

# Association Between Vitamin D Levels and Clinical and Biochemical Parameters in COVID-19 Patients

Canan Şehit Kara<sup>1</sup>, Burcu Baran Ketencioğlu<sup>2</sup>, Hümeyra Aslaner<sup>3</sup>, Zeynep Türe<sup>4</sup>, Cevat Yazıcı<sup>5</sup>, Özgür Karabıyık<sup>6</sup>, Fahri Bayram<sup>7</sup>

<sup>1</sup>Department of Endocrinology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

<sup>2</sup>Department of Pulmonary Medicine, Erciyes University Faculty of Medicine, Kayseri, Türkiye

<sup>3</sup>Department of Family Medicine, University of Health Sciences Türkiye, Kayseri City Hospital, Kayseri, Türkiye

<sup>4</sup>Department of Infectious Diseases and Clinical Microbiology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

<sup>5</sup>Department of Biochemistry, Erciyes University Faculty of Medicine, Kayseri, Türkiye

<sup>6</sup>Department of Radiology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

<sup>7</sup>Department of Endocrinology, Erciyes University Faculty of Medicine, Kayseri, Türkiye

## Abstract

**BACKGROUND/AIMS:** Both coronavirus disease 2019 (COVID-19) and vitamin D deficiency (VDD) are widespread health problems today. This study was designed to compare serum 25-hydroxyvitamin D [25(OH)D] levels among three groups: patients with COVID-19 pneumonia, patients with non-COVID-19 pneumonia, and healthy volunteers, and to investigate whether vitamin D levels correlate with laboratory findings and infection severity.

**MATERIALS AND METHODS:** This prospective case-control study was carried out at a single tertiary care centre over four consecutive months between May and August 2020. A total of 90 individuals were enrolled and assigned equally to three groups: 30 with COVID-19 pneumonia, 30 with non-COVID-19 pneumonia, and 30 healthy controls. Multiple linear regression modelling was applied to determine independent predictors of serum 25(OH)D levels.

**RESULTS:** Both pneumonia groups exhibited markedly diminished 25(OH)D concentrations relative to healthy controls, with no statistically significant difference observed between the two pneumonia cohorts. In the multivariate regression model, membership in the healthy control group emerged as the sole independent determinant of elevated 25(OH)D levels. No meaningful correlations were identified among vitamin D concentrations, laboratory indices, and illness severity.

**CONCLUSION:** VDD was common in both COVID-19 and non-COVID-19 related pneumonia groups but was not associated with disease severity. Our results indicate that VDD may influence susceptibility to lower respiratory tract infections rather than disease progression.

**Keywords:** COVID-19, pneumonia, vitamin D

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**ORCID IDs of the authors:** C.Ş.K. 0000-0002-6136-8250; B.B.K. 0000-0002-6757-3140; H.A. 0000-0002-3710-3893; Z.T. 0000-0001-6895-0318; C.Y. 0000-0003-0625-9542; Ö.K. 0000-0002-9722-4363; F.B. 0000-0002-9637-6744.



**Corresponding author:** Canan Şehit Kara  
**E-mail:** sehitanan@hotmail.com  
**ORCID ID:** orcid.org/0000-0002-6136-8250

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## INTRODUCTION

Coronavirus disease 2019 (COVID-19), which develops as a result of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection, manifests with a broad clinical spectrum, ranging from fever, fatigue, and myalgia to cough, sputum production, and respiratory distress. Although most patients are asymptomatic or have mild symptoms, severe complications can arise in a significant number.<sup>1,2</sup> Poor prognostic factors include advanced age, obesity, cancer, immunodeficiency, cardiac disorder, chronic lung disease, chronic kidney failure, and smoking.<sup>3</sup> Furthermore, it has been reported that these factors are also related to lack of vitamin D.<sup>4</sup> Although the impacts of vitamin D on the skeletal system and calcium metabolism are generally known, many studies in the literature investigate its relationship with the immune system and infectious diseases.<sup>5</sup> Prior to the COVID-19 era, two studies reported that vitamin D administration reduced respiratory tract infections, particularly in critically ill patients.<sup>6,7</sup> In addition, studies have reported that vitamin D may exhibit various biological activities against COVID-19, including immune system regulation and endothelial dysfunction protection.<sup>8</sup> Therefore, the potential linkage between vitamin D status and COVID-19 susceptibility has increasingly been investigated in clinical research. The primary objective of this study was to analyse and compare the serum 25-hydroxyvitamin D [25(OH)D] levels in patients with COVID-19-related pneumonia (CP), in patients with non-COVID-19-related pneumonia (NCP), and in healthy individuals. Furthermore, the study aimed to establish any potential relationship between 25(OH)D levels, disease severity, and laboratory data. To the best of our knowledge, no prior prospective study has simultaneously assessed 25(OH)D levels across CP, NCP, and healthy control groups while also identifying independent predictors of vitamin D status through multivariate regression analysis.

