

IMPACT OF SERUM 25(OH) VITAMIN D LEVEL ON MORTALITY IN PATIENTS WITH COVID-19 IN TURKEY

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Abstract: *Background:* Because of the lack of sufficient data, we aimed to investigate the role of serum 25(OH) vitamin D level on COVID severity and related mortality. *Methods:* This was a retrospective observational study. Data, including sociodemographic features, clinical characteristics, and laboratory data, and 25(OH) vitamin D levels were recorded for each study participant. Patients were stratified into different vitamin D groups; Normal (Serum 25(OH) vitamin D level >30 ng/mL), Vitamin D insufficiency (21-29 ng/mL), and deficiency (<20 ng/mL). The severity of COVID was classified according to the Chinese Clinical Guideline for classification of COVID-19 severity. Mortality data were determined for participants. Univariate and multivariate Logistic regression analysis was performed to determine independent predictors of in-hospital mortality. *Results:* Overall, 149 COVID-19 patients (females 45.6%, mean age 63.5 ± 15.3 (range 24-90 years) years) were included. Forty-seven patients (31.5%) had moderate COVID-19, whereas 102 patients (68.5%) had severe-critical COVID-19. The mean 25(OH) vitamin D level was 15.2 ± 10.3 ng/mL. Thirty-four (22.8%) and 103 (69.1%) patients had vitamin D insufficiency and deficiency, respectively. Mean serum 25(OH) vitamin D level was significantly lower in patients with severe-critical COVID-19 compared with moderate COVID-19 (10.1 ± 6.2 vs. 26.3 ± 8.4 ng/mL, respectively, $p < 0.001$). Vitamin D insufficiency was present in 93.1% of the patients with severe-critical COVID-19. Multivariate logistic regression analysis revealed that only lymphocyte count, white blood cell count, serum albumin and, 25(OH) vitamin D level were independent predictors of mortality. *Conclusion:* Serum 25(OH) vitamin D was independently associated with mortality in COVID-19 patients.

Key words: COVID-19, mortality, prognosis, vitamin D.

Introduction

Coronavirus disease 2019 (COVID-19) has become a pandemic and claimed more than 400.000 lives throughout the world as the time of the writing of this manuscript (1). Advanced age and underlying chronic medical conditions, particularly chronic pulmonary and cardiac diseases, appeared as the most conspicuous predisposing factors for the development of severe COVID-19 and consequent death (2, 3). However, recent observations regarding the relatively greater impact of the disease on the northern latitudes led to the generation of the hypothesis that vitamin D deficiency, to some extent, might have caused a tendency for an increased burden of the disease in vitamin D deficient COVID-19 patients, especially among the elderly (4-6).

Vitamin D is a multi-faceted hormone, the best-known effect of which is on the calcium and phosphorus metabolism. However, multiple lines of experimental and clinical evidence point to its essential regulatory role in both the innate and adaptive immune systems (7). Through several different but additive mechanisms, vitamin D produces anti-viral effects (8). Although not all included studies supported its conclusion, a meta-analysis found a protective effect of vitamin D supplementation against upper respiratory tract viral infections (9). First reports with respect to the role of vitamin D serum levels on contraction of SARS-CoV2 revealed that patients with PCR-proven COVID-19 had significantly lower serum 25(OH) D levels compared with patients without COVID-19, even after

controlling for the effect of age (10). However, a larger study did not confirm the results of this latter study (11).

To the best of our knowledge, despite the extensive discussion of the role of vitamin D in COVID-19 susceptibility and development of severe disease through editorials and review articles, only one study evaluated the effect of vitamin D status on mortality in COVID-19 patients. Raharusun and colleagues (12) reported that in 780 patients with laboratory-confirmed COVID-19 in Indonesia, vitamin D status was an independent predictor of mortality. Considering the ongoing high death toll of COVID-19 along with the prevalent nature of vitamin D deficiency, we think that it is of utmost importance to delineate the role of vitamin D status on the prognosis of patients with COVID-19.

Hence, the primary objective of this study was to evaluate the association of vitamin D status with disease severity and mortality in patients with COVID-19.

