# Serum 25(OH)D Level on Hospital Admission Associated With COVID-19 Stage and Mortality

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**Key Words:** Vitamin D deficiency; 25(OH)D; COVID-19 disease; Viral pneumonia; Laboratory analysis; Coronavirus; SARS-CoV-2

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## ABSTRACT

***Objectives:*** *Vitamin D deficiency was previously correlated with incidence and severity of coronavirus disease 2019 (COVID-19). We investigated the association between serum 25-hydroxyvitamin D (25(OH)D) level on admission and radiologic stage and outcome of COVID-19 pneumonia.*

***Methods:*** *A retrospective observational trial was done on 186 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–infected individuals hospitalized from March 1, 2020, to April 7, 2020, with combined chest computed tomography (CT) and 25(OH)D measurement on admission. Multivariate regression analysis was performed to study if vitamin D deficiency (25(OH)D <20 ng/mL) correlates with survival independently of confounding comorbidities.*

***Results:*** *Of the patients with COVID-19, 59% were vitamin D deficient on admission: 47% of females and 67% of males. In particular, male patients with COVID-19 showed progressively lower 25(OH)D with advancing radiologic stage, with deficiency rates increasing from 55% in stage 1 to 74% in stage 3. Vitamin D deficiency on admission was not confounded by age, ethnicity, chronic lung disease, coronary artery disease/hypertension, or diabetes and was associated with mortality (odds ratio [OR], 3.87; 95% confidence interval [CI], 1.30-11.55), independent of age (OR, 1.09; 95% CI, 1.03-1.14), chronic lung disease (OR, 3.61; 95% CI, 1.18-11.09), and extent of lung damage expressed by chest CT severity score (OR, 1.12; 95% CI, 1.01-1.25).*

***Conclusions:*** *Low 25(OH)D levels on admission are associated with COVID-19 disease stage and mortality.*

### Key Points

- A remarkably high fraction (59%) of patients with coronavirus disease 2019 (COVID-19) are vitamin D deficient (25(OH)D <20 ng/mL) on admission. Deficiency was most pronounced in men with advanced radiologic stages of COVID-19 pneumonia.
- Vitamin D deficiency on admission was associated with COVID-19 mortality with an odds ratio of 3.87, independent of age, chronic lung disease, coronary artery disease, hypertension, or diabetes.

In a subset of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, excessive recruitment of proinflammatory cells and cytokine release contribute to alveolar and endothelial damage, triggering a vicious cycle that evolves toward severe coronavirus disease 2019 (COVID-19).[1,2] Beside its role in calcium metabolism, 1,25-dihydroxyvitamin D is a pleiotropic regulator of the immune system.[3-5] It stimulates the expression of cathelicidins and β-defensins in respiratory epithelia as a barrier to pathogen invasion.[6,7] It acts as a protolerogenic and anti-inflammatory cytokine by inhibiting T helper 1 (Th1) proliferation and switching Th1 CD4 T cells and M1-polarized macrophages toward a type II immunity. Vitamin D deficiency (25-hydroxyvitamin D [25(OH)D] <20 ng/mL) has been associated with increased incidence of acute viral respiratory infections and asthma exacerbations.[8,9] Data are rapidly emerging that vitamin D–deficient individuals have a higher relative risk of testing positive for SARS-CoV-2 infection[10-13] than vitamin D–sufficient people or that indicate an association between low 25(OH)D levels and clinical severity of COVID-19 pneumonia.[11,14-18] More than a billion people worldwide

are vitamin D deficient,[19] with variations between sexes, ethnicities, social groups, and geographies that appear to correlate with differences in incidence and outcome of COVID-19 lung disease. Here, we investigated serum 25(OH)D levels in 186 consecutive individuals hospitalized for severe SARS-CoV-2 infection as function of radiologic stage of COVID-19 pneumonia. We studied the association between 25(OH)D status on admission and COVID-19 mortality and its possible confounding by age, sex, and known vitamin D–impacted comorbidities such as diabetes, chronic lung disease, and coronary artery disease.

