Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Evaluation of vitamin D levels in COVID-19 patients referred to Labafinejad hospital in Tehran and its relationship with disease severity and mortality☆

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SUMMARY

Background and aims: Novel Coronavirus (COVID-19) first appeared in China in late 2019 which was rapidly spread worldwide. As the COVID-19 pandemic continues to spread, it is crucial to determine the prognostic factors contributing to the development of severe disease and higher mortality. Herein we aimed to evaluate the correlation between the severity and prognosis of patients with COVID 19 with serum 25(OH)D levels.

Method: This descriptive retrospective study was performed from March to April 2020 at a referral center for patients with COVID-19, Tehran, Iran. The data collection was performed by a checklist consisting of the demographic features and laboratory assessments consisted of serum 25(OH)D were evaluated and recorded. And investigate the relationship between serum 25(OH)D and clinical outcomes of patients.

Result: 205 patients with a mean age of 59.71 years were enrolled. Our findings did not reveal a significant difference in mean levels of vitamin between improved (34.09) and deceased patients (34.54). However, in patients with severe disease, there was a considerable difference in levels of vitamin D in improved and deceased patients (P.value: 0.021). According to our results, the mortality rate was slightly higher in men (odds ratio:2.2). Furthermore, the mean age (64.20 vs. 58.51) and the presence of at least two comorbidities (odds ratio: 2.40) were significantly higher in deceased patients.

Conclusion: In this study, we did not reveal a statistical difference in mean levels of vitamin D and the outcome of patients with COVID-19. We concluded that in patients with severe disease, vitamin D deficiency could affect the course of the disease and mortality, especially in comorbidity and older people.

1. Introduction

Novel Coronavirus (COVID-19) first appeared in China in late 2019 which was rapidly spread worldwide [1,2]. The initial research was focused on the epidemiology of the newly emerging pandemic which suggested that its origin is linked to the seafood and wet animal wholesale market in Wuhan, Hubei Province, China [3,4]. The next efforts were given to the clinical, para-clinical characteristics of the disease and the therapeutic approaches [5–8]. Although the major number of infected patients were asymptomatic or presented mild symptoms like fever and upper respiratory

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tract irritation, severe cases of infection can lead to pneumonia, acute respiratory distress syndrome (ARDS), septic shock, multiple organ failure, and eventually death. Additionally, there is evidence suggesting the non-respiratory complications of the virus as gastrointestinal, cardiovascular, and neurological involvement which could worsen the final prognosis [9,10].

It should be noted that, regardless of various promising repurposing therapies and extensive research to produce vaccines, COVID-19 infection, it is still a major global challenge affecting an increasing number of patients in the world which is expected to rise moreover with the ongoing epidemic as the restricted control measures as quarantine, travel restrictions and social distance is not enforceable in many countries [11–13].

Early studies report independent associations between low serum 25-hydroxyvitanim D and susceptibility to acute respiratory tract infections [14].

Recent studies have found an association between vitamin D and COVID-19 severity and mortality which is postulated to be based on the anti-inflammatory effects of vitamin D by suppressing cytokine storm as a known pathogenic process of ARDS development [15–18].

Little is known about the role of vitamin D in preventing COVID-19 infection and fatality and more evidence is needed to recommend vitamin D supplements in the treatment of COVID-19. Also, because of the prevalence of vitamin D deficiency in Iran, it is a crucial issue that needs to be addressed [19]. As there is still no strong evidence of the effect of vitamin D status in the course of the disease, herein we aimed to evaluate the correlation between the severity and prognosis of patients with COVID 19 with serum vitamin D levels.

2. Materials and methods

This descriptive retrospective study was performed from March to April 2020 at a referral center for patients with COVID-19, Tehran, Iran. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences in Tehran, Iran. (IR.SBMU.RETECH.REC.1399.058) [20].

As this is a newly emerging pandemic pertained to COVID-19, we enrolled all patients admitted with a confirmed diagnosis of COVID-19 who fulfilled the inclusion criteria.

COVID-19 was diagnosed based on the WHO interim guidance [21]. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swab specimens or the chest computed tomography (CT).

