusted OR=1.04; 95% CI, 0.55- 1.97; p=0.90).

Vitamin D and mechanical ventilation/ICU admission

We found no significant association between vitamin D levels and need for mechanical ventilation (OR=1.23; 95% CI, 0.68 – 2.24; p=0.49) or ICU admission (OR=1.38; 95% CI, 0.81 – 2.34; p=0.23). No correlation between the need for mechanical ventilation and vitamin D levels was seen in either males (OR=1.24; 95% CI, 0.52 - 2.91; p=0.63), females (OR=1.20; 95% CI, 0.52 – 2.76; p=0.67), African Americans (OR=1.36; 95% CI, 0.71 – 2.62; p=0.34) or Caucasians (OR= 0.77; 95% CI, 0.13 – 4.49; p=0.77). The need for ICU admission was higher among males with low vitamin D levels compared to the males with normal vitamin D levels (OR=2.32; 95% CI, 1.07 – 5.03; p=0.03) in the unadjusted models, and in the models adjusted for age, BMI, and comorbidities (adjusted OR=2.60; 95% CI, 1.07 – 6.28; p=0.03). However, after Bonferroni correction was made to protect from the inflated type 1 error due to multiple comparisons, these results were noted to be statistically non-significant. No association between vitamin D levels and need for ICU admission was seen in females (OR=0.82; 95% CI, 0.38 – 1.76; p=0.61). Similarly, no significant association was noted between vitamin D levels and the need for ICU admission or mechanical ventilation among patients less than 65 years, or 65 years and older for unadjusted models as well as when the models were fully adjusted for age, sex, BMI, and presence of comorbidities. Further details on the results, unadjusted and after adjusting for age, sex, BMI, and comorbidities, are summarized in Tables 3 and 4.

Vitamin D and new DVT/PE

Vitamin D levels showed no significant association with development of new DVT or PE among COVID-19 patients (OR= 0.92; 95% CI, 0.16- 5.11; p=1.00). Further subgroup analysis was not done due to a limited number of patients developing thromboembolic episodes during the course of their admission.

Stratified vitamin D levels and clinical outcomes

The analyses performed for stratified vitamin D levels (<20ng/mL, 20-30ng/mL and >30ng/mL) showed no statistically significant association of these vitamin D levels with mortality, the need for mechanical ventilation and ICU admission in our cohort. Additionally, among patients with low vitamin D levels (<20ng/mL), no significant association was noted between vitamin D supplementation and clinical outcomes in COVID-19. More details on these results have been summarized in Table 5.

Discussion

This retrospective cohort study demonstrated no significant association between vitamin D levels and mortality among COVID-19 patients. A review of literature points toward equivocal evidence linking clinical outcomes in COVID-19 patients with low vitamin D levels. Risk factors for low vitamin D levels include elderly, obesity, and males(43), and higher mortality in

COVID-19 patients is also noticed among these patient populations(2, 17, 49). Another study suggests higher mortality seen in Italy and Spain could be attributed to a higher prevalence of low vitamin D seen in these countries(28). The study by llie et al.(21) also reports an association between vitamin D levels and COVID-19 mortality in European countries. However, these studies only provide inferred evidence based on the high prevalence of vitamin D deficiency in these countries and do not account for potential confounders like other underlying comorbidities and BMI. Also, the study by Laird et al.(28) has relied on literature and data as old as twenty years ago to derive the mean vitamin D levels in the patient population and correlated it with the current data of mortality among COVID-19 patients. Recent studies have also tried to elucidate if low vitamin D levels are associated with increased risk of testing positive for COVID-19, but the results have been conflicting(12, 20, 38).

Some of the literature suggests increased morbidity and mortality among African Americans with COVID-19(25, 48, 54) and a plausible explanation is low levels of vitamin D seen in African Americans(27). However, our study demonstrated no such correlation between low vitamin D levels and mortality among COVID-19 patients who were African Americans. Hence further studies are needed before any such link between mortality and low vitamin D levels can be established.

