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Association of vitamin D status with COVID-19 disease severity in pediatric patients: A retrospective observational study

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Abstract

Background and Aims: Vitamin D deficiency is associated with increased vulnerability to respiratory infections. This study aimed to determine the potential relationships between coronavirus disease 2019 (COVID-19) severity, serum vitamin D concentrations, and some inflammatory markers among pediatric COVID-19 patients in Iran.

Methods: A retrospective study was conducted among hospitalized pediatric COVID-19 cases in Abuzar Hospital (Ahvaz, Iran) for 6 months. The COVID-19 diagnosis was based on the real-time reverse transcription-polymerase chain reaction technique. Demographic and clinical data of patients were recorded. Patients with serum vitamin D levels lower than 20 ng/ml were assigned as Group 1 and those with serum vitamin D concentrations equal to or more than 20 ng/ml were considered as Group 2.

Results: A total of 144 patients were enrolled. Their mean age was 80 ± 49 months (range: 1–16 years). Patients in Group 1 had significantly lower levels of serum vitamin D, calcium, and lymphocytes, as well as higher fibrinogen, D-dimer, and C-reactive protein (CRP) levels compared with those in Group 2 ($p < 0.001$). In addition, they had a significantly higher dry cough, fever, chest radiographic findings, respiratory rate, and longer hospital length of stay than patients in Group 2. Serum concentrations of vitamin D were positively correlated with levels of serum calcium, lymphocytes, and neutrophils but negatively correlated with CRP, fibrinogen, and D-dimer values. Furthermore, patients with moderate or severe courses of COVID-19 had significantly higher inflammatory markers (CRP, D-dimer, and fibrinogen), as well as lower levels of serum calcium, vitamin D, lymphocytes, and neutrophils than those with mild COVID-19 ($p < 0.001$). In the multivariate analysis, fibrinogen level on admission was detected as the independent predictor of severe COVD-19 (odds ratio = 1.06, 95% confidence interval: 1.03–1.09; $p < 0.001$).

Conclusion: This study indicated associations between the severity of COVID-19, serum vitamin D concentrations, and some inflammatory markers in pediatric COVID-19 patients.

KEYWORDS
COVID-19, disease severity, Iran, pediatric, vitamin D

1 | INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) has quickly become an emerging threat and a global public health challenge.[1] The risk of death due to COVID-19 was higher in older patients and those with comorbid diseases, such as diabetes and hypertension.[2–4] It has been stated that the majority of children had milder COVID-2019 disease courses and a better prognosis compared with adults.[5]

Vitamin D insufficiency or deficiency is a worldwide health issue that afflicts over one billion adults and children globally.[6] This vitamin is a multifunctional hormone that regulates the adaptive and innate immune responses.[7] The innate immune system produces anti-inflammatory and proinflammatory cytokines in response to bacterial and viral infections.[8] It was indicated that vitamin D decreases the risk of COVID-19 illness and related mortality.[9,10] Vitamin D is contributed to the production of defensins and cathelicidins that can decrease the rate of viral replication.[8] Vitamin D deficiency is a risk factor for persistent and exaggerated inflammation and acute respiratory distress syndrome.[11] In addition, it is associated with an elevated risk of respiratory infections, including tuberculosis and influenza.[12]

Angiotensin-converting enzyme 2 (ACE2) as the functional receptor of SARS-CoV-2 (the causal agent of COVID-19) has a critical function to cause COVID-19 and facilitate viral entry into the respiratory tract of infected patients.[13] It has been reported that the metabolite of 1, 25 dihydroxy vitamin D3 (calcitriol) as one of the vitamin D receptor agonists has protective impacts on severe lung damage by regulating the gene expression of members of the renin–angiotensin system (RAS) like ACE 2 expression in lung tissues.[14] Supplementation with cholecalciferol or calcifediol as biochemically active vitamin D metabolites was suggested for the treatment and prevention of COVID-19 disease.[10]

