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RESEARCH

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Impact of vitamin D deficiency on the severity of COVID 19 infection in pediatrics: a cross-sectional study

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Abstract

Background Vitamin D has immunomodulating actions which have a major role in the regulation of the inflammatory response. In this study, we aimed to determine the presence of an association between the serum level of vitamin D (25 OH vitamin D) and the severity of symptoms and outcomes in children with COVID-19.

Results Fifty-six children who were diagnosed to have COVID-19 were selected for our study. The demographic data and clinical and laboratory parameters including vit. D serum levels were also collected. According to the WHO guidelines in COVID-19 clinical severity, only hospitalized cases will be included in this study and classified into the (1) moderate group (patients in whom pneumonia was confirmed by physical examination and radiographic imaging with or without oxygen need) and (2) severe group (consisted of hospitalized patients who need positive respiratory support). Our study found a statistically significant difference regarding vitamin D deficiency with more deficient serum levels in the severe group; also, we found a negative correlation between serum vitamin D level and the inflammatory markers in children and adolescents with COVID-19.

Conclusions This study confirms that there is a strong relationship between vit. D deficiency and COVID-19 clinical severity and outcomes in PICU-admitted pediatric population.

Keywords COVID-19, Vitamin D, Inflammation, Children, Pediatrics, Pneumonia, Immunity SARS-CoV-2

Background

Coronavirus disease 2019 (COVID-19) is a highly contagious infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified at the end of 2019 in Wuhan, China, then the disease spread as a worldwide pandemic [1–3]. The infection clinical severity in the population widely ranged from simple common cold-like symptoms to severe acute respiratory syndrome (ARDS) or even lethal outcomes [2]. At the start of the pandemic, COVID-19 was rarely to be reported among pediatric groups, and when the children become infected, they presented with a simple clinical presentation with favorable outcomes; however, with the increase in the virus mutations and variants, more children become involved with increasing severity of clinical presentation and mortality worldwide [4]. Multiple recent adult studies have postulated a relationship between the clinical severity of COVID-19 infection and low levels of vitamin D deficiency [5–7]. Vitamin D discovered to have a major role in immune response

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Table 1 Comparison between the moderate and severe groups as regards demographic data and clinical presentation ($n=56$)

Demographic data	Moderate cases ($n=24$)	Severe cases ($n=32$)	*P* value
Age (months), median (IQR)	8.5 (2.13–22.5)	5 (2.25–14.25)	0.718
Sex			
Male, *N* (%)	14 (58.3%)	18 (56.3%)	0.876
Female, *N* (%)	10 (41.7%)	14 (43.8%)	
Duration of admission (days), median (IQR)	4 (3–6.75)	5 (3.25–7)	0.235
Fever, *N* (%)	24 (100%)	31 (96.9%)	0.382
Cough, *N* (%)	16 (66.7%)	26 (81.3%)	0.212
Shortness of breath, *N* (%)	15 (62.5%)	24 (75%)	0.314
Vomiting, *N* (%)	5 (20.8%)	9 (28.1%)	0.533
Diarrhea, *N* (%)	4 (16.7%)	9 (28.1%)	0.315
Convulsion, *N* (%)	5 (20.8%)	8 (25%)	0.715
Mechanical ventilation, *N* (%)	1 (4.2%)	30 (93.8%)	0.0001*

Analyzed by the chi-square test or Fisher's exact test and Mann–Whitney test

* Significant difference at *P* value < 0.05

modulation in infections and autoimmune disorders besides its role in the maintenance of our skeleton health and calcium–phosphorus homeostasis [8, 9]. This study aims to assess if there is a potential association between vitamin D deficiency and the clinical severity of COVID-19 infection in children.

Methods

This was a cross-sectional study conducted in the pediatric department of a tertiary-level hospital from July 2021 to December 2021. The study population included 56 pediatric cases of SARS-CoV-2 aged between 1 month and 18 years. All suspected patients underwent a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay for COVID-19 for nasopharyngeal and oropharyngeal swab specimens, also confirmed by COVID-19 immunoglobulins IgG and IgM. Informed written consent was obtained from all patients' guardians before inclusion in this study. The study was approved by the Ethical Review Board of our institution (approval no.: 78:2021).

