SCIENCE PROGRESS

Vitamin D deficiency as a predictor of severity in patients with COVID-19 infection

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Abstract

Background: As an immune modulator, vitamin D has been implicated in the coronavirus disease 2019 (COVID-19) severity. This study aimed to investigate the association between vitamin D levels and the severity of COVID-19 infection.

Methods: A cross-sectional study, which included 124 patients diagnosed with COVID-19 and were selected from Ain Shams University Hospitals and assigned to two groups; mild and severe COVID-19. All patients underwent detailed history taking, clinical data, and different laboratory investigations as complete blood count, blood urea nitrogen, serum creatinine, liver enzymes, C-reactive protein, D-dimer, ferritin and serum vitamin D concentration. In addition to findings of initial chest computed tomography (CT) were recorded. COVID-19 Reporting and Data System (CO-RADS) and CT chest severity scores (CT SS) were reported.

Results: In this study of 124 COVID-19-positive individuals, a high prevalence of hypovitaminosis D was found (97.6%). Lower vitamin D levels were significantly associated with more severe COVID-19 cases (*p*-value < 0.001), higher blood levels of inflammatory markers including (D-dimer, CRP, and ferritin), a higher CT SS and longer disease duration. Serum vitamin D can be used as a predictor for the severity of COVID-19 infection with a specificity of 96.6%, and sensitivity of 45.5%.

Conclusion: The high frequency of hypovitaminosis D in severe COVID-19 patients provides further evidence of a potential link to poor prognosis and severity of the disease, so vitamin D deficiency may be a marker of poor prognosis in these patients.

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Introduction

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome-associated with coronavirus-2 (SARS-CoV-2) which caused a pandemic that has affected the lives of millions globally and has severely strained the medical community with no specific treatment available till now.[1]

COVID-19 mainly affects the respiratory tract with clinical manifestations varying from mild to severe disease that might necessitate intensive care admission. This extreme variability in clinical presentation has been a point of research to understand the disease pathogenesis.[2] It has been noted that patients with severe COVID-19 have high concentrations of proinflammatory cytokines and mediators due to the activated T-helper-1 (Th1) cell responses resulting in a cytokine storm, particularly in patients requiring ICU admission. Considering the above, the possibility of using anti-inflammatory immunomodulating treatments especially in severe cases of COVID-19 is getting increasing attention.[3]

Vitamin D, a steroid and versatile hormone, plays a crucial key role in mediating and regulating the function of both the adaptive and innate immune systems. It stimulates innate immunity, through the induction of antimicrobial peptides, for instance, cathelicidins and defensins. It inhibits the cytokine storm, diminishing the production of pro-inflammatory cytokines such as interferon (IFN) γ and tumor necrosis factor (TNF) α. In addition, it regulates the adaptive immune response, via suppressing the Th1 response and promoting Th2 cytokine production.[4]

Vitamin D deficiency is a wide-reaching condition associated with metabolic, autoimmune and infectious comorbidities[5] and many studies highlighted an association between vitamin D deficiency and an increased risk of respiratory tract infections.[6,7] Moreover, vitamin D deficiency is common in critically ill patients and associates with adverse outcomes, as found by Dancer et al.[8] in a cohort of patients with acute respiratory distress syndrome (ARDS).

According to several studies, vitamin D deficiency is found to be common among COVID-19 patients[9] moreover; recent studies showed that patients who received vitamin D supplements had less severe symptoms.[10] Another study showed that a high prevalence of hypovitaminosis D in COVID-19 patients treated in a respiratory intensive care unit and a higher risk of mortality was found in patients with severe vitamin D deficiency.[11]

The aim of this study is to investigate the association between vitamin D levels and the severity of COVID-19 infection.

