

Clinical Research Article

Vitamin D Deficiency Is Associated With Higher Hospitalization Risk From COVID-19: A Retrospective Case-Control Study

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; IQR, interquartile range; NICE, National Institute for Health and Clinical Care Excellence; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Received: 2 April 2021; Editorial Decision: 11 June 2021; First Published Online: 17 June 2021; Corrected and Typeset: 15 July 2021.

Abstract

Context: One risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is postulated to be vitamin D deficiency. To better understand the role of vitamin D deficiency in the disease course of COVID-19, we undertook a retrospective case-control study in North West England.

Objective: To examine whether hospitalization with COVID-19 is more prevalent in individuals with lower vitamin D levels.

Methods: The study included individuals with test results for serum 25-hydroxyvitamin D (25[OH]D) between April 1, 2020, and January 29, 2021, from 2 districts in North West England. The last 25(OH)D level in the previous 12 months was categorized as “deficient” if less than 25 nmol/L and “insufficient” if 25 to 50 nmol/L.

Results: The study included 80 670 participants. Of these, 1808 were admitted to the hospital with COVID-19, of whom 670 died. In a primary cohort, median serum 25(OH)D in nonhospitalized participants with COVID-19 was 50.0 nmol/L (interquartile range [IQR], 34.0–66.7) vs 35.0 nmol/L (IQR, 21.0–57.0) in those admitted with COVID-19 ($P < 0.005$). In a validation cohort, median serum 25(OH)D was 47.1 nmol/L (IQR, 31.8–64.7) in nonhospitalized vs 33.0 nmol/L (IQR, 19.4–54.1) in hospitalized patients. Age-, sex-, and season-adjusted odds ratios for hospital admission were 2.3 to 2.4 times higher among participants with serum 25(OH)D < 50 nmol/L compared with those with normal serum 25(OH)D levels, without excess mortality risk.

Conclusion: Vitamin D deficiency is associated with higher risk of COVID-19 hospitalization. Widespread measurement of serum 25(OH)D and treatment of insufficiency or deficiency may reduce this risk.

Key Words: vitamin D deficiency, COVID-19, hospitalization, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Vitamin D deficiency has been proposed as a risk factor for many viral respiratory illnesses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Despite attempts to curtail coronavirus disease 2019 (COVID-19) resulting from SARS-CoV-2 infection, there has been only limited success, even after 18 months since the beginning of the mega-pandemic in December 2019.

Vitamin D has been thought to possess immunomodulatory functions, apart from its well-known effects on bone mineral metabolism.

Several observational studies (1-10) have examined the role of vitamin D on COVID-19 infection risk or disease outcomes with conflicting results. Although with some technical flaws and discrepancies in the assessment methods, 3 systematic reviews also assessed the risk of COVID-19 and vitamin D levels, and the benefits of supplementation on morbidity and mortality reduction from the disease (11-13). These reviews suggested an overall increased risk of hospitalization (odds ratio [OR] 1.43-1.81) and mortality (OR 1.82; 95% CI, 1.6-2.58) from COVID-19 in patients with vitamin D deficiency. However, the studies included in these systematic reviews exhibited a high risk of various biases, such as inadequate evaluation of the outcome, inappropriate sample selection, and lack of uniformity of the inclusion criteria, and so the certainty of evidence emerging from these studies appears low. On the contrary, a study from Italy (14) and another from Brazil (15) clearly refute the probability of a causal link between vitamin D deficiency and susceptibility to SARS-CoV-2 infection. Therefore, it is imperative to have more evidence based on large population-based studies to reveal the risk of COVID-19 in populations with vitamin D deficiency, and multicenter randomized controlled trials to observe the potential benefits of vitamin D supplementation in treating the disease.

Most studies that have looked at prevailing vitamin D levels and COVID-19 have been performed in a small number of patients. Therefore, we set out to understand the role of vitamin D levels and the risk of developing COVID-19 in a large-cohort observational study from 2 hospital sites in North West England in the United Kingdom to uncover the uncertainties around this highly debated topic. Our primary outcome was to determine whether insufficient or deficient vitamin D status was associated with

increased risk of hospitalization from COVID-19, with due consideration of Northern hemisphere's seasonal variations of vitamin D. Our secondary outcome was to determine whether insufficient or deficient vitamin D status was associated with increased risk of inpatient death from COVID-19.