## Materials and Methods

### Study Participants

This is a retrospective observational study on 186 consecutive subjects with polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection hospitalized from March 1, 2020, to April 7, 2020, for COVID-19 pneumonia at AZ Delta General Hospital, a tertiary network hospital in Roeselare, Belgium. All 186 patients with COVID-19 were Whites of European descent (demographics summarized in Table 1). No data were available on prior vitamin D supplementation, body mass index, cancer, and general deprivation. This study was approved by the AZ Delta General Hospital ethical committee (Clinical Trial Number IRB B1172020000009) with a waiver of informed consent from study participants considering the study is based on secondary analysis of existing data.

### Procedures

*Chest Computed Tomography*

All patients with COVID-19 received a chest computed tomography (CT) on admission (detailed CT scanning protocol is shown in the supplement[20,21]; all supplementary information is available at *American Journal of Clinical Pathology* online) to determine the temporal radiologic COVID-19 disease stage by consensus evaluation of the predominant radiologic presentation: ground-glass opacities (early stage, stage 1), crazy paving pattern (progressive stage, stage 2), and consolidation (peak stage, stage 3).[21,22] Percentage of pulmonary tissue affected by COVID-19 pneumonia was expressed as CT severity score on a scale from 0 to 25, calculated by scoring loss of well-aerated functional lung tissue for each individual pulmonary lobe on a scale from 0 to 5 and summating this score for the five lobes.

*Analysis of Possibly Confounding Comorbidities*

Prevalence of diabetes was registered by anamnesis and review of electronic patient records. Chronic lung disease (emphysema, fibrosis, bronchiectasis) and coronary artery disease (coronary artery calcium scoring) were measured by noncontrast CT. Coronary artery calcium scoring is a strong independent predictor of cardiovascular mortality but also identifies individuals with hypertension requiring aggressive systolic blood pressure intervention.[23]

*Laboratory Analyses*

Serum 25(OH)D was measured using Elecsys vitamin D total II (Roche) traced to the official reference isotope dilution liquid chromatography-tandem mass spectrometry (Ghent University). All 25(OH)D data in this study represent a single time point, measured in patients with COVID-19 on admission and within 24 hours from chest CT staging. Vitamin D deficiency was defined as 25(OH)D level less than 20 ng/mL. SARS-CoV-2 infection was confirmed in all patients with COVID-19 by reverse transcription–PCR for E/N/RdRP genes (Allplex 2019-nCoV assay; Seegene) on nasopharyngeal swabs.

### Statistical Analysis

Data (not normally distributed) are expressed as medians (interquartile ranges [IQRs]), and the Mann-Whitney test was used to test statistical differences between groups. Proportions for categorical variables were compared using the $\chi^2$ test. Multivariate analysis was done by logistic regression or multiple regression as indicated. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with bivariable logistic regression for assessment of demographic characteristics and comorbidities associated with 25(OH)D deficiency and for assessment of demographic characteristics, comorbidities, vitamin D status, and CT findings on admission associated with survival outcome. The authors did not account for multiple comparisons. Statistical analyses were performed using MedCalc (version 12.2.1) and considered significant if the *P* value was less than .05.

## Results

### Vitamin D Deficiency Rates in COVID-19 Patients as a Function of Radiologic Stage

In total, 186 individuals with PCR-confirmed SARS-CoV-2 infection were hospitalized for COVID-19 pneumonia from March 1, 2020, to April 7, 2020:


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**Table 1**

**Demographics, Comorbidities, and 25(OH)D Levels of COVID-19 Patients Levels Stratified by Sex and Radiological COVID-19 Disease Stage[a]**

