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Relation between vitamin D and COVID-19 in Egyptian patients

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Abstract

Background Insufficient vitamin D (VD) levels have been linked to a higher vulnerability to acute respiratory infections and the severity of COVID-19 sickness.

Objective The purpose of this research is to investigate whether or not there is a connection between the amounts of VD produced by patients from Egypt and the severity of COVID-19, as well as the consequences of the disease.

Methods This research used a case–control design and included a total of 90 adult patients who had been diagnosed with COVID-19, as well as 90 healthy controls who were matched in terms of age and sex. Patients were classified into mild, moderate, and severe categories according to clinical and radiological criteria. The study included measuring levels of VD and analyzing their relationships with illness severity, inflammatory markers, radiological findings, and outcomes.

Results COVID-19 patient(s) had notably reduced levels of serum VD versus the control group (11.78 ± 3.24 ng/mL vs. 20.88 ± 7.76 ng/mL, $p < 0.001$). Lower VD levels were associated with more severe disease ($p < 0.001$), dyspnea ($p < 0.001$), radiological abnormalities ($p = 0.001$), and higher mortality ($p < 0.001$). A serum VD level ≤ 14.8 ng/mL could differentiate COVID-19 patients from controls with 86.67% sensitivity and 77.78% specificity (AUC = 0.881).

Conclusions COVID-19 patients often had a deficiency of VD, which was linked to more severe illness, respiratory issues, aberrant radiological findings, and higher fatality rates. VD levels may be used as a biological surrogate marker to assess the risk and predict the outcome of COVID-19.

Keywords 25(OH), Vitamin D, COVID-19

Introduction

The COVID-19 pandemic has presented the world healthcare system with unparalleled difficulties caused by the appearance of the new coronavirus SARS-CoV-2. This has led to significant rates of illness and death [1]. While efforts to combat the virus have primarily focused on vaccination and therapeutic interventions, understanding host factors influencing disease severity and outcomes remains crucial.

Functioning as a steroid hormone, VD holds pivotal importance in multiple physiological functions, encompassing bone metabolism, immune response, and respiratory well-being [2]. The latest study has shown a possible correlation between a lack of VD and the severity and result of a COVID-19 infection [3, 4].

This research aims to explore the connection between the degree of deficiency of Vit D and the severity of COVID-19 in Egyptian patients, as well as the outcome of the illness.

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Material and method

Study design and participants

This retrospective case–control research was carried out et al.-Zahraa University Hospital, affiliated with Al-Azhar University, from December 2021 to April 2022. The research had a total of 90 adult patients (aged 18–60 years) who were proven to have COVID-19 using real-time reverse transcription-polymerase chain reaction (RT-PCR) testing. Additionally, 90 controls were matched to the patients regarding age and sex. Patients were divided into three groups based on disease severity: mild ($n=30$), characterized by symptomatic cases with lymphopenia or leukopenia but without radiological signs of pneumonia confirmed by RT-PCR; moderate ($n=30$), featuring pneumonia on radiology accompanied by symptoms and/or lymphopenia or leukopenia confirmed by RT-PCR; and severe ($n=30$), necessitating intensive care unit (ICU) admission due to confirmed RT-PCR, with criteria including respiratory rate > 30 breaths/min, $SaO_2 < 92\%$ on room air, $PaO_2/FiO_2 < 300$ mmHg, or lung infiltrates > 50% on chest radiology. Additionally, outcomes were recorded as survived or not survived.

Patients were considered eligible for inclusion if they met the following criteria: The main clinical signs of COVID-19 include respiratory symptoms, fever, and rapid loss of taste and smell. Additionally, a positive SARS-CoV-2 RT-PCR test confirms the presence of the virus.

Exclusion criteria were age below 18 years or above 60 years, sarcoidosis, drug dependency, comorbidities affecting VD levels (e.g., cancer, autoimmune diseases), chronic kidney disease, chronic liver disease, pregnancy, breastfeeding, chronic obstructive pulmonary disease, chemotherapy, current use of VD or calcium supplements, malabsorption, hypercortisolism, alcoholism, parathyroid disease, and hypercalcemia.

