Lack of association between vitamin D insufficiency and clinical outcomes of patients with COVID-19 infection

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Research Article

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Abstract

Background

A protective effect of vitamin D against COVID-19 is under investigation. We aimed to analyze the effect of vitamin D sufficiency on clinical outcomes of patients with COVID-19 infection.

Methods

In this retrospective study we analyzed the vitamin D levels of COVID-19 patients who were admitted to Razi Hospital (an infectious disease referral center in Mazandaran province in north of Iran) from February to March 2020. Overall, a cutoff point of 30 ng/mL was used for the definition of vitamin D sufficiency.

Results

153 patients were analyzed in this study who had laboratory documentation of a 25(OH) D level at the time of hospitalization. In total, 62.7% (n-=96) of the patients had a 25(OH) D level of less than 30 ng/mL and 37.25% (n = 57) had a 25(OH) D level of more than 30 ng/mL. In total, 49% (n = 75) of the patients suffered from at least one underlying disease. Vitamin D sufficiency was not associated with a statistically significant lower risk of adverse clinical outcomes of COVID-19 such as duration of hospitalization, lung involvement, intensive care unit (ICU) admission, invasive and non-invasive ventilation, the severity of disease or death.

Conclusions

Sufficient vitamin D levels were not found to be protective against adverse clinical outcomes in patients infected with COVID-19.

Introduction

Coronavirus 2019 or COVID-19, a respiratory infectious disease, has led to a pandemic of pneumonia-related illness [1–3]. The clinical features of this disease vary from asymptomatic or mild (in over 80%) to severe cases leading to acute respiratory syndrome and respiratory failure, requiring hospitalization in the intensive care unit, sepsis, septic shock and death [4–6]. The rapidly increasing number of infected individuals in highly critical states requiring intensive resources is a huge public health challenge worldwide [7]. Unfortunately, no suitable antiviral treatment has been found for this disease so far, and all therapeutics used are based on hypotheses that do not have sufficient evidence to support their use. In addition, a good vaccine is not yet commercially available for this viral infection, therefore given the high economic importance of the COVID-19 pandemic, it is necessary to find methods that reduce the risk of

infection and mortality at a low cost [8]. The status of the immune system is affected by multiple factors that may contribute to the risk of viral infections such as COVID-19. There are several vitamins and essential elements that have been shown to be necessary for a robust immune system response [9]. Recent studies have highlighted a crucial supportive role for vitamin D in immune system functions, particularly in balancing the inflammatory response to viral infection [9–11]. Vitamin D is a fat-soluble vitamin that plays a key role in modulating both innate and adaptive immune responses. Previous studies have also shown that adequate levels of vitamin D have been shown to reduce the risk of viral respiratory infections and the length of hospital stay [1, 12, 13]. On the other hand, there is no accurate information about the COVID-19 virus in this field and the role of vitamin D supplementation in reducing the risk of infection is still under evaluation. Furthermore, the role of vitamin D supplementation in reducing the risk of COVID-19 infection is still under investigation, however, no clinical evidence has been reported thus far [14]. Studies about the blood level of vitamin D in Iran showed a significant prevalence of vitamin D deficiency among the Iranian population [15, 16]. Mazandaran province is located in the north of Iran, along the southern coast of the Caspian Sea with a moderate climate. In this study, we investigated the effect of vitamin D sufficiency on clinical outcomes of patients with COVID-19 infection hospitalized in Razi hospital (a referral center of COVID-19 patients in Mazandaran province).

