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Can Serum 25-Hydroxy Vitamin D Levels Predict the Severity of Multisystem Inflammatory Syndrome in Children and COVID-19?

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What is already known on this topic?

Serum vitamin D levels are lower in patients with Coronavirus disease-2019 (COVID-19) and multisystem inflammatory syndrome in children (MIS-C).

What this study adds?

The severity of COVID-19 was associated with low serum vitamin D levels. In MIS-C there was a moderate correlation between the number of affected organ systems and serum 25-hydroxy vitamin D levels. MIS-C patients who required intensive care had considerably lower vitamin D levels than those who did not.

Abstract

Objective: To determine the clinical significance of serum 25-hydroxy (OH) vitamin D levels in pediatric patients with multisystem inflammatory syndrome in children (MIS-C) and compare the vitamin D levels of these patients with those patients with Coronavirus disease-2019 (COVID-19) and healthy controls.

Methods: This study was designed for pediatric patients aged 1 month to 18 years and conducted between July 14 and December 25, 2021. Fifty-one patients with MIS-C, 57 who were hospitalized with COVID-19, and 60 controls were enrolled in the study. Vitamin D insufficiency was defined as a serum 25 (OH) vitamin D level of less than 20 ng/mL. Severe MIS-C was classified as necessitating intensive care due to cardiovascular instability, the necessity for non-invasive or invasive mechanical ventilation, and/or a diminishing Glasgow coma scale. World Health Organization definition criteria were used to describe the clinical stages of COVID-19 in children and patients were divided into four groups according to the clinical severity of COVID-19: asymptomatic, mild, moderate, and severe/critical.

Results: The median serum 25 (OH) vitamin D was 14.6 ng/mL in patients with MIS-C, 16 ng/mL in patients with COVID-19, and 21.1 ng/mL in the control group ($p < 0.001$). Vitamin D insufficiency was present in 74.5% (n = 38) of patients with MIS-C, 66.7% (n = 38) of patients with COVID-19, and 41.7% (n = 25) of the controls ($p = 0.001$). The percentage of four or more affected organ systems was 39.2% in patients with MIS-C. The correlation between the number of affected organ systems and serum 25 (OH) vitamin D levels was evaluated in patients with MIS-C and there was a moderate negative correlation ($r = -0.310$; $p = 0.027$). A weak negative correlation was found between the severity of COVID-19 and serum 25 (OH) vitamin D ($r = -0.320$, $p = 0.015$).

Conclusion: Vitamin D levels were insufficient in both the MIS-C and COVID groups. Furthermore, vitamin D levels correlated with the number of affected organ systems in MIS-C and the severity of COVID-19.

Keywords: Vitamin D, COVID-19, MIS-C, children

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Introduction

The Coronavirus disease-2019 (COVID-19) pandemic, caused by Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection, has spread rapidly worldwide. While the nature of this disease is gradually being discovered, it has been observed that the clinical course is milder in children compared with adults (1). Nevertheless, recent evidence has shown that children may develop signs of multiorgan failure several weeks after primary infection, manifesting in cardiovascular dysfunction leading to life-threatening shock and even requiring a stay in the intensive care unit (ICU) due to the systemic inflammatory response (2). This novel syndrome was later termed multisystem inflammatory syndrome in children (MIS-C) (3,4). This postinfectious process is thought to be caused by non-neutralizing antibodies through antibody-dependent amplification, causing immune system dysregulation by SARS-CoV-2 with a racial genetic predisposition (5,6).