## MATERIALS AND METHODS

A prospective case-control design was employed at a tertiary referral hospital from May through August 2020. A total of 90 participants were enrolled in three groups, each consisting of 30 consecutively recruited individuals: CP patients, NCP patients, and healthy controls. The study protocol was approved by the Erciyes University Clinical Research Ethics Committee (approval number: 2020/217, date: 29.04.2020), and written informed consent was obtained from all participants before inclusion.

**Group 1:** Patients with CP admitted to the hospital's pandemic service were included (n=30). The diagnosis of CP was established by positive SARS-CoV-2 RNA detection in nasopharyngeal swab specimens. The biospeedy COVID-19 real-time polymerase chain reaction (PCR) kit was used to detect SARS-CoV-2 RNA. In addition, thoracic computed tomography (CT) findings were compatible with COVID-19 disease, defined as bilateral, peripheral, or multifocal ground-glass opacities or consolidation patterns, as per the expert consensus criteria of Radiological Society of North America (RSNA).<sup>9</sup>

**Group 2:** Patients who had two negative SARS-CoV-2 PCR tests on nasopharyngeal swab samples and in whom CP was ruled out were included (n=30). Thoracic CT findings were compatible with pneumonia but incompatible with typical COVID-19 radiology, as per the RSNA consensus criteria.<sup>9</sup> Thoracic CT scans were performed at hospital admission (day 1).

**Group 3:** The first 30 consecutive healthy adults who applied to our hospital's endocrinology and metabolism diseases clinic, had no known

chronic diseases, and had no history of respiratory infection in the preceding three months were recruited.

Participants who were under 18 years of age, over 80 years of age, or who had taken any medication and/or supplement that may affect vitamin D metabolism in the last six months were excluded.

Socio-demographic data (age, sex), clinical symptoms (fever, headache, cough, dyspnoea, sore throat, diarrhoea), and vital signs (temperature, pulse, oxygen saturation) were recorded at hospital admission. Each participant's comorbid conditions were systematically recorded, including coronary artery disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, dyslipidemia, renal insufficiency, and malignancy. The laboratory data including complete blood count, procalcitonin, C-reactive protein (CRP), creatinine, estimated glomerular filtration rate (eGFR), ferritin, D-dimer, albumin, and inflammatory markers including systemic immune-inflammation (SII) index, neutrophil-to-lymphocyte ratio (NLR), CRP-to-albumin ratio (CAR) and platelet-to-lymphocyte ratio (PLR) were recorded at hospital admission (day 1).<sup>10,11</sup> 25(OH)D levels were measured in all participants. All pneumonia patients underwent a thoracic CT scan.

The SII index was determined using the formula listed below: SII index = (neutrophil count\*platelet count)/lymphocyte count.<sup>10,11</sup>

Serum 25(OH)D concentrations were measured in venous samples collected at admission using an electrochemiluminescence immunoassay (ECLIA) on a Cobas E601 system (Roche Diagnostics). The lowest detectable concentration of 25(OH)D was 3 ng/mL. 25(OH)D  $\geq 30$  ng/mL was considered as normal, 25(OH)D  $< 20$  ng/mL was considered as vitamin D deficiency (VDD) and 25(OH)D 20-30 ng/mL was considered as vitamin D insufficiency (VDI).<sup>12,13</sup>

Pneumonia severity was classified according to the national guideline of Türkiye,<sup>14</sup> as follows:

- Mild pneumonia: Mild clinical symptoms,  $\leq 50\%$  involvement on thoracic tomography, respiratory rate  $< 24$ /minute, and oxygen saturation  $> 93\%$ .
- Moderate pneumonia: Mild clinical symptoms,  $\leq 50\%$  involvement on thoracic tomography, and the existence of any of the two criteria: respiratory rate 24-30/minute, and oxygen saturation 90-93%.
- Severe pneumonia: The existence of any of those criteria: respiratory rate  $> 30$ /minute, oxygen saturation  $< 90\%$ , bilateral and common ( $\geq 50\%$ ) involvement on thoracic tomography.
- This study did not include patients with mild pneumonia since they were not hospitalized following the national guideline. Therefore, we classified patients into two groups with moderate and severe pneumonia.<sup>14</sup>

## Statistical Analysis

Descriptive statistics are shown as median and minimum-maximum ranges or mean  $\pm$  standard deviation (SD) for continuous data. Categorical data are reported as percentages and frequencies. Non-parametric comparisons of two groups were analysed using the Mann-Whitney U test, whereas differences among three or more groups were assessed with the Kruskal-Wallis test. If a difference was noted using the Kruskal-Wallis analysis, the Dunn test was conducted for multiple

comparisons. The chi-squared test was employed to identify relationships between categorical variables. The Spearman correlation analysis was employed to evaluate the relationship between numerical data.  $P < 0.05$  was considered statistically significant. Independent determinants of serum 25(OH)D concentrations were identified through multiple linear regression modelling. In the first model, all 90 participants were included, with age, sex, and group allocation as independent variables. In the second model, only the 60 pneumonia patients were included, and age, sex, CRP, albumin, lymphocyte count, NLR, CAR, and eGFR were evaluated as independent variables (biochemical parameters were not available for healthy controls). Regression outputs are reported as beta coefficients ( $\beta$ ), accompanied by 95% confidence intervals (CI) and corresponding p-values. A post-hoc power analysis was performed based on the observed difference in serum 25(OH)D levels between the CP group and the healthy controls (mean difference: 7.0 ng/mL, pooled SD: 9.05). With 30 participants per group and a two-tailed alpha of 0.05, the achieved statistical power was 85%, which is considered adequate for the primary comparison of this study. SPSS 26.0 (IBM Corporation, NY, US) was used to perform all statistical analyses.

## RESULTS

The study enrolled 90 participants with a mean age of  $45.5 \pm 13.9$  years (range 20-79), of whom 57.8% were male. Participants were allocated to three equal groups of 30 participants each: those with SARS-CoV-2 PCR-confirmed pneumonia, those with PCR-negative pneumonia, and those who were healthy controls. Half of the patients with pneumonia (27/60) had at least one comorbidity. The two most common comorbidities were type 2 diabetes mellitus (23.3%) and hypertension (23.3%). The main demographic and clinical features of the three groups are detailed in Table 1.

Fever (51.7%), cough (45%), and arthralgia (31.7%) were the most common symptoms. Although arthralgia was more commonly observed in CP patients, this difference was not statistically significant ( $p = 0.052$ ). Dyspnea was more frequent in NCP patients ( $p = 0.006$ ). When the vital signs of the patients at the admission were evaluated, the median fever was 36.3 (36-39.1) °C, the mean pulse was  $102 \pm 18$  rate/minute, and the median oxygen saturation was 96% (75-100%). Patients with NCP had significantly higher values of neutrophils, white blood cells, CRP, procalcitonin, D-dimer, ferritin, troponin, creatinine, NLR, SII index,

and CAR, and lower values of eGFR and albumin than CP patients. CP patients had a longer hospital stay (Table 2).

Circulating 25(OH)D values averaged  $11.9 \pm 6.7$  ng/mL in CP patients,  $11.3 \pm 6.2$  ng/mL in NCP patients, and  $18.9 \pm 10.9$  ng/mL in healthy individuals. Statistical analysis revealed that 25(OH)D levels in CP and NCP patients were lower than those in healthy controls ( $p = 0.004$  and  $p = 0.002$ , respectively). Additionally, we found that 86.7% of patients with CP had VDD, compared with 56.7% of controls. Vitamin D status and 25(OH)D levels of all participants are shown in Table 3.

