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Correlation of vitamin D level with the clinical-radiological severity of COVID-19 in geriatric patients

Hüsnü Baykal, Ayşe Füsun Ülger

Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Chest Diseases, Ankara, Turkey

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ABSTRACT

Objective: This study was planned to investigate the effect of 25-OH-Vitamin D (Vit D) deficiency on clinical and radiological findings of coronavirus disease-2019 (COVID-19) in geriatric patients hospitalized due to COVID-19.

Material and Method: Seventy-five patients who were treated for COVID-19 were reviewed retrospectively, and grouped in relation with their ages [(1) 65-74, (2) 75-84, (3) >84 years] and the severity of Vit D deficiency [(1) severe deficiency: <10 ng/mL, (2) moderate deficiency: 10-20 ng/mL, (3) minor deficiency: 21-30 ng/mL, (4) normal: >30 ng/mL]. The complaints on admission, comorbidities, intensive care unit (ICU) need, length of hospital stay, laboratory data, and mortality of the ones who had and did not have Vit D replacement (n=18/75) were recorded. The patients were analyzed for COVID-19 severity using radiological and clinical markers.

Results: Moderate Vit D deficiency (10-20 ng/mL) was frequently detected. When the disease severity and Vit D levels were analyzed, it was found that the disease was more severe (46.6%) in the Vit D <10 ng/ml group, and milder (37.5%) in the >30 ng/ml group, but there was no statistically significant difference among the groups. Low or high Vit D levels did not show any significant correlations with the severity of pneumonia or the thorax CT findings. The intensive care unit (ICU) admission rate was significantly lower in those who had Vit D replacement ($p<0.001$).

Conclusion: The ICU admission rate was lower in patients who had Vit D replacement, however, serum Vit D concentrations were not correlated with COVID-19 severity or mortality risk.

Keywords: COVID-19, vitamin D, pneumonia, elderly, intensive care unit

INTRODUCTION

Individuals of all ages have been affected by the COVID-19 pandemic worldwide; however, the COVID-19-related mortality rate is significantly higher in the elderly. Several researchers investigated potential models to reduce infection rates and reported various molecules, including Vit D (1). A European study reported an inverse correlation between serum Vit D levels and the number of COVID-19 cases and mortality, however, another study reported the correlation between Vit D supplementation with less severe disease and a lower mortality rate in the elderly hospitalized patients (2,3).

The European Food Safety Authority (EFSA) has determined that six vitamins are important for maintaining a healthy immune system: vitamins D, C, A, ß-carotene, and B vitamins (B6, folate, and B12) (4).

Vit D plays an important role in the immune system: Vit D reduces the risk of microbial and viral infections by maintaining cellular physical defense and enhancing cellular immune responses (5,6).

Vit D contributes to humoral defense and has a regulatory role in proinflammatory cytokine production. Vit D can reduce cytokine storm and improve cellular immunity in severe COVID-19 patients (7-9).

Considering the hyper-inflammatory immune response induced by COVID-19, Vit D regulates vital anti-inflammatory mediators, and current data suggest that patients with Vit D deficiency may be more susceptible to being infected by SARS-CoV-2, and they may more likely develop severe symptoms (10). The high mortality rates observed in the elderly care facilities, particularly in the Northern countries with little exposure to sunlight, suggest that Vit D deficiency increases the severity of COVID-19 (11).

Corresponding Author: Hüsnü Baykal, drhusnubaykal@hotmail.com
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Old age is an independent risk factor for Vit D deficiency (12). A recent study reported that although Vit D deficiency is common in older people, the difference between older and oldest adults is negligible. Therefore, all seniors may carry a high risk for Vit D deficiency and should have Vit D supplementation regardless of their age (13).

COVID-19 infection affects all age groups, but the elderly appear to be more severely affected. Cytokine storm and high pro-inflammatory cytokine release appear to be an important pathophysiological mechanisms in the elderly COVID-19 patients (14).