Sample size calculation

The sample size was calculated on OpenEpi program version 3 adjusting the confidence interval to 95%; the margin of error accepted was set to 5; the power of the test was set to 80%; according to a previous study done by Abrishami et al. (2020), the probability of death in patients with vitamin D deficiency [defined as 25(OH) D concentration < 25 ng/mL] was 34.6% compared with 6.4% in patients with sufficient vitamin D levels ($p < 0.05$), and according to the previous data, the minimum sample size needed for this study was found to be 29 for patients and 29 for control. We added 61 individuals in each group for better statistical analysis.

Data collection

All patients underwent a comprehensive evaluation, including personal and medical history, clinical examination, radiological assessment (computed tomography scans), and laboratory investigations (complete blood count, inflammatory markers, liver and kidney function tests, RT-PCR for SARS-CoV-2, and serum VD levels).

Principle of the test

The kit uses a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assay the level of human 25-dihydroxy vitamin D (25-OH-D) in samples. Add 25-dihydroxy vitamin D (25-OH-D) to the monoclonal antibody enzyme well, which is pre-coated with human 25-dihydroxy vitamin D (25-OH-D) monoclonal antibody, followed by incubation; then, add 25-dihydroxy vitamin D (25-OH-D) antibodies labeled with biotin and combined with streptavidin-HRP to form immune complex; then, carry out the incubation, and wash again to remove the uncombined enzyme. Then, add chromogen solutions A and B; the color of the liquid changes into the blue, and at the effect of the acid, the color finally becomes yellow. The chroma of the color and the concentration of the human substance 25-dihydroxy vitamin D (25-OH-D) of the sample were positively correlated.

Vitamin D status

ELISA, which is an abbreviation that stands for enzyme-linked immunosorbent assay, was used in order to determine the levels of VD that were present in the blood. VD levels were classified as substandard (less than 12 ng/mL), inadequate (between 12 and 20 ng/mL), acceptable (more than 30 ng/mL), or definitely high (greater than 50 ng/mL). Substandard VD levels were defined as those that were below the recommended threshold [5].

Ethical considerations

The Faculty Review Board members approved their research approval, and all participants gave their consent after being advised of the potential risks.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 27. The quantitative data were presented as mean, standard deviations, and ranges when parametric and median and inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages. The one-sample Kolmogorov–Smirnov test can be used to test

that a variable is normally distributed. The comparison between groups regarding qualitative data was done by using chi-square test and/or Fisher exact test when the expected count in any cell found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using an independent *t*-test. The comparison between more than two groups regarding quantitative data and parametric distribution was done by using one-way ANOVA test followed by post hoc analysis using Bonferroni test, while with non-parametric distribution, it was done by using Kruskal–Wallis test followed by post hoc analysis using Mann–Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The receiver operating characteristic curve (ROC) was used to assess the best cut off point with its sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC) of the studied marker. Univariate and multivariate logistic regression analyses were used to assess vitamin D levels to differentiate between the control and patient groups. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. So, the *p*-value was considered significant at level of p-value < 0.05.

Results

According to statistical research, a significant correlation was discovered between the presence of comorbidities and the severity of COVID-19 (Figs. 1, 2 and 3). In cases that were moderate or severe, the severity of diabetes mellitus (DM), hypertension (HTN), and ischemic heart disease (IHD) was considerably higher than in cases that were mild (Table 1).

After comparing the mild group to the moderate and severe groups, it was found that the moderate and severe groups had considerably greater levels of dyspnea.