High incidence of vitamin D deficiency has been reported among critically ill patients admitted to intensive care, resulting in increased length of stay and mortality(4, 14, 29, 34, 36, 51, 62). Literature review also suggests that low vitamin D levels may also be associated with worse disease outcomes especially in pneumonia(32, 44) and with the development of ARDS and acute lung injury(13, 42). A recent metanalysis by Munshi et al.(40) reported poor outcomes in COVID-19 patients with low vitamin D levels, however in their study, poor outcomes were clubbed together as the development of ARDS, mortality, need for ICU admission, and mechanical ventilation. Our study looked at each of these severe disease clinical outcomes separately to identify individual correlations. We found that the need for ICU admission was higher among males with low vitamin D levels, however, after Bonferroni correction was applied, these results failed to reach the level of statistical significance. A study conducted by Carpagnano et al.(9) noticed a high prevalence of low vitamin D among patients admitted to ICU, and the majority of patients in the vitamin D deficiency group of their study were males.

We did not find any significant correlation between low vitamin D levels and the development of new DVT or PE in COVID-19 patients. This could be, in part, due to the low number of patients in this study who developed new DVT or PE. The role of vitamin D and thromboembolism is debatable in the literature. In the past, some large population studies have shown no correlation between vitamin D levels or vitamin D supplementation, on the risk of development of thromboembolism(3, 46, 52).

Some of the literature on vitamin D levels recommends maintaining vitamin D levels at at-least 30ng/mL to achieve optimal health benefits(11). In our study, we did not see any significant association between vitamin D levels <20ng/mL, 20-30ng/mL and >30ng/mL with mortality, the need for ICU admission and the need for mechanical ventilation in COVID-19 patients.

We acknowledge that our study has several limitations that need to be addressed. Although we had a large database of over 2000 patients, a large number of patients did not have recorded vitamin D levels in the last one year. This significantly reduced the number of patients who could be included in this study. Also, we relied on electronic medical records and clinical notes to gather data including the presence of comorbidities and documentation of vitamin D levels. Hence there is a possibility of both selection and information bias. The data for this study were collected from 4 hospitals in southeast Michigan, predominantly serving the underserved population having multiple comorbidities. Our sample size consisted of very few patients with other races besides African Americans and Caucasians, thereby limiting analysis in this population group. Also, very few patients in our cohort developed new DVT or PE during their hospital stay, hence more studies with a large sample size are needed before any conclusive inference can be made in this regard. Although the use of vitamin D levels before the patient developed illness helped avoid the negative acute phase impact of the illness on vitamin D levels, it would have been ideal if we had the measurements immediately preceding the infection from COVID-19. But it was not a possibility given the nature and design of the current study. We believe that further community-based studies will provide a better understanding of the possible role of vitamin D in the disease progression and severity of symptoms in COVID 19 patients.

Conclusion

This study did not find any significant association of vitamin D levels with mortality, the need for mechanical ventilation, ICU admission and the development of thromboembolism in patients with COVID-19. Further studies are warranted before any conclusive association can be made between vitamin D levels and the clinical course of COVID 19 patients.

Conflict of Interest

All authors report no conflict of interest.

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References

1. **Adams JS, Ren S, Liu PT, Chun RF, Lagishetty V, Gombart AF, Borregaard N, Modlin RL, and Hewison M**. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. *J Immunol* 182: 4289-4295, 2009.

2. **Anderson MR, Geleris J, Anderson DR, Zucker J, Nobel YR, Freedberg D, Small-Saunders J, Rajagopalan KN, Greendyk R, Chae SR, Natarajan K, Roh D, Edwin E, Gallagher D, Podolanczuk A, Barr RG, Ferrante AW, and Baldwin MR**. Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection: A Retrospective Cohort Study. *Ann Intern Med* 29: M20-3214, 2020.

3. **Blondon M, Rodabough RJ, Budrys N, Johnson KC, Berger JS, Shikany JM, Raiesdana A, Heckbert SR, Manson JE, LaCroix AZ, Siscovick D, Kestenbaum B, Smith NL, and de Boer IH**. The effect of calcium plus vitamin D supplementation on the risk of venous thromboembolism. From the Women's Health Initiative Randomized Controlled Trial. *Thromb Haemost* 113: 999-1009, 2015.