In 2020, Ebadi and Montano-Loza reported that Vit D could suppress the expression of pro-inflammatory cytokines including IL-1α, IL-1β, and TNF-α, found Vit D deficiency in 50% of COVID-19 cases and approximately 70% of the ones who died due to COVID-19 (15).

Ilie et al. investigated the relationship of mean Vit D levels with morbidity and mortality of COVID-19 in 20 European countries and reported negative correlations of Vit D levels (mean 56 mmol/L) with the number and mortality of COVID-19 cases (2).

A study on nutritional status in COVID-19 patients reported that Vit D deficiency was the most common deficiency. The mean Vit D level was reported as 15.73 ng/dl, and there was severe deficiency (≤10 ng/dl) in 24% of the patients. 100% of mechanically ventilated COVID-19 patients had Vit D deficiency (16). It was reported that the severity of Vit D deficiency was correlated with the prognosis of COVID-19 (relative risk 1.59 if <30 ng/mL) and risk of death (relative risk 1.56) (17,18). In another study, it was reported that the 14-day mortality rate was 31.3% in older adults who did not have Vit D supplements (3).

Vit D deficiency appears to be correlated with infection severity and mortality. However, findings cannot be generalized, and there is a need for randomized controlled trials (19).

In a study on COVID-19 patients who had and did not have Vit D replacements, only 1 patient (2.7%) died in the Vit D replacement group while 24 patients (14.1%) died in the non-replacement group (p=0.038). It has been reported that a single dose of 300,000 IU Vit D may be useful in the treatment of COVID-19 (20). Unlikely, another study reported that there was no link between serum Vit D concentrations and the risk of severe COVID-19 infection or death (21).

We investigated the effect of the severity of Vit D deficiency and high dose replacement therapy on the clinical and radiological findings of COVID-19 in geriatric patients hospitalized with the diagnosis of COVID-19.

MATERIAL AND METHOD

The ethics committee approval for this study was obtained by Health Science University Keçiören Education and Training Hospital Clinical Studies Ethics Board (Date: 28/12/2021, Decision No: 2012-KAEK-15/2440). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data of the elder patients (>65 years old) with a confirmed diagnosis of COVID-19 [clinical-radiological diagnosis or with polymerase chain reaction (PCR)] and hospitalized between April 01, 2020, and March 01, 2021, were reviewed retrospectively from the electronic database of our hospital. The age groups were determined as (1) 65-74 years, (2) 75-84 years, and (3) >84 years. There were 75 patients (28 women and 47 men) included in the study. Whether the patients received Vit D replacement during the hospitalization period, their initial symptoms, comorbid diseases, hospital admission, intensive care unit (ICU) admission, length of hospital stay, mortality status, and their laboratory and radiological data were obtained from the electronic database.

The inclusion criteria were being ≥65 years old and the presence of measured Vit D levels. The ones who were younger than 65 years old and the ones who did not have Vit D level measurements were excluded.

Laboratory Data

Serum Vit D, ferritin, CRP, LDH, D-dimer, and troponin levels of the patients hospitalized for COVID-19, measured on the day of hospitalization, were recorded (previous Vit D supplementation status was unknown). The patients who had and did not have 300,000 IU Vit D replacement during hospitalization were determined. The severity of Vit D deficiency was categorized as; (1) severe Vit D deficiency: <10 ng/mL, (2) moderate deficiency: 10-20 ng/mL, (3) minor deficiency: 21-30 ng/mL, (4) normal: >30 ng/mL (22,23).

Clinical evaluation of COVID-19 severity was classified into mild, moderate, severe, or critical (WHO 2020. "Clinical management of COVID-19) [mild disease: Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia, moderate disease: clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 ≥90% on room air, severe disease: with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate >30 breaths/min; severe respiratory distress; or SpO_2 <90% on room air, critical disease: respiratory failure not fully explained by cardiac failure or fluid overload. The patients admitted to the second or tertiary intensive care units, requiring high flow oxygen (HFO) or non-invasive/invasive mechanical ventilation (NIMV/IMV) were regarded to have critical disease].