| Characteristic | COVID-19 (All) | COVID-19 (CT Stage 1) | COVID-19 (CT Stage 2) | COVID-19 (CT Stage 3) |
|---|---|---|---|---|
| All patients | | | | |
| Number | 186 | 46 | 55 | 85 |
| Age, median (IQR), y | 69 (52-80) | 74 (53-82) | 71 (60-78) | 63 (50-80) |
| Sex | | | | |
| Female | 77 (41.4) | 17 (37.0) | 25 (45.5) | 35 (41.2) |
| Male | 109 (58.6) | 29 (63.0) | 30 (54.5) | 50 (58.8) |
| Comorbidity | | | | |
| Chronic lung disease | 28 (15.1) | 8 (17.4) | 9 (16.4) | 11 (12.9) |
| Coronary artery disease | 110 (59.1) | 32 (69.6) | 32 (58.2) | 46 (54.1) |
| Diabetes | 26 (14.0) | 9 (19.6) | 7 (12.7) | 10 (11.8) |
| 25(OH)D | | | | |
| Median (IQR), ng/mL | 18.6 (12.6-25.3) | 19.7 (16.2-30.8) | 17.6 (12.0-26.0) | 16.9 (12.6-23.8)[b] |
| ≥20 ng/mL | 77 (41.4) | 22 (47.8) | 23 (41.8) | 32 (37.6) |
| <20 ng/mL | 109 (58.6) | 24 (52.2) | 32 (58.2) | 53 (62.4) |
| Female patients | | | | |
| Number | 77 | 17 | 25 | 35 |
| Age, median (IQR), y | 71 (65-74) | 68 (46-83) | 72 (64-76) | 66 (49-82) |
| Comorbidity | | | | |
| Chronic lung disease | 7 (9.1) | 0 (0.0)[c] | 3 (12.0) | 4 (11.4) |
| Coronary artery disease | 43 (55.8) | 11 (64.7) | 13 (52.0) | 19 (54.3) |
| Diabetes | 11 (14.3) | 4 (23.5) | 4 (16.0) | 3 (8.6) |
| 25(OH)D | | | | |
| Median (IQR), ng/mL | 20.7 (12.4-29.8) | 20.7 (10.4-33.0) | 20.3 (11.7-27.7) | 21.2 (15.1-29.6) |
| ≥20 ng/mL | 41 (53.2) | 9 (52.9) | 13 (52.0) | 19 (54.3) |
| <20 ng/mL | 36 (46.8) | 8 (47.1) | 12 (48.0) | 16 (45.7) |
| Male patients | | | | |
| Number | 109 | 29 | 30 | 50 |
| Age, median (IQR), y | 68 (53-79) | 74 (58-81) | 71 (59-78) | 59 (52-77) |
| Comorbidity | | | | |
| Chronic lung disease | 21 (19.3) | 8 (27.6)[c] | 6 (20.0) | 7 (14.0) |
| Coronary artery disease | 67 (61.5) | 21 (72.4) | 19 (63.3) | 27 (54.0) |
| Diabetes | 5 (13.8) | 5 (17.2) | 3 (10.0) | 7 (14.0) |
| 25(OH)D | | | | |
| Median (IQR), ng/mL | 17.6 (12.7-24.0) | 19.4 (18.2-29.8) | 16.5 (12.1-24.0)[b] | 16.0 (12.0-22.1)[b] |
| ≥20 ng/mL | 36 (33.0) | 13 (44.8) | 10 (33.3) | 13 (26.0) |
| <20 ng/mL | 73 (67.0) | 16 (55.2) | 20 (66.7) | 37 (74.0) |

COVID-19, coronavirus disease 2019; CT, computed tomography; IQR, interquartile range; 25(OH)D, 25-hydroxyvitamin D.
[a]Values are presented as number (%) unless otherwise indicated.
[b]Indicates differences with CT stage 1 patients with COVID-19 for whom *P* values less than .05 were considered statistically significant.
[c]Indicates differences of male vs female comorbidity prevalence for whom *P* values less than .05 were considered statistically significant.

109 men (median age, 68 years; IQR, 53-79 years) and 77 women (median age, 71 years; IQR, 65-74 years) (Table 1). On admission, serum 25(OH)D level was measured and the radiologic stage of COVID-19 pneumonia was determined by chest CT **Image 1**. These stages are considered a proxy for the immunologic phase of COVID-19, with an early phase of active viral replication in lower airways (stage 1) and progressive recruitment of proinflammatory cells to the lung interstitial space (stage 2), ending in consolidation with diffuse alveolar damage and fibrosis (stage 3). Most patients presented in late stage 3 (46%, 85/186), with 25% and 30% in stages 1 and 2, respectively (Table 1), with similar distribution in men and women. A remarkably high fraction (59%, 109/186) of patients with COVID-19 were vitamin D deficient (25(OH)D <20 ng/mL) on admission: 47% of women and 67% of men. Male patients with COVID-19 showed progressively lower median 25(OH)D with advancing stage, resulting in vitamin D deficiency rates increasing from 55% in stage 1, 67% in stage 2, to 74% in stage 3 ($P = .0010$) **Figure 1A**. No such stage-dependent 25(OH)D variations were seen in female patients with COVID-19 (**Figure 1B** and Table 1).