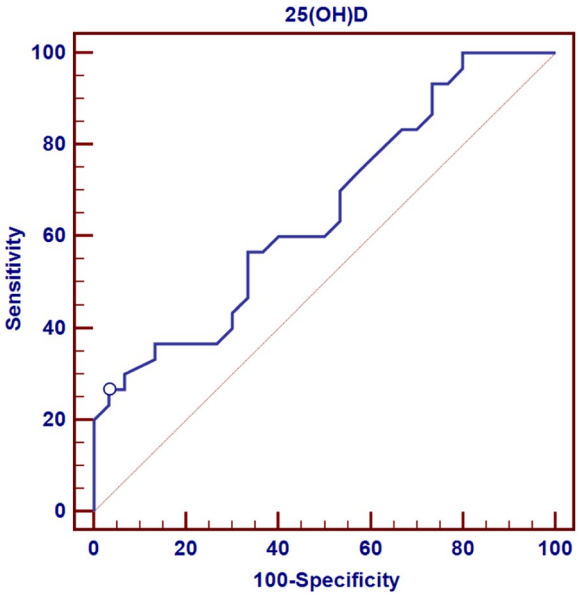

Fig. 2 Receiver operating characteristic ROC curve of 25(OH)D to differentiate between mild and moderate infections

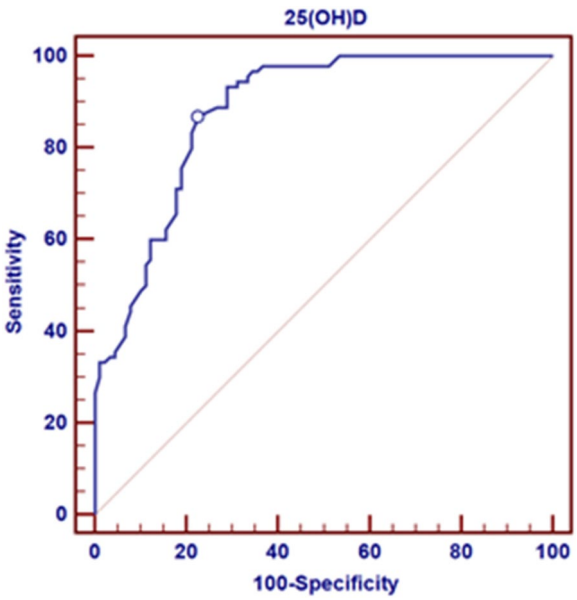

Fig. 1 Receiver operating characteristic (ROC) curve of 25(OH)D in the differentiation between the control group and patient group

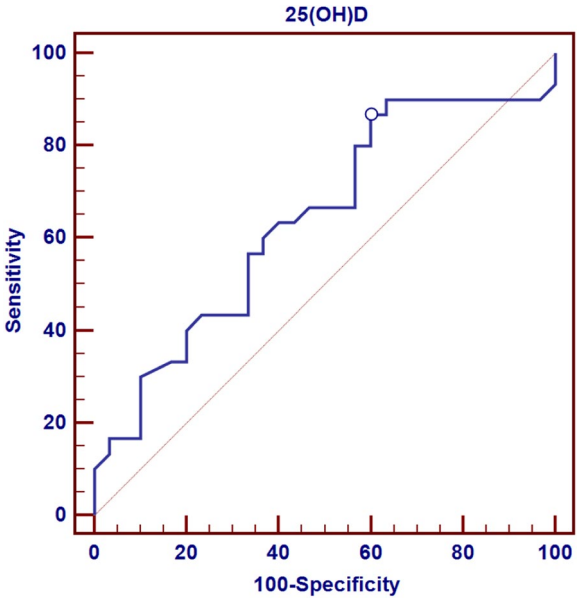

Fig. 3 Receiver operating characteristic (ROC) curve for 25(OH)D to differentiate between moderate and severe infections