Radiological Evaluation

Postero-anterior chest X-rays (CXR) and thorax computerized tomography (CT) performed at the first admission to the hospital were examined. Radiologic classification on high-resolution CT (HRCT) (typical, indeterminate, atypical, negative for pneumonia) and CXR grading of lung involvement (mild, moderate, severe) (RSNA Chest CT/ CXR findings related to COVID-19) were recorded (24).

Statistical Analysis

For the distribution of all numerical values, the Kolmogorov-Smirnov or Shapiro-Wilk test, skewness-kurtosis values, coefficient of variation, histogram, and detrended plot graphs were examined. Categorical data were analyzed with Chi-square or Fisher test, as appropriate. Categorical data were displayed as n / %. In our study group, 65-74-year-old, 75-84-year-old, and ≥85 years old groups were analyzed with ANOVA test, according to the Vit D levels. The relationship between gender and Vit D level was analyzed with Student's t-test. In our study group, the correlation between Vit D levels and COVID-19 severity (mild, moderate, severe, critical) was analyzed with an ANOVA test. Similarly, analyses of the numerical values in more than two groups were performed with Anova or the Kruskal Wallis tests, as appropriate. All analyses were performed using SPSS version 22. P values smaller than 0.05 were considered statistically significant.

RESULTS

There were 75 patients in total; 37.3% (n=28) were females and 62.7% (n=47) were males. Among the age groups, the 65-74-year-old age group comprised 48.0% (n=36) of all patients, and it was the most crowded group (Table 1). Each patient had at least one comorbid disease (%90, n=68). The most common comorbidity in women was cardiovascular disease (CVD) in 92% (n=26), and diabetes mellitus (DM) in 50% (n=14) of the females. In men, CVD was present in 78% (n=34), DM in 34% (n=14); non-pulmonary cancer 19% (n=8) and cerebrovascular disease (CVD) 21% (n=9) were also more common in men (not shown in the **Table**).

Dyspnea was present in 91.6% (n=31), 83.8% (n=26) and 87.7% (n=7), cough in 38.8% (n=14), 29% (n=9) and 62.5% (n=5), and fever was seen in 47.2% (n=17), 29% (n=9) and 12.5% (n=1) of the age groups, respectively. Dyspnea was more frequent in patients who needed ICU care (93.1%) (n=41) and in the ones who died (94.2%) (n=33), and fever was more frequent in those who did not need ICU care (41.9%) (n=13) and in those who survived (35.9%) (n=14), but there was no statistically significant difference among the groups (not shown in the **Table**). Mortality (47.2% (n=17), 46.6% (n=14), 50% (n=4), respectively) and ICU admission [(61.1% (n=22), 58% (n=18), and 50% (n=4)], respectively) were similar in the age groups studied, and no statistically significant correlations were found (not shown in **Table**).

Table 1. The distribution of the age groups and genders

	Number (n)	Percent (%)
Gender		
Female	28	37.33
Male	47	62.67
Age (years)		
65-74	36	48.00
75-84	31	41.33
85+	8	10.67

Overall, the Vit D levels were low in all age groups, and the Vit D level did not significantly decrease in parallel to aging. Moderate Vit D deficiency (10-20 ng/mL) was frequently detected. The mean Vit D was level 22.25±20.1 ng/mL (median: 16.46 ng/mL) in the 65-74-year-old age group, but the levels were not significantly different among the age groups. The mean Vit D levels were similar in males and females showing moderate Vit D deficiency, however, there was no statistically significant difference (**Table 2**).