It has been reported that serum vitamin D levels were inversely associated with mortality and severity of respiratory viral infections in adults and children.[12,15] Better COVID health outcomes were associated with higher levels of ACE2.[16] It has been proposed that vitamin D deficiency has a possible function in pathogenic mechanisms related to COVID-19.[17] Treatment of vitamin D deficiency is supposed to suppress CD26, which is assumed to be an adhesion molecule for COVID-19 host cell invasion[18] and then ameliorate respiratory failure.[19]

Vitamin D has an extensive variety of antioxidant, antifibrotic, immunomodulatory, and anti-inflammatory effects.[20] Vitamin D deficiency is related to a proinflammatory cytokine profile and chronic inflammatory state.[21] The elevated burden of infectious diseases in areas with a high prevalence rate of vitamin D deficiency is an indication of significant association with the host immune response.[22] This response to respiratory viral infections may be better by adequate levels of serum vitamin D.[23] There are limited studies related to the impact of serum vitamin D levels in pediatric COVID-19 patients.[1,3,24-26] Therefore, this study aimed to determine the potential associations between the severity of COVID-19, serum vitamin D concentrations, and some inflammatory markers in hospitalized adolescents and children with COVID-19.

2 | MATERIAL AND METHODS

This retrospective study included pediatric COVID-19 patients aged between 1 and 18 years who were admitted to Abuzar Hospital (Ahvaz, Iran) from April to September 2021. Patients with incomplete medical data and those with comorbidities and chronic diseases were excluded. The medical records of 210 infants and children were reviewed. However, documents of 144 patients with a confirmed diagnosis of COVID-19 by real-time reverse-transcription polymerase chain reaction (RT-PCR) technique were included in this study.

The severity of COVID-19 was characterized as moderate, mild, critical, severe, and asymptomatic based on the laboratory findings, clinical characteristics, and chest radiography findings.[27] Asymptomatic were considered patients without any radiological and clinical results with a positive PCR test.[3] Mild was allocated for patients with upper respiratory tract infection (URTI) symptoms, including fever, cough, myalgia, fatigue, sore throat, and nasal flow, as well as normal respiratory system examination.[3] The cases with moderate COVID-19 disease had pneumonia with cough and fever without any symptoms of hypoxemia and dyspnea or had signs of COVID-19 on chest computed tomography scan (CT) with no symptoms.[3] Patients with severe disease had cough and fever in the early stage with signs of central cyanosis and dyspnea during a week (arterial oxygen saturation less than 92%). Those with critical conditions were patients who developed acute respiratory distress or failure quickly and tended to develop myocardial affection, encephalopathy, shock, acute kidney injury, and coagulation dysfunction.[3]

After a checklist preparation, all patients' medical records were reviewed to extract demographic, laboratory, and clinical data, need

for a mechanical ventilator, hospital length of stay (LOS), condition at discharge, and any associated comorbidities. In addition, the high-performance liquid chromatography (HPLC) technique was used to determine the levels of serum vitamin D. The completeness and consistency of the records were cross-checked. Children with serum vitamin D levels of 12–20 ng/ml, below 12 ng/ml, and above 20 ng/ml were considered to have vitamin D insufficiency, deficiency, and normal vitamin D status, respectively.[28] The enrolled patients were classified into two groups. Children with serum vitamin D levels lower than 20 ng/ml were assigned as Group 1 and those with serum vitamin D concentrations equal to or more than 20 ng/ml were considered as Group 2.

2.1 | Statistical analysis

Data analysis was carried out using the SPSS software, version 25. Normal distribution was checked applying the Kolmogorov–Smirnov test. Data were explored as median (interquartile range), percentage, and mean (standard deviation). Comparisons between groups were conducted by Student t test, Kruskal–Wallis, χ^2, and Mann–Whitney tests. Spearman's correlation test was used to examine any correlation between nonparametric variables. After univariate analysis, multivariate logistic regression was applied. Variables with a $p < 0.2$ in the univariate analysis were included as independent variables. Two-tailed $p < 0.05$ were used to define statistically significant results.