Methods

Participants

Participants were recruited to a primary cohort if they had a serum 25-hydroxyvitamin D (25[OH]D) level carried out at the hospital laboratory based at Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust, between April 1, 2019, and January 29, 2021. Participants were recruited to a validation cohort if they had a serum 25(OH)D level carried out at the hospital laboratory based at Tameside General Hospital, Tameside and Glossop Integrated Care NHS Foundation Trust, between April 1, 2019, and January 29, 2021. Cases were identified from the biochemistry database of both the recruitment sites by an electronic search for a 25(OH)D test performed during the above period. COVID-19 patients were also identified from the inpatient electronic admission register. Laboratory testing for COVID-19 was carried out using throat \pm nasal swab, and samples were tested for SARS-CoV-2 viral RNA following amplification using real-time polymerase chain reaction (PCR). Patients were included if they were aged 18 years or older. Serum 25(OH)D values measured for all indications were included; information on indications was not available. The 25(OH)D measurements were carried out for a mixture of inpatients, outpatients, and primary care. Vitamin D insufficiency was defined as serum 25(OH)D levels from 25 to 50 nmol/L, and deficiency as <25 nmol/L as per the current National Institute for Health and Clinical Care Excellence (NICE), UK guidelines (16). A low vitamin D category was created by combining both vitamin D insufficient and deficient patients. Participants were recruited both from the community and inpatient stays. Inpatients who had been admitted to hospital with COVID-19 with serum 25(OH)D samples measured more than 365 days prior to eventual discharge date were excluded. Furthermore, patients with serum 25(OH)D samples carried out after discharge were also excluded, as were

COVID-19 inpatients who did not have 25(OH)D measured during the study period.

Serum 25(OH)D Measurement

Serum 25(OH)D was measured using the cobas e 801 analytical unit (Roche, Basel, Switzerland) at Royal Preston Hospital, and using the UniCel DxI 800 Access Immunoassay System (Beckman Coulter Life Sciences, Indianapolis, USA) at Tameside General Hospital. The clinical laboratories at Royal Preston Hospital participate in the Vitamin D External Quality Assessment Scheme (DEQAS) (17) to ensure analytical reliability of its 25(OH)D assays. The clinical laboratories at Tameside General Hospital participate in the Randox International Quality Assessment Scheme (RIQAS) (18) in order to ensure external quality of all assays, including 25(OH)D. Because serum 25(OH)D measurement techniques were slightly different between the 2 sites, the investigators decided to analyze the data from the 2 cohorts separately instead of pooling the data, so that findings would be internally valid within each cohort.

Statistical Methods

Patients hospitalized with a clinical diagnosis of COVID-19 identified by clinical coding (emergency use ICD code U07.1, COVID-19 confirmed by laboratory testing, and code U07.2, COVID-19 diagnosis where laboratory confirmation is inconclusive or not available) were defined as cases. Community cases of COVID-19 were not included, as the outcome measure of interest was hospitalization with COVID-19. Controls were defined as all other patients who had serum 25(OH)D measurements carried out in the above time period who were not submitted to SARS-CoV-2 testing; none of these patients were hospitalized with COVID-19.

All statistical analyses were carried out using Stata v14.0 (StataCorp LP, College Station, TX, USA). Variables were tested for skewness and kurtosis using the built-in “sktest” function in Stata in order to determine whether they were parametrically or nonparametrically distributed. A nonparametric equality of medians test was used to compare median serum 25(OH)D values between cases and controls. Odds ratios (ORs) and 95% CIs within the case-control study were estimated. The probability of association was calculated using Pearson's chi-squared test. Logistic regression was used to obtain age- and sex-adjusted ORs. Furthermore, analyses were also adjusted for the seasonality of serum 25(OH)D levels, adjusting for samples carried out in the UK's spring/summer months (March through August) vs those carried out in autumn/winter months (September through February). Finally, logistic regression was used to determine any association between vitamin D status and inpatient mortality from COVID-19, adjusting for age, sex, and whether serum 25(OH)D was measured during spring/summer.