Table 2. Vitamin D levels by age group and gender

	Vitamin D levels (ng/ml)		
	Mean	Median	p
Age (years)			0.095
65-74	22.25±20.1	16.46	
75-84	14.78±9.73	11.33	
85+	18.35±11.16	16.72	
Gender			0.322
Female	18.94±20.64	12.15	
Male	18.63±12.58	15.74	

When the disease severity and Vit D levels were analyzed, it was found that the disease was more severe (46.6%) (n=14) in the Vit D <10 ng/ml group, and milder (37.5%) (n=3) in the >30 ng/ml group, but there was no statistically significant difference among the groups. Due to the small number of patients in the groups, disease severity and Vit D levels data were divided into two subgroups to increase the number of patients and analyzed with Fisher's exact test. No statistical significance was found between the groups (**Table 3**).

Vit D level groups did not show any statistically significant correlations with the severity of pneumonia or the thorax CT findings. CXR, chest CT findings, and Vit D level data were divided into two subgroups and analyzed with Fisher's exact test. No statistical significance was found between the groups (**Table 4**).

Table 3. The clinical severity of COVID-19 and the Vitamin D levels

Vitamin D levels (ng/ml)					p*
Clinical stage	0-10 ng/ml (%)	10-20 ng/ml (%)	20-30 ng/ml (%)	>30 ng/ml (%)	
Mild n (%)	0 (0)	4 (50)	1 (12.5)	3 (37.5)	0.083
Moderate n (%)	2 (16.67)	8 (66.67)	2 (16.67)	0 (0)	
Severe n(%)	14 (46.67)	8 (26.67)	5 (16.67)	3 (10)	
Critical n(%)	7 (28)	12 (48)	3 (12)	3 (12)	
Vitamin D levels (ng/ml)					**p****
Clinical stage	<20ng/m		>20ng/m		
	n	%	n	%	
Mild-Moderate	14	25.45	6	30.00	0,452
Severe-Critical	41	74.55	14	70.00	

*Chi-square test **Fisher test ***WHO 2020. "Clinical management of COVID-19, grouped as mild, moderate, severe, or critical)

Table 4. Vitamin D level groups, pneumonia severity, and chest CT findings

Vitamin D levels (ng/ml)					**p value***
Chest X-ray pneumonia severity	0-10	10-20	20-30	30+	0.265
Normal n(%)	1(33.33)	0(0)	1(33.33)	1(33.33)	
Mild n (%)	3(12)	16(64)	4(16)	2(8)	
Moderate n(%)	14(48.28)	9(31.03)	2(6.9)	4(13.79)	
Severe n (%)	5(27.78)	7(38.89)	4(22.22)	2(11.11)	
Chest CT findings					
Typical n (%)	15(30)	23(46)	7 (14)	5(10)	
Indeterminate n (%)	3 (60)	2(40)	0 (0)	0(0)	0.265
Atypical n (%)	1(16.67)	2(33.33)	1(16.67)	2(33.33)	
Negative n (%)	0 (0)	1(100)	0 (0)	0(0)	
Chest X-ray pneumonia severity	**Vitamin D levels (ng/ml)**				**p value***
	<20 ng/m		**> 20 ng/m**		
	n	%	n	%	
Normal- Mild	20	36.36	8	40.00	0.488
Moderate-Severe	35	63.64	12	60.00	
Chest CT findings	**Vitamin D levels (ng/ml)**				**p value****
	< 20 ng/m		**> 20 ng/m**		
	n	%	n	%	
Typical-Indeterminate	43	78.18	12	60.00	0.102
Atypical-Negative	12	21.82	8	40.00	

*Chi-square test; **Fisher test; CT, Computerized tomography

Vit D groups did not show any statistically significant correlations with the lymphocyte or eosinophil counts, or CRP, D-dimer, ferritin, and troponin levels (not presented in the **Table**).

Vit D levels did not have any statistically significant correlations with mortality or ICU admission. ICU admission, mortality, and Vit D level data were divided into two subgroups and analyzed using Fisher's exact test. No statistical significance was found between the groups (**Table 5**).