Vitamin D is well-known for its role in regulating calcium and phosphorus metabolism. More recently, the role of vitamin D in non-skeletal functions, including inflammation and immune regulation, has also been investigated (7). One of the mechanistic effects of vitamin D on immune function is via the vitamin D receptor, which is expressed in most cell types and can influence genomic and non-genomic pathways related to the immune system (8). Vitamin D can induce monocyte differentiation into macrophages, increase the activity of lysosomal enzymes in macrophages, and facilitate cytotoxic activity by increasing the rate of phagocytosis (9). Many studies have provided evidence that vitamin D reduces the risk of viral infection by suppressing the release of inflammatory cytokines derived from the adaptive immune system, particularly interleukin-2 and interferon-gamma (10,11). Vitamin D has been reported to inhibit inflammatory processes by stimulating T-regulatory cells and increasing cellular immunity (10,11). Vitamin D is also known to exert direct antibacterial and antiviral effects via cathelicidin. Cathelicidin is an antimicrobial peptide that promotes the induction of reactive oxygen radical synthesis, which has direct microbicidal effects and elicits immunomodulatory responses to pathogen-associated stimuli by recruiting neutrophils, monocytes, and T cells to microbial invasion sites (12,13). The effect of vitamin D in MIS-C is thought to be due to its well-established role in modulating adaptive and innate immunity, including regulation of inflammatory cytokine release (5,6).

There are many studies on vitamin D deficiency in children with various infectious diseases (14,15). However, there are insufficient studies on vitamin D status in children with MIS-C. This study aimed to investigate the clinical significance of serum 25-hydroxy (OH) vitamin D levels in pediatric patients with MIS-C and to compare 25 (OH) vitamin D levels in patients hospitalized for COVID-19 and healthy controls.

Methods

Study Design

This prospective, observational study was designed for pediatric patients who were aged 1 month to 18 years and was conducted between July 14th and December 25th, 2021. Hospitalized patients who met the diagnostic criteria for MIS-C were enrolled in the study. During the study period, hospitalized pediatric patients with a diagnosis of COVID-19 confirmed by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) were included in the study. Healthy volunteers who were admitted to general pediatric polyclinics were defined as the control group and serum samples were during similar months to the patient group to negate the well-known seasonal effect on vitamin D levels. The control group was randomly selected, starting with the 50th patient out of roughly 3000 attendants to pediatric outpatient clinics, as well as patients who were multiples of that patient.

Patient demographics, underlying disease, medication history, symptoms, laboratory results, system involvement, and outcomes were extracted from medical records. Clinical and laboratory parameters (lymphocyte count, neutrophil count, blood pressure, respiratory rate, and heart rate) were recorded as age-specific normal ranges. The need for ICU care due to inotropic support or fluid resuscitation, the need for invasive/non-invasive mechanical ventilation, or extracorporeal membrane oxygenation were assessed. Treatment modalities were recorded. The case definition of MIS-C was used, as defined by the Centers for Disease Control and Prevention and the World Health Organization (3,4). Severe MIS-C was classified as necessitating intensive care due to cardiovascular instability, the necessity for non-invasive or invasive mechanical ventilation, and/or a diminishing Glasgow coma scale. World Health Organization definition criteria were used to describe the clinical stages of COVID-19 in children (16). Patients were divided into four groups according to the clinical severity of COVID-19: asymptomatic, mild, moderate, and severe/critical.

Cut-off values for serum 25 (OH) vitamin D have been previously published with global consensus recommendations from pediatric endocrinologists: Vitamin

D sufficiency is defined as a serum 25 (OH) vitamin D level of at least 20 ng/mL (50 nmol/L), whereas insufficiency is defined as 12 to 20 ng/mL (range, 30-50 nmol/L) and deficiency is less than 12 ng/mL (< 30 nmol/L) (17). Serum 25 (OH) vitamin D levels were measured during the first three days after hospitalization.

Patients who had taken vitamin supplements, who had bone metabolism disorders, and who did not want to participate in the study were excluded. Written informed consent was obtained from the patients and their parents. Ethical committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision no: 2021/07-14, date: 14.07.2021).

RT-PCR Assay

Combined nasopharyngeal and oropharyngeal swab specimens were collected from children with suspected COVID-19 and sent to the medical microbiology laboratory. SARS-CoV-2 was detected using RT-PCR (Bio-Speedy SARS-CoV-2 double Gene RT-qPCR Kit). Specifically, two target genes, including open reading frame 1ab (ORF1ab) and nucleocapsid protein (N), were tested during the RT-PCR assay.