Results

Cohort Characteristics

Baseline participant characteristics of both primary and validation cohorts are shown in Table 1, and that stratified by cases and controls in Table 2. A total of 58 368 participants were recruited from Lancashire Teaching Hospitals NHS Foundation Trust to the primary cohort, of whom 38 472 (65.9%) were female. Age was nonparametrically distributed in both cohorts. The median age of the primary cohort was 53.2 years [interquartile range [IQR], 36.6-69.1 years]. A total of 1036 (1.8%) participants were hospitalized with COVID-19 and defined as cases. Of the hospitalized patients, 375/1036 (36.2%) died from COVID-19. Serum 25(OH)D values were nonparametrically distributed in both cohorts. The overall primary cohort median serum

Table 1. Participant characteristics of both primary and validation cohorts

Participant characteristics	Lancashire Teaching Hospitals NHS Foundation Trust (n = 58 368)	Tameside and Glossop Integrated Care NHS Foundation Trust (n = 21 234)
Age (years), median [IQR]	53.2 [36.6-69.1]	55.1 [39.8-70.4]
Female sex, n (%)	38 472 (65.9)	14 527 (68.4)
Hospitalized patients, n (%)	1036 (1.8)	772 (3.6)
Inpatient deaths, n (%)	375 (36.9)	295 (38.2)
Serum 25(OH)D (nmol/L), median [IQR]	50.0 [34.0-66.6]	46.7 [31.3-64.4]
Time (days) between 25(OH)D measurement and admission to hospital (hospitalized participants only), median [IQR]	148 [22-265]	51 [12-187]

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; IQR, interquartile range.

25(OH)D was 50.0 nmol/L [IQR, 34.0-66.6 nmol/L]. However, when stratified by case status, median serum 25(OH)D was 50.0 nmol/L [IQR, 34.2-66.9 nmol/L] in nonhospitalized patients vs 35.0 nmol/L [IQR, 21.0-57.0 nmol/L] in hospitalized patients, and this difference was significant ($P < 0.005$). A total of 607 (58.6%) cases had serum 25(OH)D measured as an inpatient. In hospitalized patients, if serum 25(OH)D was not measured during the inpatient admission, the median time between the test being carried out and admission to hospital was 148 days [IQR, 22-265].

A total of 21 234 participants were recruited from Tameside and Glossop Integrated Care NHS Foundation Trust to the validation cohort, of whom 14 527 (68.4%) were female. The median age of the cohort was 55.1 years [IQR, 39.8-70.4 years]. A total of 772 (3.6%) participants were hospitalized with COVID-19 and defined as cases. Of the hospitalized patients, 295/772 (38.2%) died from COVID-19. The overall cohort median serum 25(OH)D was 46.7 nmol/L [IQR, 31.3-64.4 nmol/L]. However,

when stratified by case status, mean serum 25(OH)D was 47.1 nmol/L [IQR, 31.8-64.7 nmol/L] in nonhospitalized patients vs 33.0 nmol/L [IQR, 19.4-54.1 nmol/L] in hospitalized patients, and this difference was significant ($P < 0.005$). A total of 579 (75.0%) cases had serum 25(OH)D measured as an inpatient. In hospitalized patients, if serum 25(OH)D was not measured during the inpatient admission, the median time between the test being carried out and admission to hospital was 51 days [IQR, 12-187].

Case-Control Study

In the primary cohort (Lancashire Teaching Hospitals NHS Foundation Trust), low vitamin D (serum 25[OH]D < 50 nmol/L) was associated with increased odds of hospitalization with COVID-19 (OR 2.22; 95% CI, 1.93-2.53; $P < 0.005$). This remained significant following adjustment for age, sex, and whether serum 25(OH)D was measured in spring/summer (OR_{adj} 2.40; 95% CI, 2.10-2.74; $P < 0.005$). This association strengthened when only vitamin D deficient patients (serum 25[OH]D < 25 nmol/L) were considered (OR 3.77; 95% CI, 3.30-4.30; $P < 0.005$). Again, this remained significant following adjustment for age, sex, and spring/summer serum 25(OH)D measurement (OR_{adj} 3.57; 95% CI, 3.12-4.08; $P < 0.005$).

