REVIEW ARTICLE

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Clinical prognosis of coronavirus disease 2019 in children and vitamin D levels: a systematic review

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INTRODUCTION

A novel coronavirus disease 2019 (COVID-19) is a disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is declared by the World Health Organization (WHO) as a pandemic in December 2019. Since then, the pandemic of COVID-19 has caused more than 4 million deaths worldwide[1] and has been responsible for drastic changes in health systems around the world.

The pediatric population is usually more susceptible to some infectious diseases considering their still developing immune system. However, based on current observations, the susceptibility, frequency of severe cases, and fatalities from COVID-19 appear to be much lower[2,3].

The pathology of COVID-19 involves a complex interaction of the immune system, suppressing the anti-inflammatory response and activating the classical inflammation pathway, which leads to a state of hyperinflammation and cytokine storm that is responsible for the severity of the disease[4]. With the recent findings of the immunomodulatory effect of 25-hydroxyvitamin D [25(OH)D] (i.e., decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines[5]), a possible association between serum vitamin D levels and the clinical course due to COVID-19 has been hypothesized. Thus, some studies demonstrate a relationship between 25(OH)D deficiency severity and mortality from COVID-19[6,7]; however, data on this association in pediatric patients are still lacking.

OBJECTIVE

This study aimed to correlate 25(OH)D levels with the clinical prognosis of pediatric patients diagnosed with COVID-19.

METHODS

This systematic review of retrospective cohort studies evaluated the relationship between pediatric patients with COVID-19 and their serum levels of vitamin D, in the 25(OH)D form. The articles were selected according to the recommendations of the PRISMA[8] (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement, which is responsible for organizing the process of writing meta-analyses and systematic reviews. For the selection of articles, a literature search was performed in the primary databases Online Medical Literature Search and Analysis System (MEDLINE) via PubMed, Latin American and Caribbean Literature on Health Sciences (Lilacs) via the Virtual Health Library (VHL), and SciELO.

For MEDLINE, the following descriptors were used: (COVID-19) AND (vitamin D) with the filter Child-birth 18 years; LILACS: COVID-19 AND vitamin D AND children; SciELO: (COVID-19 AND vitamin D) AND (children OR infant), ((COVID-19) AND (vitamin D)) AND (paediatrics).

The inclusion criteria for this review were as follows: healthy pediatric population up to 17 years 11 months and 29 days of age with no medical history, no continuous medication use, and no vitamin D levels related to COVID-19 infection.

Exclusion criteria were non-pediatric patients, literature reviews, and studies evaluating vitamin D dosage in situations not related to COVID-19 infection.

RESULTS

After the search, 56 articles that met the inclusion criteria of this study were selected, of which 44 via MEDLINE, 3 via LILACS, and 9 via SciELO. The searches were conducted from September 30, 2021, to October 9, 2021 (Figure 1).

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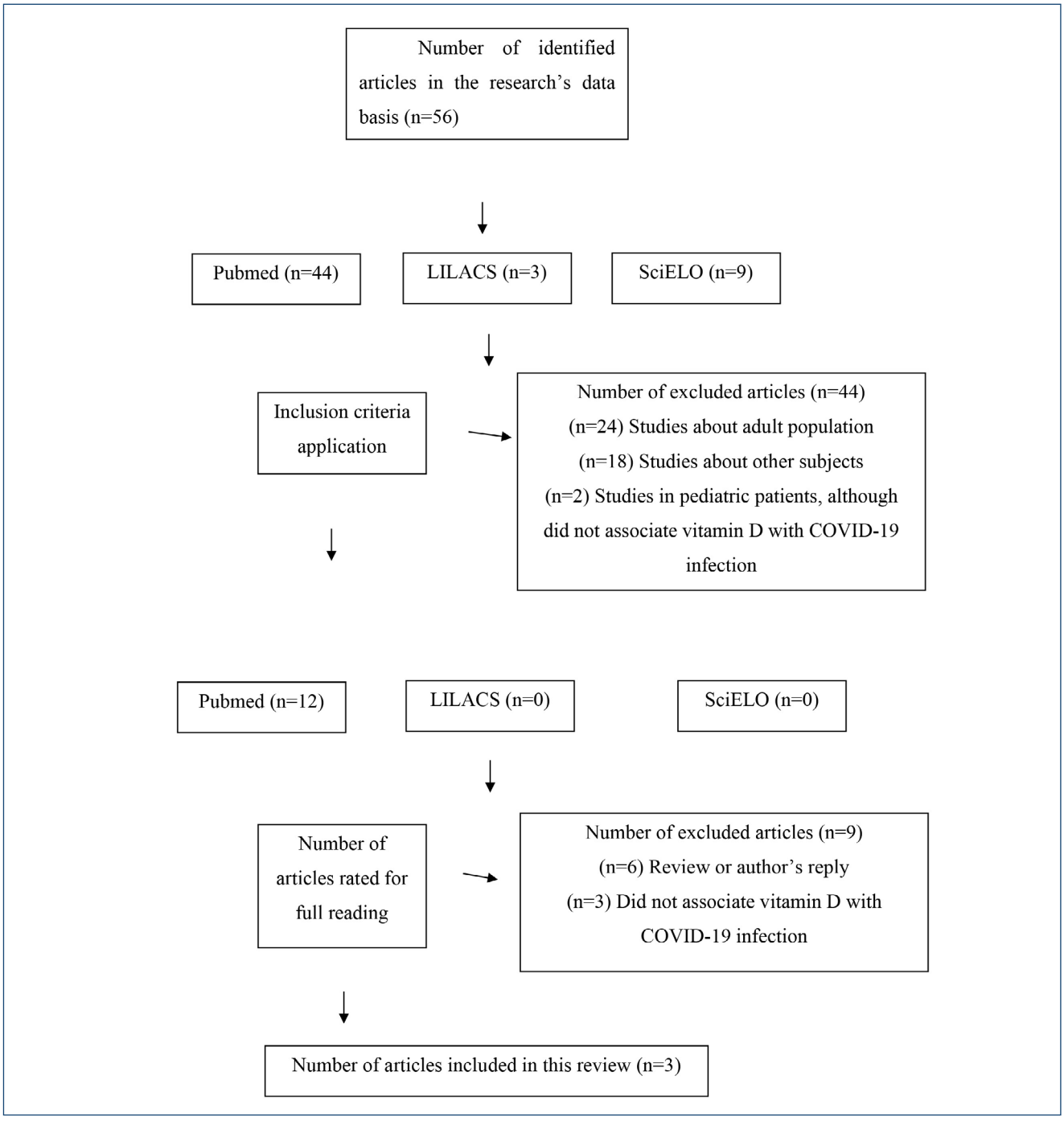