Vitamin D Assay

Blood samples were placed in gel-containing tubes with a clot activator (BD Vacutainer SST II Advance, USA) and centrifuged at 1500 g for 10 minutes to separate serum from clot. Serum 25 (OH) vitamin D was measured by chemiluminescence immunoassay on an Advia Centaur XP analyzer (Siemens Healthineers, Erlangen, Germany). The intra-assay and inter-assay coefficients of variation for the 25 (OH) vitamin D assay were less than 8% and 12%, respectively.

Statistical Analysis

The median, first quartile, and third quartile [interquartile range (IQR)] were used to represent continuous variables that were not normally distributed. Differences between two or three groups were analyzed using the Mann-Whitney U test and the Kruskal-Wallis test, respectively. An independent t-test was used to compare normally distributed data. Categorical variables were compared using the chi-square test or Fisher's exact test. A $p < 0.05$ was considered significant. Spearman's rank correlation test was performed to determine the association between serum 25 (OH) vitamin D and the severity of MIS-C or COVID-19 pneumonia. Spearman's correlation analysis was used to determine the correlation between laboratory results and serum 25 (OH) vitamin D levels. Statistical analyses were performed using Statistical Package for the Social Sciences for Windows, version 25 (IBM, Armonk, NY, USA).

Results

This prospective observational study was performed with 51 patients with MIS-C, 57 patients with COVID-19, and 60 controls. When the sex and median age distribution of the groups were evaluated, there were no statistical differences between the three groups ($p = 0.446$ and $p = 0.089$, respectively) (Table 1). The median serum 25 (OH) vitamin D level was 14.6 ng/mL in patients with MIS-C, 16 ng/mL in patients with COVID-19, and 21.1 ng/mL in the controls ($p < 0.001$). In subgroup comparison, serum 25 (OH) vitamin D levels were significantly lower in patients with MIS-C compared with controls (MIS-C vs. controls $p < 0.001$; MIS-C vs. COVID-19 $p = 0.240$; COVID-19 vs. controls $p = 0.058$). Vitamin D insufficiency was present in 74.5% (n = 38/51) of patients with MIS-C, 66.7% (n = 38/57) of patients with COVID-19, and 41.7% (n = 25/60) of the controls (Figure 1).

Table 1. Characteristics and serum vitamin D levels between patients with MIS-C, hospitalized COVID-19 and the control group

	MIS-C	COVID-19	Control group	p value	p value		
					MIS-C vs. COVID-19	MIS-C vs. control	COVID-19 vs. control
Patient number, n (%)	51	57	60	-	-	-	-
Age, years (IQR)	8.8 (5.6-12.3)	11.8 (3.8-15.7)	10 (6.2-16.4)	0.089	-	-	-
Sex, n (%)							
Boy	33 (64.7)	30 (52.6)	35 (58.3)	0.446	-	-	-
Girl	18 (35.3)	27 (47.4)	25 (41.7)				
25 (OH) vitamin D levels (IQR)	14 (9.3-20)	16 (9.1-23.4)	21.1 (13.7-27.5)	< 0.001*	0.240	< 0.001	0.058
Vitamin D status, n (%)				0.001	0.373	< 0.001	0.007
Vitamin D sufficiency	13 (25.5)	19 (33.3)	35 (58.3)				
Vitamin D insufficiency	38 (74.5)	38 (66.7)	25 (41.7)				

*Fisher's exact probability test was used for cross-classification tables.
IQR: interquartile range, 25 (OH): 25-hydroxy, MIS-C: multisystem inflammatory syndrome in children, COVID-19: Coronavirus disease-2019