These findings were replicated in the validation cohort (Tameside and Glossop Integrated Care NHS Foundation Trust). Again, low vitamin D was associated with increased odds of hospitalization with COVID-19 (OR 2.16; 95% CI, 1.83-2.54; $P < 0.005$). This remained significant following adjustment for age, sex, and whether serum 25(OH)D was measured in spring/summer (OR_{adj} 2.33; 95% CI, 1.98-2.74; $P < 0.005$). Furthermore, this association once again strengthened when only vitamin D deficient patients were considered (OR 3.36; 95% CI, 2.89-3.92; $P < 0.005$). Again, this remained significant following adjustment for age, sex, and spring/summer serum 25(OH)D measurement (OR_{adj} 2.98; 95% CI, 2.55-3.49; $P < 0.005$). Summary of associations between vitamin D status and hospitalization risk among both

Table 2. Participant characteristics of both primary and validation cohorts, stratified by cases and controls

Participant characteristics	Cases	Controls
<i>Primary cohort: Lancashire Teaching Hospitals NHS Foundation Trust (n = 59 368)</i>		
Age (years), median [IQR]	73.7 [60.3-82.6]	52.8 [36.3-68.7]
Female sex, n (%)	472 (45.6)	38 000 (66.3)
Serum 25(OH)D (nmol/L), mean (SD)	35.0 [21.0-57.0]	50.0 [34.2-66.9]
<i>Validation cohort: Tameside and Glossop Integrated Care NHS Foundation Trust (n = 21 234)</i>		
Age (years), median [IQR]	72.5 [60.1-81.5]	54.5 [39.3-69.7]
Female sex, n (%)	345 (44.7)	14 182 (69.3)
Serum 25(OH)D (nmol/L), mean (SD)	33.0 [19.4-54.1]	47.1 [31.8-64.7]

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; IQR, interquartile range.

Table 3. Summary of associations between vitamin D status and hospitalization, both cohorts

Variable of interest	Primary cohort		Validation cohort	
	OR (95% CI)	P value	OR (95% CI)	P value
Serum 25(OH)D < 50 nmol/L	2.22 (1.93-2.53)	< 0.005	2.16 (1.83-2.54)	< 0.005
Serum 25(OH)D < 50 nmol/L, adjusted	2.40 (2.10-2.74)	< 0.005	2.33 (1.98-2.74)	< 0.005
Serum 25(OH)D < 25 nmol/L	3.77 (3.30-4.30)	< 0.005	3.36 (2.89-3.92)	< 0.005
Serum 25(OH)D < 25 nmol/L, adjusted	3.57 (3.12-4.08)	< 0.005	2.98 (2.55-3.49)	< 0.005

Where odds ratios have been adjusted, these have been adjusted for age, sex, and whether serum 25(OH)D measurement was carried out in UK spring/summer months (March through August).

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

cohorts are shown in Table 3, and the detailed subanalysis stratified by age, sex, and season is available in Table 4.

There was no association between low vitamin D levels and inpatient hospital mortality among patients admitted with COVID-19 in either cohort, both unadjusted and following adjustment for age, sex, and spring/summer 25(OH)D measurement.

Discussion

This is one of the largest studies to date to investigate the role of vitamin D in the severity of COVID-19 infection. In this retrospective large-scale case-control observational study, we demonstrated an association between

suboptimal serum 25(OH)D levels and risk of hospitalization from COVID-19. Our study utilizes a large number of community-based patients as well as hospital inpatients and outpatients, and the findings replicate across 2 independent cohorts. We found no association between 25(OH)D levels or vitamin D status and inpatient mortality from COVID-19.

Previous systematic reviews have clearly showed an inverse nonlinear association between 25(OH)D concentration and acute respiratory tract infections, including community-acquired pneumonias (19, 20), but these studies were not specifically focused on SARS-CoV-2 infection. Similar to our findings, a study from the UK by Panagiotou et al. found that low serum 25(OH)D levels in COVID-19 inpatients were associated with a more severe disease course (21), but this study included only 134 patients.