Table 1 Comparison between studied patient groups as regards comorbidities

		Mild No. = 30	Moderate No. = 30	Severe No. = 30	Test value	*p* -value	Sig.
Associated comorbidities	**No**	25 (83.3%)	10 (33.3%)	10 (33.3%)	20.000[a]	**< 0.001**	HS
	Yes	5 (16.7%)	20 (66.7%)	20 (66.7%)			
	DM	1 (3.3%)	11 (36.7%)	11 (36.7%)	11.681[a]	0.003	HS
	HTN	3 (10.0%)	9 (30.0%)	14 (46.7%)	9.844[a]	0.007	HS
	IHD	0 (0.0%)	6 (20.0%)	0 (0.0%)	12.857[a]	0.002	HS
	Obesity	0 (0.0%)	0 (0.0%)	2 (6.7%)	4.091[a]	0.129	NS
	Asthma	0 (0.0%)	1 (3.3%)	0 (0.0%)	2.022[a]	0.364	NS
Multi-comparison between groups							
		Mild vs moderate	**Mild vs severe**	**Moderate vs severe**			
Associated comorbidities		**< 0.001**	**< 0.001**	**1.000**			
DM		**0.001**	**0.001**	**1.000**			
HTN		**0.053**	**0.002**	**0.184**			
IHD		**0.010**	**–**	**0.010**			

p-value > 0.05: non-significant *(NS)*; *p*-value < 0.05: significant *(S)*; *p*-value < 0.01: highly significant *(HS)*

[a] Chi-square test

However, there was no significant difference between the moderate and severe groups. Compared to the moderate group, the proportion of patients with fever was considerably higher in both the mild and severe risk categories. The severity of this difference was more pronounced in the severe group than in the moderate group, as seen in Table 2.

Compared to mild cases, there was a significant rise in the levels of lactate dehydrogenase (LDH), ferritin, and C-reactive protein (CRP) in the blood of severe and moderate cases. This indicates that the levels of inflammatory markers were higher. The D-dimer levels exhibited a similar pattern, with a significant increase in severe and moderate cases in contrast to mild cases. On the other hand, as can be shown in Table 3, there was no noticeable difference between the moderate and severe groups.

Table 4 demonstrates that the group of patients saw a substantial decrease in serum VD levels compared to the

Table 2 The main symptoms in the patient groups

		Mild No. = 30	Moderate No. = 30	Severe No. = 30	Test value	*p* -value	Sig.
Cough	**No**	1 (3.3%)	1 (3.3%)	2 (6.7%)	0.523[a]	0.770	NS
	Yes	29 (96.7%)	29 (96.7%)	28 (93.3%)			
Dyspnea	**No**	12 (40.0%)	3 (10.0%)	3 (10.0%)	11.250[a]	0.004	HS
	Yes	18 (60.0%)	27 (90.0%)	27 (90.0%)			
Fever	**No**	11 (36.7%)	21 (70.0%)	3 (10.0%)	22.816[a]	< 0.001	HS
	Yes	19 (63.3%)	9 (30.0%)	27 (90.0%)			
Chest pain	**No**	29 (96.7%)	30 (100.0%)	30 (100.0%)	2.022[a]	0.364	NS
	Yes	1 (3.3%)	0 (0.0%)	0 (0.0%)			
Anosmia and ageusia	**No**	17 (56.7%)	16 (53.3%)	13 (43.3%)	1.156[a]	0.561	NS
	Yes	13 (43.3%)	14 (46.7%)	17 (56.7%)			
Multi-comparison between groups							
		Mild vs moderate	**Mild vs severe**	**Moderate vs severe**			
Dyspnea		0.007	0.007	1.000			
Fever		0.010	0.015	< 0.001			

p-value > 0.05: non-significant *(NS)*; *p*-value < 0.05: significant *(S)*; *p*-value < 0.01: highly significant *(HS)*

[a] Chi-square test

Table 3 Results of inflammatory markers in the studied patients

		Mild No. = 30	Moderate No. = 30	Severe No. = 30	Test value	*p* -value	Sig.
D-dimer **(microgram/ml)**	Median (IQR)	0.4 (0.3–0.5)	1.2 (0.7–1.5)	0.75 (0.5–1.2)	32.240[a]	< 0.001	HS
	Range	0.2–1.2	0.2–2.3	0.4–2			
LDH (U/L)	Median (IQR)	196.5 (123–248)	236 (197–334)	450.5 (230–570)	24.120[a]	**< 0.001**	HS
	Range	67–340	128–976	128–1276			
Ferritin (micro/liter)	Median (IQR)	131 (95–215)	314 (213–370)	546 (373–824)	37.091[a]	**< 0.001**	HS
	Range	58–1953	65–543	167–2592			
CRP (mg/dL)	Median (IQR)	11.5 (4–16)	16 (9–30)	57.8 (24–96)	38.009[a]	**< 0.001**	HS
	Range	1.8–128	6–173	12–210			
Multi-comparison between groups							
		Mild vs moderate	**Mild vs severe**	**Moderate vs severe**			
D-dimer		**< 0.001**	**< 0.001**	0.132			
LDH		**0.004**	**< 0.001**	**0.008**			
Ferritin		**0.001**	**< 0.001**	**< 0.001**			
CRP		**0.012**	**< 0.001**	**< 0.001**			

