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# Vitamin D levels have a potential role in predicting the disease severity in COVID-19 positive pediatric patients

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## ABSTRACT

**Background and Objective:** The contagious and invasive nature has made coronavirus disease-19 (COVID-19) a critical health issue for the community. The lower respiratory tract is the major site of inflammation seen in COVID-19-positive individuals. Vitamin D (Vit D) has been proposed to have a positive role in immunomodulation, hence, this study aimed to determine the association between Vit D levels and the severity of COVID-19 in infected pediatric patients presenting at a secondary healthcare hospital in Pakistan.

**Methods:** This cross-sectional analytical study was conducted on 100 pediatric patients of the age range 1-18 years from March to December 2021. These patients were hospitalized and diagnosed with coronavirus disease with confirmed results on a real-time reverse transcription-polymerase chain reaction. Blood samples of the patients were taken to monitor the baseline levels of markers of acute infection and Vit D levels. Patients with serum Vit D levels  $\leq 20$  ng/ml were labeled with deficiency, those with levels 21-29 ng/ml were presumed to have Vit D insufficiency whereas levels  $\geq 30$  ng/ml were considered normal.

**Results:** There were 57 (57%) males and 43 (43%) female pediatric patients. The mean age of the patients was  $10.46 \pm 4.25$  years (1-18 years). The deficient Vit D level group had a greater frequency of pyrexia, weakness, cough, anosmia, headache, myalgia, and diarrhea. The levels of Vit D and severity of the disease were significantly associated ( $p$ -value = 0.027).

**Conclusion:** Pediatric patients with COVID-19 having optimum levels of Vit D were less likely to develop complications associated with the severity of the disease.

**Keywords:** COVID-19, pediatric, vitamin D, severity, disease, complications.

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## Introduction

Coronavirus disease-19 (COVID-19) associated morbidity and fatality has nearly devastated the world population in the preceding year. Coronavirus disease in particular attacks the respiratory tract, however, severe complications including hematological, renal, acute respiratory failure, and/or septic shock have also been well reported in the literature.<sup>1</sup> Around 40% of the patients with COVID-19 require admission in the critical care units while the mortality is reported as high as 15%.<sup>2</sup> Although due to rapid mutations of the organism still many aspects of the pathogenesis and evolution of the disease process remain debatable; however, the disease severity and complications are few and far reported among the pediatric population.<sup>3,4</sup>

COVID-19 infection triggers the release of enormous amounts of inflammatory markers especially the cytokines

which cause destruction of the lungs' parenchyma leading to acute respiratory distress syndrome. Recent research has revealed an upsurge of cases and complications in pediatric patients, hence, warranted for the exploration of safe and non-invasive treatment modalities and empirical therapies among this vulnerable group of population.<sup>5,6</sup>

Vitamin D (Vit D) has a significant role in the development of bones and metabolism at the skeletal level. It also has a significant role in immunomodulation. To enhance innate immunity Vit D is critical for the augmentation of antimicrobial peptides, cathelicidin, and beta-defensin. Cathelicidin and beta-defensin have elucidated pleiotropic ramifications in the induction of immunomodulatory reaction to infectious and pathogenic triggers with a significant impact on T-lymphocytes by downregulation and upregulation of type 1 and type 2 T cells

respectively.<sup>7,8</sup> Vit D also plays an indirect stimulatory role in the antigen-presenting capacity of the T-lymphocytes by inducing or inhibiting a cascade of interleukins and cytokines.<sup>9,10</sup>

On the basis of this immunomodulatory role, the serum Vit D levels are considered a significant biomarker of disease progression and prognostication in COVID-19 patients of both adult and pediatric age groups.<sup>11-13</sup> Thus, this study aimed to determine the association between Vit D levels and the severity of COVID-19 in COVID-19-infected pediatric patients presenting at a local secondary health care hospital of Pakistan so as to prescribe this vitamin as a potential empirical treatment in COVID-19 patients.

## Methods

This cross-sectional analytical study was performed at the Tehsil Headquarters Hospital Gujar Khan, Rawalpindi, Pakistan from March to December 2021 after approval of the ethical review board. The calculated sample size for the study was 84 with the comparison of two means of Vit D levels with a 95% confidence interval, power of 80%, and margin of error of 5% as per a study conducted by Alpcan et al.<sup>13</sup> Sampling was done through non-probability consecutive technique.