Conversely, a study using the UK Biobank looked at 348 598 participants, of whom only 449 had a confirmed diagnosis of COVID-19 as defined by a positive laboratory test for SARS-CoV-2 (only 0.13% of the study population), and they did not find any association between 25(OH)D and risk of COVID-19 infection (22). In addition to the low number of patients with COVID-19, other weaknesses in this study included heterogeneity in severity and management of COVID-19 cases (likely a mixture of inpatient and community, instead of focusing on COVID-19 cases in only one setting), serum 25(OH)D measurement between 2006 and 2010, and not contemporaneously with COVID-19 infection 10 to 14 years after recruitment to the UK Biobank, and no mention of validation of 25(OH)D measurement.

In terms of 25(OH)D and COVID-19 disease severity, a study from India of 154 patients admitted to hospital with COVID-19 reported that the mean 25(OH)D level was <30 ng/mL (insufficient range), and patients admitted to the intensive care unit and those that died from COVID-19 were more deficient in vitamin D than survivors (23). Another study from Belgium (n = 186) reported similar findings of greater deficiency rates in patients with more severe disease (24). Similarly, a study from Switzerland demonstrated that 25(OH)D concentrations were significantly lower in patients with COVID-19 than in those without the disease (25).

Other studies have also demonstrated a correlation between vitamin D deficiency and COVID-19 infection, contrary to the study using patients from the UK Biobank. A study from Israel with 7807 subjects demonstrated that 25(OH)D concentrations were significantly lower among those who tested positive for COVID-19 than those who were COVID-19 negative (26). A study from Wuhan, China, showed in a multivariable logistic regression that vitamin D deficiency (<30 nmol/L) was significantly associated with COVID-19 severity (27).

Table 4. Subgroup analyses for the Primary and validation cohorts

A. Primary cohort subanalysis		
<i>Serum 25(OH)D < 50 nmol/L and association with hospitalization</i>		
Subgroup	OR (95% CI)	P value
Female	2.15 (1.78-2.61)	<0.005
Male	2.10 (1.75-2.52)	<0.005
Age ≥ 60 years	2.46 (2.12-2.86)	<0.005
Age < 60 years	2.68 (2.02-3.55)	<0.005
25(OH)D measured in spring/summer	2.14 (1.69-2.72)	<0.005
25(OH)D measured in autumn/winter	2.19 (1.87-2.57)	<0.005
<i>Serum 25(OH)D < 25 nmol/L and association with hospitalization</i>		
Subgroup	OR (95% CI)	P value
Female	3.56 (2.91-4.35)	<0.005
Male	3.59 (3.00-4.28)	<0.005
Age ≥ 60 years	3.68 (3.15-4.31)	<0.005
Age < 60 years	4.11 (3.17-5.32)	<0.005
25(OH)D measured in spring/summer	4.54 (3.58-5.75)	<0.005
25(OH)D measured in autumn/winter	3.42 (2.91-4.01)	<0.005
B. Validation cohort subanalysis		
<i>Serum 25(OH)D < 50 nmol/L and association with hospitalization</i>		
Subgroup	OR (95% CI)	P value
Female	2.15 (1.70-2.72)	<0.005
Male	1.92 (1.54-2.40)	<0.005
Age ≥ 60 years	2.47 (2.06-2.97)	<0.005
Age < 60 years	2.39 (1.71-3.36)	<0.005
25(OH)D measured in spring/summer	2.30 (1.71-3.10)	<0.005
25(OH)D measured in autumn/winter	2.05 (1.69-2.48)	<0.005
<i>Serum 25(OH)D < 25 nmol/L and association with hospitalization</i>		
Subgroup	OR (95% CI)	P value
Female	3.30 (2.62-4.16)	<0.005
Male	2.93 (2.38-3.59)	<0.005
Age ≥ 60 years	3.19 (2.67-3.82)	<0.005
Age < 60 years	3.43 (2.53-4.64)	<0.005
25(OH)D measured in spring/summer	4.28 (3.25-5.64)	<0.005
25(OH)D measured in autumn/winter	3.00 (2.50-3.61)	<0.005

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio.