p-value > 0.05: non-significant *(NS)*; *p*-value < 0.05: significant *(S)*; *p*-value < 0.01: highly significant *(HS)*

[a] Kruskal–Wallis test

Table 4 Comparison between control and patient groups regarding 25(OH)D level of the studied subjects

25(OH)D (ng/ml)	Control group No. = 90	Patients group No. = 90	Test value	*p*-value	Sig.
Mean ± SD	20.88 ± 7.76	11.78 ± 3.24	10.266[b]	**< 0.001**	HS
Range	10–49	3–20			
Deficiency	7 (7.8%)	41 (45.6%)	66.794[a]	< 0.001	HS
Insufficiency	41 (45.6%)	49 (54.4%)			
Sufficient	42 (46.7%)	0 (0.0%)			

p-value > 0.05: non-significant *(NS)*; *p*-value < 0.05: significant *(S)*; *p*-value < 0.01: highly significant *(HS)*

[a] Chi-square test

[b] Independent *t*-test

Table 5 Comparison of serum 25(OH)D among the studied groups

		Mild No. = 30	Moderate No. = 30	Severe No. = 30	Test value	*p*-value	Sig.
25(OH)D (ng/ml)	**Mean ± SD**	13.55 ± 2.73	11.68 ± 2.75	10.10 ± 3.33	10.289[b]	**< 0.001**	HS
	Range	9–20	6.5–15.2	3–15.5			
	Deficiency	9 (30.0%)	13 (43.3%)	19 (63.3%)	6.809[a]	0.033	S
	Insufficiency	21 (70.0%)	17 (56.7%)	11 (36.7%)			
	Sufficient	0 (0.0%)	0 (0.0%)	0 (0.0%)			
Post hoc analysis by Bonferroni test and multi-comparison between groups							
		Mild vs moderate	**Mild vs severe**	**Moderate vs severe**			
25(OH)D		0.048	< 0.001	0.122			
		0.284	0.010	0.120			

p-value > 0.05: non-significant *(NS)*; *p*-value < 0.05: significant *(S)*; *p*-value < 0.01: highly significant *(HS)*

[a] Chi-square test

[b] One-way ANOVA test

group that served as the control. In addition, as can be seen in Table 5, there was a significant reduction in the levels of VD in both the severe and moderate groups compared to the mild group.

Furthermore, a statistically significant association was seen between the levels of VD, dyspnea, radiological findings, patient outcomes, and the severity of the illness (Table 6). In the patient groups, the correlation analysis indicated a significant negative connection between serum VD and respiratory rate, LDH, CRP, D-dimer, and ferritin (Table 7). This link was seen within the patient groups.

When it comes to the accuracy of diagnostics, a serum VD threshold that is less than or equal to 14.8 (ng/ml) demonstrated an area under the curve of 0.881, demonstrating remarkable sensitivity and specificity in distinguishing between the control group and the sick group (Table 8). Similarly, cutoff values were determined to differentiate between distinct severity groups. These cutoff values were as follows: < 9.17 (ng/ml) for mild instances against moderate cases and ≤ 13.3 (ng/ml) for moderate cases versus severe cases. These cutoff values were accompanied by matching sensitivity, specificity, and predictive values, as shown in Tables 9 and 10.

The univariate logistic regression shows that 25OHD ≤ 14.8 was statistically significant associated with diseased group, and the adjusted multivariate shows that the most associated factor was 25OHD ≤ 14.8 with odds ratio (OR) and 95% confidence interval of 22.729 (10.198–50.662) as shown in Table 11.

