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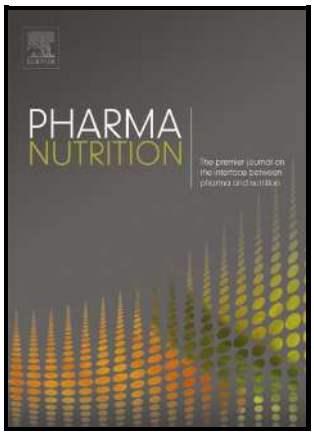

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Vitamin D status can affect COVID-19 outcomes also in pediatric population.

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Abstract

Background

vitamin D influences the immune system and the inflammatory response. It is known that vitamin D supplementation reduces the risk of acute respiratory tract infection. In the last two years, many researchers have investigated vitamin D’s role in the pathophysiology of COVID-19 disease.

Results

the findings obtained from clinical trials and systematic reviews highlight that most patients with COVID-19 have decreased vitamin D levels and low levels of vitamin D increase the risk of severe disease. This evidence seems to be also confirmed in the pediatric population.

Conclusions

further studies (systematic review and meta-analysis) conducted on children are needed to confirm that vitamin D affects COVID-19 outcomes and to determine the effectiveness of supplementation and the appropriate dose, duration and mode of administration.

Keywords

vitamin D, COVID-19, SARS-CoV-2 infection, children, immunity.

Abbreviations

dendritic cells=DCs, vitamin D receptors=VDRs, interleukin=IL, Treg cells=regulatory T cell, cluster of differentiation=CD, reduce interferon-gamma=IFN-γ, Toll-like receptors=TLRs, renin-angiotensin system=RAS, angiotensin-converting enzyme 2=ACE2, immunoglobulin E=IgE, pathogen-associated molecular patterns=PAMPs, damage-associated molecular patterns=DAMPs, pattern recognition receptors=PRRs, tumor necrosis factor-α=TNF-α, intensive care unit=ICU, natural killer=NK, randomized control trials=RCTs, risk ratio=RR, confidence interval=CI, odds ratio=OR, Hazard Risk=HR, mean difference=MD.

1. Exploring the immune link between vitamin D and SARS-CoV-2

Vitamin D is the collective name for cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2); the active hormonal form is calcitriol or 1,25-dihydroxyvitamin D, obtained by hydroxylation in the liver and kidney [1]. Vitamin D plays a crucial role in the regulation of the metabolism of calcium and phosphates, regulating bone growth and the maintenance of mineral homeostasis, as well as acting on different peripheral organs and tissues such as kidneys, bones, parathyroids, skin, thymus, pituitary glands, uterus, placenta, and various cellular elements of the immune system. Vitamin D works on the adaptive and innate immune systems, with anti-inflammatory and immunomodulating activity [2]. Cells of the adaptive immune system are not only targets of vitamin D metabolites, but they are also able to activate and inactivate vitamin D metabolites. Both monocytes and dendritic cells (DCs) express vitamin D receptors (VDRs). Surface costimulatory molecules like CD40,

CD80, and CD86 are decreased in monocytes cultured with 1,25(OH)2D[3]. 1,25$(OH)_2$D inhibits the differentiation of monocytes into immature DCs. Studies show that DCs matured in vitro in the presence of 1,25$(OH)_2$D, have an altered cytokine and chemokine profile: the release of Th1 and Th17 inducing cytokines, interleukin (IL)-12 and IL-23, is inhibited, while the production of IL-10 (anti-inflammatory cytokine) and Treg cells (regulatory T cell) is enhanced [4,5]. Altogether these results show that vitamin D can block DC maturation, IL-12 production and enhance the production of IL-10 and Treg cells. Most in vitro studies on human cluster of differentiation (CD) 4+ T cells show that 1,25(OH)2D is able to reduce interferon-gamma (IFN-γ) secretion, inhibit Th1 cells and Th2 cell differentiation, and enhance the secretion of IL-4 by the already differentiated Th2 cells [2,6]. Vitamin D has been shown to interact with the innate immune system by activating Toll-like receptors (TLRs) or increasing the levels of cathelicidins and β-defensins. TLRs play an important role in recognizing viral particles and activating the innate immune system. Vitamin D increases TLR2 and TLR4 on the cord blood monocytes, TLR2/6 on the keratinocytes and TLR2, TLR3, TLR8 on the immune cells, strengthening the immune responses against microbial infections [7]. Different TLRs, like TLR2, TLR3, TLR4, TLR6, TLR7, TLR8, and TLR9 are potentially important in COVID-19 infection**,** representing a potential target in controlling the infection in the early stages of the disease [8]. Adequate vitamin D levels are also required in order to reduce renin-angiotensin system (RAS) activity and increase angiotensin-converting enzyme 2 (ACE2) concentrations in acute lung injury [9]. Furthermore, low circulating vitamin D levels have been associated with the risk of asthma, atopic dermatitis, and elevated total immunoglobulin E (IgE) [10-15].