The World Health Organization (WHO) guidelines classified COVID-19 severity into mild, moderate, and severe. Mild cases are clinically symptomatic patients without evidence of hypoxemia or viral pneumonia. Moderate cases are patients with clinical manifestations of pneumonia and pneumonic findings in chest imaging but with O_2 saturation $\geq 90\%$ on room air and do not need positive O_2 pressure or circulatory support. Severe cases involve patients with clinical manifestations of pneumonia and one of the following: increased respiratory rates, severe distress, or O_2 saturation $< 90\%$ on room air and need positive O_2 pressure and cardiac support or have multiorgan failure.

Table 2 Comparison between the moderate and severe groups as regard GCS, degree of stress, CT finding, PCR, and prognosis

	Moderate cases with positive PCR ($n=24$)	Severe cases with positive PCR ($n=32$)	*P* value
Level of suspicion COVID (%)			
N	2 (8.3%)	2 (6.3%)	0.6
Low	7 (29.2%)	5 (15.6%)	
Indeterminate	9 (37.5%)	11 (34.4%)	
High	3 (12.5%)	8 (25.0%)	
Very high	3 (12.5%)	6 (18.8%)	
Degree of respiratory distress, *N* (%)			
0	4 (16%)	–	**0.0001***
I	2 (8.3%)	1 (3.1%)	
II	13 (54.2%)	4 (12.5%)	
III	5 (20.8%)	18 (56.3%)	
VI	–	9 (28.1%)	
V	–	–	
GCS (mean ± SD)	13.29 ± 1.98	11 ± 1.93	**0.001***
Prognosis (%)			
Improved	24 (100%)	4 (12.5%)	**0.0001***
Died	–	28 (87.5)	

Analyzed by the independent samples *t* test and chi-square test or Fisher's exact test

* Significant difference at *P* value < 0.05

Exclusion criteria

Mild or asymptomatic COVID-19 children who were isolated and managed at home and patients with comorbidities (TB infection, chronic renal failure, etc.) that may affect the presentation and the clinical course of COVID-19.

Table 3 Comparison between the moderate and severe groups regarding laboratory parameters

Laboratory investigations	Moderate cases with positive PCR ($n=24$), mean ± SD	Severe cases with positive PCR ($n=32$), mean ± SD	*P* value
Hemoglobin	10.85 (9.15–12.8)	10.1 (9.52–11.3)	**0.337**
Leukocytic count	7.7 (5.55–12.9)	6.8 (4.47–10.8)	**0.220**
Platelet	300 (214.25–416.25)	201.5 (83.2–347.7)	**0.066**
Lymphocyte	2.2 (1.8–2.6)	1.64 (1.12–2.38)	**0.048***
Neutrophil	70 (55–79)	75 (61.7–82.2)	**0.044***
CRP	24 (22.5–48)	48 (36–96)	**0.006***
Urea	27.5 (23.2–34.7)	33 (25.2–53.7)	**0.063**
Creatinine	0.6 (0.5–0.7)	0.8 (0.6–1.3)	**0.014***
ALT	33 (20.2–44.7)	50.5 (33–148.5)	**0.007***
AST	44 (23.2–74)	66 (42.2–192.5)	**0.015***
D-dimer	1.5 (1–2)	3.4 (2.5–5.95)	**0.0001***
Ferritin	148 (99.7–281.7)	282.5 (214–392.7)	**0.003***
LDH	698.5 (514–912.7)	1042 (898–1375)	**0.0001***