### Analysis of Possible Confounding by Vitamin D–Impacted Comorbidities

The high vitamin D deficiency rate and its association with the COVID-19 radiologic stage might be confounded by underlying differences in comorbidities



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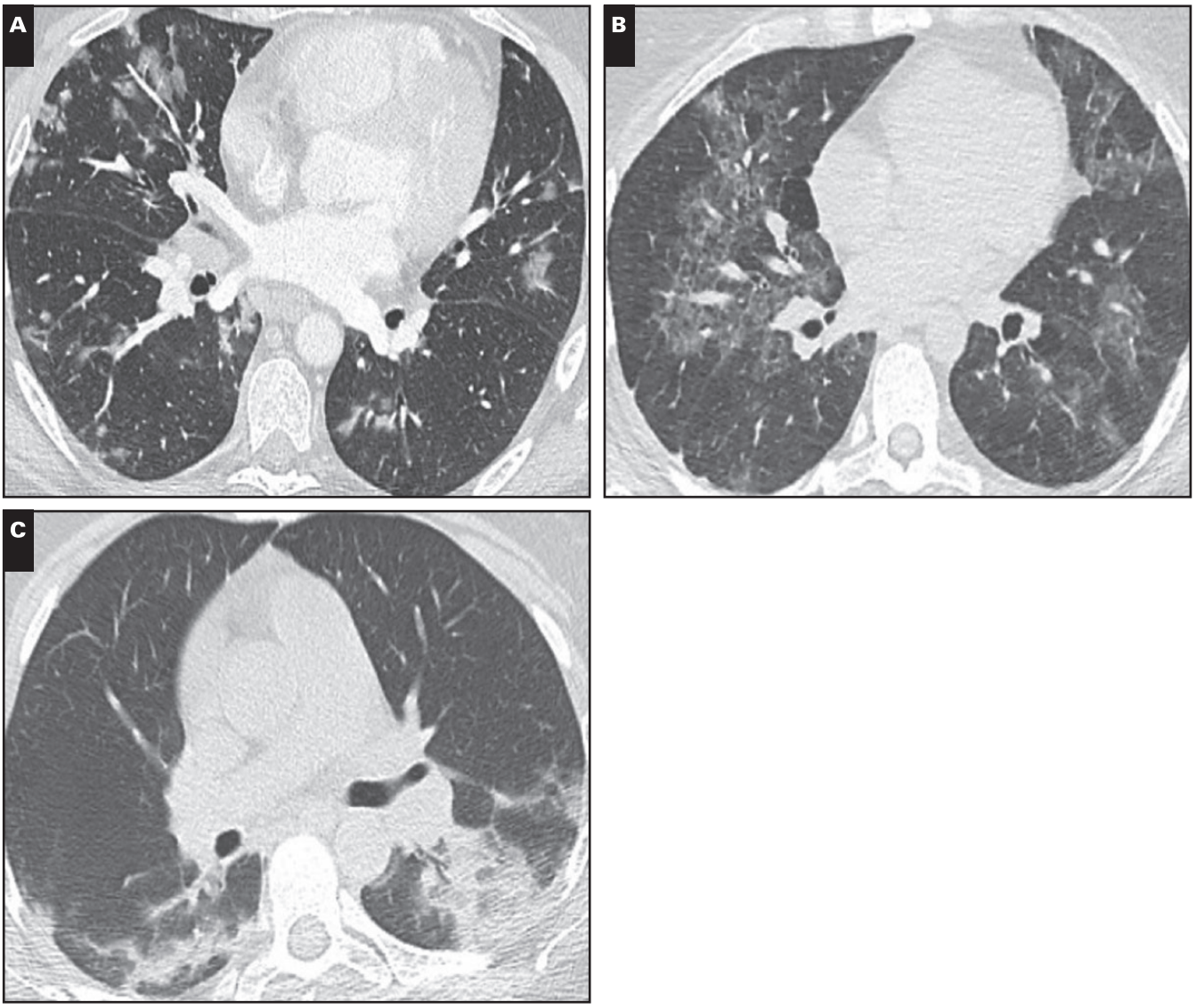