4. **Braun A, Chang D, Mahadevappa K, Gibbons FK, Liu Y, Giovannucci E, and Christopher KB**. Association of low serum 25-hydroxyvitamin D levels and mortality in the critically ill. *Crit Care Med* 39: 671-677, 2011.

5. **Brodin E, Lerstad G, Grimnes G, Brækkan SK, Vik A, Brox J, Svartberg J, Jorde R, and Hansen JB**. Serum levels of vitamin D are not associated with future risk of venous thromboembolism. The Tromsø Study. *Thromb Haemost* 109: 885-890, 2013.

6. **Brøndum-Jacobsen P, Benn M, Tybjaerg-Hansen A, and Nordestgaard BG**. 25-Hydroxyvitamin D concentrations and risk of venous thromboembolism in the general population with 18,791 participants. *J Thromb Haemost* 11: 423-431, 2013.

7. **Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, and Giovannucci E**. Epidemic influenza and vitamin D. *Epidemiol Infect* 134: 1129-1140, 2006.

8. **Cantorna MT, Snyder L, Lin YD, and Yang L**. Vitamin D and 1,25(OH)2D regulation of T cells. *Nutrients* 7: 3011-3021, 2015.

9. **Carpagnano GE, Di Lecce V, Quaranta VN, Zito A, Buonamico E, Capozza E, Palumbo A, Di Gioia G, Valerio VN, and Resta O**. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J Endocrinol Invest* 9: 1-7, 2020.

10. **Charan J, Goyal JP, Saxena D, and Yadav P**. Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. *J Pharmacol Pharmacother* 3: 300-303, 2012.

11. **Charoenngam N, and Holick MF**. Immunologic Effects of Vitamin D on Human Health and Disease. *Nutrients* 12: 2020.

12. **D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, Keller F, and Cantù M**. 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. *Nutrients* 12: 2020.

13. **Dancer RC, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, Park D, Bartis DG, Mahida R, Turner AM, Sapey E, Wei W, Naidu B, Stewart PM, Fraser WD, Christopher KB, Cooper MS, Gao F, Sansom DM, Martineau AR, Perkins GD, and**

Thickett DR. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). *Thorax* 70: 617-624, 2015.

14. **de Haan K, Groeneveld AB, de Geus HR, Egal M, and Struijs A**. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. *Crit Care* 18: 014-0660, 2014.

15. **Forrest KY, and Stuhldreher WL**. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 31: 48-54, 2011.

16. **Ginde AA, Mansbach JM, and Camargo CA**. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 169: 384-390, 2009.

17. **Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, and Pesenti A**. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. *Jama* 323: 1574-1581, 2020.

18. **Greiller CL, and Martineau AR**. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients* 7: 4240-4270, 2015.

19. **Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, and Hunninghake GW**. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. *J Immunol* 181: 7090-7099, 2008.

20. **Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, Niedzwiedz CL, Jani BD, Welsh P, Mair FS, Gray SR, O'Donnell CA, Gill JM, Sattar N, and Pell JP**.

Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr* 14: 561-565, 2020.

21. **Ilie PC, Stefanescu S, and Smith L**. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res* 32: 1195-1198, 2020.

22. **Janssens W, Bouillon R, Claes B, Carremans C, Lehouck A, Buysschaert I, Coolen J, Mathieu C, Decramer M, and Lambrechts D**. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 65: 215-220, 2010.

23. **Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, Walker LS, Lammas DA, Raza K, and Sansom DM**. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol* 183: 5458-5467, 2009.

24. **Jolliffe DA, Griffiths CJ, and Martineau AR**. Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. *J Steroid Biochem Mol Biol* 136: 321-329, 2013.

25. **Khunti K, Singh AK, Pareek M, and Hanif W**. *Is ethnicity linked to incidence or outcomes of covid-19?* BMJ. 2020 Apr 20;369:m1548. doi: 10.1136/bmj.m1548.

26. **Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMP, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, and Endeman H**. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 191: 145-147, 2020.

27. **Kohlmeier M**. Avoidance of vitamin D deficiency to slow the COVID-19 pandemic. *BMJ Nutrition, Prevention & Health* bmjnph-2020-000096, 2020.