Materials And Methods

This was a retrospective study analyzing vitamin D levels of COVID-19 patients who were admitted to Razi Hospital (an infectious disease referral center in Mazandaran province in north of Iran) from February to March 2020. The study was approved by the Ethics Committee of Mazandaran University of Medical Science, Ramsar international branch (IR.MAZUMS.RIB.REC.1399.019).In this study all applied methods were carried out in accordance with relevant guidelines and regulations. The definitive diagnosis of COVID-19 infection was based on a positive PCR test of the nasopharyngeal swab sample. A total of 3 cc of whole blood was taken from each patient and the serum was removed and the vitamin D levels were measured by a high performance liquid chromatography method. Overall, a cutoff point of 30 ng/mL was used for the definition of vitamin D sufficiency [17]. All demographic, clinical, and diagnostic data of the patients and their vitamin D levels were recorded. Definitions of disease severity were based on the Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19 including : 1- Mild stage; 2- Non-severe or moderate (patient with a oxygen saturation (SpO2) > 94% not requiring supplemental oxygen); 3- Severe stage (patients with SpO2 ≤ 94% on room air, including patients on supplemental oxygen; 4- Critical (patients on mechanical ventilation and extracorporeal mechanical oxygenation, acute respiratory distress syndrome, end organ dysfunction and sepsis/septic shock). Severe and critical categories were defined as “severe” in our study. Statistical analysis was performed using the Stata software version 14.0. Differences between groups (patients with serum level 25(OH) D level ≥ 30 and patients with serum level 25(OH) D level ≤ 30) were determined by the chi-square test or Fisher's exact test. Multivariable analysis was performed using logistic regression to identify the relationship of socio-demographic characteristics and preexisting comorbidities and the level of vitamin D with adverse outcomes of COVID-19. Ordinal logistic regression was used to determine the

association between variables and severity of diseases. The descriptive values below 5% (P value < 0.05) were considered statistically significant. In cases with a statistically significant difference, adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

Results

A total of 841 patients with COVID-19 were admitted to Razi Hospital from February 2 to March 20, 2020, of which 153 patients were analyzed in this study who had laboratory documentation of a 25(OH) D level at the time of hospitalization. All patients had CT imaging findings typical of COVID-19 and a SARS-CoV-2 PCR-positive result. In total, 62.7% (n = 96) of the patients had a 25(OH) D level of less than 30 ng/mL and 37.25% (n = 57) had a 25(OH) D level of more than 30 ng/mL. To assess the role of vitamin D status in relation to the disease, socio-demographic features, comorbidity factors, and clinical outcomes, all data were classified into two subgroups based on 25(OH) D levels. The socio-demographics and comorbidities and clinical outcomes of COVID-19 patients are presented in Tables 1 and 2.

Table 1
Socio-demographics and Comorbidity of COVID-19 Patients Based on Vitamin D Level

		Total (N = 153) N (%)	25(OH) D level ≥ 30 (N = 57) N (%)	25(OH) D level ≤ 30 (N = 96) N (%)	P value	Odds ratio	95% CI
Socio-demographic characteristics							
Gender	Female	66 (43.13)	23(40.35)	43 (44.79)	0.6	NA	
	Male	87(53.86)	34(59.64)	53 (55.2)			
Age > 50		98 (64.05)	44 (77.19)	54(56.25)	0.009	2.63	1.258–5.509
Body mass index (BMI)		29.909 ± 5.81	29.15 ± 5.71	29.92 ± 5.92	0.32	NA	
Living area	Rural	57(37.25)	20(35.08)	37 (38.54)	0.73	NA	
	Urban	96 (62.7)	37(64.91)	59(61.45)			
Preexisting comorbidities							
Diabetes		41(26.79)	19 (38.59)	22 (22.91)	0.18	NA	
Hypertension		44 (28.75)	26 (45.61)	18 (18.75)	0.001	3.63	1.750–7.549
Cardiovascular disease		30 (19.6)	17(29.82)	13(13.54)	0.02	2.7	1.201–6.129
Dyslipidemia		10 (6.53)	1(1.75)	9 (9.37)	0.09	NA	
Hypothyroidism		9 (5.88)	0	9 (9.37)	0.02	0.906	0.850–0.966
Asthma		6 (3.92)	0	6 (6.25)	0.08	NA	
Malignancy		3 (1.96)	2	1 (1.04)	0.55	NA	
Chronic liver disease		2 (1.3)	1(1.75)	1 (1.04)	1	NA	
Chronic Kidney Disease		1 (0.65)	1(1.75)	0	0.37	NA	
NA: not applicant; CI: confidence interval							