Materials and methods

Patients (COVID-19 may also be asymptomatic)

This is a cross-sectional study, which included 124 patients diagnosed with COVID-19 randomly enrolled from Ain Shams University Hospitals. The study

was conducted during the period from September 2020 to January 2021. Patients were diagnosed based on the WHO interim guidance[12]; A confirmed case of COVID-19 was defined as a positive result on real-time reverse transcriptase -polymerase-chain reaction (RT-PCR) of nasopharyngeal and oropharyngeal swab specimens. Patients had a history of liver disease, chronic renal disease, inflammatory disease, parathyroid disease, acute and chronic infection, hypercortisolism, cancer, hematological diseases, malabsorption, alcoholism, autoimmune disease, current use of vitamin D or calcium preparations, and pregnancy or breastfeeding were all excluded from the study.

Patients were divided into mild and severe groups according to the WHO guidance.[12] (The mild group had clinical symptoms of fever, fatigue, cough, anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, and headache. The severe group: respiratory distress, respiratory rate $\geqslant 30$ beats/min resting state, mean oxygen saturation $\leq 93\%$ and arterial blood oxygen partial pressure (PaO$_2$)/ oxygen concentration (FiO$_2$) ≤ 300 mmHg).

Ethical considerations

This study was conducted in accordance with the principles outlined in the World Medical Association's Declaration of Helsinki. The local ethics committee of Ain Shams University approved the study protocol. Informed consent was obtained from each participant after receiving an explanation about the study's aim and procedures.

Methods

All patients were subjected to detailed history taking with a particular emphasis on age, sex, duration of disease, and clinical symptoms. laboratory investigations including relevant Complete blood count (CBC) parameters (hemoglobin (Hb), White Blood Counts (WBC); neutrophil, lymphocyte count and Platelet count)), inflammatory parameters (C-reactive protein (CRP), Ferritin, D-dimer), liver and kidney function tests (AST, ALT and BUN, Creatinine), in addition to serum 25-hydroxy (OH) vitamin D were performed. Blood samples (5 ml) from our recruited PCR positive patients were obtained, left to clot completely, and centrifuged at $3500 \times g$ for 20 min at $+4°C$ and serum was stored at $-20°C$ until analysis. Routine biochemical parameters were measured by standard automated methods at Central Laboratories at Ain Shams Hospitals by standard automated methods on AU680 Beckman Coulter autoanalyzer (Beckman Coulter, Inc., Brea, CA). Serum 25-hydroxy (OH) vitamin D concentrations were detected by automated competitive electrochemiluminescence protein binding assay for a quantitative determination of total 25-OH vitamin D (both 25-OH D3 and 25-OH D2) in human serum using Roche Diagnostics, GmbH, Mannheim, Germany. The detection limit was 4 ng/mL. Vitamin D mild, moderate, and severe deficiency were

defined as 25(OH) vitamin D levels of 20–29, 10–19, and <10 ng/mL, respectively.[13]

Intra assay coefficient variation at mean concentration 15.4 ng/mL CV = 4.8% and at 29 ng/mL the CV was 3.6%, inter-assay precision at mean concentration 15.4 ng/mL the CV = 8.4% and at 29 ng/mL the CV was 5.4% using quality control material provides by Roche Diagnostics according to our assay verification records. Daily internal and monthly external quality control is performed using quality control material provides by Roche Diagnostics and EQAS provided by BIO-RAD.

Imaging investigations

All patients underwent non-contrast-enhanced chest CT in radiology department of Ain Shams University by expert radiologists using a Siemens 16-channel scope (CTAWP92544; Siemens Healthineers, Erlangen, Germany). All volumetric chest CT were assessed at lung window of 1500 WW and − 500 WL and mediastinal window of 400 WW and 60 WL using 2D coronal and sagittal planes for better assessment of the extent of the disease. The following parameters in each CT chest were assessed:

1. CO-RADS score based on CT findings

CO-RADS score grades the level of suspicion of pulmonary involvement of COVID-19 infection as follows:

CO-RADS 1: COVID-19 is highly unlikely, CT is normal, or there are findings indicating a non-infectious disease. CO-RADS 2: the level of suspicion of COVID-19 infection is low, and CT findings are consistent with other infections. CO-RADS 3: COVID-19 infection is unsure or indeterminate, and CT abnormalities indicate infection but are unsure whether COVID-19 is involved. CO-RADS 4: the level of suspicion is high, and most CT findings are suspicious but not extremely typical as unilateral ground glass, confluent, or multifocal consolidations without a typical location or any other typical findings. CO-RADS 5: the level of suspicion is high with typical CT findings.[14]