**Image 1** Levels of 25-hydroxyvitamin D (25(OH)D) in male and female patients with coronavirus disease 2019 (COVID-19) grouped by radiologic COVID-19 disease stage. **A-C**, Representative images of radiologic stages of COVID-19 lung disease with predominantly ground-glass opacities in early stage 1 (**A**), crazy paving patterns in progressive stage 2 (**B**), and consolidation in peak stage 3 (**C**).

known to be correlated with low 25(OH)D. We therefore compared prevalences of chronic obstructive lung disease,[24,25] diabetes, and coronary artery disease in male vs female patients (Table 1) and in vitamin D–deficient vs vitamin D–sufficient patients with COVID-19 **Table 2**. Prevalences of chronic lung disease, coronary artery disease, and diabetes in all patients with COVID-19 were 15%, 59%, and 14%, respectively, with no differences across COVID-19 disease stages (Table 1). The high prevalence of coronary artery disease in patients with COVID-19 was strongly correlated to patients' age ($r_s$ = 0.655; 95% CI, 0.565-0.730; $P$ < .0001). Male patients with COVID-19 showed similar prevalence of diabetes and coronary artery disease and a tendency toward more chronic lung diseases, reaching significance only in male COVID-19 stage 1 patients. The latter difference, however, was not related to differences in 25(OH)D status: male and female patients with COVID-19 with sufficient or deficient 25(OH)D status showed comparable prevalence of chronic lung disease, coronary artery disease, and diabetes (Table 2). Bivariable logistic regression analysis showed that vitamin D deficiency on admission was independently predicted only by male sex (OR, 2.43; 95% CI, 1.32-4.50; $P$ = .0046) but not by age or any of the listed possibly confounding comorbidities.


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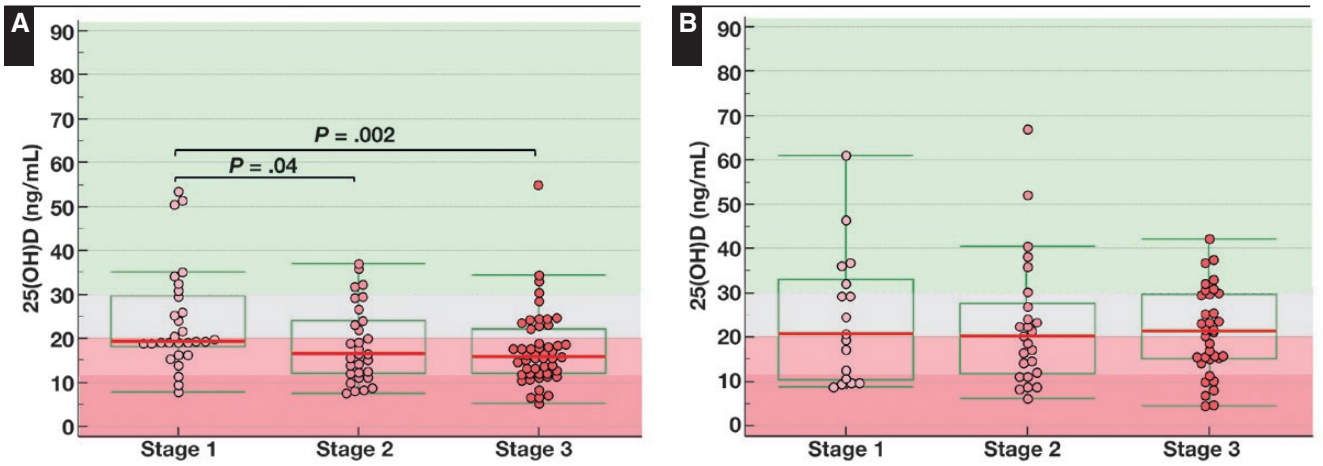