28. **Laird E, Rhodes J, and Kenny RA**. Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. *Ir Med J* 113: 81, 2020.

29. **Lee P, Eisman JA, and Center JR**. *Vitamin D deficiency in critically ill patients*. N Engl J Med. 2009 Apr 30;360(18):1912-4. doi: 10.1056/NEJMc0809996.

30. **Lei GS, Zhang C, Cheng BH, and Lee CH**. Mechanisms of Action of Vitamin D as Supplemental Therapy for Pneumocystis Pneumonia. *Antimicrob Agents Chemother* 61: 2017.

31. **Lemire JM, Adams JS, Kermani-Arab V, Bakke AC, Sakai R, and Jordan SC**. 1,25-Dihydroxyvitamin D3 suppresses human T helper/inducer lymphocyte activity in vitro. *J Immunol* 134: 3032-3035, 1985.

32. **Leow L, Simpson T, Cursons R, Karalus N, and Hancox RJ**. Vitamin D, innate immunity and outcomes in community acquired pneumonia. *Respirology* 16: 611-616, 2011.

33. **Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, and Modlin RL**. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 311: 1770-1773, 2006.

34. **Lucidarme O, Messai E, Mazzoni T, Arcade M, and du Cheyron D**. *Incidence and risk factors of vitamin D deficiency in critically ill patients: results from a prospective observational study*. Intensive Care Med. 2010 Sep;36(9):1609-11. doi: 10.1007/s00134-010-1875-8. Epub 2010 Apr 7.

35. **Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganmaa D, Ginde AA, Goodall EC, Grant CC, Griffiths CJ, Janssens W, Laaksi I, Manaseki-Holland S, Mauger D, Murdoch DR, Neale R, Rees JR,

Simpson S, Stelmach I, Kumar GT, Urashima M, and Camargo CA. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 356: i6583, 2017.

36. **McKinney JD, Bailey BA, Garrett LH, Peiris P, Manning T, and Peiris AN**. Relationship between vitamin D status and ICU outcomes in veterans. *J Am Med Dir Assoc* 12: 208-211, 2011.

37. **Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, and HLH Across Speciality Collaboration UK**. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 395: 1033-1034, 2020.

38. **Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, and Solway J**. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA Netw Open* 3: 19722, 2020.

39. **Moore JB, and June CH**. Cytokine release syndrome in severe COVID-19. *Science* 368: 473-474, 2020.

40. **Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, Youssef MR, Omar M, Attia AS, Fawzy MS, Killackey M, Kandil E, and Duchesne J**. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *J Med Virol* 27: 26360, 2020.

41. **Olliver M, Spelmink L, Hiew J, Meyer-Hoffert U, Henriques-Normark B, and Bergman P**. Immunomodulatory effects of vitamin D on innate and adaptive immune responses to Streptococcus pneumoniae. *J Infect Dis* 208: 1474-1481, 2013.

42. **Parekh D, Thickett DR, and Turner AM**. Vitamin D deficiency and acute lung injury. *Inflamm Allergy Drug Targets* 12: 253-261, 2013.

43. **Pearce SH, and Cheetham TD**. Diagnosis and management of vitamin D deficiency. *BMJ* 340: b5664, 2010.

44. **Remmelts HH, van de Garde EM, Meijvis SC, Peelen EL, Damoiseaux JG, Grutters JC, Biesma DH, Bos WJ, and Rijkers GT**. Addition of vitamin D status to prognostic scores improves the prediction of outcome in community-acquired pneumonia. *Clin Infect Dis* 55: 1488-1494, 2012.

45. **Schwalfenberg GK**. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. *Mol Nutr Food Res* 55: 96-108, 2011.

46. **Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, and Camargo CA, Jr.** Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. *JAMA Cardiol* 2: 608-616, 2017.

47. **Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, and Xue X**. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system. *Sci Rep* 7: 3312, 2017.

48. **Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, Tie Y, and Fullerton KE**. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep* 69: 759-765, 2020.

49. **Tartof SY, Qian L, Hong V, Wei R, Nadjafi RF, Fischer H, Li Z, Shaw SF, Caparosa SL, Nau CL, Saxena T, Rieg GK, Ackerson BK, Sharp AL, Skarbinski J, Naik TK, and Murali SB**. Obesity and Mortality Among Patients Diagnosed With COVID-19: Results From an Integrated Health Care Organization. *Ann Intern Med* 12: M20-3742, 2020.