2. Semiquantitative scoring system for severity (CT severity score)

A semi-quantitative scoring system was used to quantitatively estimate the pulmonary involvement of all these abnormalities based on the area involved for disease severity. The CT severity score (CT-SS) was calculated based on the extent of lobar involvement. Each of the five lung lobes was visually scored on a scale of 0–5, with 0 indicating no involvement, 1 indicating less than 5% involvement, 2 indicating 5–25% involvement, 3 indicating 26–49% involvement, 4 indicating 50–75% involvement, and 5 indicating more than 75% involvement. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement).[15,16]

Statistical analysis

Statistical analyses were made using the statistical software SPSS version 15. Data were expressed as the median and interquartile range (IQR) while categorical variables as number (*n*) and percentage (%) of patients were calculated for study groups. Wilcoxon Rank Sum's Test and Ranked Spearman's Correlation Test were used. Pearson's chi-squared test (χ^2) was applied to sets of categorical data when groups were compared ($p > 0.05$ = insignificant, $p \leq 0.05$ = significant, $p \leq 0.001$ = highly significant).

Receiver-operating characteristic (ROC) curve analysis was used to examine the diagnostic value of serum vitamin D the area under the ROC curve (AUC) for Diagnostic/predictive value was interpreted as follows:

(0.9–1.0 Excellent, 0.8–0.89 Good, 0.7–0.79 Fair, 0.6–0.69 Poor, < 0.6 Fail)

Sensitivity, or the probability that the test results will be positive when the disease is present (true positive rate), is presented as a percentage. Specificity, or the probability that the test results will be negative when the disease is absent (true negative rate), is expressed as a percentage.

Results

A total of 124 patients whose RT-PCR tests for COVID-19 positive were recruited. We divided patients into two groups: mild and severe COVID-19; out of total of 124 patients; 58 patients (46.7%) were classified as mild COVID-19 (median age: 43 years, IQR: 35–52.5 range) and 66 patients (53.3%) were classified as severe COVID-19 (median age: 50 years, IQR: 43–56). There was a highly significant statistical difference between both groups with median age higher in the severe group ($p < 0.001$) Table 1.

Patients with severe COVID-19 ($n = 66$) showed a statistically significant higher median disease duration of 8 days (IQR: 6–11), while the remaining 58 mild cases had a median duration of 5 days (IQR: 4–9) ($p < 0.001$). The results of laboratory tests in all groups are reported in Table 1. We noticed also high serum levels of inflammatory parameters including CRP, D-dimer and ferritin in both groups, however, their levels in severe COVID-19 patients were significantly higher than that of the mild Group ($p < 0.001$). There were no significant differences between both groups regarding total WBC, neutrophil, lymphocyte counts, HGB, PLT, creatinine, ALT, AST. The median CT-SS was significantly higher in severe group (median = 15, IQR: 8.75–20) compared to mild COVID-19 (median = 3, IQR: 2–8) ($p < 0.001$).

In this cohort, we found a high prevalence of hypovitaminosis D (97.6%). Of total 124 patients, only 2.4% of patients had no hypovitaminosis D (normal; vitamin D >30 ng/ml), while 97.6% of cases showed a degree of vitamin D deficiency; 46.8% showed mild insufficiency, 46.8% had a moderate deficiency and 4% had severe deficiency Figure 1.