No significant relationship was detected between 25(OH)D levels and any inflammatory parameters, including CRP, procalcitonin, ferritin, D-dimer, troponin, white blood cell, neutrophil, and lymphocyte counts (all p-values  $> 0.050$ ). Additionally, derived inflammatory indices such as PLR, NLR, CAR, and SII index did not exhibit correlations with serum 25(OH)D levels (all  $p > 0.050$ ).

Multivariate linear regression analysis revealed that membership in the healthy control group was the only independent predictor of higher serum 25(OH)D levels compared with the CP group ( $\beta = 6.278$ , 95% CI: 1.94-10.62,  $p = 0.005$ ). Age and sex were not independent predictors of 25(OH)D levels. In the second model, including only pneumonia patients, none of the biochemical or inflammatory parameters were independently associated with serum 25(OH)D levels (all  $p > 0.05$ , Adjusted  $R^2 = -0.022$ ) (Table 4).

## DISCUSSION

In this study, VDD was found in 90% of NCP patients and 86.7% of CP patients, compared with only 56.7% of healthy controls. When the groups were compared, pneumonia patients demonstrated markedly reduced 25(OH)D concentrations relative to age- and sex-matched healthy individuals. The 25(OH)D levels were similar between the CP and NCP groups. Consistent with our univariate findings, multivariate linear regression analysis confirmed that group allocation, specifically membership in the healthy control group, was the only independent predictor of higher serum 25(OH)D levels ( $\beta = 6.278$ , 95% CI: 1.94-10.62,  $p = 0.005$ ). Neither demographic variables (age, sex) nor inflammatory and biochemical parameters (CRP, albumin, NLR, CAR, eGFR, lymphocyte count) were independently associated with 25(OH)D levels. These findings suggest that pre-existing VDD may contribute to

**Table 1. Main demographic and clinical characteristics of all participants**

Variables	COVID-19 patients (n=30)	Non-COVID-19 patients (n=30)	Healthy controls (n=30)	p-value
Age (years), median (min-max)	40.5 (20-76)	51 (20-79)	41 (25-61)	0.074
Sex (male), n (%)	14 (46.7%)	22 (73.3%)	16 (53.3%)	0.094
Current smoker, n (%)	5 (16.7%)	8 (26.7%)	5 (16.7%)	0.535
Comorbidities	10 (33.3%)	17 (56.6%)	N/A	0.069
Diabetes mellitus	10 (33.3%)	4 (13.3%)	N/A	0.67
Hypertension	7 (23.3%)	7 (23.3%)	N/A	1
Coronary artery disease	5 (16.7%)	4 (13.3%)	N/A	0.71
Chronic obstructive pulmonary disease	0	5 (16.7%)	N/A	0.062
Dyslipidemia	1 (3.3%)	1 (3.3%)	N/A	1
Chronic renal disease	3 (10%)	6 (20%)	N/A	0.472
Malignancy	1 (3.3%)	3 (10%)	N/A	0.61

N/A: not applicable, COVID-19: Coronavirus disease 2019.