The characteristics of patients with MIS-C according to adequate/inadequate serum 25 (OH) vitamin D levels are shown in Table 2. Thirty-eight (74.5%) patients had vitamin D insufficiency and 13 (25.5%) had vitamin D sufficiency. The median (IQR) age of patients with MIS-C was 8.8 (5.6-12.3) years. Patients with adequate serum 25 (OH) vitamin D levels were younger compared with patients with inadequate serum 25 (OH) vitamin D (6 vs. 10.3 years; p = 0.034) (Table 2). Thirty-three (64.7%) patients with MIS-C were male and 28.9% (n = 15) were overweight-obese. The median length of hospital stay was eight days in the inadequate vitamin D group and five days in the adequate vitamin D group (p = 0.085). In the evaluation of admission symptoms (fever, fatigue, muscle ache, any gastrointestinal symptoms, conjunctival inflammation mucous membrane changes, rash, arthralgia, any respiratory symptoms), there were no statistically significant differences between the adequate and inadequate vitamin D groups with MIS-C (p > 0.05 for all).

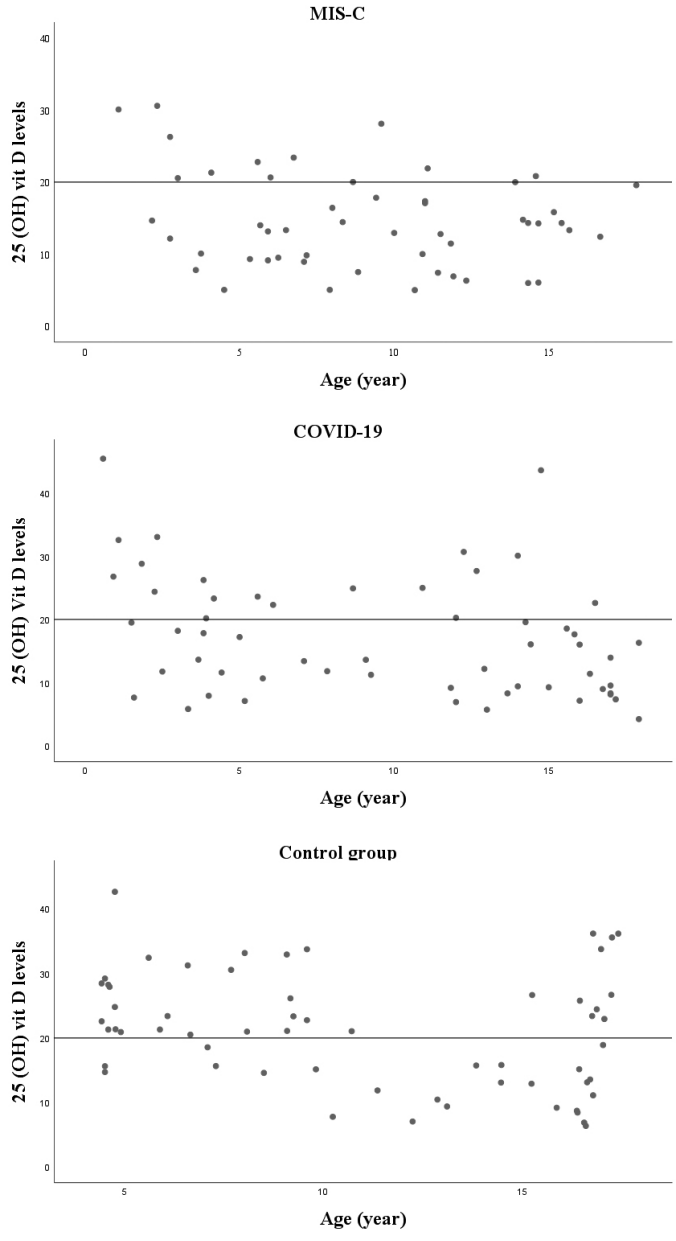

Figure 1. Serum 25-hydroxy vitamin D values in patients with MIS-C, COVID-19, and healthy controls

COVID-19: Coronavirus disease-2019, MIS-C: multisystem inflammatory syndrome in children, 25 (OH): 25-hydroxy