50. **Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, and Ida H**. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 91: 1255-1260, 2010.

51. **Venkatram S, Chilimuri S, Adrish M, Salako A, Patel M, and Diaz-Fuentes G**. Vitamin D deficiency is associated with mortality in the medical intensive care unit. *Crit Care* 15: 10, 2011.

52. **Vučković BA, van Rein N, Cannegieter SC, Rosendaal FR, and Lijfering WM**. Vitamin supplementation on the risk of venous thrombosis: results from the MEGA case-control study. *Am J Clin Nutr* 101: 606-612, 2015.

53. **Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, and Peng Z**. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *Jama* 323: 1061-1069, 2020.

54. **Webb Hooper M, Nápoles AM, and Pérez-Stable EJ**. COVID-19 and Racial/Ethnic Disparities. *JAMA* 323: 2466-2467, 2020.

55. **Wei R, and Christakos S**. Mechanisms Underlying the Regulation of Innate and Adaptive Immunity by Vitamin D. *Nutrients* 7: 8251-8260, 2015.

56. **Wu WX, and He DR**. Low Vitamin D Levels Are Associated With the Development of Deep Venous Thromboembolic Events in Patients With Ischemic Stroke. *Clin Appl Thromb Hemost* 24: 69S-75S, 2018.

57. **Xu J, Yang J, Chen J, Luo Q, Zhang Q, and Zhang H**. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep* 16: 7432-7438, 2017.

58. **Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, and Zhou Y**. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis* 94: 91-95, 2020.

59. **Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, and Stanciu LA**. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol* 27: 2017.

60. **Zhang C, Wu Z, Li JW, Zhao H, and Wang GQ**. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents* 55: 29, 2020.

61. **Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, and Goleva E**. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol* 188: 2127-2135, 2012.

62. **Zhang YP, Wan YD, Sun TW, Kan QC, and Wang LX**. Association between vitamin D deficiency and mortality in critically ill adult patients: a meta-analysis of cohort studies. *Crit Care* 18: 014-0684, 2014.

63. **Zhou J, Du J, Huang L, Wang Y, Shi Y, and Lin H**. Preventive Effects of Vitamin D on Seasonal Influenza A in Infants: A Multicenter, Randomized, Open, Controlled Clinical Trial. *Pediatr Infect Dis J* 37: 749-754, 2018.

Legends for figures

Figure 1- Flowchart depicting patient inclusion criteria. Adult patients (≥18 years of age) with a confirmed COVID-19 diagnosis and a documented vitamin D level in the past 12 months were included. Patients under the age of 18, any readmission during the time frame, ambulatory surgery and pregnant patients were excluded from the study.