Table 5. Vitamin D levels, ICU admission, and mortality

		Vitamin D levels (ng/ml)				**p***
		0-10	**10-20**	**20-30**	**30+**	
ICU n(%)	Not admitted	5(16.13)	16 (51.61)	6(19.35)	4(12.9)	0.141
	Admitted	18(40.91)	16(36.36)	5(11.36)	5(11.36)	
Mortality n(%)	Died	12(34.29)	14(40)	5(14.29)	4(11.43)	0.956
	Survived	11(28.21)	17(43.59)	6(15.38)	5(12.82)	
ICU admission, and mortality		Vitamin D levels (ng/ml)				p**
		<20ng/m		>20ng/m		
		n	%	n	%	
ICU		26	48.15	9	45.00	0,509
Mortality		28	51.85	11	55.00	

*Chi-square test **Fisher test, ICU: Intensive care unit

The days of hospitalization were determined as 13.7 days, 14.5 days, 11.3 days, and 10.2 days, in the Vit D level groups <10 ng/mL, 10-20 ng/mL, 21-30 ng/mL, and >30 ng/mL, respectively. There was no significant difference among the Vit D groups (not shown in the Table).

In the first hospitalization period, high-dose vit D replacement was given to only 18 patients with low serum Vit D levels. The analysis of Vit D replacement status (n=18/75) and ICU admission showed a statistically significant difference (p<0.001). Those who had Vit D replacement had a lower ICU admission rate, however, no statistically significant difference was observed in the mortality rates (**Table 6**). The number of days of hospitalization did not show any statistically significant correlation with the laboratory parameters (CRP, LDH, D-dimer, troponin) when the groups that had and did not have Vit D replacement were compared (not shown in the table).

Table 6. ICU admission and mortality in patients who had and did not have Vitamin D supplementation.

		No Vitamin D supplementation		**Had Vitamin D supplementation**		**p**
		n	**%**	**n**	**%**	
Survival	Died	28	50.00	7	38.89	0.292
	Survived	28	50.00	11	61.11	
ICU admission	No	18	31.58	13	72.22	<0.001
	Yes	39	68.42	5	27.78	

ICU: Intensive care unit

DISCUSSION

Vit D plays a key role in modulating the immune system, and its deficiency is associated with immune system disorders (5). Vit D reduces the risk of bacterial and viral infections with both the continuity of cellular physical defense and the strengthening of innate and adaptive cellular immunity.6 Bulut et al. found that Vit D deficiency is a frequent occurrence in COPD and is correlated with the frequency of exacerbation and hospitalization in COPD patients (25).

Due to the hyper-inflammatory nature of COVID-19, the anti-inflammatory mediator regulatory capacity of Vit D is noteworthy. In terms of regulation of anti-inflammatory mediators, one may suggest that patients with Vit D deficiency may be more susceptible to COVID-19, and the disease may be more severe (10). Higher number of cases and higher mortality were reported in the ones with Vit D deficiency and COVID-19, however higher disease severity and higher survival rates were reported in the ones who had Vit D supplementation (3,4).

In our study, the Vit D levels were generally low in all age groups. Consistent with the literature, moderate Vit D deficiency (10-20 ng/mL) was determined. The mean Vit D level was the highest at 22.25±20.1 ng/ml (median: 16.46 ng/ml) in the 65-74-year-old age group, however, there was no significant difference among the age groups. The mean Vit D levels were similar in males and females, and both genders had moderate Vit D deficiency (26).

The age groups (the old and the oldest) did not show severe Vit D deficiency or decrease in Vit D levels parallel to aging, however, there are dissimilar results in the literature (13).

Bassatne et al. (27) reported that they observed an increasing trend in COVID-19 disease severity in patients with serum 25(OH) D <30 ng/ml (RR=3.0, 95% CI) in their meta-analysis.