Table 2. Clinical characteristics and laboratory data of all cases with pneumonia				
Variables	Total (n=60)	COVID-19 patients (n=30)	Non-COVID-19 patients (n=30)	p-value
<b>Onset symptoms</b>				
Fever	31 (51.7%)	16 (53.3%)	15 (50%)	0.796
Cough	27 (45%)	12 (40%)	15 (50%)	0.436
Dyspnea	14 (23.3%)	2 (6.7%)	12 (40%)	<b>0.006</b>
Sore throat	14 (23.3%)	7 (23.3%)	7 (23.3%)	1
Headache	9 (15%)	5 (16.6%)	4 (13.3%)	0.718
Arthralgia	19 (31.7%)	13 (43.3%)	6 (20%)	0.052
Nausea-vomiting	3 (5%)	3 (10%)	0	0.237
Diarrhoea	4 (6.7%)	3 (10%)	1 (3.3%)	0.612
<b>Vital signs</b>				
Fever	36.3 (36-39.1)	36.2 (36-38.8)	36.6 (36-39.1)	0.224
Pulse	102±18	101.8±16.6	101.5±19.8	0.800
Oxygen saturation	96 (75-100)	96 (88-100)	94.5 (75-99)	0.056
<b>Laboratory data</b>				
White blood cell count (mm <sup>3</sup> )	6485 (630-18960)	5130 (3180-11100)	9580 (630-18960)	< <b>0.0001</b>
Neutrophil count (mm <sup>3</sup> )	4175 (140-15200)	2985 (1780-8700)	6865 (140-15200)	< <b>0.0001</b>
Lymphocyte count (mm <sup>3</sup> )	1504±808	1503±607	1505±980	0.992
Platelet count (x10 <sup>3</sup> /mm <sup>3</sup> )	226,5 (99-548)	226 (103-548)	231 (99-454)	0.953
Haemoglobin (g/dL)	14 (7.2-17)	13 (10-17)	14.3 (7.2-16.7)	0.320
Creatinine (mg/dL)	0.88 (0.43-5.22)	0.80 (0.43-1.35)	1.04 (0.53-5.22)	< <b>0.0001</b>
eGFR (mL/min)	93.5 (13-132.4)	97.1 (49.1-132.4)	84.8 (13-122)	<b>0.002</b>
CRP (mg/L)	18.7 (0.2-316)	5.4 (0.2-144.7)	48.2 (2.6-316)	< <b>0.0001</b>
Procalcitonin (ng/mL)	0.07 (0-16)	0.05 (0-0.21)	0.12 (0.03-16)	< <b>0.0001</b>
D-dimer (µgram/L)	530 (189-11160)	385 (189-1520)	740 (189-11160)	< <b>0.0001</b>
Ferritin(ng/mL)	173.5 (6.6-989)	132 (6.6-989)	222 (18.5-620)	<b>0.039</b>
Troponin (ng/mL)	0.006 (0.002-0.770)	0.004 (0.002-0.026)	0.01 (0.002-0.770)	< <b>0.0001</b>
Albumin (g/dL)	4.4 (2.8-5.2)	4.5 (3.7-5.2)	4.2 (2.8-5)	<b>0.011</b>
<b>Clinical severity scores</b>				
NLR	3.1 (0.4- 62)	1.8 (1.1-11.3)	4.65 (0.4-62)	<b>0.001</b>
PLR	175.9 (58.5-1655)	175.9 (58.5-473.5)	183.2 (80-1655)	0.626
SII index	720.8 (82.4-20522)	500.1 (146.3-3402.6)	953 (82.4-20522)	<b>0.003</b>
CAR	4.3 (0-83.4)	1.1 (0-35.4)	12.1 (0.5-83.4)	< <b>0.0001</b>
<b>Outcome</b>				
Length of hospital stay (days)	6 (2-14)	8 (3-14)	5 (2-14)	<b>0.001</b>
Oxygen need	16 (26.6%)	5 (16.7%)	11 (36.7%)	0.072
ICU admission	2 (3.3%)	0	2 (6.6)	0.246
Mechanical ventilation	2 (3.3%)	0	2 (6.6)	0.246
Death	2 (3.3%)	0	2 (6.6)	0.246
<b>Disease severity</b>				
Moderate pneumonia	53 (88.3%)	25 (83.3%)	28 (93.3%)	0.424
Severe pneumonia	7 (11.7%)	5 (16.7%)	2 (6.7%)	

Values are expressed as n (%), mean ± SD or median (min-max).  
COVID-19: Coronavirus disease 2019, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: Systemic immune-inflammation, CAR: CRP to albumin ratio, ICU: Intensive care unit, SD: Standard deviation.

**Table 3. 25(OH)D levels and vitamin D status of all participants**

25(OH)D level and status	COVID-19 patients (n=30)	Non-COVID-19 patients (n=30)	Healthy controls (n=30)	p <sup>a</sup> -value	p <sup>b</sup> -value	p <sup>c</sup> -value
25(OH)D (ng/mL) (mean ± SD)	11.9±6.7	11.3±6.2	18.9±10.9	0.958	0.004	0.002
Vitamin D status				<b>0.002</b>		
Vitamin D deficiency	26 (86.7%)	27 (90%)	17 (56.7%)			
Vitamin D insufficiency	4 (13.3%)	3 (10%)	7 (23.3%)			
Vitamin D sufficiency	0	0	6 (20%)			

p<sup>a</sup>COVID-19 vs. non-COVID-19 patients, p<sup>b</sup>COVID-19 patients vs. controls, p<sup>c</sup>Non-COVID-19 patients vs. controls according to vitamin D status (<20 vs. ≥20 ng/mL).  
COVID-19: Coronavirus disease 2019, SD: Standard deviation.