3 | RESULTS

A total of 144 COVID-19 patients were enrolled in this study. More than half of them were males. Their mean age was 80 ± 49 months (range: 1–16 years). Groups 1 and 2 consisted of 73 and 71 Patients, respectively. There were significant age-related differences between the two groups, while no significant gender differences were found between them. The mean serum levels of vitamin D in Groups 1 and 2 were 15 ± 3 ng/ml (9.90–19.83) and 32 ± 13 ng/ml (3.8–77.42) respectively. In addition, 21 and 52 patients in Group 1 had deficient and insufficient vitamin D serum levels, respectively. Furthermore, 29 patients with low vitamin D levels received intensive care unit (ICU) treatment. A comparison between clinical and demographic characteristics of patients in both groups is summarized in Table 1.

Patients in Group 1 had significantly lower levels of serum vitamin D, calcium, and lymphocytes, as well as higher D-dimer, fibrinogen, and C-reactive protein (CRP) levels compared with those in Group 2 ($p < 0.001$). In addition, they had a significantly higher dry cough, fever symptoms on admission, chest CT findings, respiratory rate, and longer hospital LOS than patients in Group 2 ($p < 0.001$) (Table 1).

The distribution of COVID-19 disease severity according to serum vitamin D levels between the two groups was significantly different ($p < 0.001$) (Table 2). The prevalence of vitamin D deficiency in patients with mild, moderate, and severe COVID-19

TABLE 1 Comparison between the two groups of patients based on their serum vitamin D levels ($n = 144$)

Parameters	Group 1 (73)	Group 2 (71)	p Value
Age (years)		**n (%)**	
1–2	14 (19.2)	28 (39.4)	0.006
>2	59 (80.8)	43 (60.6)	
Gender			
Male	34 (46.6)	43 (60.6)	0.06
Female	39 (53.4)	28 (39.4)	
Fever >38°C	49 (67.1)	13 (18.3)	<0.001
Dry cough	44 (60.3)	18 (25.4)	<0.001
Chest CT findings	45 (61.6)	7 (9.9)	<0.001
ICU ward	29 (39.7)	5 (7)	<0.001
		Mean ± SD	
Age (month)	80 ± 46	61 ± 51	<0.05
Serum vitamin D (ng/ml)	15 ± 3	32 ± 13	<0.001
Length of hospital stay (in days) (range)	9 ± 4 (3–16)	6 ± 1 (4–8)	<0.001
		Median (IQR)	
Neutrophil count (10^3 μl)	2.80 (2.58–2.96)	3.20 (2.7–3.71)	0.13
Lymphocyte count (10^3 μl)	2.10 (1.80–2.32)	2.30 (2.20–2.77)	<0.05
CRP (mg/dl)	17.50 (16.50–18.30)	2.60 (2.30–7.50)	<0.001
D-dimer (mg/L)	1.16 (0.76–1.26)	0.63 (0.35–0.83)	<0.001
Fibrinogen (mg/dl)	354 (328–410)	321 (254–328)	<0.001
Calcium (mg/dl)	9.50 (9.30–9.90)	10.10 (9.80–10.10)	<0.01
Respiratory rate	25 (11)	21 (9)	<0.01

Note: Group 1, pediatric COVID-19 patients with deficient and insufficient levels of vitamin D; Group 2, pediatric COVID-19 patients with normal serum levels of vitamin D.