Discussion

Within the scope of this research, the association between VD level and the severity and consequences of COVID-19 was investigated. In contrast to the healthy control group, patients with COVID-19 exhibited

Table 6 Association between 25(OH)D level and other studied parameters among the studied patients

		(25OHD)		Test value	*p*-value	Sig.
		Mean ± SD	Range			
Gender	Female	11.46 ± 3.01	3.3–20	−1.025[a]	0.308	NS
	Male	12.17 ± 3.51	3–19.8			
Cough	No	10.95 ± 2.59	8–14.3	−0.520[a]	0.605	NS
	Yes	**11.82 ± 3.28**	**3–20**			
Dyspnea	**No**	**14.13 ± 3.09**	**7–20**	**3.684**[a]	**0.001**	**HS**
	Yes	**11.19 ± 3.02**	**3–15.9**			
Associated comorbidities	No	12.27 ± 3.14	3.3–20	1.459[a]	0.148	NS
	Yes	11.28 ± 3.3	3–19.8			
DM	No	11.99 ± 3.37	3–20	1.069[a]	0.288	NS
	Yes	11.15 ± 2.8	6.1–15.2			
HTN	No	12.17 ± 2.98	3.3–20	1.819[a]	0.072	NS
	Yes	10.81 ± 3.7	3–19.8			
IHD	No	11.7 ± 3.27	3–20	−0.891[a]	0.376	NS
	Yes	12.92 ± 2.77	8–15.2			
Obesity	No	11.78 ± 3.27	3–20	−0.010[a]	0.992	NS
	Yes	11.8 ± 2.12	10.3–13.3			
Radiology	**No finding**	**13.5 ± 2.7**	**9–20**	**5.771**[b]	**0.001**	**HS**
	GGO	**10.98 ± 3.36**	**3–15.5**			
	Pneumonic patches	**10.05 ± 2.21**	**7.6–13.7**			
	Lower opacity	**12.85 ± 1.91**	**11.5–14.2**			
Outcome	**Survive**	**12.28 ± 2.87**	**6.5–20**	**4.287**[b]	**0.001**	**HS**
	Arrest	**8.19 ± 3.63**	**3–15.2**			
Severity	**Mild**	**13.55 ± 2.73**	**9–20**	**10.289**[b]	**0.001**	**HS**
	Moderate	**11.68 ± 2.75**	**6.5–15.2**			
	Severe	**10.1 ± 3.33**	**3–15.5**			

p-value > 0.05: non-significant; *p*-value < 0.05: significant; *p*-value < 0.01: highly significant

[a] Independent *t*-test

[b] One-way ANOVA test

Table 7 Correlation between 25(OH)D level and other studied parameters among the studied patients

	(25OHD)	
	r	***p*** **-value**
Age	−0.069	0.518
Temperature	−0.027	0.802
Pulse	−0.155	0.145
Systolic BP	0.081	0.445
Diastolic BP	0.084	0.433
RR	**−0.251***	**0.018**
Hb	0.045	0.673
WBCs	0.047	0.661
Lymph	0.183	0.085
Neutrophil	0.177	0.094
N/L ratio	**−0.221***	**0.037**
PLT	−0.107	0.316
Albumin	0.169	0.111
D-dimer	**−0.319****	**0.002**
LDH	**−0.260***	**0.013**
Ferritin	**−0.382****	**< 0.001**
CRP	**−0.268***	**0.011**
ALT	−0.067	0.532
AST	−0.082	0.443
Creatinine	−0.029	0.789

p-value > 0.05: non-significant; *p*-value < 0.05: significant; *p*-value < 0.01: highly significant

Spearman correlation coefficient

* means significant

** means highly significant

Table 8 Receiver operating characteristic (ROC) curve of 25(OH)D in the differentiation the between control group and patient group

Cut off point	AUC	Sensitivity	Specificity	+PV	−PV
≤ 14.8	0.881	86.67	77.78	79.6	85.4