**Table 4. Multivariate linear regression analysis for independent predictors of serum 25(OH)D levels**

Variable	β	SE	95% CI	p-value
<b>Model 1: All participants (n=90) - Dependent variable: 25(OH)D; R<sup>2</sup>=0.157, Adjusted R<sup>2</sup>=0.118</b>				
Non-COVID-19 pneumonia (vs. COVID-19)	-1.977	2.321	-6.59 to 2.64	0.397
Healthy controls (vs COVID-19)	6.278	2.183	1.94 to 10.62	0.005
Age	0.115	0.067	-0.02 to 0.25	0.089
Sex	-1.543	1.876	-5.27 to 2.19	0.413
<b>Model 2: Pneumonia patients only (n=60) - Dependent variable: 25(OH)D; R<sup>2</sup>=0.116, Adjusted R<sup>2</sup>=-0.022</b>				
Age	0.112	0.075	-0.04 to 0.26	0.142
Sex	0.227	1.870	-3.53 to 3.98	0.904
CRP	0.132	0.158	-0.19 to 0.45	0.408
Albumin	3.224	2.877	-2.55 to 9.00	0.268
Lymphocyte count	1.278	1.214	-1.16 to 3.72	0.298
NLR	0.121	0.118	-0.12 to 0.36	0.313
CAR	-0.530	0.635	-1.81 to 0.75	0.408
eGFR	0.025	0.046	-0.07 to 0.12	0.582

Reference category for group comparison: COVID-19 pneumonia.  
β: Unstandardized beta coefficient, SE: Standard error, CI: Confidence interval, CRP: C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, CAR: CRP-to-albumin ratio, eGFR: Estimated glomerular filtration rate, COVID-19: Coronavirus disease 2019, 25(OH)D: 25-hydroxyvitamin D.

susceptibility to lower respiratory tract infections, independent of the acute inflammatory response.

In a retrospective study in Switzerland, D'Avolio et al.<sup>15</sup> found that 25(OH)D concentrations were considerably lower in SARS-CoV-2 PCR positive patients than in SARS-CoV-2 PCR negative patients and healthy controls. The control group consisted of people with 25(OH)D levels measured one year ago, and the clinical severity of the patients was not mentioned. Unlike that study, our investigation was conducted prospectively; all included patients had pneumonia; and the control group consisted of healthy individuals evaluated during the same period. Similarly, the healthy control group had higher 25(OH)D levels, but no difference was observed between the SARS-CoV-2 PCR-positive and PCR-negative groups. These findings suggest that reduced vitamin D levels may represent a risk factor not only for COVID-19 but also for lower respiratory tract infections.

In another retrospective cohort, COVID-19 cases exhibited mean 25(OH)D levels of 13.8±7.2 ng/mL, substantially below the 20.9±7.4 ng/mL observed in the healthy comparators. VDD was found in 82.2% of COVID-19 patients and 47.2% of control subjects.<sup>16</sup> Similarly, 25(OH)D levels were 11.9±6.7 ng/mL in CP patients and 18.9±10.9 ng/mL in healthy controls, and the 25(OH)D levels of control groups were higher

than in CP patients in our study. VDD was detected in 86.7% of CP patients and 56.7% of controls. These findings indicate that VDD may be associated with increased susceptibility to pneumonia. In the previous study, 19 of 216 COVID-19 patients received vitamin D supplements. However, the researchers reported that these 19 patients were analysed as a separate group. Because vitamin D supplementation may bias the results, patients who had taken a vitamin D supplement for at least 6 months were excluded from our study.

Ye et al.<sup>17</sup> conducted a study in China including 62 COVID-19 patients and 80 healthy controls. Similarly, they found that VDD in COVID-19 patients was considerably greater than in controls. In addition, they compared 25(OH)D concentrations between mild/moderate and severe/critical groups, and reported that these concentrations were lowest in the severe/critical groups. In our study, patients who met the hospitalization criteria of the Ministry of Health Guide were included and therefore mainly belonged to the moderate and severe disease groups. Contrary to the study of Ye et al.,<sup>17</sup> vitamin D levels and VDD status were similar in the two disease groups (p=0.748, p=0.188, respectively).