Methods

Patients, study design and data collection

This was a retrospective observational study that included adult COVID-19 patients in Health Sciences University, Bagcilar Training and Research Hospital, Istanbul, Turkey between April 1st, 2020 and May 20th, 2020. The study protocol was approved by the Hospital Clinical Studies Ethical Committee (2020.06.1.01.072 and 12 June 2020).

The primary outcome measure of the study was all-cause

VITAMIN D AND MORTALITY IN COVID-19 IN TURKEY

mortality in COVID-19 patients.

Data, including sociodemographic features, clinical characteristics, and laboratory data comprising complete blood counts, serum albumin, calcium, and 25(OH) vitamin D levels were retrieved from the hospital electronic database system and recorded for each study participant.

Patients who did not have 25(OH) vitamin D values, who had clinical presentation compatible with COVID-19, but did not have a positive PCR-based test for SARS-CoV2, and pediatric patients were excluded from the study.

Measurement of serum 25(OH) vitamin D level and Vitamin D groups

Serum 25(OH) vitamin D levels were studied by electrochemiluminescence method. Patients were stratified into different groups according to their serum 25(OH) vitamin D levels. Serum 25(OH) vitamin D level >30 ng/mL was accepted as normal. Vitamin D insufficiency and deficiency were defined as serum 25(OH) vitamin D levels of 21-29 ng/mL and <20 ng/mL, respectively (13).

Classification of the severity of COVID-19

We used the Chinese Clinical Guideline for classification of COVID-19 severity, which was devised by the China Health Committee (14). According to this guideline, COVID-19 has four levels of the severity: mild, moderate, severe, and critical. Patient symptoms, laboratory values, and results of imaging studies performed at admission are used to determine severity of COVID-19. Based on this classification system, disease severity groups were defined as follows;

- Mild disease: Mild clinical symptoms and normal lung on radiologic imaging
- Moderate disease: Fever and pulmonary symptoms along with pneumonia on radiologic imaging
- Severe disease: The presence of any of the following criteria: i) respiratory distress (≥ 30 breaths/min); ii) oxygen saturation $\leq 93\%$ at rest; iii) $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg or chest imaging shows obvious lesion progression $> 50\%$ within 24-48 hours)
- Critical disease: The presence of any of the following criteria: i) respiratory failure and need for mechanical ventilation; ii) shock; iii) other organ failures that requires ICU care.

Since patients with mild COVID-19 were not hospitalized according to our National guidelines, our study did not involve any patient with mild disease. Furthermore, for practical purposes for our study aims, we combined severe and critical COVID-19 in a single group named “severe-critical disease”. In the end, we stratified all included patients either to moderate or critical-severe COVID-19 groups.

Statistical analysis

In summarization of the study data, descriptive statistics were presented for continuous variables as either mean \pm standard deviation or median-interquartile range depending on the distribution type of the data. Categorical variables were reported as numbers and percentages. The normality check of numerical variables was performed via the Kolmogorov-Smirnov test. According to groups, to compare categorical variables, chi-square/Fisher exact test used, while Independent Samples t-test or Mann-Whitney U tests was used for continuous variables in case of normal and non-normal distribution, respectively. To evaluate the bivariate correlation between the serum 25(OH) vitamin D level and inflammatory marker, Pearson’s correlation was used. We also constructed univariate and multivariate logistic regression analyses to determine the independent associates of mortality. SPSS 26.0 (IBM Corporation, NY, US) was used to perform all statistical analyses. A P-value <0.05 was considered as statistically significant.

Results

Patient characteristics and baseline laboratory values

Overall, 149 COVID-19 patients (females 45.6%) were included. The mean age of the patients was 63.5 ± 15.3 (range 24-90 years) years. The most frequent comorbid condition was hypertension, which was followed by diabetes mellitus (40.9%) and dyslipidemia (26.2%). Almost one-fifth of the whole group had chronic kidney disease, and the mean estimated glomerular filtration rate (eGFR) was 74.7 ± 33.7 mL/minute.

Sixty-two patients (41.6%) had critical COVID-19, whereas forty patients had severe disease. Baseline laboratory values of the entire study cohort were shown in table-1.