**Table 1.** Comparison between mild and severe COVID-19 patients' groups regarding all the tested parameters.

	Mild COVID-19 (n = 58) Median (IQR)	Severe COVID-19 (n = 66) Median (IQR)	Z	p-Value
Age (years)	43 35–52.5	50 42.75–56.25	−3.24	0.001
Duration of disease (days)	5 4–9	8 6–11	−3.703	<0.001
WBC count (10^9/l)	5.5 4.275–10.5	7.8 4.75–10.4	−1.022	0.307
Neutrophil count (10^9/l)	4 2.7–6.89	5.5 2.9–8.3	−1.663	0.096
Lymphocyte count (10^9/l)	1.24 0.85–1.68	1.1 0.79–1.53	−0.621	0.534
Platelet count (10^9/l)	229 194.5–259.25	246 167.75–330.25	−0.621	0.535
CRP (mg/l)	22 11.75–48.5	83 29–222.25	−4.512	<0.001
Ferritin (ng/ml)	227 126.7–289.5	778 454.5–1225	−7.855	<0.001
D-dimer (ng/ml)	336 230–451	1200 569.5–1451	−7.087	<0.001
Vitamin D (ng/ml)	22 18.75–25.25	16 12–22	−5.057	<0.001
HGB (g/dl)	14.2 11.925–15.4	14 13.15–15	−0.581	0.561
BUN (mg/dl)	14 11.45–16.85	15.9 11.7–22.25	−2.156	0.031
Serum creatinine (mg/dl)	0.8 0.7–1.03	0.9 0.7–1.05	−0.543	0.587
AST IU/l	23 15.5–37.25	34 18–43.25	−1.845	0.065
ALT IU/l	27 15–51	34 17.75–54	−0.963	0.336
CORAD score	1 0-2	4 3–5	−8.095	<0.001
CT-SS	3 2-8	15 8.75–20	−6.823	<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Bun: blood urea nitrogen; CO-RADS score: COVID-19 Reporting and Data System score; CRP: C-reactive protein; CT-SS: CT chest severity score.
Statistical method: Wilcoxon Rank Sum's Test.
p-value >0.05: non significant (NS); p-value <0.05: significant (S); p-value <0.01: highly significant (HS).

Patients with mild COVID-19; 3.4% (2/58 cases) showed normal vitamin D levels (>30 ng/ml) while in the severe COVID-19 group 1.5% (1/66 cases) showed normal vitamin D levels. Mild vitamin D deficiency was seen in 65.5% (38/58) versus 30.3% (20/66) in both mild and severe groups, respectively. Moderate and severe
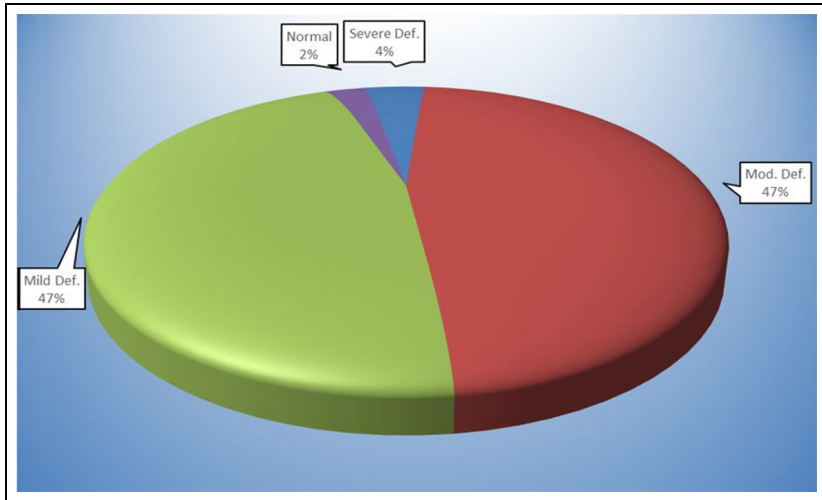
Figure 1. Distribution of vitamin D level among studied COVID-19 patients (*n* = 124).

Table 2. Distribution of vitamin D concentration across both mild and severe COVID-19 patients' groups.