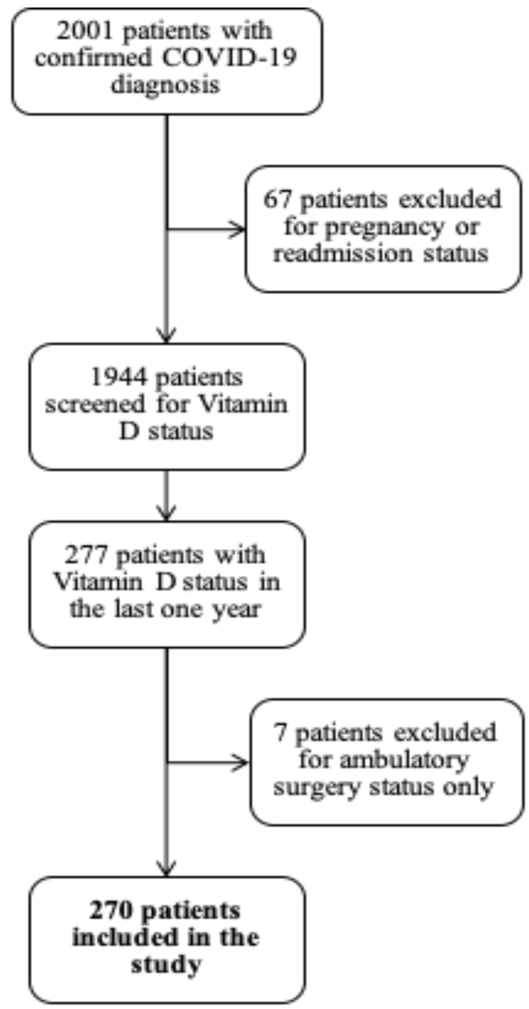


Figure 1- Flowchart depicting patient inclusion criteria

Table 1: Baseline Characteristic of patients

Characteristic	Cohort (n=270)
Age group, n (%)	
18-30 years	5 (1.9)
31-45 years	26 (9.6)
46-64 years	100 (37)
65+ years	139 (51.5)
Sex, n (%)	
Male	117 (43.3)
Female	153 (56.7)
Race/ ethnicity, n (%)	
African American	216 (80)
Caucasian	48 (17.8)
Asian	3 (1.1)
Middle Eastern	3 (1.1)
Number of Comorbidities, n (%)	
0	14 (5.2)
1	30 (11.1)
2	39 (14.4)
3 or 3+	187 (69.3)
Vitamin D levels, n (%)	
>20ng/mL	175 (64.8)
<20ng/mL	95 (35.2)
BMI categories, n (%)	
Underweight (BMI<18.5)	5 (1.9)
Normal (18.5-<25)	52 (19.3)
Overweight (25-<30)	74 (27.4)
Obese (>30)	139 (51.5)
Vitamin D supplementation, n (%)	
≥20ng/mL	58 (33.1)
<20ng/mL	26 (27.4)

Table 2- Admission characteristics of patients, n (%)	
Mortality	72 (26.7)
Mechanical Ventilation	59 (21.9)
ICU Admission	87 (32.2)
Admission Disposition	
ER Visit Only (Discharged from ER)	10 (3.7)
Inpatient Admission	220 (81.5)
Direct ER to ICU Admission	40 (14.8)
Maximum supplemental oxygen during admission	
Room air only	51 (18.9)
Nasal Canula	100 (37)
Venti-mask	15 (5.6)
Non-Rebreather	37 (13.7)
High Flow Oxygen	7 (2.6)
BPAP/CPAP*	1 (0.4)
Mechanical Ventilation	59 (21.9)
New DVT or PE	6 (2.2)

*BPAP- Bilevel positive airway pressure

*CPAP- Continuous positive airway pressure

Table 3- Association Between Vitamin D levels and Mortality, Mechanical ventilation and ICU admission*

Characteristic	Mortality		ICU Admission		Mechanical ventilation	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Total cohort	0.69 (0.39-1.24)	0.21	1.38 (0.81-2.34)	0.23	1.23 (0.68-2.24)	0.49
Males	1.10 (0.46-2.63)	0.83	2.32 (1.07-5.03)	0.03	1.24 (0.52-2.91)	0.63
Females	0.49 (0.22-1.09)	0.08	0.82 (0.38-1.76)	0.61	1.20 (0.52-2.76)	0.67
Less than 65 years	0.90 (0.37-2.18)	0.81	1.39 (0.66-2.94)	0.39	1.81 (0.75-4.40)	0.19
65+ years	0.83 (0.35-1.92)	0.66	1.67 (0.74-3.75)	0.21	1.04 (0.42-2.59)	0.94
African Americans	0.78 (0.41-1.48)	0.44	1.33 (0.73-2.41)	0.35	1.36 (0.71-2.62)	0.34
Caucasian	0.51 (0.12-2.19)	0.36	2.56 (0.74-8.89)	0.14	0.77 (0.13-4.49)	0.77

*unadjusted Odds ratio

Table 4- Association between Vitamin D levels and Mortality, Mechanical ventilation and ICU admission*