In COVID-19 pathogenesis, SARS-CoV-2 is able to activate both the innate and adaptive immune response. The viral particle attaches to ACE2 receptor, which is present on lung cells, reduces ACE2 expression and then enters via endocytosis [16]. ACE2 regulates RAS, thus its downregulation breaks RAS homeostasis, affecting blood pressure, electrolyte balance, increasing inflammation and vascular permeability in the airways. Innate immune cells detect the pathogen-

associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) present on the virus particle using pattern recognition receptors (PRRs), which include TLRs, and generate local inflammation and releasing cytokines and chemokines including IFN-γ, IL-6, MCP1, and IP-10. SARS-CoV-2-specific CD4+ T cells display IFN-γ, tumor necrosis factor-α (TNF-α), IL-2 chemokines, enhancing the activation of Th1 immune response and cell-mediated immunity [9,17]. T cells, CD4+, Th1 and Th17, and CD8 + T cells play a critical role in the adaptative immunity response. It consists in promoting the secretion of pathogen-specific antibodies by inducing T-dependent B cells and killing the virus-infected cells. Furthermore, virus-specific memory CD8 + T cells have a significant role in host protection from lethal SARS-CoV-2 infection by the production of IFN-γ, TNF-α, IL-2, and cytolytic molecules, such as granzyme B [18] [*Fig.1*]. In a case-control study by Bayraktar et al., the role and relationship between the cytokine profile and vitamin D were investigated. The serum cytokine levels IL-1, IL-6, IL-10, IL-21, TNF-α and vitamin D were measured in the COVID-19 patient group (intensive care unit (ICU) patients with severe illnesses) and the control group (individuals without a history of serious illness or infection): in the COVID-19 group cytokine levels were significantly higher than control groups, while serum vitamin D was significantly low [19].

The pathophysiological and clinical disparities between children and adults with COVID-19 may be due to different factors. Children have a more potent innate immune response with more natural killer (NK) cells, which serves as the initial line of defence against SARS-CoV-2 [20]. Another significant element is "trained immunity," which is the process by which innate immune cells undergo epigenetic reprogramming as a result of exposure to specific stimuli, such as infections and immunizations, and develop "memory." Children also have greater proportions of lymphocytes and absolute numbers of T and B cells in connection to adaptive immunity, while ageing is linked to a decline in thymic activity and a decline in naive T cell numbers [21]. Children may also be protected by more frequent concurrent and recurrent infections, innate immunity to coronaviruses, variations

in their microbiome, increased melatonin levels, and protective off-target effects of live vaccinations [21].