	Severity COVID-19 groups		Total 124
	Mild *n* = 58	Severe *n* = 66	
Vitamin D level			
Normal	3.4%	1.5%	2.4%
	2/58	1/66	3/124
Mild deficiency.	65.5%	30.3%	46.8%
	38/58	20/66	58/124
Moderate deficiency.	31%	60.6%	46.8%
	18/58	40/66	58/124
Severe deficiency.	0.0%	7.6%	4.0%
	0/58	5/66	5/124
Total			
Pearson Chi-square	Value	*p*	
	18.827	0.000	

Statistical method: Pearson's chi-squared test (χ^2).

vitamin D deficiency was seen in 31% (18/58) versus 68.2% (45/66) in both mild and severe COVID-19 groups respectively, with zero cases showing severe vitamin D deficiency in the mild group in contrast to seven cases with severe vitamin D deficiency in severe COVID-19 group ($p < 0.001$) (Table 2).

Using Ranked Spearman Correlation (Table 3), Vitamin D showed a significant negative correlation with age ($r = -0.218$, $p = 0.015$) a significant negative

Table 3. Correlation between vitamin D concentration and all of studied parameters.

Different parameters	Vitamin D	
	r	p-Value
Age (years)	−0.218	0.015
Duration of disease (days)	−0.182	0.043
WBC count (10^9/l)	−0.117	0.194
Neutrophil count (10^9/l)	−0.153	0.09
Lymphocyte count (10^9/l)	0.066	0.469
Platelet count (10^9/l)	−0.139	0.123
C-reactive protein (mg/l)	−0.556	<0.001
HGB (g/dl)	−0.003	0.974
BUN (mg/dl)	−0.205	0.022
Serum creatinine (mg/dl)	−0.16	0.075
AST IU/l	0.031	0.731
ALT IU/l	0.021	0.815
CORAD score	−0.37	<0.001
CT-SS	−0.307	0.001
Ferritin (ng/ml)	−0.438	<0.001
D-dimer (ng/ml)	−0.32	<0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; Bun: blood urea nitrogen; CO-RADS score: COVID-19 Reporting and Data System score; CRP: C-reactive protein; CT-SS: CT chest severity score.
Statistical method: Rank Sum's Test and Ranked Spearman's Correlation Test.
p-Value >0.05: non-significant (NS); p-value <0.05: significant (S); p-value <0.01: highly significant (HS).

correlation with the duration of hospital stay in COVID-19 patients ($r = -0.182$, $p = 0.043$). A highly significant negative correlation with all inflammatory indices including CRP ($r = -0.556$, $p < 0.001$), ferritin ($r = -0.438$, $p < 0.001$), and D-dimer ($r = -0.32$, $p < 0.001$). Vitamin D showed a highly significant negative correlation with CORAD score ($r = -0.37$, $p = 0.001$) and CT-SS ($r = -0.307$, $p = 0.001$) Figure 2.

Receiver operating curve (ROC) showing performance of vitamin D in predicting severity in COVID-19 patients, cutoff value and performance are presented in Figure 3. For a value <18 ng/ml, vitamin D could predict a poor prognosis with a specificity of 75.9%, sensitivity of 60.6%, positive predictive value of 74.1%, negative predictive value of 62.9%, efficiency of 67.7%, area under curve (AUC) of 0.783, and p-value was <0.001.