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computerized tomography; IQR, interquartile range.

were 9.3%, 49%, and 86.5%, respectively. In addition, patients with severe or moderate courses of COVID-19 had significantly higher inflammatory markers (D-dimer, CRP, and fibrinogen), as well as lower levels of serum calcium, vitamin D, lymphocytes, and neutrophils than those with mild COVID-19 ($p < 0.001$). Furthermore, serum concentrations of vitamin D were positively correlated with levels of serum calcium ($r = 0.35$, $p < 0.001$), lymphocytes ($r = 0.43$, $p < 0.001$), and neutrophils ($r = 0.31$, $p < 0.001$) but negatively correlated with CRP ($r = -0.55$, $p < 0.001$), fibrinogen ($r = -0.52$, $p < 0.001$), and D-dimer ($r = -0.49$, $p < 0.001$) values. In the multivariate analysis, fibrinogen level on admission was detected as the independent predictor of

TABLE 2 Comparison between patients based on COVID-19 disease severity (n = 144)

Parameters	The severity of COVID-19 disease			P value
	Mild (43)	**Moderate (49)** n (%)	**Severe (52)**	
Group 1	4 (9.3)	24 (49)	45 (86.5)	<0.001
Group 2	39 (90.7)	25 (51)	7 (13.5)	
Gender				
Male	26 (60.5)	26 (53.1)	25 (48.1)	0.48
Female	17 (39.5)	23 (46.9)	27 (51.9)	
		Median (IQR)		
Neutrophil (10^3 µl)	3.47 (2.80–4.40)	3.34 (2.75–3.65)	2.63 (2.44–2.82)	<0.001
Lymphocyte (10^3 µl)	2.50 (2.27–3.00)	2.30 (2.10–2.70)	1.86 (1.70–2.10)	<0.001
CRP (mg/dl)	2.30 (2.30–2.50)	8.30 (7.00–17.00)	17.50 (16.50–19.50)	<0.001
D-dimer (mg/L)	0.38 (0.26–0.46)	0.76 (0.73–0.86)	1.26 (1.17–1.36)	<0.001
Fibrinogen (mg/dl)	300 (254–321)	328 (321–347)	400 (354–421)	<0.001
Calcium (mg/dl)	10.10 (9.90–10.20)	9.80 (9.50–10.10)	9.40 (9.30–9.90)	<0.001
		Mean ± SD		
Age (month)	73 ± 51	52 ± 48	86 ± 44	0.16
Level of serum vitamin D (ng/ml)	29 ± 12	26 ± 14	17 ± 9	<0.001

Note: Group 1, pediatric COVID-19 patients with deficient and insufficient levels of vitamin; Group 2, pediatric COVID-19 patients with normal serum levels of vitamin D.

Abbreviations: CRP, C-reactive protein; COVID-19, coronavirus disease 2019; IQR, interquartile range.

TABLE 3 Multivariate logistic regression analysis of factors associated with severe COVID-19

Variables	Odds ratio (95% CI)	p Value
Serum vitamin D	0.99 (0.94–1.03)	0.65
Neutrophils	1.16 (0.34–3.90)	0.80
Lymphocytes	0.22 (0.02–1.77)	0.15
Fibrinogen	1.06 (1.03–1.09)	<0.001
Calcium	0.37 (0.07–1.84)	0.22

Abbreviation: CI, confidence interval.

severe COVD-19 (odds ratio = 1.06, 95% confidence interval: 1.03–1.09; p < 0.001) (Table 3).

4 | DISCUSSIONS

This study indicated associations between the severity of COVID-19, serum vitamin D concentrations, and some inflammatory markers in pediatric COVID-19 patients. It was revealed that serum concentrations of vitamin D were positively correlated with levels of serum calcium, lymphocytes, and neutrophils but negatively correlated with fibrinogen, CRP, and D-dimer values. In addition, patients with moderate or severe courses of COVID-19 had significantly higher inflammatory markers (CRP, D-dimer, and fibrinogen), as well as lower levels of serum calcium, vitamin D, lymphocytes, and neutrophils than those with mild COVID-19. Fibrinogen level on admission was detected as the independent predictor of severe COVID-19. These findings are similar to those recently reported from a retrospective study among 103 adolescents and children with COVID-19 in Turkey.[25]