2. Does vitamin D deficiency increase the risk and severity of COVID-19?

Several studies have investigated a possible association between vitamin D serum levels and the risk and severity of SARS-CoV-2 infection. The most important evidence on the link between vitamin D and COVID-19 comes from systematic reviews and meta-analyses. In the meta-analysis by Rawat et al., 5 studies (3 randomized control trials (RCTs) and 2 Quasi-experimental) including 467 patients were included: vitamin D didn't reduce mortality (risk ratio (RR) 0.55, 95% confidence interval (CI) 0.22 to 1.39, p = 0.21), ICU admission rates (RR 0.20, 95% CI 0.01-4.26, p = 0.3) and need for invasive ventilation (RR 0.24, 95% CI 0.01-7.89, p = 0.42) [22]. In the systematic review by Pereira et al., vitamin D deficiency was not associated with a higher chance of infection by COVID-19 (OR= 1.35; 95% CI = 0.80-1.88), but severe cases of COVID-19 present 64% (OR = 1.64; 95% CI = 1.30-2.09) more vitamin D deficiency compared with mild cases. Vitamin D concentration insufficiency increased hospitalization (OR = 1.81, 95% CI = 1.41-2.21) and mortality from COVID-19 (OR = 1.82, 95% CI = 1.06-2.58) [23]. Twenty-three studies containing 11901 participants entered into the meta-analysis by Ghasemian et al. 41% of COVID-19 patients were suffering from vitamin D deficiency (95% CI, 29%-55%), and in 42% of patients, levels of vitamin D were insufficient (95% CI, 24%-63%). The serum 25-hydroxyvitamin D concentration was 20.3 ng/mL among all COVID-19 patients (95% CI, 12.1-19.8). The odds of getting infected with SARS-CoV-2 were 3.3 times higher among individuals with vitamin D deficiency (95% CI, 2.5-4.3), while the chance of developing severe COVID-19 was about five times higher in patients with vitamin D deficiency (OR: 5.1, 95% CI, 2.6-10.3). There was no significant association between vitamin D status and higher mortality rates (OR: 1.6, 95% CI, 0.5-4.4) [24]. In the systematic review by Kazemi et al., thirty-nine studies were included: fifteen studies evaluated associations between vitamin D deficiency and composite severity. In the studies that were adjusted

(OR: 2.57; 95% CI: 1.65, 4.01; I2 = 0.0%) and nonadjusted for confounders (OR: 10.61; 95% CI: 2.07, 54.23; I2 = 90.8%) there was a higher severity in the vitamin D deficiency group. Analysis of studies with crude OR (OR: 2.62; 95% CI: 1.13, 6.05; I2: 47.9%), and adjusted studies that used the Cox survival method (HR: 7.67; 95% CI: 3.92, 15.03; I2: 0.0%) indicated a significant association of vitamin D deficiency with mortality, while in adjusted studies that used logistic regression, no relation was observed (OR: 1.05; 95% CI: 0.63, 1.75; I2: 76.6%). The results of studies that examined relations between vitamin D deficiency and ICU admission, pulmonary complications, hospitalization, and inflammation were inconsistent [25]. In October 2021 Petrelli et al. assessed the association between vitamin D and risk, severity, and mortality for COVID-19 infection, through a review of 43 observational studies. Among subjects with deficient vitamin D values, risk of COVID-19 infection was higher compared to those with replete values (OR = 1.26; 95 % CI, 1.19-1.34; P < .01). Vitamin D deficiency was also associated with worse severity and higher mortality than in nondeficient patients (OR = 2.6; 95 % CI, 1.84-3.67; P < .01 and OR = 1.22; 95 % CI, 1.04-1.43; P < .01, respectively) [26]. According to the review by Pal et al., vitamin D use in COVID-19 was significantly associated with reduced ICU admission/mortality (OR 0.41, 95% CI: 0.20, 0.81, p = 0.01, I2 = 66%, random-effects model) and decreased the risk of adverse outcomes (pooled OR 0.27, 95% CI: 0.08, 0.91, p = 0.03, I2 = 80%, random-effects model). Subgroup analysis showed that vitamin D supplementation was associated with improved clinical outcomes only in patients receiving the drug post-COVID-19 diagnosis and not in those who had received vitamin D before diagnosis [27]. In 2022 the meta-analysis of Shah et al. showed that vitamin D supplementation reduces the risk of mortality (OR: 0.48, 95% CI: 0.346-0.664; p < 0.001), the need for ICU (OR: 0.35; 95%CI: 0.28-0.44; p < 0.001) and mechanical ventilation (OR: 0.54; 95% CI: 0.411-0.708; p < 0.001) requirement in COVID patients [28]. In an adult population-based study, the researchers observed that in comparison to non-supplemented 25-hydroxyvitamin D-deficient patients, those receiving cholecalciferol treatment and achieving vitamin D levels 30 ng/ml had a lower risk of SARS-CoV2 infection, a lower risk of severe COVID-19, and a lower risk of COVID-19 mortality