Discussion

Many studies focused on the role of inflammatory markers as predictors of severity in COVID-19, including lymphocyte counts, CRP, D-dimer and ferritin.[17–19] Vitamin D, through nuclear vitamin D receptor, is known to be involved in both innate and acquired immune system modulation and production of antimicrobial peptides, such as cathelicidin and human β-defensin-2.[4] Considering the above, the
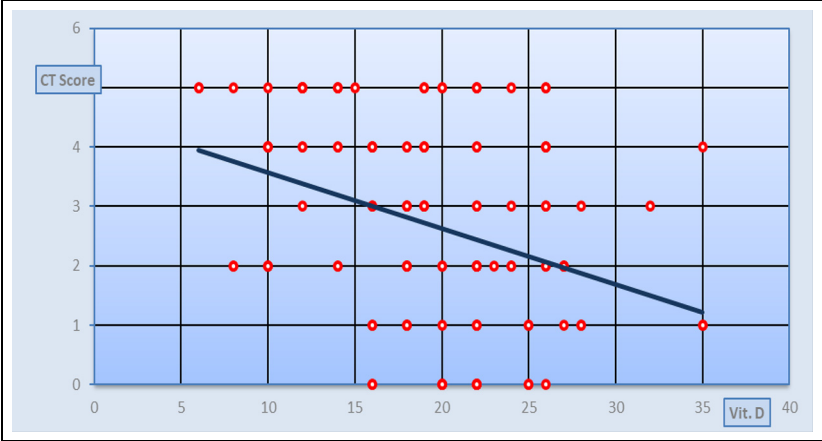
Figure 2. Correlation between vitamin D and CT severity score in COVID-19 patients.
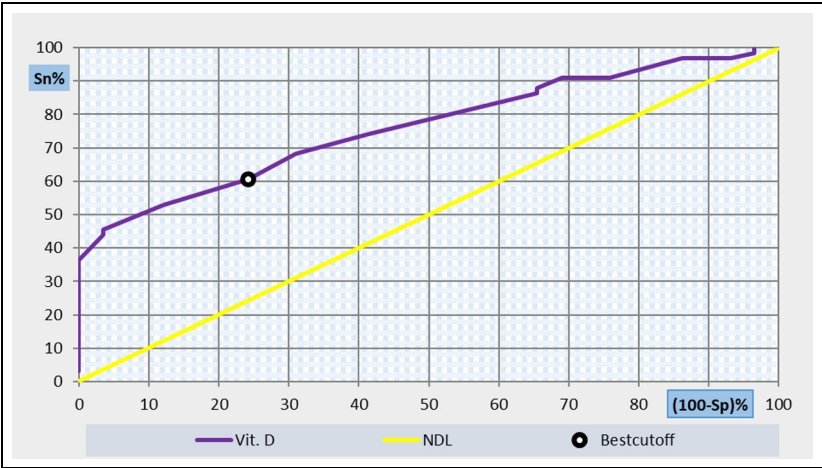

Figure 3. ROC showing the performance of vitamin D in predicting severity in COVID-19 patients.

current study aimed to evaluate the potential association between vitamin D level and the severity of COVID-19 infection.

In this study of 124 COVID-19-positive individuals, we found a high prevalence of hypovitaminosis D (97.6%). Of total 124 patients, 97.6% of cases showed a degree of vitamin D deficiency and only 2.4% of patients had no hypovitaminosis D (vitamin D >30). Nearly 50% percent of the patients had moderate to severe deficiency (46.8% showed moderate deficiency, 4% severe deficiency) in addition 46.8% showed mild insufficiency. This agreed with results from various studies

showing significant associations between vitamin D levels and the number of COVID-19 cases, severity and mortality rate.[20,21] A retrospective study of 107 cases showed significantly lower vitamin D levels in PCR positive COVID-19.[22]

In this study cohort, our median vitamin D concentration was 19 (range: 6–35) nearly 95% of our cohort showed vitamin D deficiency (120/124) only four patients had vitamin D >30. This was supported by a study of 489 patients whose vitamin D levels were measured within a year of COVID-19 testing, the relative risk for COVID-19 positivity was 1.77 times higher in vitamin D deficient cases versus those with sufficient vitamin D.[23]

According to Demir et al.,[24] COVID-19 positivity was higher in individuals with vitamin D deficiency where 94.27% of COVID-19 cases had vitamin D levels <30 ng/ml. Furthermore, they noted a substantially higher incidence of severe vitamin D deficiency in COVID-19-positive cases (44%) versus non-COVID-19 (31%). These findings showed a strong association between vitamin D deficiency and COVID-19 PCR positivity, which was consistent with other studies investigating the association between vitamin D deficiency and COVID-19.[25,26]

We found significantly higher vitamin D deficiency rates among severe cases of COVID-19 versus mild cases ($p < 0.001$). That was in coordination with a retrospective observational study aimed to investigate vitamin D levels and their correlation with COVID-19 severity in West Flanders, Belgium and found higher vitamin D–deficiency rates among severe cases of COVID-19 (58.6% vs 45.2%, $p = 0.0005$).[27]

In this cohort, according to our correlation analysis, a decrease in vitamin D levels was associated with more severe COVID-19 cases, with significantly higher blood levels of inflammatory markers; D-dimer CRP, ferritin, a higher CT SS and longer disease duration.