The inclusion criteria in our study were as follows:

1. Age 18 years or older
2. Presence of clinical symptoms leading to hospitalization regarding the national protocol which included patients with moderate and severe conditions (RR > 30 times/min, Oxygen saturation in room air, less than 93%, Partial pressure ratio of arterial oxygen to air pressure, concentration Inspired by oxygen, (PaO2/FiO2)less than 300 mm Hg) [22].
3. A positive test for the nucleotide acid of SARS-COV-2 in a Nasopharyngeal swab specimen by (RT-PCR) or chest CT scan compatible with COVID-19 patterns.

Our criteria for considering COVID-19 patients were positive PCR and if negative, cases with Covid-19 symptoms and CT scan changes according to Covid-19 were regrading as Covid-19 patients.

In the following, the data collection was performed by a checklist consisting of the demographic features like age, sex, past medical history (DM, HTN, CKD, COPD), clinical symptoms as fever, myalgias, coughs, dyspnea, vital sign such as temperature, pulse rate, respiratory rate, saturation, duration of hospitalization and clinical outcome.

Additionally, laboratory assessments consisted of a complete blood count, C-reactive protein (CRP) (adult normal range: 0.08–3.1 mg/L), and serum 25(OH)D were evaluated and recorded.

In this study, serum 25(OH)D were considered as “very low” below 10 ng/ml, “insufficient” at 10–30 ng/ml, “sufficient” at 30–100 ng/ml, and “toxic” above 100 ng/ml, respectively.

Vitamin D deficiency is considered by most articles to be below 30 ng/dL [23–25], but in some studies, under 10 ng/ml class as “very low”, which is associated with cardiovascular disease [26,27] and a significant predictor for community-acquired pneumonia [28], as well as lower bone mineral densitometry and T scores than those with insufficient or normal values [29]. Because of these systemic effects, in patients with vitamin D deficiency, less than 10 ng/dL was considered “very low”.Severe COVID-19 is defined as dyspnea, a respiratory rate of 30 or more breaths per minute, a blood oxygen saturation of 93% or less, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao2: Fio2) of less than 300 mm Hg, or infiltrates in more than 50% of the lung field within 24–48 h from the onset of symptoms [30].

Eventually, the statistical analysis was performed using IBM SPSS© software version 19.0. For statistical analysis of the variability and mean of the variables, two-sample-tests or Chi-square tests were performed. To investigate the relationship between serum level 25 (OH) D and clinical outcomes of patients, a multivariate logistic regression test was used. A two-side P-value <0.05 was considered statistically significant.

3. Results

205 patients with the mean age of 59.71 ± 14.92 years were enrolled, of whom 126 (68.46%) were males. *From the total patients, 59* (28.78%) did not have comorbidity and 95 (46.34%) had at least one comorbidity. We revealed that the mean CRP level at presentation was 3.90 ± 2.01 *mg/L*. Regarding the PCR assay, 113 patients (55.12%) were PCR positive.

More ever, based on our results, the main clinical presentation was dyspnea (62.44%) followed by cough and fever. The mean saturation at arrival was 88.31(STD: 4.78).

In terms of disease severity, the patients were categorized into moderate (162 patients) and severe groups (43 patients). The mean level of vitamin D was 33.86 ± 26.42 in the moderate group and 35.41 ± 21.25 in the severe group, a difference which was not statistically significant (p.value = 0.347).

The summary of the clinical, para-clinical characteristics of the patients, and association with vitamin D levels are brought in Table 1.

Additionally, we Observed that 162 patients improved and 43 patients died. The mean duration of hospitalization was 9.75 ± 5.47 days. Our findings did not reveal a significant difference in mean levels of vitamin between improved (mean: 34.09 ± 24.51) and deceased patients (mean:34.54 ± 28.74) (P-value = 0.226).

However, in patients with severe disease, there was a considerable difference in mean levels of vitamin D in improved patients (36.8 ± 17.54) and deceased patients (31.04 ± 22.61) (P.value: 0.021, CI 95% = 48.43-33.88). Furthermore, we revealed that the mortality rate was more evident in patients with very low levels of vitamin D (36%).

The summary of the association of vitamin D levels and mortality is brought in Table 2.