Moderate and severe-critical COVID-19

Forty-seven patients (31.5%) had moderate COVID-19, whereas 102 patients (68.5%) had severe-critical COVID-19. Patients with severe-critical COVID-19 had significantly higher rates of coronary artery disease, hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease, chronic atrial fibrillation, and congestive heart failure compared to patients who had moderate COVID-19. Interestingly, chronic obstructive pulmonary disease frequency was comparable between the groups. Patients with severe-critical COVID-19 had significantly lower eGFR, lower hemoglobin, higher neutrophil and lymphocyte counts, and higher serum C-reactive protein values compared to those of patients with moderate COVID-19. Table-2 summarizes the comorbid disease rates and laboratory values in moderate and severe-critical COVID-19 patients.

25(OH) Vitamin D levels and vitamin D status

The mean 25(OH) vitamin D level was 15.2 ± 10.3 ng/mL. The numbers of patients with vitamin D insufficiency and

Table 1

Mean age, sex distribution, comorbid conditions, baseline laboratory values and serum 25(OH) vitamin D levels in the whole study cohort

		Min-Max	Median	Mean \pm SD /Number (%)	
Age (years)		24.0	- 90.0	65.0	63.5 \pm 15.3
Sex	Female				68 (45.6%)
	Male				81 (54.4%)
Smoking					51 (34.2%)
Coronary artery disease					32 (21.5%)
Hypertension					85 (57.0%)
Dyslipidemia					39 (26.2%)
Diabetes mellitus					61 (40.9%)
Cerebrovascular accident					9 (6.0%)
Chronic obstructive pulmonary disease					15 (10.1%)
Malignancy					23 (15.4%)
Chronic kidney disease					29 (19.5%)
Chronic atrial fibrillation					15 (10.1%)
Congestive heart failure					18 (12.1%)
Acute kidney injury					16 (10.7%)
eGFR (mL/minute)		3.0	- 141.0	81.0	74.7 \pm 33.7
Hemoglobin (g/dL)		5.0	- 17.0	12.1	12.0 \pm 2.1
Neutrophil count (x10 ³ /mm ³)		0.50	- 31.20	5.60	6.82 \pm 4.84
Lymphocyte count (x10 ³ /mm ³)		0.32	- 27.20	1.78	4.08 \pm 4.69
White blood cell count (x10 ³ /mm ³)		0.20	- 21.10	4.09	4.23 \pm 3.37
Platelet count (x10 ³ /mm ³)		46.0	- 688.0	208.0	227.3 \pm 96.1
C-reactive protein (mg/dL)		0.5	- 317.3	55.0	83.8 \pm 77.8
Albumin (g/dL)		1.9	- 4.6	3.3	3.3 \pm 0.5
Calcium (mg/dL)		6.3	- 9.6	8.2	8.2 \pm 0.6
25(OH) vitamin D (ng/mL)		1.6	- 57.1	11.7	15.2 \pm 10.3
Vitamin D status	\leq 20 (Deficiency)				103 (69.1%)
	21-29 (Insufficiency)				34 (22.8%)
	\geq 30 (Normal)				12 (8.1%)
COVID-19 severity	Moderate				47 (31.5%)
	Severe				40 (26.8%)
	Critical				62 (41.6%)

deficiency were 34 (22.8%) and 103 (69.1%), respectively. Only 8.1% of the entire study cohort had a normal level of serum 25(OH) vitamin D (table-1).

Mean serum 25(OH) vitamin D level was significantly lower in patients with severe-critical COVID-19 compared to that of patients with moderate COVID-19 (10.1 \pm 6.2 vs. 26.3 \pm 8.4 ng/mL, respectively, $p < 0.001$). Vitamin D insufficiency was present in 93.1% of the patients with severe-critical COVID-19 (table-2, figure-1).

Mean serum 25(OH) vitamin D level was significantly lower among deceased patients compared with the surviving patients

(10.4 \pm 6.4 vs. 19.3 \pm 11.2 ng/mL, respectively, $P < 0.001$). A significantly higher ratio of the deceased patients had vitamin D deficiency compared with surviving patients (92.8% vs. 48.8%, $P < 0.001$) (table-3, figure-2).