(56/9474 [0.6%] vs 96/7616 [1.3%]; Hazard Risk (HR) 0.66 [CI 95% 0.46-0.93], p = 0.018). In the entire cohort (n = 134,703), calcifediol use was not linked to a lower incidence of SARS-CoV2 infection or mortality. When compared to 25-hydroxyvitamin D-deficient patients not receiving vitamin D supplements, patients on calcifediol treatment who achieved serum vitamin D levels 30 ng/ml also had a lower risk of SARS-CoV2 infection, a lower risk of severe COVID-19, and a lower risk of COVID-19 mortality (88/16276 [0.5%] vs 96/7616 [1.3%]; HR 0.56 [CI 95% 0.42-0.76], p < 0.001) [29]. In the analysis by Wang et al., including 17 observational studies with 2756 individuals, in comparison to non-deficient vitamin D status, vitamin D deficiency was linked to significantly higher rates of mortality (OR: 2.47, 95%, CI 1.50-4.05; 12 studies; HR: 4.11, 95% CI: 2.40-7.04; 3 studies), higher rates of hospital admissions (OR: 2.18, 95% CI: 1.48-3.21; 3 studies), and longer hospital stays (0.52 days, 95% CI: 0.25-0.80; 2 studies) [30]. In the review by Teshome et al., the pooled analysis showed that individuals with vitamin D deficiency were 80% more likely to acquire COVID-19 infection as compared to those who have sufficient vitamin D levels (OR = 1.80; 95% CI: 1.72, 1.88) [31]. In a systematic review conducted in Sri Lanka, 72 observational studies were included (n = 1 976 099). Vitamin D deficiency/insufficiency increased the odds of developing COVID-19 (OR=1.46; 95% CI, 1.28-1.65; *P* < 0.0001), severe disease (OR 1.90; 95% CI, 1.52-2.38; *P* < 0.0001), and death (OR 2.07; 95% CI, 1.28-3.35; *P* = 0.003). Patients with COVID-19 had lower 25-hydroxy vitamin D concentrations than controls (mean difference [MD] -3.85 ng/mL; 95 % CI, -5.44 to -2.26; P = 0.0001), patients with severe COVID-19 had lower 25-hydroxy vitamin D concentrations than controls with non-severe COVID-19 (MD -4.84 ng/mL; 95 % CI, -7.32 to -2.35; P = 0.002) [32]. In the systematic review by Hosseini et al., including 23 randomized and non-randomized control studies, vitamin D supplementation was significantly associated with a reduced risk of ICU admission (RR = 0.35, 95% CI: 0.20, 0.62) and mortality (RR = 0.46, 95% CI: 0.30, 0.70), but it had no significant impact on the risk of COVID-19 infection [33]. Also in the study by Tentolouris et al., including a total of 11 studies with 22,265 COVID-19 patients, the findings implied that vitamin D supplementation improved COVID-19 outcomes:

vitamin D supplementation was associated with a reduction in intensive care unit admission rate (OR 0.27; 95% CI: 0.09–0.76, p = 0.010, I2 = 70%, random-effect modelling); reduction of the need for mechanical ventilation (OR 0.34; 95% CI: 0.16–0.72, p = 0.005, I2 = 61%, random-effect modelling) and reduction of mortality from COVID-19 (OR 0.37; 95% CI: 0.21–0.66, p < 0.001, I2 = 50%, random-effect modelling) [34]. In the systematic review by Akbar et al., consisting of 14 studies comprising of 999,179 participants, when compared to the control group, COVID-19 patients had lower serum vitamin D (OR = 2.71 [1.72, 4.29], p < 0.001; I2: 92.6%). Higher rate of severe COVID-19 was observed in patients with low serum 25-OHD (OR = 1.90 [1.24, 2.93], p = 0.003; I2: 55.3%). Decreased serum vitamin D was associated with higher mortality (OR = 3.08 [1.35, 7.00], p = 0.011; I2: 80.3%), with a sensitivity of 85% and specificity of 35%. Male gender and diabetes were found to be factors in the connection between low serum 25-OHD and mortality (OR = 1.22 [1.08, 1.39], p = 0.002 and OR = 0.88 [0.79, 0.98], p = 0.019, respectively) [35].