Based on age group patients were distributed in three groups including 35.94% (n = 55) less 50 years old, 34.64% (n = 53) in the range 50–65 years and 28.75% (n = 44) more than 65 years old respectively; 58.2% (n = 89) of patients were male, and 41.8% (n = 64) were female. Of the 98 patients who were 50 years and

older, 56.25% had a blood level of 25(OH) D < 30 ng/mL (p = 0.009). There were no differences between the two groups (patients with serum level 25(OH) D level ≥ 30 and patients with serum level 25(OH) D level ≤ 30) in regards to gender and living area. Most of the patients had multiple underlying disorders. The most common underlying illnesses were hypertension 26.8% (n = 44), diabetes 26.8% (n = 41), cardiovascular disease19.6% (n = 30), dyslipidemia 6.5% (n = 10), hypothyroidism 5.9% (n = 9), asthma 5.9% (n = 9), malignancy 1.96% (n = 3) and chronic liver disease 1.3% (n = 2), respectively. In total, 49% (n = 75) of patients suffered from at least one underlying disease. Significant differences between the two groups were noted to be preexisting comorbidities such as hypertension, cardiovascular disease, and hypothyroidism (p < 0.05). Hypertension (17/30) and cardiovascular disease (13/30) were mostly noted among patients with blood level 25(OH) D level ≥ 30 ng/mL, while hypothyroidism was only seen in patients with blood level 25(OH) D level ≤ 30 ng/mL.

Table 2
The COVID-19 Clinical Outcomes of Patients Based on Vitamin D Level

Outcomes of patients		**Total (N = 153) N (%)**	**25(OH) D level ≥ 30 (N = 57) N (%)**	**25(OH) D level ≤ 30 (N = 96) N (%)**	**P value**
Duration of hospitalization (days) Mean ± SD		6.3 ± 4.12	6.36 ± 4.35	6.25 ± 4.01	0.8
Bilateral lung involvement		28(17.64)	10(17.54)	18(17.7)	0.3
ICU admission		10(6.53)	3(5.26)	7(7.29)	0.5
Invasive mechanical ventilator use		3(1.96)	1(1.75)	2(2.083)	1
Non-invasive ventilation		15(9.08)	5(8.77)	10(10.41)	1
Severity of disease	Mild	85(55.6)	27 (47.36)	58(60.41)	0.08
	Moderate	51(33.3)	21(36.84)	30(31.25)	
	Severe	17(11.1)	9(15.78)	8(8.33)	
Death		5(3.26)	2(3.57)	3(3.12)	1

The average hospitalization stay of patients were 6.3 ± 4.12 days. Bilateral lung involvement was seen in 17.64% of patients. In total, 6.53% of patients were admitted to the ICU. Invasive mechanical ventilator was utilized for 1.96% of patients while 9.08% of patients were under non-invasive ventilation. Based on severity of disease, 55.6% of patients were categorized into the mild form of COVID-19 disease, while 33.3% and 11.1% experienced the moderate and severe / critical forms of COVID-19, respectively. Overall, 3.26% of patients involved expired. Vitamin D sufficiency was not associated with a statistically

significant lower risk of adverse clinical outcomes of COVID-19 such as duration of hospitalization, lung involvement, ICU admission, invasive and non-invasive ventilation, severity of disease or death.

Ordinal logistic regression showed that male patients (OR 2.5, 95% CI (1.241, 5.301), P = 0.011) and patients with diabetes (OR 3.98, 95% CI (1.34, 11.86), P = 0.013) experienced the severe form of COVID-19 infection more often than other patients. Multiple logistic regression showed that patients with cardiovascular disease were more at risk of requiring non-invasive ventilation (OR 4.37, CI (1.44, 13.26), P = 0.009). There was no significant association between other effective predisposing risk factors such as socio-demographic characteristics and preexisting comorbidities on the outcome of COVID-19.