Mean serum 25(OH) vitamin D level was negatively correlated with increasing age ($r = -0.3$, $p < 0.001$).

Correlation of 25(OH) vitamin D and inflammatory markers

Mean serum 25(OH) vitamin D level was significantly and negatively correlated with serum C-reactive protein level ($r = -0.253$, $P = 0.002$). Mean serum 25(OH) vitamin D level was significantly and negatively correlated with neutrophil

VITAMIN D AND MORTALITY IN COVID-19 IN TURKEY

Table 2

Comparison of age, sex distributions, frequency of comorbid conditions, laboratory values and 25(OH) vitamin D levels between the COVID-19 patients with moderate and severe-critical disease

		Moderate COVID-19 (n=47)		Severe-Critical COVID-19 (n=102)		P-value	
		Mean ± SD /n (%)	Median	Mean ± SD /n (%)	Median		
Age		56.1 ± 15.2	55.0	67.0 ± 14.1	69.0	<0.001	t
Sex	Female	24 (51.1%)		44 (43.1%)		0.367	X ²
	Male	23 (48.9%)		58 (56.9%)			
Smoking		10 (21.3%)		41 (40.2%)		0.024	X ²
Coronary artery disease		3 (6.4%)		29 (28.4%)		0.002	X ²
Hypertension		15 (31.9%)		70 (68.6%)		<0.001	X ²
Dyslipidemia		3 (6.4%)		36 (35.3%)		<0.001	X ²
Diabetes mellitus		12 (25.5%)		49 (48.0%)		0.009	X ²
Cerebrovascular accident		2 (4.3%)		7 (6.9%)		0.535	X ²
Chronic obstructive pulmonary disease		4 (8.5%)		11 (10.8%)		0.668	X ²
Malignancy		6 (12.8%)		17 (16.7%)		0.540	X ²
Chronic kidney disease		2 (4.3%)		27 (26.5%)		0.001	X ²
Chronic atrial fibrillation		0 (0.0%)		15 (14.7%)		0.006	X ²
Congestive heart failure		0 (0.0%)		18 (17.6%)		0.002	X ²
Acute kidney injury		1 (2.1%)		15 (14.7%)		0.021	X ²
eGFR		94.4 ± 24.7	101.0	65.6 ± 33.5	71.0	<0.001	m
Hemoglobin		12.7 ± 2.0	13.0	11.7 ± 2.1	12.0	0.005	m
Neutrophil count		3.6 ± 1.8	3.4	8.3 ± 5.1	7.2	<0.001	m
Lymphocyte count		1.4 ± 0.6	1.3	5.3 ± 5.2	3.9	<0.001	m
White blood cell count		5.5 ± 2.0	5.4	3.6 ± 3.7	1.7	<0.001	m
Platelet count		219.3 ± 96.8	199.0	231.0 ± 96.1	212.0	0.476	m
C-reactive protein		44.2 ± 59.5	17.5	102.1 ± 78.7	83.1	<0.001	m
Albumin		3.6 ± 0.5	3.6	3.2 ± 0.5	3.1	<0.001	t
Calcium		8.6 ± 0.5	8.6	8.1 ± 0.6	8.0	<0.001	t
25(OH) vitamin D		26.3 ± 8.4	25.8	10.1 ± 6.2	8.4	<0.001	m
Vitamin D status	≤20	8	17.0%	95	93.1%	<0.001	X ²
	21-29	27	57.4%	7	6.9%		
	≥30	12	25.5%	0	0.0%		
Death	(-)	46	97.9%	34	33.3%	<0.001	X ²
	(+)	1	2.1%	68	66.7%		

m. Mann-Whitney U test / t Independent Samples t-test/ X² Chi-Squared test

count ($r=-0.419$, $P<0.001$) and lymphocyte count ($r=-0.348$, $P<0.001$).