A total of 100 patients, of both genders, were recruited in the study with an age range of 1-18 years. The patients were diagnosed with coronavirus disease using polymerase chain reaction as a gold standard test for identification of the virus. Informed assent for the study was taken from the parents. However, patients with non-consenting parents, asymptomatic coronavirus disease, with a history of co-morbidities (e.g., bone metabolism disorders, bleeding disorder, tuberculosis, etc.), and a history of recent Vit D intake as a supplement before the diagnosis of COVID-19, were excluded from the study.

The patient's demographic profile, medical history, clinical features, and laboratory parameters were recorded. On presentation to the hospital, blood samples were collected to monitor the baseline laboratory investigations including markers of infection [erythrocyte sedimentation rate, C-reactive protein (CRP), D-dimer] and levels of Vit D. Vit D levels in the blood were estimated in Cobas E411 and enzyme-linked immunosorbent assay using the protocol as per available commercial kits. Patients with serum Vit D levels  $\leq 20$  ng/ml (Group A) were labeled with deficiency, those with levels 21-29 ng/ml (Group B) were presumed to have Vit D insufficiency, whereas levels  $\geq 30$  ng/ml (Group C) were considered as normal.<sup>14</sup> Patients were further classified into asymptomatic, mild, moderate, and severe COVID-19 based on the criteria<sup>15</sup> as shown in Table 1.

## Statistical analysis

Data entry and analysis were done using the data management software IBM SPSS (version 23.0). Frequencies

**Table 1.** Disease severity criteria.<sup>15</sup>

Symptoms	Features
Asymptomatic	Positive reverse transcription-polymerase chain reaction test without clinical and radiological features
Mild	Infection of the upper respiratory tract without associated findings on respiratory system examination
Moderate	Fever, cough, dyspnea, tachypnea, oxygen saturation $>90\%$ on room air
Severe	Fever, cough, dyspnea, tachypnea, central cyanosis, oxygen saturation $>90\%$ on room air, respiratory rate $>30$ breaths/minute, severe distressful respiration
Critical	Acute respiratory distress or respiratory failure or one of the following: septic shock and acute thrombosis

and percentages were used for descriptive variables, while, mean  $\pm$  SD was given for continuous variables. The chi-square test was used to compare the variables and a  $p$  value of  $\leq 0.05$  was considered statistically significant.

## Results

There were 57 (57%) males and 43 (43%) female pediatric patients. The mean age of the patients was  $10.39 \pm 4.21$  years (1-18 years). Mean Vit D levels in all 100 patients were  $16.6515 \pm 8.79328$  ng/ml. Patients with deficient Vit D levels had a greater frequency of pyrexia, weakness, cough, anosmia, headache, myalgia, and diarrhea, however association was statistically insignificant ( $p > 0.05$ ). Chest X-ray findings and acute respiratory distress were abundantly found in Group A (deficient Vit D levels) as compared to the other groups and were statistically significant ( $p$ -value  $< 0.02$ ). The levels of Vit D and severity of the disease (Table 2) was significantly associated ( $p$ -value = 0.027) (Figure 1).

The frequency of symptoms, laboratory parameters, and their association with disease severity is given in Table 2.

## Discussion

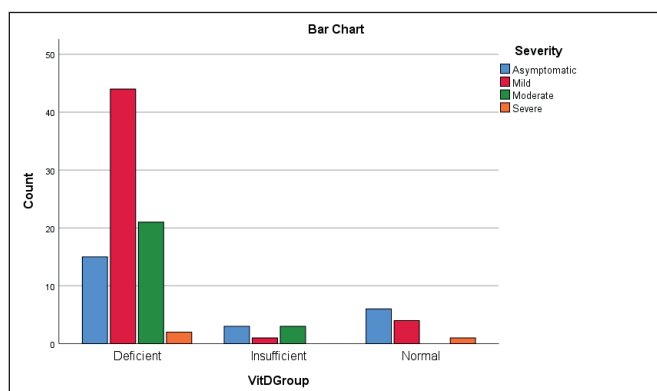
This study shows a significant association between levels of Vit D and the disease severity in COVID-19 patients. One of the commonest adversity reported with the COVID-19 pandemics in the communities was a hampered natural lifestyle leading to home isolation with subsequent minimal exposure to sunlight causing a decreased Vit D synthesis, especially in the pediatric population.<sup>16</sup>