Analyzed by the Mann–Whitney test

* Significant difference at *P* value < 0.05

All patients were subjected to analytic history taking emphasizing sociodemographic data including age, sex, residence, and parents' consanguinity, and medical history of any associating comorbidities. Analysis of the presenting symptoms including fever, cough, shortness of breath, vomiting, diarrhea, and convulsions. A thorough clinical examination was done starting by taking vital data on presentation including pulse, respiratory rate, temperature, and blood pressure, and their values were adjusted according to their age and referred to the normal ranges: anthropometric measurements and general examination including Glasgow Coma Scale (GCS). Detailed chest examination was done, and oxygen saturation was measured using pulse oximetry. The laboratory investigations included peripheral blood smear, C-reactive protein (CRP), markers of inflammations (D-dimer, serum ferritin, LDH), renal and hepatic function tests, COVID-19 (PCR) through nasopharyngeal swabs, and COVID-19 immunoglobulins IgG and IgM.

25-Hydroxyvitamin D (25 OH vit. D) was measured, and according to the Institute of Medicine (IOM) and the American Academy of Pediatrics (AAP), both define vitamin D normal levels when above 20 ng/ml, insufficiency when (25 OH vit. D) concentrations between 16 and 20 ng/mL, and deficiency when less than 15 ng/mL in the pediatrics population [10, 11].

Statistical analysis

Data was statically analyzed using the IBM SPSS 26.0 statistical package software (IBM; Armonk, New York, USA). The data normality was tested using the Kolmogorov–Smirnov tests. Our data were expressed as median and interquartile ranges (IQR) for quantitative measures; in addition, we used both numbers and percentages for the categorized data. To compare two independent group nonparametric data, we used the Mann–Whitney *U* test, and we used the chi-square test or Fisher's exact test to compare the categorical variables. A *P*-value lower than 0.05 was considered significant.

Results

A total of 56 children whose PCR test revealed COVID-19 were included in our study, 24 in the moderate group, and 32 in the severe group. Vitamin D serum levels and laboratory markers were measured in all

Table 4 Comparison between the moderate and severe groups as regards vitamin D level

Vit. D level	Moderate cases ($n=24$)	Severe cases ($n=32$)	*P* value
Median (IQR)	55 (30–76.75)	17 (13–23)	**0.0001***
Normal, *N* (%)	21 (87.5%)	13 (40.6%)	**0.0001***
Insufficiency, *N* (%)	1 (4.2%)	9 (28.1%)	
Deficiency, *N* (%)	2 (8.3%)	10 (31.3%)	

Analyzed by the chi-square test or Fisher's exact test

* Significant difference at *P* value < 0.05

patients. Fever was the most common associated symptom in both groups. Respiratory symptoms in both groups were more prevalent in presentation than gastrointestinal symptoms (Table 1). No significant difference in the suspicion level of COVID-19 infection at clinical presentation before confirming by PCR tests between the two groups while there were significant differences in the disease course and outcome between both groups with lower scores of GCS, items of respiratory distress, and survival rates in the severe group with 100% mortality in this group (Table 2). Comparisons between laboratory parameters including inflammatory markers and organ function tests in both groups were shown in Table 3.

Our study found that the severe group had by far the lowest median 25 OH vit. D levels compared to the moderate group (Table 4). Correlations between serum levels of 25 OH vit. D and CRP, serum ferritin, and D dimer levels are shown in (Figs. 1, 2, and 3).

Discussion

The current study compared the severity of the clinical course of COVID-19 infection in pediatric patients with vitamin D serum levels including different health-related scores, inflammatory markers, and organ function tests.

On analyzing the demographic data of the cases, the ages of our children ranged from 1 month to 18 years with a median age of 6 months (2.13–17.3 mo) with a non-significant difference between moderate and severe positive PCR cases. This finding suggests that all ages of childhood were susceptible to COVID-19 and this agreed with Dong et al. and Kamidani et al. [12, 13] who showed that children of all ages were susceptible to COVID-19.