**Figure 1** Box-and-whisker plots of 25-hydroxyvitamin D (25(OH)D) in male patients with coronavirus disease 2019 (COVID-19) (**A**) and female patients with COVID-19 (**B**) grouped according to radiologic stage (stage 1, early stage ground-glass opacities; stage 2, progressive stage, crazy paving pattern; stage 3, peak stage, consolidation). Background color in boxplots indicates normal vitamin D status (green, 25(OH)D >30 ng/mL), vitamin D deficiency (pale red, 25(OH)D <20 ng/mL), severe vitamin D deficiency (darker red, 25(OH)D <12 ng/mL), and a gray zone (20 ng/mL ≤ 25(OH)D ≤ 30 ng/mL). *P* values indicate statistical differences between groups calculated by the Mann-Whitney test. Exact *P* values are listed in the supplementary information.[20]

**Table 2**

**Prevalence of Comorbidities Within Patients With COVID-19 Stratified for Sex and Vitamin D Deficiency Status[a]**

| Characteristic | 25(OH)D ≥20 ng/mL | 25(OH)D <20 ng/mL | *P* Value |
|---|---|---|---|
| All patients (n = 186) | | | |
| Number | 77 | 109 | |
| Age, median (IQR), y | 73 (53-81) | 67 (52-79) | .2692 |
| Sex | | | .0092[b] |
| Female | 41 (53.2) | 36 (33.0) | |
| Male | 36 (46.8) | 73 (67.0) | |
| Chronic lung disease | 13 (16.9) | 15 (13.8) | .7085 |
| Coronary artery disease | 48 (62.3) | 62 (56.9) | .5575 |
| Diabetes | 11 (14.3) | 15 (13.8) | .9063 |
| Multivariate analysis, OR (95% CI) | | | |
| Age | 1.00 (0.97-1.02) | | .6601 |
| Male sex | 2.43 (1.32-4.50) | | .0046[b] |
| Chronic lung disease | 0.69 (0.30-1.61) | | .3880 |
| Coronary artery disease | 0.87 (0.38-1.99) | | .7441 |
| Diabetes | 0.99 (0.42-2.34) | | .9798 |
| Female patients (n = 77) | | | |
| Number | 41 | 36 | |
| Chronic lung disease | 4 (9.8) | 3 (8.3) | .8660 |
| Coronary artery disease | 25 (61.0) | 18 (50.0) | .4594 |
| Diabetes | 7 (17.1) | 4 (11.1) | .6714 |
| Male patients (n = 109) | | | |
| Number | 36 | 73 | |
| Chronic lung disease | 9 (25.0)[c] | 12 (16.4)[c] | .4163 |
| Coronary artery disease | 23 (63.9)[c] | 44 (60.3)[c] | .8776 |
| Diabetes | 4 (11.1)[c] | 11 (15.1)[c] | .7838 |

CI, confidence interval; COVID-19, coronavirus disease 2019; IQR, interquartile range; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D.
[a]Values are presented as number (%) unless otherwise indicated.
[b]*P* values less than .05 were considered statistically significant.
[c]Additional male to female comparisons for prevalence of comorbidities showed no statistical differences (*P* > .05).



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**Table 3**

**Demographic Characteristics, Comorbidities, and 25(OH)D and CT Findings on Admission Associated With Death vs Survival Outcome of Patients With COVID-19[a]**