Wong et al.<sup>17</sup> enrolled (303) infants and toddlers (2-24 months) via random stratification protocol for 6 months to determine the impact of the COVID-19 outbreak on serum Vit D levels in an interrupted time series paradigm. Their analysis concluded a steep decline in Vit D levels with the progression of the pandemic with a rate of  $-6.32$  nmol/l per

**Table 2.** Association of severity of COVID-19 disease with gender and age groups.

Asymptomatic		Severity				Total	
		Mild	Moderate	Severe			
Gender	Male	13 (22.8%)	29 (50.87%)	13 (22.8%)	2 (3.5%)	57	0.061
	Female	11 (25.58%)	20 (46.51%)	11 (25.58%)	1 (2.32%)	43	0.076
Age groups (years)	1-5	9 (37.5%)	11 (45.83%)	4 (16.66%)	0 (%)	24 (%)	0.314
	6-12	4 (10.81%)	22 (59.46%)	9 (24.32%)	2 (5.40%)	37 (%)	0.112
	13-18	11 (28.20%)	16 (41.02%)	11 (28.20%)	1 (2.56%)	39 (%)	0.091
Total		24	49	24	3	100	

\*Chi square test: No significant association was seen.



**Figure 1.** Distribution of Vit D level groups with reference to the severity of the disease ( $p = 0.027$ ).

month, categorically prevalent in the younger age group (2-6 months). The authors thereby proposed a cautious increase in the intake of Vit D by pregnant women during the pandemic.<sup>17</sup>

Davoudi et al.<sup>18</sup> conducted a trial on (153) patients in Iran to ascertain the association between Vit D levels and clinical presentation of coronavirus disease. The reference standard of adequate Vit D was set up at 30 ng/ml. The mean average Vit D levels of the participants were  $27.19 \pm 20.17$  ng/ml with 96 (62.7%) had values below the cutoff.<sup>18</sup>

Vit D is recognized to play its role as an immunomodulator in inflammatory conditions. Bayramoğlu et al.<sup>19</sup> estimated the 25(OH)D levels in (103) pediatric patients with COVID-19 of variable disease severity. They found higher levels of inflammatory markers (CRP, procalcitonin, fibrinogen, and D-dimer) and deficient Vit D levels in 70.6% of patients with moderate-to-severe disease ( $p < 0.001$ ). Concurrent results were also reported from other studies in adults as well.<sup>20,21</sup>

Darren et al.<sup>22</sup> reported the Vit D status of children with the pediatric inflammatory multisystem syndrome in (18) (0.3-14.6 years) patients in the United Kingdom. Black, Asian, and minority ethnicity were considered to have a greater susceptibility to the syndrome and 72% of the patients with Vit D deficiency had serious complications.

Numerous studies have reported an elaborated prophylactic role of Vit D in the reduction of COVID-19 and respiratory tract infections through major clinical trials. Therefore, a targeted serum evaluation and engagement of Vit D as a prophylactic and treatment modality have been reported in COVID-19 patients.<sup>23-25</sup> To date, no standard guidelines for prescribing Vit D to pediatric COVID-19 patients have yet been published from Pakistan. Prophylactic and therapeutic use of Vit D by pediatricians is widely accepted in our country however there is a need for further studies emphasizing the potential utility of these cost-effective nutritional supplements in managing patients with COVID-19.

## Conclusion

Pediatric patients with COVID-19 having optimum levels of Vit D are less likely to develop complications related to the severity of the disease.

## Limitations of the Study

This study has a small sample size and no intervention is carried out. Further studies with large population size and randomized clinical trials focusing on dose-dependent effects of Vit D in COVID-19 patients are recommended to support the findings of this study.

## Acknowledgement

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## List of Abbreviations

COVID-19	Coronavirus disease-19
Vit-D	Vitamin D
CRP	C-reactive protein

## Conflict of interest

None to declare.

## Grant support and financial disclosure

None to disclose.

### Ethical approval

The study is approved by the Institutional Ethics Committee of the Tehsil Headquarters Hospital Gujar Khan, Rawalpindi, Pakistan vide Letter No. 681/THQ/21, dated 02-02-2021.

### Authors' contributions

**MH:** Conception and design of study, acquisition of data, and drafting of manuscript with critical intellectual input.

**IB:** Acquisition and analysis of data and drafting of manuscript.

**HM:** Critically revised the manuscript with intellectual input.

**MJ, UA:** Acquisition of data and drafting of manuscript.

**ALL AUTHORS:** Approval of the final version of the manuscript to be published.

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