Our study's strengths lie in the usage of relatively recent serum 25(OH)D testing (ie, carried out within 12 months of inpatient admission with COVID-19), and the use of 2 large cohorts of patients ($n = 80\ 670$ combined). We have clearly demonstrated that vitamin D insufficiency and deficiency exponentially increase the risk of the disease by a factor of 2.3 to 3.6, even after adjustments for age and sex. However, we did not find any association between low 25(OH)D levels or vitamin D status and excess mortality risk, as observed in previous studies (6, 8, 11, 12).

Vitamin D deficiency has been recognized as a risk factor for developing COVID-19, a disease that has affected over 1 billion people worldwide and has led to over 2.82 million deaths. Vitamin D deficiency is a global problem, more so in countries with colder climates, especially those above the 35th parallel. This is in support of our UK-based study, which also showed that vitamin D deficiency was associated with more severe COVID-19 that required admission to hospital, increasing the risk approximately 3-fold when compared with people with normal 25(OH)D levels.

Vitamin D is a pluripotent secosteroid hormone that is important for bone health, but it is also known to regulate cellular functions throughout the body. Vitamin D, specifically, is of 2 types: vitamin D2 (ergocalciferol), derived mainly from plant sources, and vitamin D3 (cholecalciferol), which is present in higher animals and constitutes 80% to 90% of the body's vitamin D (28). The role of vitamin D in the immune system could partially explain the relationship between vitamin D deficiency and COVID-19 incidence and disease severity. Vitamin D is anti-inflammatory, and it has been shown to modulate the immune system by upregulating a complex set of proteins and inducing the expression of defense peptides such as cathelicidin and β -defensins (29).

One of the factors associated with the apparently high mortality risk from the COVID-19 pandemic in the temperate and cold regions of the world compared to the tropics may be vitamin D deficiency. Several previous studies clearly demonstrated high prevalence of low 25(OH)D levels in European populations, especially during winter months (30–33). As the association between vitamin D deficiency and usual respiratory illnesses/mortality was not sizable, public health measures for nutritional supplementation, at least during winter months, were not a major agenda at the time of writing. With the emergence of a mega-pandemic such as COVID-19, with high morbidity and case fatality risk with few treatment options currently, urgent attention to this important issue now becomes crucial.

Vitamin D supplementation has been shown to reduce the risk of respiratory infections in both a previous and

recent meta-analyses (34). We have recently demonstrated that high-dose cholecalciferol treatment was associated with reduced mortality among hospitalized patients with COVID-19 infections (2). In another study from Spain, Entrenas Castillo et al. found that in a cohort of patients treated with calcifediol (hydroxylated cholecalciferol or 25-hydroxyvitamin D₃), fewer patients required admission to the intensive care unit (35).

There has been a lot of discussion on the role of vitamin D in COVID-19. With its effect on macrophage function and innate immunity, vitamin D may alter the disease manifestations of COVID-19. In the absence of highly effective prevention and treatment strategies for the pandemic currently, any medical intervention, including vitamin D supplementation/treatment, becomes relevant. With the easy availability and very economic pricing of the drug, vitamin D supplementation should be an important consideration for deficient populations at risk.

To understand and improve outcomes, risk scores are being devised. Two such scores (QCOVID (36) and OURMAPCN (37)) for risk of hospital admission and mortality from COVID-19 have been developed, and these include patient demographics and biochemical parameters, as well as a range of comorbidities. However, vitamin D was not included in the analysis, and given widespread, independent findings regarding 25(OH)D levels and risk for severity and mortality from COVID-19, the inclusion of serum 25(OH)D levels should be considered for future algorithms.

We acknowledge certain limitations of our study, which are inherent to the retrospective design of the data collection, being recruitment from only 2 large district hospitals in the UK, and lack of availability of other confounding factors such as comorbid illnesses that might have increased the hospitalization rates in patients with COVID-19. However, the large sample size compared with most other published data, examining the association between 25(OH)D levels and COVID-19, as well as validation between 2 independent cohorts, make our data unique. As we obtained data of COVID-19 cases from respective hospital admissions registers from both sites, we were unable to assess the risk of asymptomatic COVID-19 in people with vitamin D deficiency in the community. We were also unable to exclude other potential confounding factors (such as obesity) which are associated with vitamin D deficiency and higher morbidity from COVID-19 (38, 39). Even with these limitations, our observations may have important public health implications for planning and policymaking to prevent and treat COVID-19, the enigmatic disease that still threatens normal human life across the globe.