The association between vitamin D deficiency and increased risk of inflammation and respiratory infections was stated in many studies; a study by Lehouck et al.[28] showed the role of high vitamin D supplements in reducing COPD exacerbations. In addition to a study conducted by Kaya et al.[29] who reported the strong association between vitamin D with ESR as a marker of inflammation in diabetic patients. Furthermore, Panfili et al.,[30] stated that vitamin D deficiency contributes to acute respiratory distress syndrome (ARDS), and indicated that vitamin D has a role in preventing lung fibrosis which is a common complication and a long-term concern in these patients.

COVID-19 might be implicated in an aggressive pro-inflammatory response leading to endothelial cells dysfunction and excessive thrombin formation.[31] Elevated D-dimer represents microangiopathy and hypercoagulable state in COVID-19 patients.[32] Similarly, CRP is an acute phase reactant synthesized in response to pro-inflammatory cytokines mainly tumor necrosis factor (TNF), interleukin (IL-6), so it is an indicator of cytokine storm.[33] In this study, D-dimer level and CRP were significantly higher in cases with severe COVID-19, and there was a highly significant negative correlation with vitamin D levels. The above findings were in line with those reported in several studies.[34,35]

Ferritin is another crucial immune response mediator that showed a statistically significant increase in severe COVID-19 cases and showed a highly significant negative correlation with vitamin D levels. Increased ferritin levels could cause a cytokine storm by exerting direct immunosuppressive and pro-inflammatory effects.[19] Thus, our COVID-19 patients had a high prevalence of vitamin D deficiency, and serum 25OHD levels significantly and negatively correlated with ferritin indicating that vitamin D might have a beneficial role on the systemic inflammatory state of this viral disease.

Interestingly, we noticed that in cases with lower vitamin D levels, there were more lung segments with ground-glass opacity, which is the common CT feature in COVID-19 pneumonia.[36] COVID-19 is known to causes downregulation of ACE2 causing Angiotensin II accumulation, elevated pulmonary vascular permeability, pulmonary edema, oxidative stress, eventually leading to inflammation and fibrosis.[37] Xu et al.[38] and Cui et al.[39] reported that vitamin D provides protective effects in acute lung injury through increasing ACE2 expression and down regulating the injurious pathway; renin, ACE and Angiotensin II levels.

According to our results, a longer disease duration was seen in patients with severe vitamin D deficiency. In agreement with Ilie et al.[21] who observed a negative correlation between vitamin D levels and longer hospital stay and mortality in COVID-19 patients. Our study revealed that the better cut-off point for vitamin D to predict a poor prognosis of COVID-19 infection was 18 ng/ml, with a specificity of 75.9%, sensitivity of 60.2%. Our results were close to Bennouar et al.[40] who reported sensitivity of 76% and specificity of 69% with a cut-off value of 39 nmol/l. Meanwhile, Abrishami et al.[26] reported an optimal cut-off level <25 ng/mL, with 75% specificity and 72% sensitivity. These results provide evidence of a potential link between vitamin D deficiency and poor prognosis of COVID-19 infection.

Conclusion

The high frequency of hypovitaminosis D in severe COVID-19 patients provides further evidence of a potential link to poor prognosis, so vitamin D deficiency may be a marker of poor prognosis in these patients and thus it might be possible that vitamin D supplementation may attenuate severity and improve prognosis. Further multi-center studies need to be conducted on a larger scale to demonstrate the real influences of vitamin D deficiency on the severity of COVID-19 and if treatment with vitamin D might be effective in improving the disease outcome and reducing mortality.

Limitations of the study

This single-centered study, patients were from only our country, analysis was done on a modest sample size, this may have limited the results of statistical analyzes and did not give our study variability of the results.

Declaration of conflicting interests

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