Characteristic	Mortality		ICU Admission		Mechanical ventilation	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Total cohort adjusted^	1.04 (0.55-1.97)	0.9	1.51 (0.85-2.69)	0.16	1.36 (0.71-2.60)	0.35
Males**	1.94 (0.72-5.25)	0.19	2.60 (1.07-6.28)	0.03	1.32 (0.51-3.43)	0.56
Females**	0.62 (0.26-1.49)	0.28	0.91 (0.40-2.05)	0.82	1.29 (0.52-3.20)	0.58
Less than 65 years^	1.14 (0.43-2.99)	0.79	1.31 (0.58-2.99)	0.51	2.00 (0.75-5.34)	0.16
65+ years^	0.96 (0.40-2.31)	0.93	1.66 (0.73-3.79)	0.23	0.99 (0.39-2.53)	0.99
African American^	1.17 (0.57-2.39)	0.66	1.36 (0.71-2.60)	0.36	1.48 (0.72-3.02)	0.29
Caucasian^	0.86 (0.16-4.53)	0.86	3.71 (0.81-16.91)	0.09	1.08 (0.15-7.66)	0.94

*Adjusted model

^adjusted for age, sex, BMI and comorbidities

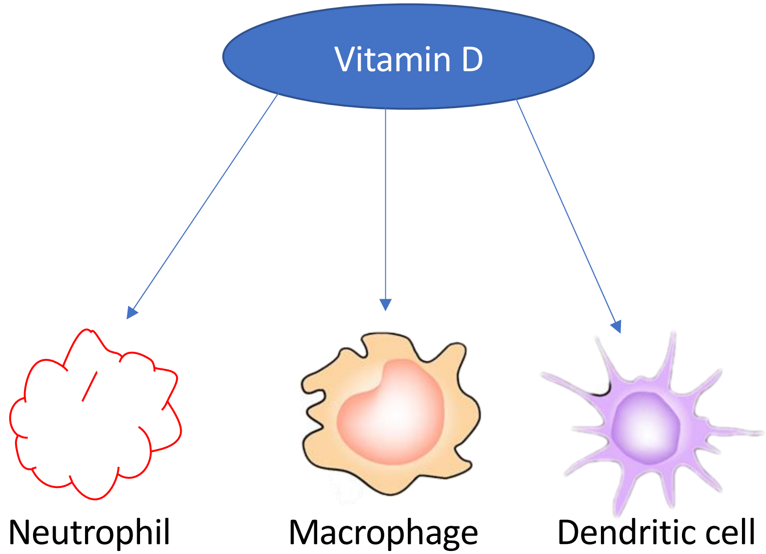
**Adjusted for age, BMI and comorbidities

Table 5- Association of stratified vitamin D levels/ vitamin D supplementation with Mortality, Mechanical Ventilation and ICU admission*

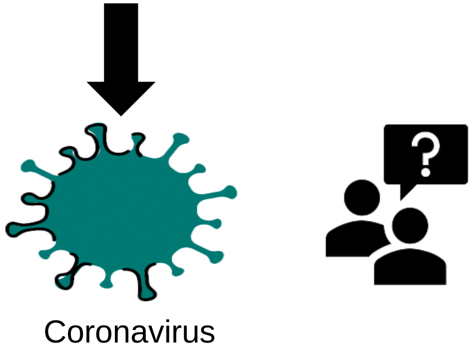
Characteristic	**Mortality**		**ICU Admission**		**Mechanical ventilation**	
	Odds ratio (95% CI)	**p-value**	**Odds ratio (95% CI)**	**p-value**	**Odds ratio (95% CI)**	**p-value**
Vitamin D supplements (among patients with low vitamin D levels)						
Supplements (Yes v/s No)	0.86 (0.26-2.80)	0.8	0.96 (0.35-2.59)	0.93	0.68 (0.22-2.13)	0.51
Stratified vitamin D levels						
<20ng/ml	1 (Ref)		1 (Ref)		1 (Ref)	
20-30ng/mL	1.20 (0.57-2.54)	0.63	0.70 (0.35-1.40)	0.31	0.69 (0.31-1.53)	0.36
>30ng/mL	0.81(0.39-1.66)	0.56	0.63 (0.33-1.22)	0.17	0.77 (0.37-1.60)	0.48