Discussion

The association between vitamin D status and seasonal respiratory infections has been proven in several studies [11, 18, 19]. Optimizing vitamin D status could improve the immune response and has been suggested as possibly protective in COVID-19 infection [20, 21]. The COVID-19 outbreak began during the winter and a common feature of the inhabitants of all countries north of the 42nd parallel is a vitamin D insufficiency [22]. These facts resulted in the concept of using vitamin D for the prevention of COVID-19 infection or using vitamin D as an intervention strategy in COVID-19 patients [3, 18]. In our study, only 37.25% of patients with documented COVID-19 infection had a sufficient blood level of vitamin D. However, after categorizing all patients based on a cutoff point of 30 ng/mL for 25(OH) D to assess the association between vitamin D sufficiency and severity of COVID-19 infection, we found a lack of effect of vitamin D insufficiency on clinical outcomes in patients with COVID-19 infection. Studies investigating the association of circulating levels of 25(OH) D and incidence and severity of COVID-19 are currently limited and prospective studies published to date are conflicting. Maghbooli et al. reported vitamin D sufficiency reduced the risk for adverse clinical outcomes in patients with COVID-19 infection, and Panagiotou1 et al. reported low serum 25(OH) D levels in patients hospitalized with COVID-19 are associated with greater disease severity [12, 13]. Consistent with our study findings, the study by Hastie et al. did not support a potential link between vitamin D concentrations and risk of COVID-19 infection [20]. Older age and co-morbidities are linked to an insufficient vitamin D supply [23, 24]. It is notable that 64.05% of our patients were greater than 50 years old. Therefore the high rate of patients in our study with blood 25(OH) D level ≤ 30 ng/mL may be due to the aging population. Unlike our study, where the severity of COVID-19 infection was not associated with lower blood levels of 25(OH) D, Baktash et al. assessed the potential relationship between vitamin D deficiency and COVID-19 severity in hospitalized older adults and found that older patients with lower serum concentrations of 25(OH) D, when compared with aged-matched vitamin D-replete patients, may demonstrate worse outcomes from COVID-19[23]. Moreover, a meta-analysis by Zhao et al. on 53000 COVID-19 patients, co-morbidities and old age showed a relationship with the renin angiotensin-aldosterone-system, vitamin D status and COVID-19 infection [25]. In our study, 19.6% of patients suffered from cardiovascular disease and after adjusting for socio-demographic features, comorbidity variables, and vitamin D level, multivariate logistic regression results have shown an increased need for ventilation in patients with cardiovascular disease. Other studies have shown increased risk of hospitalization stay and severe conditions requiring ventilation in patients with

diabetes and hypertension [20, 26, 27]. Several studies have reported that a higher prevalence of vitamin D deficiency was observed in patients with worse COVID-19 outcomes [12–14, 28]. In our study, there was no evidence to suggest that assessment of vitamin D can serve as an indicator of the outcomes of COVID-19 infection. In line with our findings, Hastie et al. reported that measurement of vitamin D would not be useful to evaluate the risk of COVID-19 in clinical practice [20].

Conclusion

Despite the fact that the number of patients with an insufficient blood level of vitamin D were greater in our study, and approximately 44% of patients fell into the moderate and severe/critical categories, some requiring invasive/non-invasive ventilation, ICU admission, longer hospitalization and death, there was no statically significant evidence that insufficient blood levels of vitamin D might play a role in adverse outcomes of COVID-19 infection. Larger prospective studies are needed however to support or refute our observations.

Abbreviations

Odds ratio: OR; Confidence interval: CI; Peripheral oxygen saturation:SPO2; Body mass index: BMI; Intensive care unit: ICU

Declarations

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Authors' contributions

AD, NN and FA designed the project, collected data, wrote and performed the critical review of the manuscript. MA, AT, HI, ZS, LD, RN, NV and ZD contributed to clinical data collection. MA and RN carried out statistical interpretation. All authors read and approved the final manuscript.

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Availability of data and materials

All data analysed during this study are included in this published article.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ramsar international branch of Mazandaran University of Medical Sciences with code: IR.MAZUMS.RIB.REC.1399.019. In addition, written informed consent was obtained from all subjects or, if subjects are under 18, from a parent and/or legal guardian.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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