2.1. Vitamin D and COVID-19 in children

Pandemic-related restrictions have caused a significant decrease in vitamin D levels in children, in particular school-aged children and adolescents [36]. Despite, in the pediatric population, most cases of SARS-CoV-2 infection are asymptomatic or paucisymptomatic [37-39], even five months after discharge and beyond, children who have *long-COVID* might experience debilitating symptoms [40-42]. Many studies show that allergy and asthma, if under control, did not represent risk factors for the susceptibility to SARS-CoV-2 [43-46]. The role of spirometry, in the COVID era, still remains fundamental in the diagnosis and follow-up of respiratory diseases, in compliance with current containment measures [47].

The role of vitamin D in SARS-CoV-2 infection was also investigated in the pediatric population. In the systematic review by Shah et al., eight eligible studies were included: in infected pediatric patients, low levels of vitamin D increased the risk of severe disease (OR -5.5; 95% CI: 1.560-

19.515; P = 0.008). It was also found that children and adolescents having vitamin D deficiency had a greater risk of COVID infection as compared to patients with normal vitamin D levels [48]. In a study by Yilmaz et al., 40 children hospitalized with COVID-19 and 45 healthy controls were divided into two groups; those with vitamin D levels <20 ng/ml were classified as Group 1, and those with ≥20 ng/ml as Group 2. Children with COVID-19 had significantly lower vitamin D levels than the controls (p < .001). The symptom of fever was significantly higher in COVID-19 patients who had deficient and insufficient vitamin D levels than in patients who had sufficient vitamin D levels (p = .038) [49]. In the retrospective study by Bayramoğlu et al., consisting of 103 pediatric cases with COVID-19, low 25OH vitamin D levels were linked to higher inflammatory indicators (C-reactive Protein, procalcitonin, fibrinogen, D-dimer) and more severe clinical course [50]. In a turkish report, including seventy-five 1-18 years old patients, the mean serum vitamin D level was significantly lower in the COVID-19 group than the control group (21.5 ± 10.0 vs. 28.0 ± 11.0 IU, P < 0.001). In comparison to the control group, the COVID-19 group had a considerably higher percentage of patients who were vitamin D deficient (44% vs. 17.5%, P < 0.001). Patients with low levels of vitamin D were older than those with normal levels of vitamin D (11.6 ± 4.9 vs. 6.2 ± 1.8 years, P = 0.016). There was a significant male preponderance in the normal vitamin D group compared with the low vitamin D group (91.7% vs. 50.8%, P = 0.03). C-reactive protein level was higher in the low vitamin D group, although the difference did not reach statistical significance (9.6 ± 2.2 vs. 4.5 ± 1.6 mg/l, P = 0.074) [51]. *[Table.1]*

Current evidence suggests that taking a vitamin D supplement to maintain a serum concentration of 25-OH vitamin D of at least 30 ng/mL (preferred range 40–60 ng/mL), can help reduce the risk of COVID-19 and its severe outcomes, including mortality [52]. According to evidence on the paediatric population, although robust systematic and meta-analyses are lacking, it can be recommended in any case to maintain adequate levels of vitamin D (>30 ng/mL) in order to maintain a healthy immune system.

3. Conclusion

In conclusion, although the examined studies were different in methods and statistical approach, most of them indicated a significant relation between vitamin D serum levels and SARS-CoV-2 infection, clinical outcomes and mortality. Even in children with COVID-19, insufficient levels of vitamin D have been found and low levels of vitamin D would seem to be associated with worse outcomes. While there is currently insufficient evidence to support the use of vitamin D as a therapeutic treatment for SARS-CoV-2 infection, those who may be deficient should raise their levels through diet, lifestyle changes, and supplementation because it is affordable and generally safe, in order to achieve any potential prophylactic benefits, but more significantly because preserving appropriate vitamin D levels is crucial for overall wellness.