There was no statistically significant difference among the Vit D groups for COVID-19 severity, but the number of severe stage patients was higher in the severe Vit D deficiency (<10 ng/ml) group, and the number of mild stage patients was higher in the normal Vit D level group (11).

Although a negative correlation was reported between Vit D level and radiological pulmonary involvement in the literature (26), no statistically significant correlation was found between Vit D level and CXR pneumonia severity or chest CT findings in our study.

D-dimer is one of the most important indicators associated with mortality risk in COVID-19. Studies have reported a negative correlation between Vit D and D-dimer levels. In our study, Vit D groups did not show any negative or positive correlations with D-dimer, CRP, lymphocyte, eosinophil, ferritin, or troponin values (28,29).

Bassatne et al. (27) pooled data from three individual studies (30-32) (n=480) and found that the risk of intensive care unit admission was increased in COVID-19 patients with low 25(OH) D levels (<20 ng/ml). However, in conclusion, none of the outcomes evaluated showed a clear and strong correlation between vitamin D status on COVID-19 health-related outcomes.

Similar to literature data, the ICU admission rate was higher (40%) (n=18) in the group with severe Vit D deficiency (0-10 ng/ml), but the difference among the Vit D groups was not statistically significant (16,33).

The highest mortality rate in the Vit D subgroups was observed in the moderate (10-20 ng/ml) 40% (n=14) and severe deficiency (0-10 ng/ml) 34.2% (n=12) groups. However, no significant difference was found among the Vit D subgroups in terms of mortality. Our results are not in line with the previous studie (18,19,29).

Hernandez et al. (31) reported significantly longer hospital stays in COVID-19 patients with low serum 25(OH)D (<20 ng/ml) than in the normal group (p=0.013). But Baktash et al. (28) found no significant difference between Vit D groups in COVID-19 patients in terms of mean hospital stay.

In our study, the number of hospitalization days was 13.7 days in the severe Vit D deficiency group and 10.2 days in the normal Vit D level group. There was no significant difference among the Vit D groups for this parameter.

In a meta-analysis involving hospitalized COVID-19 patients, it was found that there was no statistically significant difference in mortality in patients who received vitamin D supplementation compared to patients who did not receive it (p=0.87) (34).

Our results (mortality rate 38% (n=7) in the group that had Vit D replacement, 50% (n=28) in the group that did not have it) were not similar to the previously reported results in terms of mortality, hospitalization days, and laboratory values (CRP, LDH, D-dimer, troponin) when the patients who had and did not have Vit D replacement were compared (35).

In a meta-analysis (n=532) of data from two randomized controlled trials and a retrospective case-control study involving hospitalized COVID-19 patients, it was reported that patients who received vitamin D supplementation had a statistically (p<0.0001) lower ICU requirement than patients who did not (34).

Tan et al. (36) In their prospective cohort study, it was observed that 17 patients with COVID-19 who received 1000 IU of vitamin D3, magnesium, and B complex daily for up to 14 days had a reduced risk of admission to ICU compared to 26 patients who did not receive.

Similar to the studies in the literature, a statistically significant difference was found when the status of having a Vit D replacement (n=18/75) and ICU admission were compared (p<0.001). Those who had Vit D replacement had a lower ICU admission rate (ICU admission rate was 27.7% (n=5) in the group that had Vit D replacement, 68.4% (n=39) in the group that did not have Vit D replacement) (3).

However, contrary to the results of these studies; there is also a study reporting that a single oral supplement of vitamin D3 (200,000 IU of vitamin D3) (n=120/120) did not improve COVID-19-related health outcomes, such as mortality, intensive care unit admission, and need for mechanical ventilation, compared to placebo (37).