Mortality and its determinants

In total, 69 out of 149 patients (46.3%) died during the study period. The deceased patients were significantly older compared with surviving patients. As expected, the mortality

rate was significantly higher among patients with severe-critical COVID-19 compared with moderate COVID-19 patients (66.7% vs. 2.1%, respectively, $P<0.001$) (Figure-3).

Figure 1

Box and whisker graph showing 25(OH) vitamin D levels in patients with moderate and severe-critical COVID-19

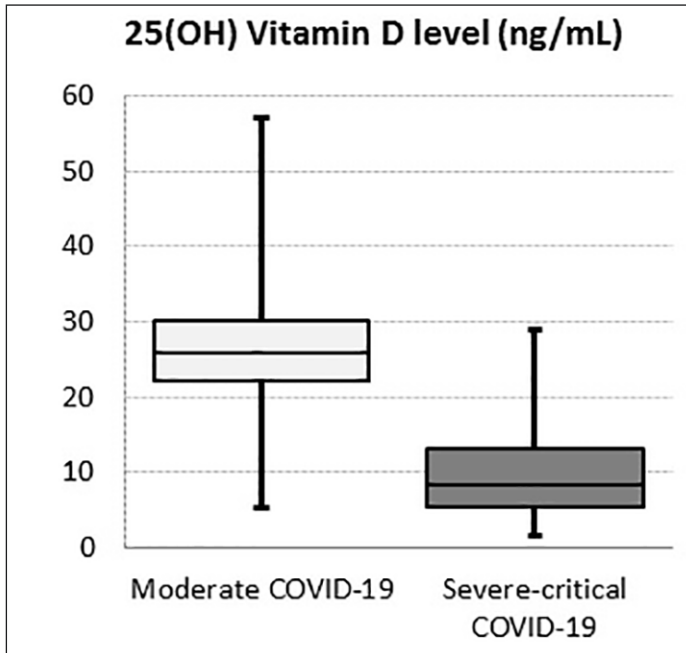
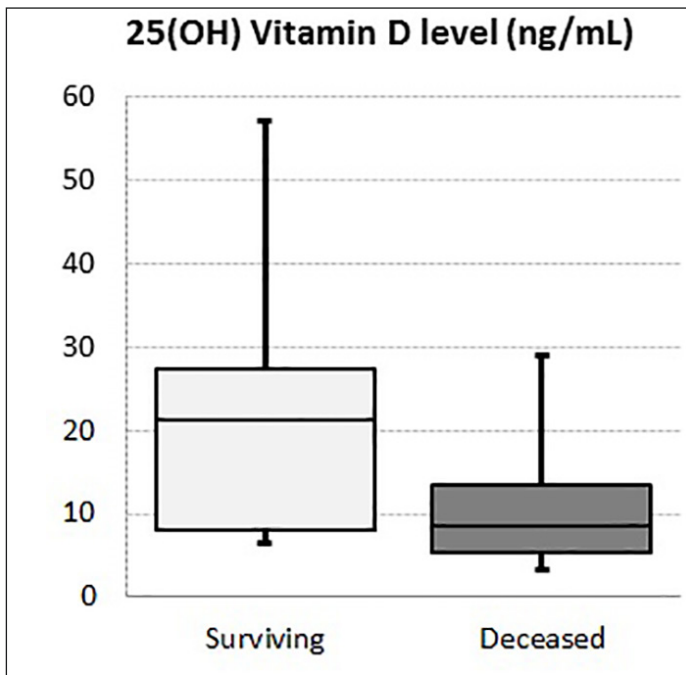


Figure 2

Box and whisker graph showing 25(OH) vitamin D levels in the surviving and deceased patients