Conclusion

Vitamin D insufficiency or deficiency is associated with 2.3 to 3.6 times higher risk of severe SARS-CoV-2 infection necessitating hospital admission. However, there is no association between vitamin D deficiency and excess mortality in COVID-19. Urgent action is required to address the high prevalence of vitamin D deficiency that increases COVID-19-related morbidity. Future studies should also investigate any potential role of vitamin D sufficiency in the prevention of SARS-CoV-2 infection.

Acknowledgments

Financial Support: No funding was received for this work.

Additional Information

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Disclosures: None to declare in relation to this work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Data Availability: Full data of this research work is available with the corresponding author and can be viewed by interested parties on request.

References

- Katz J, Yue S, Xue W. Increased risk for COVID-19 in patients with vitamin D deficiency. *Nutrition*. 2021;84:111106.
- Ling SF, Broad E, Murphy R, et al. High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with COVID-19: a cross-sectional multi-centre observational study. *Nutrients*. 2020;12(12):3799.
- Jevalikar G, Mithal A, Singh A, et al. Lack of association of baseline 25-hydroxyvitamin D levels with disease severity and mortality in Indian patients hospitalized for COVID-19. *Sci Rep*. 2021;11(1):6258.
- Sulli A, Gotelli E, Casabella A, et al. Vitamin D and lung outcomes in elderly COVID-19 patients. *Nutrients*. 2021;13(3):717.
- Pugach IZ, Pugach S. Strong correlation between prevalence of severe vitamin D deficiency and population mortality rate from COVID-19 in Europe. *Wien Klin Wochenschr*. 2021;1-3. doi:10.1007/s00508-021-01833-y
- Angelidi AM, Belanger MJ, Lorinsky MK, et al. Vitamin D status is associated with in-hospital mortality and mechanical ventilation: a cohort of COVID-19 hospitalized patients. *Mayo Clin Proc*. 2021:S0025-6196(21)00001-X. doi:10.1016/j.mayocp.2021.01.001
- Gavioli EM, Miyashita H, Hassaneen O, Siau E. An evaluation of serum 25-hydroxy Vitamin D levels in patients with COVID-19 in New York City. *J Am Coll Nutr*. 2021;1-6. doi:10.1080/07315724.2020.1869626
- Yadav D, Birdi A, Tomo S, Charan J, Bhardwaj P, Sharma P. Association of Vitamin D status with COVID-19 infection and mortality in the Asia Pacific region: a cross-sectional study. *Indian J Clin Biochem*. 2021;1-6. doi:10.1007/s12291-020-00950-1
- Li S, Cao Z, Yang H, Zhang Y, Xu F, Wang Y. Metabolic healthy obesity, vitamin D status, and risk of COVID-19. *Aging Dis*. 2021;12(1):61-71.
- Ma H, Zhou T, Heianza Y, Qi L. Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank. *Am J Clin Nutr*. 2021:nqaa381. doi:10.1093/ajcn/nqaa381
- Yisak H, Ewunetei A, Kefale B, et al. Effects of Vitamin D on COVID-19 infection and prognosis: a systematic review. *Risk Manag Healthc Policy*. 2021;14:31-38.
- Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Crit Rev Food Sci Nutr*. 2020;1-9. doi:10.1080/10408398.2020.1841090
- Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;104:58-64.
- Ferrari D, Locatelli M, Faraldi M, Lombardi G. Changes in 25-(OH) Vitamin D levels during the SARS-CoV-2 outbreak: lockdown-related effects and first-to-second wave difference-an observational study from Northern Italy. *Biology (Basel)*. 2021;10(3):237.
- Brandão CMÁ, Chiamolera MI, Biscolla RPM, et al. No association between vitamin D status and COVID-19 infection in São Paulo, Brazil. *Arch Endocrinol Metab*. 2021:2359-3997000000343. doi:10.20945/2359-3997000000343.
- National Institute for Health and Clinical Care Excellence (NICE). Vitamin D deficiency in adults - treatment and prevention. <https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention/>. Accessed April 09, 2021.
- Vitamin D External Quality Assessment Scheme. DEQAS. Accessed March 20, 2021. <http://www.deqas.org/>
- Randox Laboratories Ltd. Randox International Quality Assessment Scheme (RIQAS). Accessed March 20, 2021. <https://www.randox.com/external-quality-assessment/>
- Zhou YF, Luo BA, Qin LL. The association between vitamin D deficiency and community-acquired pneumonia: a meta-analysis of observational studies. *Medicine (Baltimore)*. 2019;98(38):e17252.
- Pham H, Rahman A, Majidi A, Waterhouse M, Neale RE. Acute respiratory tract infection and 25-Hydroxyvitamin D concentration: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2019;16(17):3020.
- Panagiotou G, Tee SA, Ihsan Y, et al. Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. *Clin Endocrinol (Oxf)*. 2020;93(4):508-511.
- Hastie CE, Mackay DF, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr*. 2020;14(4): 561-565.
- Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically

- ill COVID-19 patients and its correlation with inflammatory markers. *Sci Rep*. 2020;10(1):20191.
24. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. *Am J Clin Pathol*. 2021;155(3):381-388.
 25. D'Avolio A, Avataneo V, Manca A, et al. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. *Nutrients*. 2020;12(5):1359.
 26. Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. *Febs J*. 2020;287(17):3693-3702.
 27. Luo X, Liao Q, Shen Y, Li H, Cheng L. Vitamin D deficiency is associated with COVID-19 incidence and disease severity in Chinese people [corrected]. *J Nutr*. 2021;151(1):98-103.
 28. Holick MF. Cancer, sunlight and vitamin D. *J Clin Transl Endocrinol*. 2014;1(4):179-186.
 29. Bilezikian JP, Bikle D, Hewison M, et al. MECHANISMS IN ENDOCRINOLOGY: Vitamin D and COVID-19. *Eur J Endocrinol*. 2020;183(5):R133-R147.
 30. Niculescu DA, Capatina CAM, Dusceac R, Caragheorgheopol A, Ghemigian A, Poiana C. Seasonal variation of serum vitamin D levels in Romania. *Arch Osteoporos*. 2017;12(1):113.
 31. Duarte C, Carvalheiro H, Rodrigues AM, et al. Correction to: Prevalence of vitamin D deficiency and its predictors in the Portuguese population: a nationwide population-based study. *Arch Osteoporos*. 2020;15(1):55.
 32. Baauw A, Kist-van Holthe J, Slattery B, Heymans M, Chinapaw M, van Goudoever H. Health needs of refugee children identified on arrival in reception countries: a systematic review and meta-analysis. *BMJ Paediatr Open*. 2019;3(1):e000516.
 33. Manios Y, Moschonis G, Lambrinou CP, et al. A systematic review of vitamin D status in southern European countries. *Eur J Nutr*. 2018;57(6):2001-2036.
 34. Jolliffe DA, Camargo CA Jr, Sluyter JD, et al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomised controlled trials. *Lancet Diabetes Endocrinol*. 2021;9(5):276-292.
 35. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". *J Steroid Biochem Mol Biol*. 2020;203:105751.
 36. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. *BMJ*. 2020;371:m3731.
 37. Chen Z, Chen J, Zhou J, et al. A risk score based on baseline risk factors for predicting mortality in COVID-19 patients. *Curr Med Res Opin*. 2021;1-11. doi:10.1080/03007995.2021.1904862.
 38. Aghili SMM, Ebrahimpur M, Arjmand B, et al. Obesity in COVID-19 era, implications for mechanisms, comorbidities, and prognosis: a review and meta-analysis. *Int J Obes (Lond)*. 2021;45(5):998-1016.
 39. Charoenngam N, Shirvani A, Reddy N, Vodopivec DM, Apovian CM, Holick MF. Association of vitamin D status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. *Endocr Pract*. 2021;27(4):271-278.