It is not possible to generalize the results of this single-center study. We could not obtain data related to Vit D deficiency including obesity, socioeconomic status, population demographics, and exposure to sunlight. We believe that these factors would influence the results of the study (12). We did not have any information on the Vit D replacement statuses of the patients before they had COVID-19. We were unable to distinguish whether Vit D deficiency was a pre-existing deficiency in patients with COVID-19, or the decrease was due to the inflammatory process as a result of rapid metabolism of Vit D, and/or because Vit D is a negative acute-phase reactant (19).

CONCLUSION

The results of the systematic review and meta-analysis revealed inconclusive evidence of a relationship between low serum 25(OH) D levels (<20 ng/ml) and the risk of mortality, admission to the intensive care unit, mechanical ventilation, and the need for non-invasive ventilation. puts it. In addition, no associations were found between disease severity and risk of ARDS, and length of hospital stay.

Although the ICU admission rate was found to be low in patients who had Vit D replacement in our study, our findings do not support a potential link of Vit D concentrations in general with disease severity or mortality risk of COVID-19 infection in hospitalized elderly patients. To achieve statistical significance in disease severity, mortality, and the benefit of Vit D replacement, expanding the sample size at the national level may be helpful. New studies should be conducted to determine whether a low Vit D level is the cause or consequence of the COVID-19-related inflammatory process.

ETHICAL DECLARATIONS

Ethics Committee Approval: The ethics committee approval for this study was obtained by Health Science University Keçiören Education and Training Hospital Clinical Studies Ethics Board (Date: 28/12/2021, Decision No: 2012-KAEK-15/2440).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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REFERENCES

1. Glinsky GV. Tripartite combination of candidate pandemic mitigation agents: vitamin D, Quercetin, and Estradiol manifest properties of medicinal agents for targeted mitigation of the COVID-19 pandemic defined by genomics-guided tracing of SARS-CoV-2 targets in human cells. Biomedicines 2020; 8: 129.
2. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020; 32: 1195-98.
3. Annweiler G, Corvaisier M, Gautier J, et al. Vitamin D supplementation associated to better survival in hospitalized frail elderly COVID-19 patients: The GERIA-COVID quasi-experimental study. Nutrients 2020; 12: 3377.
4. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA). Scientific Opinion on the substantiation of health claims related to vitamin D and normal function of the immune system and inflammatory response (ID 154, 159), maintenance of normal muscle function (ID 155) and maintenance of normal cardiovascular function (ID 159) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA J 2010; 8: 1-17.
5. Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. Nutrients 2018; 10: 1656.
6. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020; 12: 988.
7. Sloka S, Silva C, Wang J, Yong VW. Predominance of Th2 polarization by vitamin D through a STAT6-dependent mechanism. J Neuroinflammation 2011; 8: 56.
8. Bertoldi G, Gianesello L, Calò LA. Letter: ACE2, Rho kinase inhibition and the potential role of vitamin D against COVID-19. Aliment Pharmacol Ther 2020; 52: 577-8.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
10. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. Aging Clin Exp Res 2020; 32: 2141-58.
11. Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity-plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. J Intern Med 2021; 289: 97-115.
12. Wyskida M, Wieczorowska-Tobis K, Chudek J. Prevalence and factors promoting the occurrence of vitamin D deficiency in the elderly. Postepy Hig Med Dosw (Online) 2017; 71: 198-204.
13. Cheng Q, Du Y, Hong W, et al. Factors associated to serum 25-hydroxyvitamin D levels among older adult populations in urban and suburban communities in Shanghai, China. BMC Geriatr 2017; 17: 246.
14. Zhao M. Cytokine storm and immunomodulatory therapy in COVID-19: Role of chloroquine and anti-IL-6 monoclonal antibodies. Int J Antimicrob Agents 2020; 55: 105982.
15. Ebadi M, Montano-Loza AJ. Perspective: improving vitamin D status in the management of COVID-19. Eur J Clin Nutr 2020; 74: 856-9.