Credit list

M.M.d.G. wrote and conceptualized the manuscript. C.I. revised the manuscript. G.D. contributed to drafting the introduction. F.D. revised the manuscript. A.D. contributed to the research in the literature. A.K. supervisioned the manuscript. All authors have read and agreed to the published version of the manuscript.

Declaration of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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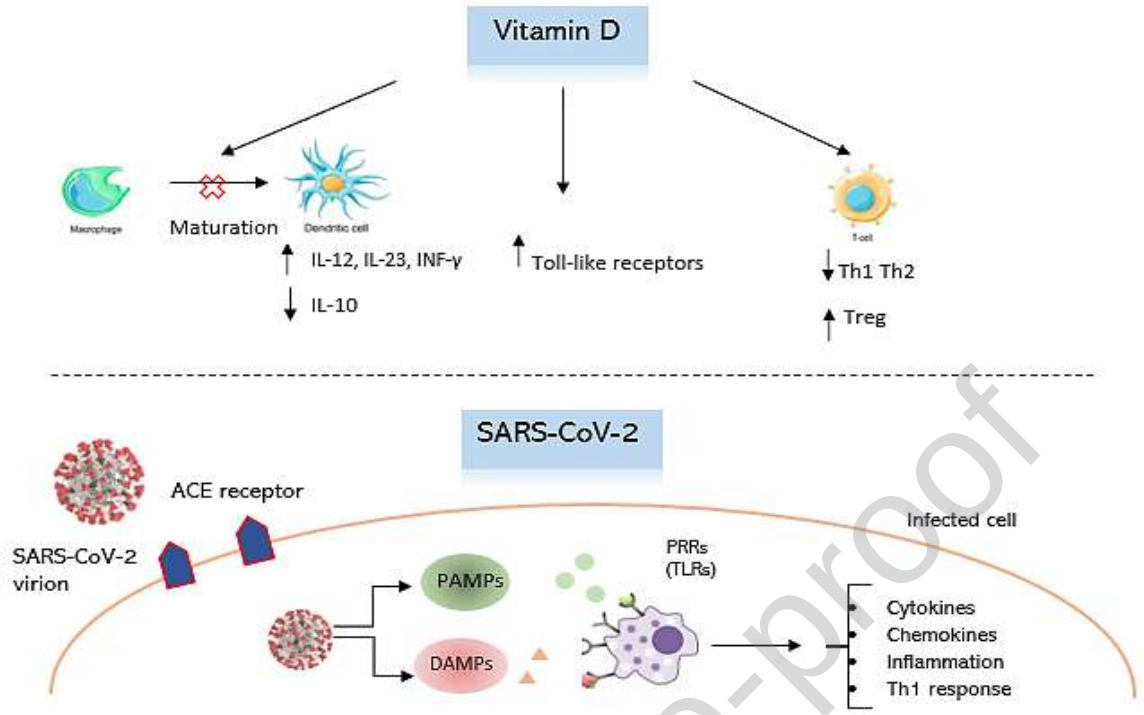

Fig.1. Comparison of the immune response induced by vitamin D administration and SARS-CoV-2 infection. Vitamin D increases the production of Toll-like receptors (TLRs), IL-10 (anti-inflammatory cytokine) and Treg cells (regulatory T cell), while the release of Th1 and Th17 inducing cytokines, interleukin (IL)-12 and IL-23, is inhibited. In the COVID-19 pathogenesis, pattern recognition receptors (PRRs), which include TLRs, are used by innate immune cells to recognize the pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) found on virus particles. This mechanism triggers local inflammation and the release of cytokines and chemokines such as IFN- γ (interferon-gamma***)***, IL-6, MCP1, and IP-10. IFN- γ, tumor necrosis factor (TNF), and IL-2 chemokines are expressed on SARS-CoV-2-specific CD4+ T cells, which promote the activation of the Th1 immune response and cell-mediated immunity.

Table.1. Comparison of current evidence on vitamin D and COVID-19 in pediatric population, based on retrospective studies and a systematic review.