The clinical presentation of cases widely varies as fever, cough, shortness of breath, vomiting, diarrhea, and convulsions with more prevalence in the severe group rather than the moderate group. This is following Mustafa et al. [14] who found that the COVID-19-infected children exhibited a large spectrum of respiratory and gastrointestinal involvement and some exhibited severe clinical

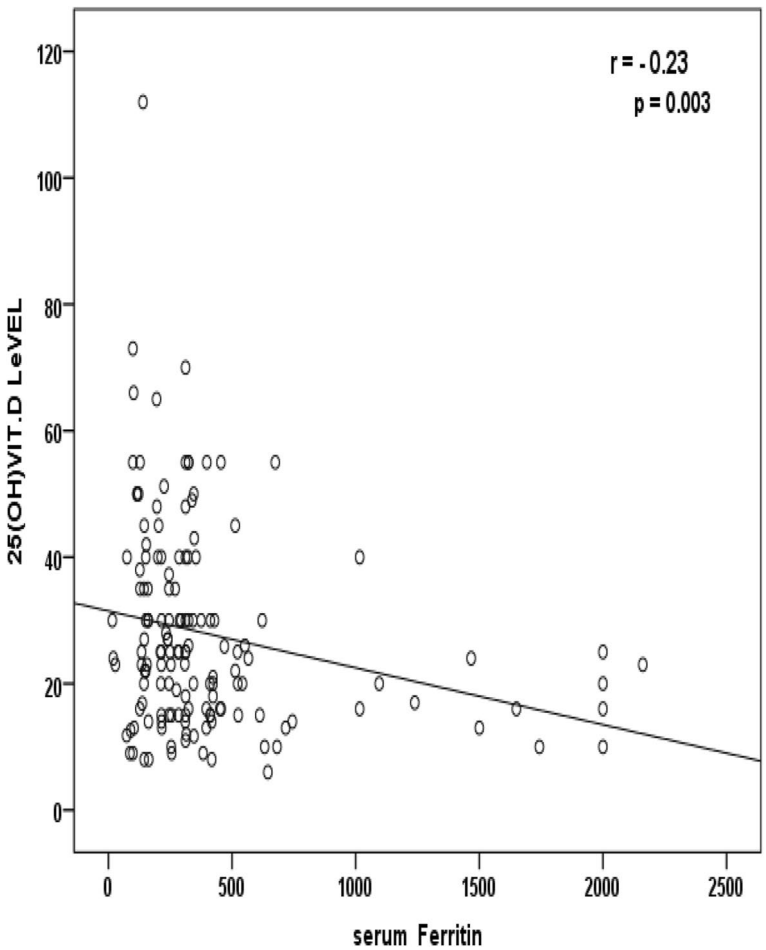

Fig. 1 Correlation between vit. D level and serum ferritin

course. Also, Oualha et al. [15] reported varieties of respiratory symptoms from an isolated cough and minor hypoxia to severe pneumonia with the need for invasive and prolonged mechanical ventilation without any associating comorbidities. Their findings can be explained by our study as we found that the children in the severe group exhibited severe clinical course without any associated comorbidities that can be attributed to the prevalence of decreased vitamin D serum levels in this group.

Our study found a significant increase in inflammatory markers in severe pediatric COVID-19 cases regarding CRP, D-dimer, ferritin, and LDH. These inflammatory markers have some tracing and detecting accuracy for disease severity and fatality as mentioned by Wu et al. [16]. Also, significant differences were found in our study between moderate and severe COVID-19 cases regarding decreased lymphocyte and increased neutrophil count. These results are consistent with 2 studies from Europe and the USA where significantly increased neutrophil counts were found in multisystem inflammatory syndrome in children (MIS-C) patients [17, 18]; however, Huang et al. [19] found lymphopenia was the most consistent laboratory finding, but it did not have prognostic value.

Organ involvement was found in most children affected by COVID-19 as observed by a cross-sectional study from south India as Sai et al. [20] found that 45% of children had laboratory evidence of liver dysfunction as increased SGOT, SGPT, or both. In our study, we also found hepatic dysfunction by elevated ALT and AST which was observed more in severe COVID-19 patients rather than a moderate group which indicates more liver injury. Our finding is also supported by Lei et al. [21] who found that AST elevation was associated with increased mortality risk compared with the other markers of liver injury along the disease course during hospitalization. Common parameters associated with elevated liver injury were decreased lymphocytic count and increased neutrophil count, these findings are matching with results of our study.