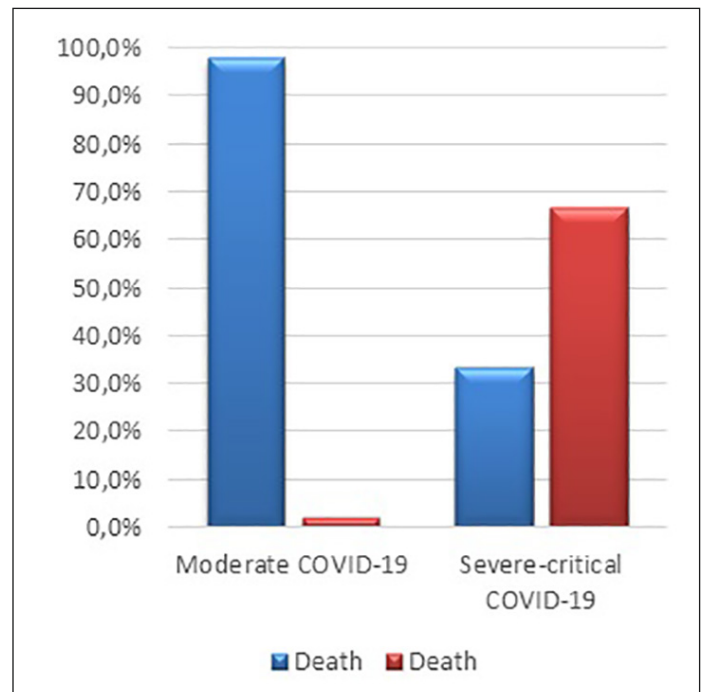


The deceased COVID-19 patients had significantly higher rates of dyslipidemia, diabetes mellitus, chronic kidney disease, chronic atrial fibrillation, and congestive heart failure compared

with surviving patients. The deceased COVID-19 patients had significantly lower eGFR, lower hemoglobin, higher neutrophil and lymphocyte counts, and higher C-reactive protein values compared with their surviving counterparts. The comorbid conditions and laboratory results of the deceased and surviving patients were shown in table-3.

Figure 3

Multiple bar chart showing mortality rates in patients with moderate and severe-critical COVID-19



Multivariate logistic regression analysis revealed that only lymphocyte count, white blood cell count, serum albumin, and 25(OH) vitamin D level were independent predictors of mortality. An increase in lymphocyte count, but a decrease in white blood cell count, serum albumin, and 25(OH) vitamin D level was associated with increased mortality in COVID-19 patients (table-4).

Discussion

The salient findings of the present study were as follows: (i) Vitamin D insufficiency (22.8%) and deficiency (69.1%) were quite common among patients with COVID-19. Only 8.1% of the entire study cohort had a normal level of serum 25(OH) vitamin D. (ii) Patients with more severe COVID-19 had lower mean serum 25(OH) vitamin D levels. (iii) A significantly higher ratio of the deceased patients had vitamin D deficiency compared with surviving patients (92.8% vs. 48.8%, $P < 0.001$). (iv) Serum 25(OH) vitamin D level was independently associated with increased mortality in COVID-19 patients in multivariate logistic regression.

VITAMIN D AND MORTALITY IN COVID-19 IN TURKEY

Table 3

Comparison of age, sex distributions, frequency of comorbid conditions, laboratory values and 25(OH) vitamin D levels between the deceased and surviving COVID-19 patients