The affected organ systems (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, or neurologic) were assessed in patients with MIS-C. The percentage of four or more affected organ systems was 39.2% among patients with MIS-C. It was found that the prevalence of patients with ≥4 involved organ systems was significantly higher in the group with inadequate vitamin D (47.4%, n = 18) compared with the group with adequate vitamin D (15.4%, n = 2) (p = 0.041). When the correlation between the number of affected organ systems and serum 25 (OH) vitamin D levels was evaluated, there was a moderate negative correlation (r = -0.310; p = 0.027). ICU stay was required in 15.7% (n = 8) of patients with MIS-C, and all of these patients were in the inadequate vitamin D group (p = 0.096). The pediatric ICU (PICU) group had significantly lower serum 25 (OH) vitamin D levels compared with the non-PICU group (11.8 vs. 15.1; p = 0.039) (Figure 2). Similarly, hypotension was noted in 34.2% (n = 13) of patients, and shock developed in 26.3% (n = 10) of patients; all of these patients were in the inadequate vitamin D group (p = 0.023 and p = 0.048, respectively). There were no deaths in the study population.

The characteristics of patients with COVID-19 are shown in Table 3. Thirty-eight (66.7%) of 57 hospitalized COVID-19 patients had vitamin D insufficiency. The median (IQR) age was 11.8 years (3.8-15.7) and 52.6% (n = 30) of patients were male. When evaluating the clinical characteristics of the patients, dry cough was significantly more frequent in the group with inadequate serum vitamin D levels (73.7% vs. 47.4%, respectively; p = 0.049). When evaluating the laboratory results, the lymphocyte count was significantly lower in the group with inadequate serum vitamin D levels (1300 vs. 2200 cells/uL, p = 0.049). When evaluating the correlation between the severity of COVID-19 and serum 25 (OH) vitamin D, a weak negative correlation was found (r = -0.320, p = 0.015) and this was also found for the length of hospital stay (r = -0.304, p = 0.022). The correlation between serum 25 (OH) vitamin D levels and laboratory results was evaluated. There was a moderate positive correlation between serum 25 (OH) vitamin D levels and aspartate aminotransferase levels (r = 0.530; p < 0.001),

and a weak positive correlation with lactate dehydrogenase levels (r = 0.269, p = 0.043).

Discussion

To the best of our knowledge, this is one of the first studies to analyze vitamin D levels in pediatric patients with MIS-C and a hospitalized pediatric COVID-19 group. In the present study, the median serum 25 (OH) vitamin D level was inadequate in both patients with MIS-C and COVID-19 compared with the control group. It was lowest in the MIS-C group followed by COVID-19 and then healthy controls.

There are few published studies on vitamin D status in patients with MIS-C. In a study by Darren et al. (18), 16 of 18 (89%) patients with MIS-C had vitamin D insufficiency, and the mean 25 (OH) vitamin D level was 6.8 ng/mL. They also reported that the PICU group (n = 12) tended to have lower mean 25 (OH) vitamin D levels compared with the non-PICU group (8.9 vs. 5.6 ng/mL, respectively; p = 0.110), but these results were not significant. Zengin et al. (19) compared the serum vitamin D levels of 34 MIS-C patients requiring ICU with those of 34 control patients in a retrospective study. They reported that patients with MIS-C had considerably lower serum 25 (OH) vitamin D levels than those without MIS-C (9 vs. 19 ng/mL). Consistent with previous reports, 75% of patients in the present study with MIS-C had either vitamin D deficiency or vitamin D insufficiency and all patients who required ICU stay (n = 8/51, 21%) were in the vitamin D insufficiency group. The PICU group had significantly lower 25 (OH) vitamin D levels than the non-

Table 2. Characteristics of the patients with MIS-C according to serum 25-hydroxy vitamin D levels