Renal involvement in pediatric COVID-19 cases in the form of elevated serum creatinine (low urine output or high creatinine) was noted in many studies as Sai et al. [20] who found 25.7% of children had renal function impairment as evidenced by increased serum urea or creatinine or both and 1patient (1.3%) required hemodialysis. Our study found elevated renal functions mainly with severe COVID-19 cases in comparison with moderately

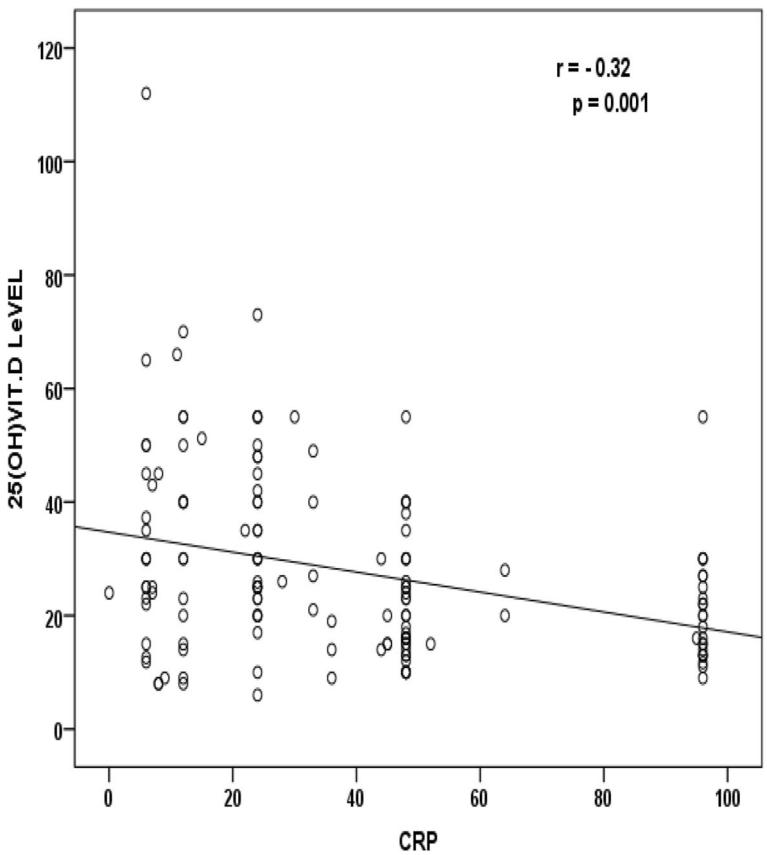

Fig. 2 Correlation between vit. D level and CRP

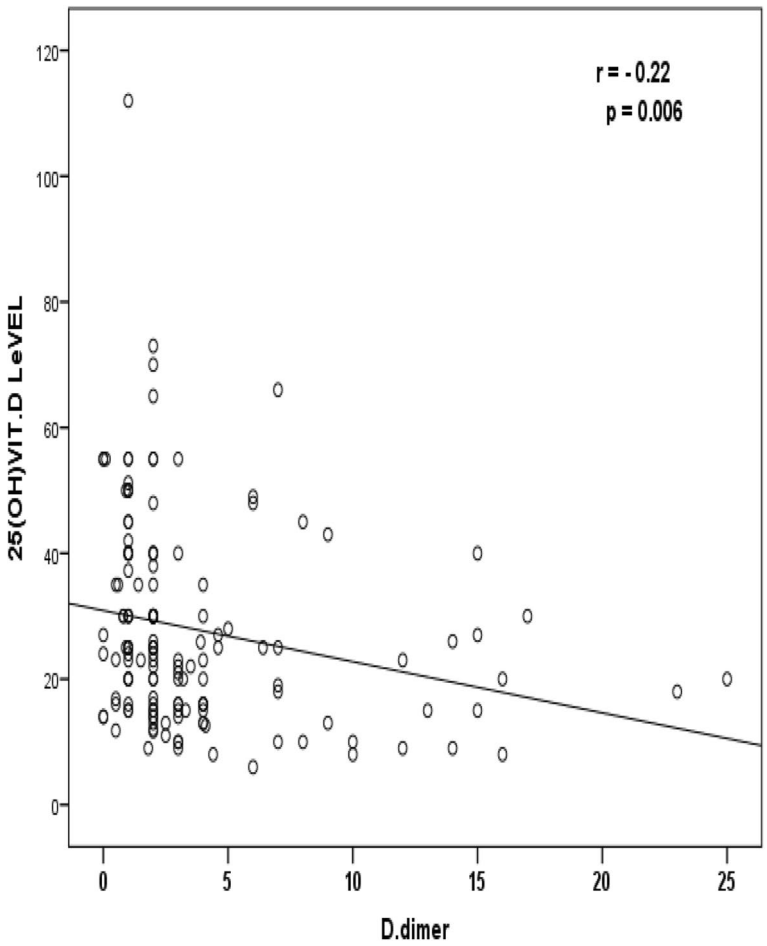

Fig. 3 Correlation between vit. D level and D-dimer

affected cases. Similar findings have been shown by Chao et al. [22] who found an elevation in serum level of creatinine and decreased creatinine clearance in clinically severe patients who had significantly higher markers of inflammation. Also, Samprathi and Jayashree [23] found a progressive increase in creatinine serum levels in severe cases.

We observed a significant difference in GCS with more decrease in severe pediatric COVID-19 cases than moderate cases and these findings coincide with Oualha et al. [15] who showed that the degree of deterioration in GCS is positively correlated to the severity of COVID-19 infection.

Our study found significant respiratory distress in patients with severe COVID-19, and this agrees with many researches done in COVID-19 presentation analysis [24–27]; these studies reported that concomitant hyperinflammation has been linked to severe pulmonary dysfunction. Notz et al. [26] found IL-6 was massively increased to the levels that block lymphopoiesis and induce lymphocyte death.

Siddiqui et al. [28] showed that high doses of calcitriol supplementation in healthy human subjects (1 μg twice per day for 7 days) leads to a dramatic reduction in the levels of pro-inflammatory cytokine IL-6 secreted by peripheral mononuclear cells, and this may support our finding that patients with severe respiratory symptoms and mechanically ventilated have lower values of vit. D and increased levels of inflammatory markers.