A few studies have been conducted on the association between COVID-19 infection and vitamin D levels in Türkiye. In a study, the mean 25(OH)D

level was  $15 \pm 10.3$  ng/mL. VDD and VDI were found in 69.1% and 22.8%, respectively.<sup>18</sup> In our study, the mean 25(OH)D level was lower, and no COVID-19 patient had a sufficient level of 25(OH)D. Despite higher vitamin D levels in that cohort, their reported mortality rate (46.3% vs. 0%) was substantially higher than ours. This may be explained by other confounding factors, such as comorbidities, gender, smoking status, and by a higher proportion of severe/critical disease in their population (68.5% vs. 16.7%).

While the association between circulating 25(OH)D concentrations and COVID-19 has been widely investigated, the present study is, to the best of our knowledge, the first prospective investigation to compare vitamin D status across CP, NCP, and healthy control groups simultaneously. This study analysed laboratory parameters, clinical outcomes, and pneumonia severity. We found that vitamin D levels and clinical outcomes were similar between the two groups, except for hospital stays. However, biochemical parameters, especially inflammation-related markers, were higher in NCP patients. This observation suggests that although the clinical outcomes of COVID-19 and other lower respiratory tract infections may be comparable, systemic inflammation may be more pronounced in NCP. This difference may be attributable to the distinct pathophysiological mechanisms underlying bacterial and viral pneumonia. NCP is more commonly caused by bacterial pathogens, which typically elicit a more robust innate immune response characterized by marked elevations of CRP, procalcitonin, and neutrophil-predominant inflammation.<sup>19,20</sup> In contrast, SARS-CoV-2 has been shown to actively evade innate immune defenses through suppression of interferon responses and is often associated with relatively lower early inflammatory biomarker levels despite substantial lung involvement.<sup>21,22</sup>

Several studies have documented an association between lower 25(OH)D levels and worse COVID-19 outcomes. In a retrospective study of 88 hospitalized patients using LC-MS/MS methodology, Nguyen et al.<sup>23</sup> found that VDD was independently associated with longer hospital stay and higher adjusted odds of in-hospital mortality and mechanical ventilation. Similar associations between low 25(OH)D levels and greater disease severity or adverse clinical outcomes have also been reported in other COVID-19 cohorts.<sup>24,25</sup> In our cohort, however, no meaningful association was identified between 25(OH)D concentrations and either disease severity or clinical outcomes. This discrepancy may be attributable to several factors. First, our cohort included only moderate and severe cases of pneumonia, which may have limited the detectable gradient in vitamin D levels across severity groups. Second, whereas Nguyen et al.<sup>23</sup> measured 25(OH)D using LC-MS/MS, we used an ECLIA immunoassay, which may underestimate vitamin D levels in certain patients. Finally, the modest sample size may have reduced the ability to detect statistically significant associations with clinical outcomes.

Despite the absence of a supplementation intervention in our study, markedly reduced 25(OH)D concentrations were consistently observed in both pneumonia groups relative to healthy controls. Supporting a potential preventive role of vitamin D against respiratory infections, Jolliffe et al.<sup>26</sup> conducted a comprehensive meta-analysis of 43 randomized controlled trials and reported a modest but statistically significant protective effect of vitamin D supplementation against acute respiratory tract infections (odds ratio 0.92, 95% CI: 0.86-0.99).<sup>26</sup> However, this meta-analysis focused on acute respiratory tract infections

in general, and the evidence remains heterogeneous and not specific to pneumonia or COVID-19. Therefore, further targeted randomized controlled trials are required to determine whether correction of VDD through supplementation can reduce the risk of pneumonia in high-risk populations.

We found that serum 25(OH)D concentrations were significantly diminished in pneumonia patients, irrespective of COVID-19 status, compared with healthy individuals. Nevertheless, the absence of any correlation with laboratory parameters or disease severity points to VDD as a predisposing condition rather than a driver of clinical deterioration. Larger multicenter studies are warranted to confirm these findings and to improve generalizability to different populations.