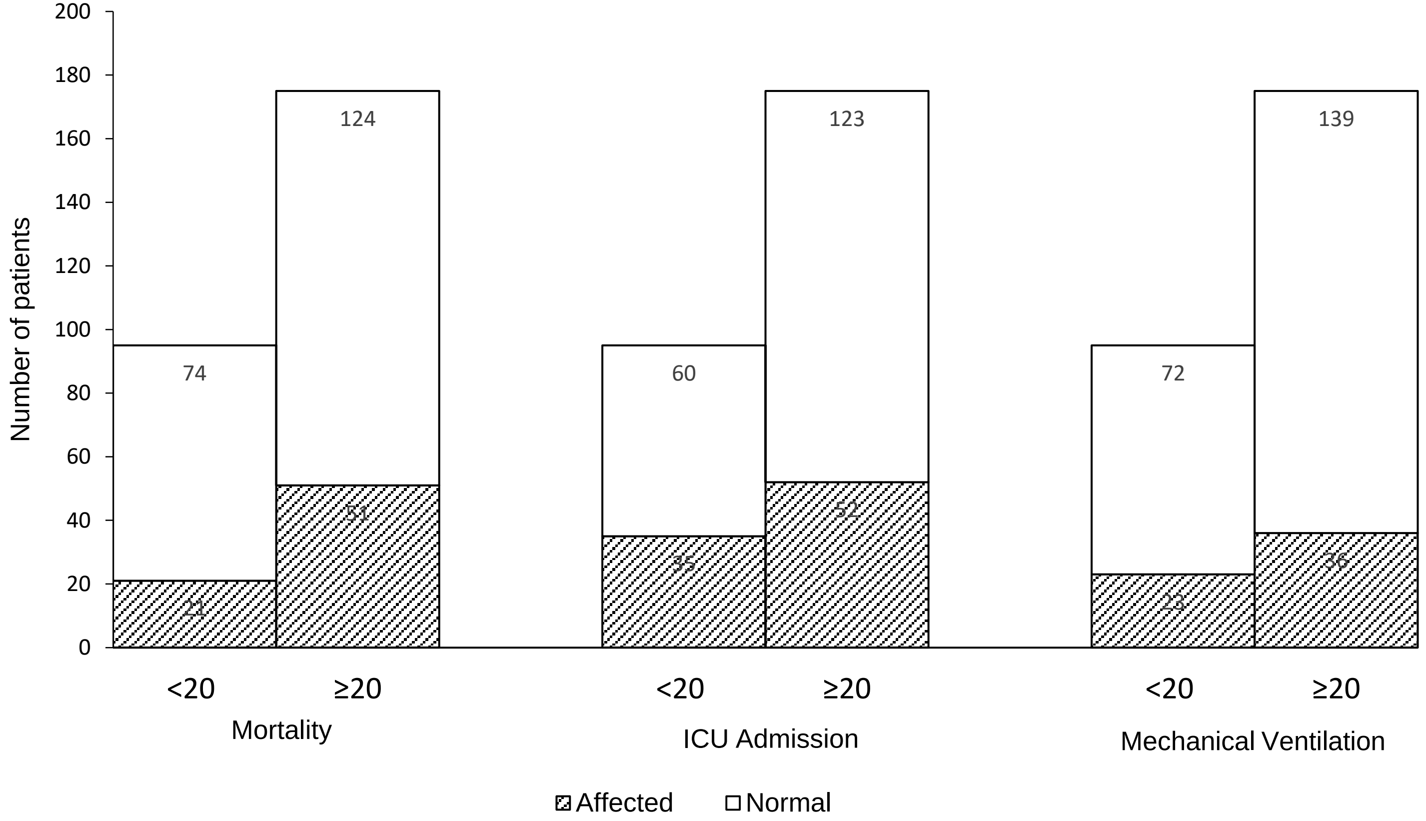
*adjusted Odds ratio for age, sex, BMI and comorbidities

Exploring the link between Vitamin D and clinical outcomes in COVID-19



Vitamin D binds to these cells and immunomodulates gene expression enhancing innate immunity and modulating adaptive immunity





Severe disease outcomes in relation to Vitamin D Levels

Question- Does Vitamin D help decrease the severity of clinical outcomes in COVID-19?

Conclusion- No significant association found between Vitamin D levels and clinical outcomes in COVID-19.