| Characteristic | Death Outcome | Survival Outcome | *P* Value |
|---|---|---|---|
| Number (%) | 27 (14.5) | 159 (85.5) | |
| Age, median (IQR), y | 81 (72-87) | 67 (51-77) | <.0001[b] |
| Sex | | | .4744 |
| Female | 9 (33.3) | 68 (42.8) | |
| Male | 18 (66.7) | 91 (57.2) | |
| Chronic lung disease | 9 (33.3) | 19 (12.0) | .0102[b] |
| Coronary artery disease | 22 (81.5) | 88 (55.4) | .0188[b] |
| Diabetes | 4 (14.8) | 22 (13.8) | .8715 |
| 25(OH)D | | | |
| Median (IQR), ng/mL | 15.2 (11.1-19.9) | 18.9 (13.9-26.4) | .0227[b] |
| ≥20 ng/mL | 7 (25.9) | 70 (44.0) | .1201 |
| <20 ng/mL | 20 (74.1) | 89 (56.0) | .1201 |
| CT stage | | | |
| CT stage 1 | 7 (25.9) | 39 (24.5) | .9320 |
| CT stage 2 | 9 (33.3) | 46 (28.9) | .8140 |
| CT stage 3 | 11 (40.7) | 74 (46.5) | .7260 |
| CT severity score (0-25), median (IQR) | 15 (10-17) | 11 (8-14) | .0460[b] |
| Multivariate analysis, OR (95% CI) | | | |
| Age | 1.09 (1.03-1.14) | | .0014[b] |
| Male sex | 1.02 (0.37-2.84) | | .9684 |
| Chronic lung disease | 3.61 (1.18-11.08) | | .0247[b] |
| Coronary artery disease | 0.90 (0.24-3.44) | | .8801 |
| Diabetes | 1.16 (0.32-4.15) | | .8197 |
| 25(OH)D <20 ng/mL | 3.87 (1.30-11.55) | | .0154[b] |
| CT stage (I, II, III) | 0.93 (0.51-1.69) | | .8050 |
| CT severity score (0-25) | 1.12 (1.01-1.25) | | .0283[b] |

CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; IQR, interquartile range; OR, odds ratio; 25(OH)D, 25-hydroxyvitamin D.
[a]Values are presented as number (%) unless otherwise indicated.
[b]*P* values less than .05 were considered statistically significant.

### 25(OH)D Levels on Admission Are Independently Correlated With COVID-19 Mortality

Finally, we studied if the patients' 25(OH)D status on admission was associated with mortality. Of patients with COVID-19, 15% (27/186) died, of whom 67% were men. Patients who died were older (median age, 81 vs 67 years; $P < .0001$), had higher prevalence of chronic lung disease (33% vs 12%; $P = .01$) and coronary artery disease (82% vs 55%, $P = .02$), and showed higher CT severity scores (15 vs 11; $P = .046$) and lower median 25(OH)D level (15.2 vs 18.9 ng/mL; $P = .02$) Table 3 than survivors. Bivariable logistic regression analysis indicated that mortality was independently associated with higher age, higher CT severity score, presence of chronic lung diseases, and presence of vitamin D deficiency (OR, 3.87; 95% CI, 1.30-11.55) but not with sex, prevalence of diabetes and coronary artery disease, or CT stage.

## Discussion

This study is one of several emerging reports that correlate vitamin D deficiency to incidence or severity of COVID-19 pneumonia. Retrospective epidemiologic studies in Israel and the United States involving hundreds[10] to thousands[11,13] of individuals showed an association between prior vitamin D deficiency—defined as 25(OH)D below 20 to 30 ng/dL—and the possibility of testing positive by SARS-CoV-2 PCR. Case-control studies in Switzerland and China indicated lower median 25(OH)D in patients with COVID-19 vs healthy controls.[12,17] Also, several studies involving tens to hundreds of patients in Iran, Germany, Israel, Spain, China, and the United Kingdom reported correlations between low 25(OH)D levels and various indicators of clinical severity of COVID-19 pneumonia such as intensive care unit (ICU) admission, ventilation dependency, and death.[11,14-18] A meta-analysis on six such studies, including the data reported in the preprint version of the present study, indicated heterogeneity in methodology, outcome measures, and analysis of confounders but overall supported the association between vitamin D deficiency and severity of COVID-19 pneumonia.[26]

The current study shows that a surprisingly high fraction (59%) of patients requiring hospitalization for severe COVID-19 pneumonia are vitamin D deficient (25(OH)D <20 ng/mL) and that presence of vitamin D deficiency on admission is associated with COVID-19 mortality.