Table 9 Receiver operating characteristic ROC curve of 25(OH)D to differentiate between mild and moderate infections

Cut off point	AUC	Sensitivity	Specificity	+PV	−PV
≤ 9.17	0.654	26.67	96.67	88.9	56.9

Table 10 Receiver operating characteristic (ROC) curve for 25(OH)D to differentiate between moderate and severe infections

Cut off point	AUC	Sensitivity	Specificity	+PV	−PV
≤ 13.3	0.639	86.67	40.00	59.1	75.0

significantly lower serum VD concentrations. Furthermore, there was a correlation between reduced levels of VD and increased severity of COVID-19 infection, increased dyspnea, presence of radiological abnormalities, and elevated mortality rates. Furthermore, a serum VD concentration of 14.8 ng/mL or less demonstrated a commendable accuracy in distinguishing between COVID-19 patients and controls.

The lower levels of VD seen in people with COVID-19 align with previous research in other groups, indicating a possible link between insufficient VD and vulnerability to SARS-CoV-2 infection, as well as the progression of severe COVID-19 symptoms [2, 6, 7]. Bae et al. suggest that VD and its metabolites might potentially affect both the infection of SARS-CoV-2 and the severity of COVID-19 via several pathways. These factors include effects on the body's immunological responses, inflammatory processes, fibrotic pathways, the renin–angiotensin–aldosterone system (RAAS), acute lung damage, glucose management, and cardiovascular health [3].

Furthermore, the findings of our investigation provide credence to the findings of other studies that show a negative association between the levels of VD in the blood and the severity of COVID-19 [3, 4, 8]. The immune-modulating effects of VD on cytokine assembly and the modulation of the renin-angiotensin system are two of the possible pathways that might be responsible for this connection [9]. If a person is deficient in VD, they may be more likely to have cytokine storms and acute respiratory distress syndrome, both of which are characteristics of severe COVID-19 [10]. In addition, VD has been shown to have a role in the control of the production of angiotensin-converting enzyme 2 (ACE2), which is the cellular receptor that facilitates entrance for SARS-CoV-2. The existence of this connection suggests that VD may play a role in the modulation of viral entrance and replication processes [11]. The results from our study support the previous research that has shown a negative correlation between blood VD levels and the severity of COVID-19.

As a consequence of the association between decreased levels of VD and symptoms such as trouble breathing, abnormal findings on medical imaging, and mortality in persons with COVID-19, the multifaceted influence of VD deficiency on the progression and outcomes of the disease is brought to light. Our results are in line with those of previous research carried out by Demir and others before us [12] and Abrishami et al. [13], who found that patients with VD levels < 30 ng/mL had more lung segments with ground-glass opacity appearance. Furthermore, Mostafa et al. [14] and Ilie et al. [15] brought attention to the fact that there is a correlation between lower levels of VD and increased death rates among those who have severe COVID-19 infection. The results that we

Table 11 Univariate and multivariate logistic regression analysis to assess vitamin D level to differentiate between cases and control groups adjusted to age and gender

	Univariate				Multivariate			
	p-value	Odds ratio (OR)	95% C.I. for OR		*p*-value	Odds ratio (OR)	95% C.I. for OR	
			Lower	Upper			Lower	Upper
(25OHD) ≤ 14.8	< 0.001	22.750	10.376	49.880	< 0.001	22.729	10.198	50.662

obtained are in agreement with the findings that were presented by Yilmaz and Şen [16]. They claimed that VD might potentially reduce the incidence of inflammatory markers that are predictive of unfavorable outcomes in patients who were diagnosed with COVID-19.

However, it is essential to remember that a number of research have found contradictory outcomes. The researchers Ozturk et al. [17] discovered no significant connection between the concentration of VD and the severity of COVID-19 or inflammatory markers. Likewise, Almehamadi et al. [18] and Ali [8] could not find any correlation between the circulating VD concentrations and the severity of the illness despite the fact that there was a significant prevalence of VD insufficiency among hospitalized COVID-19 patients.