In the current study, 50.7% of COVID-19 patients (n = 73) had low or insufficient concentrations of serum vitamin D and 29 of them received ICU treatment. Patients in Group 1 with deficient and insufficient values of vitamin D had significantly lower levels of serum calcium, vitamin D, and lymphocytes, as well as higher D-dimer, fibrinogen, and CRP levels compared with those in Group 2 with normal vitamin D status. In addition, they had a significantly higher dry cough, fever, chest CT findings, respiratory rate, and LOS than patients in Group 2. In contrast, a similar retrospective study among 40 pediatric COVID-19 patients in Turkey did not report any significant differences related to the abovementioned variables between the two groups.[3] However, there was a negative correlation between fever symptoms and serum concentrations of vitamin D similar to that found in the present study.

The prevalence of vitamin D insufficiency and deficiency in this study was higher in patients with severe ($n = 45$) and moderate COVID-19 ($n = 24$) compared to those with a mild COVID-19 course ($n = 4$). A retrospective study in Turkey intended to examine the association between serum vitamin D levels, the severity of COVID-19, and related mortality. Patients with critical or severe COVID-19 had significantly lower mean levels of serum vitamin D than those with moderate COVID-19 severity.[29] In addition, serum vitamin D level was related to mortality in COVID-19 patients.[29] Another retrospective study was carried out among 61 COVID-19 patients in Italy to find the association between the severity of COVID-19 illness and serum vitamin D status.[30] It was reported that vitamin D deficiency was linked to more respiratory failure and severe systemic inflammatory response among those patients;[30] its findings are in agreement with the results of this study.

In a cohort study with a retrospective design among 260 COVID-19 patients, vitamin D deficiency was related to greater COVID-19 risk.[31] The results were similar to the outcomes of the present study. Patients with sufficient levels of vitamin D had a considerably shorter hospital stay and lower inflammatory markers, CRP, D-dimer, and incidence of pulmonary ground-glass opacity (GGO) in chest CT images.[31]

A significant negative correlation between vitamin D levels, the number of COVID-19 patients, and related mortality rate have been reported.[16] However, there was no death among patients in the current study. Another study revealed that more than half of COVID-19 cases had serum vitamin D levels lower than 30 ng/ml.[32] The lower levels of serum vitamin D in the current study were associated with lower lymphocyte count and higher inflammatory markers, such as CRP and D-dimer. Consequently, vitamin D deficiency may contribute to hyper inflammation and related low lymphocyte counts in COVID-19.[25] In addition, significant reductions in lymphocyte counts have been extensively found in patients with severe COVID-19.[33]

In response to proinflammatory cytokines, CRP as an acute-phase plasma protein is produced;[34] thus, CRP is a sign of inflammation and cytokine storm.[31] The cytokine storm can lead to quick multiple organ damage.[35] Very high CRP levels were detected among many COVID-19 patients.[36] Higher levels of CRP linked to vitamin D deficiency might be related to an elevated risk of severe COVID-19[36] and mortality.[37] Serum vitamin D concentrations lower than 30 ng/ml were found in COVID-19 patients with very high CRP levels.[31] Vitamin D deficiency can cause the generation of proinflammatory cytokines, which may result in increased levels of CRP and induction of inflammation.[36] Vitamin D could decrease anti-inflammatory effects and CRP. Therefore, sufficient serum vitamin D concentrations may reduce the occurrence of cytokine storms in COVID-19 patients and the severity of COVID-19 illness.[31]

It was reported in a meta-analysis and systematic review that pediatric COVID-19 patients with vitamin D deficiency had a higher risk of COVID-19 disease and poorer outcomes than cases with normal levels of vitamin D levels.[38] Improvement in the severity of COVID-19 through supplementation with vitamin D was also stated.[38] Nearly half of the pediatric COVID-19 patients had vitamin

D deficiency.[38] These findings were similar to the results of the current study.