Reference	Study design	Objectives	Population	Methods	Results
48	systematic review	To study the relationship between vitamin D level, risk and severity of Coronavirus disease of 2019 (COVID-19) infection in pediatric population	8 studies involving children (age ≤18) reporting vitamin D status and COVID-19 infection in pediatric patients.	-	In infected pediatric patients, low levels of vitamin D increased the risk of severe disease (odds ratio-5.5; 95% CI: 1.560-19.515; P = 0.008). It was also found that children and adolescents with vitamin D deficiency had a greater risk of COVID infection than patients with normal vitamin D levels.
49	Retrospective study.	Vitamin D deficiency prevalence and the association between vitamin D deficiency and clinical and inflammatory markers in patients hospitalized for COVID-19 infection.	85 children between the ages of 1 month to 18 years 40 COVID-19+ (101.76 ± 27.91 months range, 3 months-18 years)	Vitamin D status was assessed retrospectively using accredited laboratory methods. Patients with 25-OH vitamin D levels below 20 ng/ml (<50 nmol/l) were considered to have vitamin D deficiency; those with 25-OH vitamin D levels between 21 and 29 ng/ml (52.5 and 72.5 nmol/l) were considered to have vitamin D insufficiency; and those with 25-OH vitamin D levels above 30 ng/ml were considered to have a normal vitamin D level.	72.5% of cases were vitamin D deficient or insufficient, and 2 patients in need of treatment in the ICU had the vitamin D level of below 10 ng/ml, and had comorbid diseases, but there were no reported cases of mortality. In the study, the distribution of disease severity according to vitamin D levels was not found significantly different (p = 0.097)
50	Retrospective study.	To evaluate the relationship between vitamin D levels and clinical severity and inflammation markers in children and	103 children. The mean age was 12.2 ± 4.92 (range 1–17) years and 52.4% (n = 54) were male.	Data were assessed retrospectively. Patients were grouped according to their clinical severity (asymptomatic, mild, and	The serum vitamin D level was associated with clinical severity and markers of inflammation in children and adolescents with COVID-19.

		adolescents with COVID-19.		moderate-to-severe) and vitamin D levels (25 OH vitamin D serum levels sufficient (> 20 ng/mL), deficient (12–20 ng/mL), and insufficient (<12 ng/mL)).	Interestingly, these associations were observed especially when there was a deficiency (i.e., 25 OH vit D) vitamin D insufficiency was not found to be associated with disease severity or inflammation markers in COVID-19
51	Retrospective study.	To compare the vitamin D levels of paediatric patients with mild/moderate coronavirus disease 2019 (COVID-19) disease and a healthy control group	75 COVID-19 patients and 80 healthy controls. The mean age of the COVID-19 patients was 10.7 ± 5.5 years (range 1–18 years); 43 (57.3%) patients were male The control group was composed of 43 (53.8%) males and 37 (46.2%) females and had a mean age of 9.9 ± 4.6 years (range 1–17 years)	Vitamin D status was assessed retrospectively using accredited laboratory methods. Patients with 25-OH vitamin D levels below 20 ng/ml (<50 nmol/l) were considered to have vitamin D deficiency; those with 25-OH vitamin D levels between 21 and 29 ng/ml (52.5 and 72.5 nmol/l) were considered to have vitamin D insufficiency; and those with 25-OH vitamin D levels above 30 ng/ml were considered to have a normal vitamin D level	The mean serum vitamin D level was significantly lower in the COVID-19 group than the control group (21.5 ± 10.0 vs. 28.0 ± 11.0 IU, P < 0.001). In comparison to the control group, the COVID-19 group had a considerably higher percentage of patients who were vitamin D deficient (44% vs. 17.5%, P < 0.001). Patients with low levels of vitamin D were older than those with normal levels of vitamin D (11.6 ± 4.9 vs. 6.2 ± 1.8 years, P = 0.016). There was a significant male preponderance in the normal vitamin D group compared with the low vitamin D group (91.7% vs. 50.8%, P = 0.03). C-reactive protein level was higher in the low vitamin D group, although the difference did not reach statistical significance (9.6 ± 2.2 vs. 4.5 ± 1.6 mg/l, P = 0.074)

Graphical abstract