	All patients n = 51	Vitamin D insufficiency n = 38	Vitamin D sufficiency n = 13	p value
Age, years, median (IQR)	8.8 (5.6-12.3)	10.3 (6.1-13)	6 (2.6-10.3)	0.034
Overweight/obese n/total (%)	13/45 (28.9)	10/35 (28.6)	3/10 (30)	0.608
Sex, n (%)				
Girl	18 (35.3)	15 (39.5)	3 (21.1)	0.336
Boy	33 (64.7)	23 (60.5)	10 (76.9)	
25 (OH) vitamin D levels, median (IQR)				
Girl	11.6 (6.7-18.2)	9.8 (6.3-12.7)	20.6 (20.5--)	-
Boy	14.4 (10.7-20.4)	13.3 (9.3-14.6)	23.1 (20.6-28.6)	-
Underlying medical condition, n (%)	17 (33.3)	14 (36.8)	3 (23.1)	0.502
Duration of hospitalization, median (IQR)	7 (4-11)	8 (5-13.2)	5 (3-8.5)	0.085
Number of organ systems involvements				
2-3	31 (60.8)	20 (52.6)	11 (84.6)	**0.041**
≥4	20 (39.2)	18 (47.4)	2 (15.4)	
Treatment				
Intravenous immunoglobulin n (%)	36 (70.6)	28 (73.7)	8 (61.5)	0.487*
Corticosteroids n (%)	31 (60.8)	26 (68.4)	5 (38.5)	0.098*
Anticoagulants n (%)	39 (76.5)	32 (84.2)	7 (53.8)	0.053*
Acetyl salicylic acid n (%)	5 (9.8)	3 (7.9)	2 (15.4)	0.591*
Inotropes n (%)	9 (17.6)	8 (21.1)	1 (7.7)	0.417*
Immunomodulatory therapy n (%)	4 (7.8)	4 (10.5)	0	0.561*
Need for oxygen n (%)	10 (19.6)	10 (26.3)	0	0.048*
Outcomes				
Hypotension n (%)	13 (25.5)	13 (34.2)	0	**0.023***
Extracorporeal membrane oxygenation n (%)	3 (5.9)	3 (7.9)	0	0.561*
Prone position n (%)	4 (7.8)	4 (10.5)	0	0.342*
Plasma exchange n (%)	4 (7.8)	4 (10.5)	0	0.295*
NIMV/MV n (%)	4 (7.8)	4 (10.5)	0	0.561*
Shock n (%)	10 (19.6)	10 (26.3)	0	**0.048***
Need for ICU n (%)	8 (15.7)	8 (21.1)	0	0.096*

*Fisher's exact probability test was used for cross-classification tables.
IQR: interquartile range, ICU: intensive care unit, NIMV/MV: non-invasive mechanical ventilation/mechanical ventilation, 25 (OH): 25-hydroxy, MIS-C: multisystem inflammatory syndrome in children

ICU group (11.8 vs. 15.1 ng/mL, respectively). This finding warrants further investigation in larger MIS-C cohorts.

Although studies on vitamin D status in patients with MIS-C are limited, some studies focused on its relation to disease severity. In the study by Torpoco Rivera et al. (20), the authors found that the seriousness of MIS-C, especially cardiac involvement, was associated with severe vitamin D deficiency [25 (OH) vitamin D level < 10 ng/mL]. In the study conducted by Mamishi et al. (21), 122 patients with MIS-C were divided into two groups (mild-moderate and severe). Mild-to-moderate MIS-C was present in 97, while severe MIS-C was present in 25. Serum 25 (OH) vitamin D levels were considerably lower in patients with severe MIS-C (8.5 vs. 20.5 ng/mL). In a review by Feketea et al. (22), the authors concluded that serum vitamin D levels might help predict severe forms of MIS-C and that correction of abnormal levels in severe MIS-C could influence the progression of the syndrome. Consistent with these speculations, we found a moderate negative correlation between serum 25 (OH) vitamin D and the number of affected organ systems in patients with MIS-C. These results suggest that patients with inadequate vitamin D status had a more severe disease course. However, vitamin D is an acute-phase reactant, and its blood level might decrease during the inflammatory process. MIS-C disease is known to occur as a result of cytokine storms. It is thought that an excess of cytokines could lead to more severe inflammation and cause a further decrease in serum vitamin D levels. Similarly, in a study by Peterson and Heffernan (23), the authors found serum concentrations of tumor necrosis factor-alpha or C-reactive protein were inversely correlated with serum vitamin D concentrations. As another mechanism, it is worth noting that the need for active vitamin D, which has an anti-inflammatory effect, increases when a severe inflammatory process occurs. Therefore, the turnover of vitamin D from serum and cells involved in immunomodulation increases, resulting in a decrease of inactive vitamin D from serum. From this point of view, the low serum vitamin D level in severe disease could be a consequence of severity and not a predisposing factor (24).