		Surviving patients		Deceased patients		P-value	
		Mean \pm SD /n (%)	Median	Mean \pm SD /n (%)	Median		
Age		60.0 \pm 15.5	60.0	67.7 \pm 14.1	68.5	0.002	t
Sex	Female	40 (50.0%)		28 (40.6%)		0.250	X ²
	Male	40 (50.0%)		41 (59.4%)			
Smoking		21 (26.3%)		30 (43.5%)		0.027	X ²
Coronary artery disease		13 (16.3%)		19 (27.5%)		0.124	X ²
Hypertension		41 (51.3%)		44 (63.8%)		0.078	X ²
Dyslipidemia		13 (16.3%)		26 (37.7%)		0.003	X ²
Diabetes mellitus		25 (31.3%)		36 (52.2%)		0.010	X ²
Cerebrovascular accident		2 (2.5%)		7 (10.1%)		0.051	X ²
Chronic obstructive pulmonary disease		8 (10.0%)		7 (10.1%)		0.977	X ²
Malignancy		9 (11.3%)		14 (20.3%)		0.128	X ²
Chronic kidney disease		9 (11.3%)		20 (29.0%)		0.006	X ²
Chronic atrial fibrillation		2 (2.5%)		13 (18.8%)		0.001	X ²
Congestive heart failure		4 (5.0%)		14 (20.3%)		0.004	X ²
Acute kidney injury		4 (5.0%)		12 (17.4%)		0.015	X ²
eGFR		85.1 \pm 31.8	94.5	62.7 \pm 32.0	70.0	<0.001	m
Hemoglobin		12.4 \pm 1.9	12.5	11.6 \pm 2.2	12.0	0.027	m
Neutrophil count		4.7 \pm 3.1	4.1	9.3 \pm 5.3	7.8	<0.001	m
Lymphocyte count		1.7 \pm 2.0	1.2	6.8 \pm 5.4	5.4	<0.001	m
White blood cell count		5.8 \pm 2.9	5.5	2.4 \pm 2.9	1.0	<0.001	m
Platelet count		224.3 \pm 92.9	205.0	230.7 \pm 100.3	211.0	0.771	m
C-reactive protein		62.4 \pm 71.2	31.3	108.7 \pm 78.3	90.0	<0.001	m
Albumin		3.5 N \pm 0.5	3.5	3.1 \pm 0.5	3.0	<0.001	t
Calcium		8.4 \pm 0.6	8.5	8.0 \pm 0.6	8.0	<0.001	t
25(OH) vitamin D		19.3 \pm 11.2	21.3	10.4 \pm 6.4	8.6	<0.001	m
Vitamin D status	\leq 20	39 (48.8%)		64 (92.8%)		<0.001	X ²
	21-29	29 (6.3%)		5 (7.2%)			
	\geq 30	12 (15.0%)		0 (0.0%)			

m Mann-Whitney U test / t Independent Samples t-test/ X² Chi-Squared test

Vitamin D has important immune functions. Considering in a context of a viral infection, the beneficial anti-viral effect of vitamin D can be grouped into three categories: enhancing physical barrier against the viruses and beneficial effects on innate and adaptive immunity (15, 16). Vitamin D supports the innate immune system by means of inducing the secretion of several antimicrobial peptides such as defensins. In addition, the active form of vitamin D, calcitriol, has itself several virus suppressive effects. Cytokine storm was found to play an important role in the rapid deterioration of some patients with COVID-19 (17). Importantly, vitamin D can limit the

devastating effects of cytokine storm via reducing the release of proinflammatory Th1 derived cytokines such as TNF-alpha and interferon-gamma (18, 19). Last but not least, vitamin D also has an important favorable impact on the adaptive immune system, particularly through the actions of calcitriol. Calcitriol stimulates T regulatory lymphocytes and suppresses cytokine release both from Th1 and Th2 lymphocytes (20, 21).

COVID-19 loaded a proportionately heavy burden on the elderly (22, 23). One of the main reasons for this was the common occurrence of chronic medical conditions in this age group. Moreover, both the presence of comorbidities and

Table 4

Univariate and multivariate logistic regression analysis showing independent predictors of in-hospital mortality

	Logistic regression analysis					
	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.036	1.012 - .060	0.003			
Smoking	2.161	1.085 - 4.304	0.028			
Hyperlipidemia	3.116	1.446 - 6.717	0.004			
Diabetes mellitus	2.400	1.230 - 4.682	0.010			
Chronic kidney disease	3.220	1.353 - 7.661	0.008			
Chronic atrial fibrillation	9.054	1.965 - 41.718	0.005			
Congestive heart failure	4.836	1.510 - 15.491	0.008			
Acute kidney injury	4.000	1.226 - 13.051	0.022			
eGFR	0.979	0.968 - 0.989	<0.001			
Hemoglobin	0.822	0.699 - 0.968	0.018			
Neutrophil count	1.408	1.226 - 1.617	<0.001			
Lymphocyte count	1.743	1.419 - 2.142	<0.001	1.375	1.092 - 1.731	0.007
White blood cell count	0.640	0.551 - 0.744	<0.001	0.815	0.679 - 0.979	0.029
C-reactive protein	1.008	1.004 - 1.013	0.001			
Albumin	0.158	0.071 - 0.353	<0.001	0.196	0.067 - 0.572	0.003
Calcium	0.267	0.141 - 0.506	<0.001			
25(OH) vitamin D	0.896	0.858 - 0.936	<0.001	0.927	0.875 - 0.982	0.010

Logistic Regression (Forward LR), CI: Confidence interval OR: Odds ratio

advancing age per se are associated with reduced 25(OH) vitamin D levels (24). We should take the effects of the lockdown and avoidance of sun exposure into account on the already insufficient 25(OH) vitamin D levels.