Our findings were in agreement with Tay et al. [29] who reported similar results that lower vitamin D levels were associated with clinical severity and higher inflammatory markers (i.e., CRP and ferritin) and a decreased lymphocytic count. Also, Daneshkhah et al. [30] found that treating severely vitamin D-deficient individuals lowers the risk of increased CRP levels which are used as a marker of cytokine storm, which

usually happens in severe COVID-19 cases. All these studies support our finding of the presence of a relationship between the severity and mortality of COVID-19 infection with vit. D status in the body at the infection time.

Conclusion

Although the effects of 25 OH vitamin D on the immune system are quite complex, the available information support that adequate vitamin D levels improve the defense process against bacterial and viral infections and prevent hyperinflammation. In our study, it has been shown that low serum vitamin D level in the body at the time of infection was associated with severe clinical course and higher mortality in children and adolescents with COVID-19.

One of the limitations of this research was the small sample size; also, the current study was carried out in one center, and conducting this research in multiple centers can lead to more accurate conclusive results.

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Authors' contributions
MIA, SHMR, and WAE conceived the study. MIA, ISA, SHMR, and IFA collected the data and performed the statistical analysis. ISA and MI reviewed the literature and drafted the initial version of the manuscript which was critically reviewed by ISA. All authors contributed to the drafting of the manuscript and approved the final version of the manuscript. ISA shall act as the corresponding author of the paper.

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Availability of data and materials
The data used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical Review Board of Minia University Hospital (approval no.: 78:2021).

Consent for publication
Written informed consent was obtained from parents/legal guardians.

Competing interests
The authors declare that they have no competing interests.

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