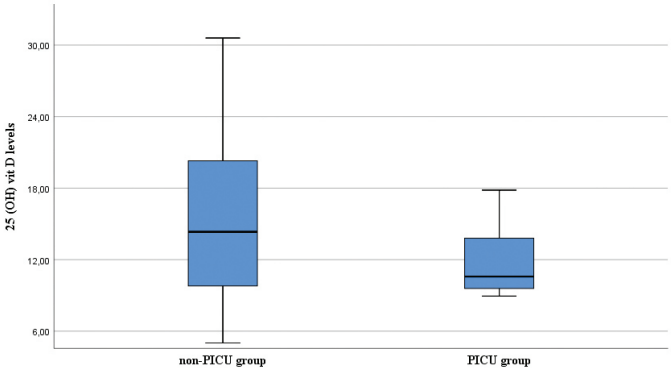

Figure 2. The comparison of serum 25-hydroxy vitamin D levels of patients with MIS-C according to a need for a stay in an intensive care unit

PICU: pediatric intensive care unit, 25 (OH): 25-hydroxy, MIS-C: multisystem inflammatory syndrome in children

Apart from the well-known effect of vitamin D on calcium metabolism in humans, it regulates immune responses by increasing the production of anti-inflammatory cytokines,

Table 3. Characteristics of hospitalized patients with COVID-19 according to serum 25-hydroxy vitamin D levels

	All patients n = 57	Vitamin D insufficiency n = 38	Vitamin D sufficiency n = 19	p value
Age, years, median (IOR)	11.8 (3.8-15.7)	13.3 (4.8-16.2)	5.5 (2.2-12.2)	**0.007**
Sex, n (%)				0.091
Girl	27 (47.4)	21 (55.3)	6 (31.6)	-
Boy	30 (52.6)	17 (44.7)	13 (68.4)	-
25 (OH) vitamin D levels, median (IQR)				-
Girl	11.2 (8.1-19.5)	9.2 (7.6-13.7)	25.8 (23.5-32.9)	-
Boy	17.7 (12-25.3)	13.3 (9.8-16.7)	26.2 (22.4-31.6)	-
Underlying medical condition, n (%)	20 (35.1)	15 (39.5)	5 (26.3)	0.326
Duration of hospitalization, median (IQR)	5 (3-7)	5 (2.7-7)	4 (3-6)	0.274
Severity of COVID-19 pneumonia n (%)				0.292*
Mild	17 (29.8)	9 (23.7)	8 (42.1)	-
Moderate	22 (38.6)	15 (39.5)	7 (36.8)	-
Severe/critical	18 (31.6)	14 (36.9)	4 (21.1)	-
Need for oxygen treatment n (%)	18 (31.6)	14 (36.8)	4 (21.1)	0.227
Need for ICU n (%)	5 (8.8)	3 (7.9)	2 (10.5)	1.000*

*Fisher's exact probability test was used for cross-classification tables.
IQR: interquartile range, ICU: intensive care unit, COVID-19: Coronavirus disease-2019, 25 (OH): 25-hydroxy