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A strength of our study is the simultaneous assessment of 25(OH)D status and the extent of pulmonary involvement and radiologic stage of viral pneumonia as measured by structured chest CT.[21] The latter indicated a clear correlation between 25(OH)D level and temporal stages of viral pneumonia, particularly in male patients, with lower 25(OH)D levels on admission associated with a more advanced stage. It also allowed a correction for possible confounding comorbidities. Chronic lung diseases are known to alter 25(OH) metabolism or sequestration.[24,25] Vitamin D deficiency has also been correlated to coronary artery disease, arterial hypertension, and diabetes,[27] known risk factors for COVID-19 survival.[28,29] Chest CT allowed an objective measurement of preexisting lung emphysema and fibrosis, as well as overall burden of coronary artery disease by coronary artery calcium scoring. The latter also corrects possible confounding by arterial hypertension since it identifies hypertensive individuals requiring aggressive antihypertensive treatment.[23] Our data confirm that preexisting chronic lung disease is associated with COVID-19 mortality. But they also disclose a strong association between vitamin D deficiency and mortality with an OR of 3.87, independent of coronary artery disease, chronic lung disease, and diabetes. Of note, all 25(OH)D levels analyzed in our study were single time points, measured on admission, and are thus not biased by secondary decreases during hospitalization due to inflammatory consumption of 25(OH)D[30] or dilutions due to therapeutic interventions such as fluid resuscitation, extracorporeal oxygenation, or dialysis. Our data indicate that 25(OH)D is a meaningful parameter in addition to markers for inflammation, coagulation, and tissue damage[31,32] in prognostic models for COVID-19.

Our study has limitations. First, we lacked data to correct for some other risk factors for COVID-19 mortality known to be correlated to vitamin D deficiency, such as obesity and socioeconomic deprivation, as identified by the OpenSAFELY study.[28] Black, Asian, and ethnic minority ethnicity was also identified as a major risk factor for COVID-19 severity and is known to be correlated to lower 25(OH)D status. Our cohort of 186 patients with COVID-19 was uniformly composed of Whites, ruling out racial makeup as confounder in our study. Second, we had no data on prior vitamin D supplementation and cannot differentiate whether the high rate of vitamin D deficiency in patients with COVID-19 on admission reflects preexisting deficiency or rather an accelerated metabolism of 25(OH)D in an inflammatory context between onset of SARS-CoV-2 infection and hospitalization. Third, our cohort of patients with COVID-19 was biased toward more severe clinical presentations that required hospitalization. Therefore, we cannot determine if vitamin D deficiency also influences the prevalence of SARS-CoV-2 infection as recently reported[10-13] or milder COVID-19 presentations.

Vitamin D is a steroid hormone with many nonclassical actions that mediate immunologic response to respiratory viruses and survival of critically ill patients.[5] Emerging evidence suggests that severe COVID-19 can be conceptualized as an unbalance between proinflammatory type I and tolerogenic type II response.[1,2,33] Vitamin D stimulates cathelicidin/defensin expression in respiratory barriers[6] and exerts a tolerogenic M2-polarizing effect by dampening excessive inflammation.[7] Vitamin D is also studied as a modifiable risk factor for mortality in critical illness, both via its effect on bone health[34] and via nonclassical actions.[35,36] Prior meta-analysis indicated that vitamin D supplementation reduces the incidence of acute respiratory infections but only in those patients with a deficient vitamin D level at the start, as measured by 25(OH)D.[37] The largest randomized controlled trial (RCT) in ICU patients to date, VITdAL-ICU, showed a protective effect of high-dose 25(OH)D but only in individuals with starting 25(OH)D less than 12 ng/mL.[35,38] A recent pilot RCT indicated that oral calcifediol reduced the need for ICU treatment in hospitalized patients with COVID-19.[39] Larger RCTs are now needed, ideally guided by baseline 25(OH)D measurements.

In conclusion, our study shows an association between vitamin D deficiency on admission and mortality of COVID-19 pneumonia, independent of vitamin D–impacted comorbidities such as chronic lung disease, coronary artery disease, and diabetes. It highlights the need for RCTs targeting specifically vitamin D–deficient patients at intake and makes a call for general avoidance of vitamin D deficiency as a safe and inexpensive possible mitigation of the SARS-CoV-2 pandemic.

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