Eventually, we evaluated the other factors correlated with a higher mortality rate. According to our results, the mortality rate was slightly higher in men (odds ratio:2.2 (P.value = 0.034, CI

Table 1
The demographic, clinical and paraclinical characteristics of patients with COVID19 and their association with vitamin D levels.

Vitamin D classification (N)		Very low(25)	Insufficient(85)	Sufficient(88)	Toxicity(7)	TOTAL(205)
Mean Age(St.D)		52.04 (14.86)	58.01 (14.39)	62.68 (14.68)	70.29 (11.04)	59.71 (14.93)
Sex	Male	7	24	36	2	69
	Female	18	61	52	5	136
rRT -PCR test	Positive	11	41	36	4	92
	Negative	14	44	52	3	113
Severity of disease	Moderate	24	67	65	6	162
	Severe	1	18	23	1	43
Symptom	Dyspnea	14	53	57	4	128
	Fever	10	40	42	4	96
	Cough	9	48	52	5	114
	Myalgia	6	33	25	2	66
	GI	5	12	11	0	28
Comorbidity	DM	9	26	34	3	72
	HTN	12	30	46	3	91
	CKD	14	16	16	2	48
	IHD	6	21	23	1	51
	CANCER	2	4	3	2	11
	Hypothyroidism	1	4	2	1	8
	Autoimmune	0	2	3	0	5
	COPD	0	4	8	1	13
	TOTAL (%)	20 (80.0%)	52 (61.18%)	68 (77.27%)	6 (85.71%)	146 (71.22%)
Laboratory data	Mean WBC count (× 1000) (St.D)	7.69 (4266)	6.64 (3757)	6.70 (3758)	5.74 (2047)	6.76 (3774)
	Mean Hb(g/dL) (St.D)	12.92 (2.68)	13.09 (2.28)	12.69 (1.99)	12.81 (2.36)	12.89 (2.21)
	Mean Lymphocyte COUNT (St.D)	1353 (773.06)	1279 (614.65)	1419 (1012.02)	924 (547.82)	1336 (826.00)
	Mean CRP level (mg/L) (St.D)	4.34 (2.17)	4.11 (2.28)	3.55 (1.70)	4.00 (1.51)	3.90 (2.02)
	Mean O2 sat% (St.D)	88.68 (3.83)	88.18 (5.10)	88.43 (4.38)	87.14 (8.55)	88.31 (4.78)
Outcome	Died	9	15	17	2	43
	Improved	16	70	71	5	162

St.D: standard deviation, rRT -PCR test: real-time reverse transcription-polymerase chain reaction test, GI: gastro-intestinal, DM: diabetic Mellitus, HTN: hypertension, CKD: chronic kidney disease, IHD: ischemic heart disease, COPD: Chronic obstructive pulmonary disease, WBC: white blood cell, Hb: hemoglobin, CRP: C-reactive protein.

95% = 1.72–2.54)). Furthermore, the mean age (64.20 vs. 58.51 with P.value = 0.014, CI 95% = 76.72-59.23) and presence of At least two comorbidities (including diabetes mellitus, hypertension, ischemic heart disease, cancer, and thyroid disease) (odds ratio: 2.40 (P.value = 0.028, CI 95% = 1.92–2.84)) were significantly higher in deceased patients. The most common "1 < comorbidity" associated with mortality are Diabetic Mellitus and Ischemic Heart Disease.

The summary of factors potentially influencing the mortality is listed in Table 3.

4. Discussion

Our study of 205 patients illustrated no statistical difference in mean levels of vitamin D between patients with COVID-19 (92 patients who confirmed and 113 cases suspected for Covid-19) who died at the hospital and those improved. However, in subgroup analysis, in patients with severe disease, we estimated a considerable link between the mean vitamin D levels and mortality rate mean levels of vitamin D in improved patients (36.8 ± 17.54) and deceased patients (31.04 ± 22.61) (P.value: 0.021, CI 95% = 48.43-33.88). Additionally, we revealed that the mortality rate was more evident in patients with very low levels of vitamin D (36%).

It should be noted that the previous observational studies reported meaningful associations between low serum concentration of vitamin D and susceptibility to acute respiratory tract infections as a meta-analysis of 25 randomized controlled studies that confirmed the possible role of vitamin D in the prevention of acute respiratory tract infection [31].