reducing plasma cells and the release of immunoglobulins, decreasing the production of proinflammatory cytokines, and thus stimulating the production of antimicrobial peptides in the respiratory system (7,25). One such study by Katz (26) examined 987,849 patients, 887 individuals tested positive for COVID-19, while 31,950 were diagnosed with vitamin D deficiency. Additionally, 87 patients had both vitamin D deficiency and COVID-19. They found that patients with vitamin D deficiency were 4.6 times more likely to have positive COVID-19 status than patients without deficiency [95% confidence interval (CI), 3.713-5.783]. Many studies conducted on adult patients showed a significant association between vitamin D deficiency and the severity of COVID-19 (26,27,28). In contrast, there are few studies in children because of the milder clinical course of COVID-19. A study by Alpcan et al. (29) retrospectively analyzed serum 25 (OH) vitamin D levels in 75 pediatric patients with COVID-19 and 80 healthy controls. The mean serum vitamin D level was significantly lower in the COVID-19 group than in the control group (21.5 vs. 28.0 ng/mL). They also showed that 84% of patients with COVID-19 had vitamin D insufficiency, as in the study by Karakaya Molla et al. (30), which reported a rate of 82% (29). Similar to previous reports, 66.7% of hospitalized patients with COVID-19 had vitamin D insufficiency in our population. Although the median serum vitamin D level was lower in the hospitalized COVID-19 group than in the control group, this was not significant, although there was a weak negative correlation between the severity of COVID-19 and serum vitamin D levels.

In a recent study comparing clinical features associated with COVID-19, according to vitamin D status, dyspnea, weakness, anosmia, headache, myalgia, and loss of taste were significantly more common in the insufficient vitamin D group (29). Regression analysis showed that low vitamin D level was a risk factor for the occurrence of dyspnea (Odds ratio = -0.268, 95% CI: -15.920 to -1.406) (29). The present study showed that only dry cough was significantly more frequent in the group with insufficient vitamin D in patients with COVID-19 (73.7% vs. 47.4%). In a study evaluating laboratory results and serum vitamin D levels, vitamin D was positively correlated with leukocyte count, lymphocyte count, and platelet count. In contrast, it was negatively correlated with age and length of hospital stay (30). Our results showed that there was a moderate positive correlation between serum 25 (OH) vitamin D and aspartate aminotransferase and a weak positive correlation with lactate dehydrogenase levels. Importantly, we found a weak negative correlation between serum 25 (OH) vitamin D levels and length of hospital stay.

Study Limitations

First, serum vitamin D levels were taken during the active inflammation phase. Serum vitamin D levels decrease during active inflammation in the human body. A more valid comparison would be possible if these patients' serum vitamin D levels before infection and inflammation were known. However, it is practically impossible to know in advance which patient will have MIS-C or COVID-19, unless widespread population studies are performed.

Conclusion

This study sheds light on the relationship between vitamin D status in patients with MIS-C and COVID-19. Serum 25 (OH) vitamin D levels were correlated with the severity of MIS-C, as represented by patients with >4 involved organ systems and severity of COVID-19. However, it is unclear whether low vitamin D status is more common in patients with MIS-C than in the general population because there are no clinical trial data. Our study is the first to compare vitamin D levels in patients with MIS-C and healthy controls. Evaluation of serum vitamin D status of patients with MIS-C and COVID-19 before and during the disease will provide a better understanding of the pathophysiologic mechanism of this issue.

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Ethics

Ethics Committee Approval: Ethical committee approval was obtained from University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision no: 2021/07-14, date: 14.07.2021).

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yıldız Ekemen Keleş, Dilek Yılmaz, Gülnihan Üstündağ, Ayşegül Elvan Tuz, Ahu Kara Aksay, Ayfer Çolak, Concept: Yıldız Ekemen Keleş, Dilek Yılmaz, Selin Taşar, Aslıhan Şahin, Ayşegül Elvan Tuz, Aslıhan Arslan Maden, Eda Karadağ Öncel, Ayfer Çolak, Design: Yıldız Ekemen Keleş, Dilek Yılmaz, Ahu Kara Aksay, Eda Karadağ Öncel, Ayfer Çolak, Data Collection or Processing: Yıldız Ekemen Keleş, Dilek Yılmaz, Selin Taşar, Gülnihan Üstündağ, Ayşegül Elvan Tuz, Aslıhan Şahin, Aslıhan Arslan Maden, Ahu Kara Aksay, Analysis or Interpretation: Eda

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