16. Im JH, Je YS, Baek J, Chung MH, Kwon HY, Lee JS. Nutritional status of patients with COVID-19. Int J Infect Dis 2020; 100: 390-3.
17. Maghbooli Z, Sahraian MA, Ebrahimi M, et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PLoS One 2020; 15: e0239799.
18. Hastie CE, Mackay DF, Ho F, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr 2020; 14: 561-5.
19. Oscanoa TJ, Amado J, Vidal X, Laird E, Ghashut RA, Romero-Ortuno R. The relationship between the severity and mortality of SARS-CoV-2 infection and 25-hydroxyvitamin D concentration-a metaanalysis. Adv Respir Med 2021; 89: 145-57.
20. Yildiz M, Senel MU, Kavurgaci S, Ozturk FE, Ozturk A. The prognostic significance of vitamin D deficiency in patients with COVID-19 pneumonia. Bratisl Lek Listy 2021; 122: 744-7.
21. Hastie CE, Pell JP, Sattar N. Vitamin D and COVID-19 infection and mortality in UK Biobank. Eur J Nutr 2021; 60: 545-8.
22. Kweder H, Eidi H. Vitamin D deficiency in elderly: Risk factors and drugs impact on vitamin D status. Avicenna J Med 2018; 8: 139-46.
23. Hanley DA, Cranney A, Jones G, et al; Guidelines committee of the scientific advisory council of osteoporosis Canada. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. CMAJ 2010; 182: E610-8.
24. Simpson S, Kay FU, Abbara S, et al. Radiological Society of North America Expert Consensus Statement on Reporting Chest CT Findings Related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA-Secondary Publication. J Thorac Imaging 2020; 35: 219-27.
25. Bulut S, Karamanlı H, Şahin ME, Çelik D, Biber Ç. Association between vitamin D levels and frequency of disease exacerbations and hospitalizations in patients with COPD. J Health Sci Med 2022; 5: 471-7.
26. De Smet D, De Smet K, Herroelen P, Gryspeerdt S, Martens GA. Serum 25(OH)D level on hospital admission associated with COVID-19 stage and mortality. Am J Clin Pathol 2021; 155: 381-8.
27. Bassatne A, Basbous M, Chakhtoura M, El Zein O, Rahme M, El-Hajj Fuleihan G. The link between COVID-19 and Vitamin D (VIVID): a systematic review and meta-analysis. Metabolism 2021; 119: 154753.
28. Baktash V, Hosack T, Patel N, et al. Vitamin D status and outcomes for hospitalized older patients with COVID-19. Postgrad Med J 2021; 97: 442-7.
29. Sulli A, Gotelli E, Casabella A, et al. Vitamin D and lung outcomes in elderly COVID-19 patients. Nutrients 2021; 13: 717.
30. Cereda E, Bogliolo L, Klersy C, Lobascio F, Masi S, Crotti S. Vitamin D 25OH deficiency in COVID-19 patients admitted to a tertiary referral hospital. Clin Nutr 2021; 40: 2469-72.
31. Hernandez JL, Nan D, Fernandez-Ayala M, Garcia-Unzueta M, Hernandez-Hernandez MA, Lopez-Hoyos M. Vitamin D status in hospitalized patients with SARS-CoV-2 infection. J Clin Endocrinol Metab 2021; 106: e1343. e135.
32. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Sci Rep 2020; 10: 1-8.
33. Ohaegbulam KC, Swalih M, Patel P, Smith MA, Perrin R. Vitamin D supplementation in COVID-19 patients: a clinical case series. Am J Ther 2020; 27: e485-90.
34. Shah K, Saxena D, Mavalankar D. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. QJM 2021; 114: 175-81.
35. Panagiotou G, Tee SA, Ihsan Y, et al. Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. Clin Endocrinol (Oxf) 2020; 93: 508-11.
36. Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, Thien SY. A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. medRxiv 2020
37. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CS. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA 2021; 17: 2021.