### Study Limitations

The present study is subject to a number of limitations. First, the modest sample size of 30 participants per group may have constrained the statistical power of our analyses and increased the likelihood of a type II error, thereby reducing the capacity to identify genuine associations between 25(OH)D levels and clinical or disease severity parameters. Second, the study was conducted between May and August 2020, during the summer months in Türkiye, when sun exposure is typically highest. This seasonal factor may have elevated baseline 25(OH)D levels across all groups, thereby masking differences that might be observed during winter months. Third, the single-center nature of this study, conducted at a tertiary institution in Türkiye, may limit the applicability of our findings to broader populations and diverse clinical settings. Fourth, only hospitalized patients with moderate or severe pneumonia were included; findings cannot be extrapolated to patients with mild or asymptomatic COVID-19. Fifth, serum 25(OH)D levels were measured only at hospital admission, and no longitudinal follow-up measurements were performed. In addition, acute illness may influence vitamin D-binding protein levels and, consequently affect 25(OH)D concentrations, possibly affecting measured vitamin D levels at admission. Finally, key determinants known to affect vitamin D status, including nutritional habits, duration of sun exposure, physical activity level, and socioeconomic background, were not systematically collected and may constitute unmeasured sources of confounding.

### CONCLUSION

Patients with pneumonia had substantially lower serum 25(OH)D concentrations than age- and sex-matched healthy individuals. No meaningful difference in vitamin D levels was observed between the CP and NCP groups, and a multivariate regression analysis identified group allocation as the sole independent predictor of serum 25(OH)D levels. No association was identified among vitamin D levels, the severity of infection, and laboratory parameters. These findings suggest that VDD may be more relevant as a predisposing factor for lower respiratory tract infections rather than a determinant of disease severity once pneumonia develops. Although a causal relationship cannot be established from this observational study, vitamin D supplementation and food fortification strategies may represent preventive approaches in high-risk populations. Future large-scale randomized controlled trials are warranted to better clarify the interplay between vitamin D status, supplementation strategies, and clinical outcomes in COVID-19.

## MAIN POINTS

- Circulating 25-hydroxyvitamin D [25(OH)D] concentrations were markedly lower in patients with pneumonia, irrespective of severe acute respiratory syndrome-coronavirus-2 status, compared with healthy individuals.
- Vitamin D levels did not differ significantly between patients with coronavirus disease 2019 (COVID-19)-related pneumonia and patients with non-COVID-19-related pneumonia.
- No meaningful relationship was identified between 25(OH)D concentrations and inflammatory biomarkers, biochemical parameters, or clinical severity.
- Vitamin D may be associated with susceptibility to lower respiratory tract infections, including COVID-19, but does not appear to influence clinical severity once pneumonia develops.
- Multivariate regression analysis identified healthy control status as the only independent predictor of higher 25(OH)D levels, suggesting that VDD in pneumonia patients likely reflects a pre-existing condition rather than a consequence of acute illness.

## ETHICS

**Ethics Committee Approval:** This study was approved by the Erciyes University Clinical Research Ethics Committee (approval number: 2020/217, date: 29.04.2020).

**Informed Consent:** All participants provided informed consent prior to their inclusion in the study.

## Footnotes

### Authorship Contributions

Concept: C.Ş.K., F.B., Design: C.Ş.K., H.A., F.B., Data Collection and/or Processing: C.Ş.K., B.B.K., Z.T., Analysis and/or Interpretation: C.Ş.K., B.B.K., H.A., Z.T., Literature Search: C.Ş.K., C.Y., Ö.K., Writing: C.Ş.K., B.B.K., Z.T., C.Y., Ö.K., F.B.

## DISCLOSURES

**Conflict of Interest:** No conflict of interest was declared by the authors.

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### Declaration Regarding the Use of AI and AI-Assisted Technologies:

In the course of drafting this manuscript, Grammarly was employed as an AI-assisted writing tool to enhance linguistic clarity, improve textual coherence, and refine sentence structure for academic communication. All scientific content, including data interpretation, statistical evaluations, and conclusions, was solely generated by the authors. The authors take complete responsibility for the originality, accuracy, and integrity of the work. The use of this tool had no bearing on the research design, data acquisition process, or interpretation of the outcomes.

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