It has been reported in observational studies that low serum concentrations of vitamin D were associated with an increased rate of respiratory viral infections.[39] Vitamin D supplementation was suggested as a potential preventive measure against respiratory tract infections (RTIs) in children.[40] Vitamin D has various functions in the immune system that can regulate the body's response to infections.[1] The immunomodulatory role of vitamin D has been established.[41] Adequate concentrations of vitamin D could conquer inflammation and decrease the severity of COVID-19.[41] Supplementation with vitamin D may have significant impacts on decreasing the effects of the COVID-19 pandemic.[41,42] However, calcifediol or calcitriol has been recently proposed as a potential treatment for COVID-19 patients rather than high-dose vitamin D3.[10,43–45] Calcifediol or 25-hydroxyvitamin D, the main metabolite of vitamin D could decrease the severity of COVID-19 disease in a pilot randomized clinical trial.[45] It was significantly associated with lower in-hospital mortality[44] and it significantly reduced the requirement for ICU treatment of hospitalized COVID-19 patients.[45]

A systematic review and meta-analysis of observational studies with nearly 2 million adults suggested that vitamin D insufficiency or deficiency may increase susceptibility to COVID-19 and its severity.[46] It has been also discussed that systemic inflammation decreases vitamin D levels in patients with infectious diseases such as COVID-19.[47] Vitamin D levels start to decline after the initiation of a systemic inflammatory response.[47] Consequently, the developing inflammatory response in COVID-19 patients may reduce vitamin levels before in-hospital measurements.[47] The findings emphasized that reverse causality could explore the possible associations between low vitamin D levels in patients with COVID-19.[47]

The findings of the present study in line with the results of two similar studies in Turkey[3,26] suggest that vitamin D levels may be linked to the incidence and management of the COVID-19 illness in the pediatric population. The current study was the first research to examine the potential associations between the severity of COVID-19, serum vitamin D concentrations, and some inflammatory markers among Iranian pediatric COVID-19 patients. Even though the roles of vitamin D on the immune system are rather multifaceted, the existing data propose that sufficient serum vitamin D concentrations facilitate the defense procedure against viral or bacterial infections and prevent hyperinflammation.

Routine vitamin D supplementation in Iran is allocated during infancy. Thus, infants under 1-year-old were omitted from this study. There were some limitations in this study. The data may probably be incorrect or incomplete due to the retrospective design of this study. In addition, some of the clinical parameters may not be possible to be evaluated. Furthermore, it was conducted in a single center and the sample size in each group may be small. However, it can offer better insight into other studies to assess the association between vitamin D deficiency and the occurrence of COVID-19. There is no confirmed data related to the treatment of COVID-19 through supplementation with vitamin D.[3] Additional studies and

randomized controlled trials are required to evaluate the impact of supplementation with vitamin D on the treatment and prevention of COVID-19.[3]

CONCLUSIONS

This study indicated associations between the severity of COVID-19, serum vitamin D concentrations, and some inflammatory markers in pediatric COVID patients. Further studies are required among these patients to determine the association between serum vitamin D levels and clinical consequences of COVID-19 infection, as well as the impact of supplementation with vitamin D on the management and incidence of COVID-19 disease.

AUTHOR CONTRIBUTIONS

Solmaz Heidari: conceptualization; data curation; investigation; methodology; project administration; resources; supervision; writing – review and editing. **Shooka Mohammadi**: data curation; formal analysis; writing – original draft; writing – review and editing. **Mohammadreza Fathi**: conceptualization; data curation; investigation; methodology; project administration; resources; supervision; writing – review and editing. **Shayan Cigary**: data curation; investigation; project administration; writing – review and editing. **Mohsen Alisamir**: project administration; resources; supervision; writing – review and editing. **Mohammadreza Mirkarimi**: project administration; supervision; writing – review and editing. **Majid Aminzadeh**: methodology; project administration; supervision; writing – review and editing.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets, which were analyzed for this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The Medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS) approved the protocol of the study (IR.AJUMS.REC.1399.824).

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