The relationship between VD and inflammatory diseases is still a topic of continuous debate due to the limited knowledge of the mechanism that connects low VD levels with increased amounts of inflammatory cytokines [18]. Additionally, according to the findings by Yousefizadeh et al. [19], it is possible that the VD levels that are measured during acute illness may not offer an appropriate depiction of the overall VD status. This is because there may be fluctuations in the levels of VD-binding protein (DBP). The interpretation of VD concentrations in the circulation may become more complicated as a result of these alterations. Due to the fact that the amount of VD is recognized as a harmful acute-phase reactant, its efficiency as a biomarker for VD status may be diminished during acute inflammatory events [18].

Interestingly, the research conducted by Huanu and colleagues [20] showed that lower levels of VD were associated with the development of more severe symptoms of COVID-19 [20]. On the other hand, their research did not uncover any significant correlations between the levels of VD and inflammatory indicators or mortality, highlighting this link's complex nature.

The fact that a level of VD that is equal to or less than 14.8 ng/mL is able to differentiate COVID-19 patients from controls successfully highlights the potential relevance of VD status as a marker for risk assessment and prognosis. In spite of this, the study into finding the optimal threshold for VD levels in predicting COVID-19 cases and outcomes is still at an ongoing stage. Yosef and others [21] identified ≤ 30 ng/mL as the optimal cutoff for predicting COVID-19 cases, achieving 100% sensitivity and specificity. On the other hand, Teama et al. [22], on the other hand, suggested 18 ng/mL as the preferable cutoff for predicting poor COVID-19 prognosis, with a specificity of 75.9% and a sensitivity of 60.2%. Meanwhile, Abrishami et al. proposed a 25 ng/mL cutoff, with specificity and sensitivity rates of 75% and 72%, respectively. These divergent cutoff values underscore the necessity for more extensive prospective studies to establish optimal thresholds and their predictive efficacy for COVID-19 outcomes across diverse populations and contexts.

Among the many features of our research are the case–control design, the complete data collection, and the incorporation of radiological and laboratory characteristics. It is crucial to keep in mind that there are certain restrictions. In the first place, the research was carried out in a single location, which may restrict the extent to which the results may be generalized. In the second place, we did not investigate other possible confounding variables, such as food habits, sun exposure, and genetic determinants of VD status.

Conclusion

The deficiency of VD has been shown to be associated with increased severity, respiratory problems, radiological abnormalities, and mortality in patients who have COVID-19, according to the findings of this study, which gives empirical proof of this link. It is important to note that the findings highlight the potential role that VD might have as an immunomodulatory and protective factor against severe COVID-19 responses. It is necessary to do more research in order to investigate the underlying mechanisms and assess the therapeutic advantages of VD supplementation in the treatment of COVID-19.

Abbreviations

VD	25-Hydroxyvitamin D
AUC	Area under the curve
(DBP)	Vitamin D-binding protein
(ACE2)	Angiotensin-converting enzyme 2
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
RAAS	Renin-angiotensin-aldosterone system
CRP	C-reactive protein
(LDH)	Lactate dehydrogenase
DM	Diabetes mellitus

ELISA	Enzyme-linked immune sorbent assay
HTN	Hypertension
IH	Ischemic heart disease
ICU	Intensive care units
ROC	Receiver operating characteristic curve
RT-PCR	Real-time reverse transcriptase-polymerase chain reaction

Supplementary Information

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Supplementary Material 1. Availability of data and materials

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Authors' contributions
Dr. Mona Ramadan Abdel Aziz, Idea and general supervision, Dr. Alshaimaa Mohamed Mosaad Soliman, Data analysis, supervision, and revision, Dr. Sarah Younes Abdel Aziz, Laboratory part of the work, Nour Hussein Hammam, Data collection and analysis of results, Eman Hussein Soliman Altaweel, Data collection and analysis of results, Asmaa M. A Omran, Data collection and analysis of results. Dr. Mervat Ragab Abdel Rahman Nassar, Final revision for the manuscript and did all corrections & recommendations required by the reviewers & did the extra statistics wanted.

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Declarations

Competing interests
The authors declare no competing interests.

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