Following the advent of COVID- 19, attention was drawn to the role of vitamin D status in disease severity as the study of Brown et al. who related the higher mortality rate of COVID-19 in southern European countries to vitamin D deficiency in comparison to northern European [32] or the study of Llie et al. who examined the status of vitamin D in 20 European countries with cases and mortality caused by COVID-19. Their results revealed a negative correlation between mean levels of vitamin D and the number of COVID-19 cases in each country [33]. Similarly, in a cohort study of 780 confirmed cases of COVID-19 in Indonesia, Raharusuna et al. revealed a considerable association between vitamin D deficiency and mortality even considering the other contributing factors as age, pre-existing comorbidity, and gender [34]. In another study, Lau et al. assessed vitamin D levels in twenty COVID-19 patients admitted in the intensive care unit which demonstrated the evidence of vitamin D deficiency in 11 subjects supporting the association of vitamin D deficiency and COVID-19 severity [35].

However, there is still no exclusive consensus on the role of vitamin D and mortality in COVID-19.

In our study, we did not show a negative relationship between total mortality and mean levels of vitamin D. However, similar to previous studies, we revealed that in patients with severe disease the vitamin D deficiency was significantly correlated with mortality. Besides, in patients with a very low level of vitamin D, the mortality rate was higher. Eventually, we illustrated the pre-existing comorbidity, old age, male sex as a risk factor of higher mortality which was in line with previous studies.

It is noteworthy that, vitamin D deficiency is a major public health problem worldwide in all age groups which considerably

Table 2
The association between vitamin D levels and clinical outcome in patients with COVID-19.

Vitamin D levels	Dead (N = 43)	Improved (N = 162)	Total	P.Value
Very low	9.88%	20.93%	12.20%	0.002
Insufficient	43.21%	34.88%	41.46%	0.126
Sufficient	43.83%	39.53%	42.93%	0.035
Toxicity	3.09%	4.65%	3.41%	0.276

Table 3
Analysis of factors associated with mortality.

		death(n=43)	Improved(n=162)	P.value
Age(St.D)		64.20 (15.17)	58.51 (14.68)	0.002
Gender	Male (%)	34 (79.07)	102 (62.96)	0.425
	Female (%)	9 (20.93)	60 (37.04)	0.331
Mean Lymphocyte count		1029 (498)	1416 (876)	0.016
Comorbidity 1<(%)		25 (58.14)	75 (46.29)	0.046
Severe disease (%)		11 (25.58)	32 (19.75)	0.026
Mean WBC counts (× 1000) (St.D)		6.91 (4186)	6.72 (3774)	0.212

deteriorates with age that is important concerning COVID-19 as case-fatality rates surge with age [36].

Overall, in this retrospective study, we observed the relationship between the deficit of vitamin D and COVID-19 severity and mortality. Although there are still some limitations as a low sample size of our study which hampers the decisive conclusion. Additionally, we did not adjust other factors that can affect the severity of the disease along with vitamin D deficiency as old age and pre-existing comorbidity. Despite these limitations, our work is unique as it is the first article in Iran on the status of vitamin D in patients with COVID-19 and It has also been shown that in patients with high severity of onset, vitamin D deficiency can be a risk factor for increased mortality.

Taking all considerations into account, apart from the prophylactic effect of vitamin D, regarding the importance of quarantine at home during the COVID-19 era, it is in paramount of importance to consider the bone metabolism health which relays on vitamin D supplementation, exposure to sunlight, and exercise.

5. Conclusion

In this study, we did not reveal a statistical difference in mean levels of vitamin D and the outcome of patients with COVID-19. However, we concluded that in patients with severe disease, vitamin D deficiency could affect the course of the disease and mortality. Additionally, we identified older age, male gender, and pre-existing comorbidities as other contributing factors of higher mortality.

Author contribution

Shabnam Tehrani: Conceptualization, Investigation, Validation, Project administration, Writing - Review & Editing; **Neda Khabiri**: Conceptualization, Resources; **Hamideh Moradi**: Resources, Methodology, Validation; **Mina Sadat Mosavat**: Methodology, Formal analysis; **Seyyed Saeed Khabiri**: Methodology, Formal analysis, Writing - Original Draft, Project administration.

Declaration of competing interest

The authors did not declare any conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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