Hypothesis regarding the potential deleterious roles of vitamin D deficiency on COVID-19 patients initially originated from the studies in which 25(OH) vitamin D was shown to be related to increased susceptibility to infection (25, 26). However, some studies did not show the beneficial effects of vitamin D supplementation on the prevention and treatment of viral respiratory infections (27, 28). Then, some authors reported that the mean level of 25(OH) vitamin D level was inversely correlated with COVID-19 infection rates and mortality in 20 European countries (5). The authors emphasized the possible association of severely deficient vitamin D status and very high case fatality rates among the elderly in Spain and Italy. Some others also speculated that COVID-19 related mortality was lower in countries south of Latitude 35 degrees north might be related to vitamin D deficiency that is more prevalent due to limited sun exposure (29).

Despite all the experimental evidence regarding the antiviral and immunity supporting roles of vitamin D, along with indirect clinical evidence showing the potential detrimental effect of vitamin D deficiency on upper respiratory viral infections, to

our knowledge, only a few studies evaluated the vitamin D and mortality association in COVID-19 patients. Daneshkhah et al. (30) reported that in COVID-19 patients, serum C-reactive protein levels were inversely correlated with serum 25(OH) D levels. The authors concluded that since CRP is a marker of inflammation, vitamin D deficiency might be related to increased inflammation and cytokine storm in these patients. Alipio first reported the independent association between vitamin D deficiency and increased mortality(31). In another retrospective study, Raharusun and colleagues showed that 25(OH) vitamin D value was an independent predictor of mortality.

Our results present important data regarding the relationship between vitamin D deficiency and prognosis of COVID-19. First of all, the prevalence of vitamin D deficiency/insufficiency was very high among hospitalized moderate-to-severely ill COVID-19 patients. The mean level of 25(OH) vitamin D was 15.2 ± 10.3 ng/mL. Moreover, as COVID-19 severity increased, the level of 25(OH) vitamin D further reduced. Multivariable logistic regression analysis revealed that 25(OH) vitamin D level was independently associated with mortality, even after controlling for age and comorbid diseases was performed. Serum 25(OH) vitamin D level was positively correlated with serum C-reactive protein levels and negatively correlated with

VITAMIN D AND MORTALITY IN COVID-19 IN TURKEY

both neutrophil and lymphocyte counts. Thus, the unfavorable effects of low serum vitamin D levels in terms of disease severity and mortality might be partly due to the increased inflammation. Our results also showed that mean serum 25(OH) vitamin D level was negatively correlated with increasing age ($r=-0.3$, $p<0.001$). Thus, we speculate that disproportionately unfavorable clinical outcomes seen in the elderly may be, in part, due to the age-related vitamin D deficiency.

Some limitations of the present study deserve mention. First, since this study was a retrospective analysis, we did not control all the factors that potentially might have impacted the mortality rate. Our sample size is relatively small. However, it should be kept in mind that we only included patients who have moderate-to-severe COVID-19.

Conclusion

In conclusion, our analysis revealed that vitamin D insufficiency/deficiency was quite prevalent among hospitalized COVID-19 patients. The level of 25(OH) vitamin D level was inversely related to the severity of the COVID-19. Moreover, vitamin D level was an independent predictor of COVID-19 related mortality. Since it is still rampant in many areas of the world, and considering the lack of an effective vaccine and specific drugs, measures to strengthen the immune system might be strongly considered. Before recommending the routine application of high-dose vitamin D in vulnerable populations, controlled studies investigating the effects of vitamin D supplementation on the COVID-19 severity and mortality are warranted.

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical standards: The study protocol was approved by the Hospital Clinical Studies Ethical Committee (2020.06.1.01.072 and 12 June 2020).

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