Figure 1. Flowchart of the study inclusion process.

The three selected articles are retrospective cohort studies, whose patients' data were obtained from their medical records. All patients were tested positive for SARS-CoV-2 infection by RT-PCR (polymerase chain reaction) test.

In the study by Alpcan et al.[9], 155 patients were analyzed, of which 75 carried COVID-19 and 80 were from the healthy control group. Patients with metabolic bone disorders and patients with a positive but asymptomatic COVID-19 test were not included.

Bayramoğlu et al.[10] applied the exclusion criteria such as carrying comorbidities and less than 1 year of age and data from 103 patients were obtained for the study. There was only the classification in the 25(OH)D levels as to their sufficiency of all patients

affected by COVID-19. This separation, made according to the clinical course of the patients, allowed the categorization into asymptomatic (n=29), mild (n=40), and moderate to severe (n=34).

Yılmaz and Şen[11] conducted a study on 85 patients and classified them into COVID-19 carriers (40 patients) and healthy controls (45 patients). The patients with COVID-19 were further divided into two groups subsequently in order to discern the 25(OH)D sufficiency levels in each category. Patients less than 1 year and older than 18 years, chronically ill patients, and those with comorbidities were excluded from the study.

Several studies evaluated the 25(OH)D dosages and divided patients according to the sufficiency level in their blood and their clinical courses. Alpcan et al.[9] classified the patients as follows: deficiency <20 ng/dL, insufficiency 21–29 ng/dL, and sufficiency >30 ng/dL; Yılmaz and Şen[11] and Bayramoglu et al.[10] classified the patients as follows: deficiency <12 ng/dL, insufficiency 12–20 ng/dL, and sufficiency >20 ng/dL (Table 1).

Alpcan et al.[9] reported that serum 25(OH)D levels were lower in the group of patients with COVID-19 (21.5±10.0 IU) (p<0.001). Within this group, 12 patients had normal vitamin D levels, 33 patients had deficiency, and 30 patients had insufficiency.

Yılmaz and Şen[11] divided the patients confirmed for SARS-CoV-2 as follows: group 1 as those having 25(OH)D deficiency and insufficiency (n=29, 72.5%) and group 2 as those with normal levels (n=11, 27.5%). In group 1, 18 children were deficient and 11 were insufficient, with a mean 25(OH)D value of 10.83 (4.19–17.69; p<0.001). The overall 25(OH)D levels in COVID-19 patients were 13.14 µg/L (4.19–69.28) (p<0.001).

Bayramoğlu et al.[10] reported that the prevalence of 25(OH) D deficiency was 17.2% in asymptomatic cases, 35.2% in mild cases, and 70.6% in moderate-to-severe cases. In addition, the authors concluded that the level of 25(OH)D deficiency was 16.3 ng/ml (12.6–19.1) in the asymptomatic cases (p=NS), 13.95 ng/ml (10.0–17.2) in mild cases (p<0.001), and 9.95 ng/ml (7.9–12.9) in moderate-to-severe cases (p=0.001) (Table 1).

Regarding the categorization of the clinical picture, different criteria were used in different studies to categorize the patients. Bayramoglu et al.[10], as previously mentioned, divided the patients into asymptomatic, mild, and moderate-to-severe groups.

Yilmaz and Şen[11] expanded and divided the study subjects into asymptomatic, mild, moderate, severe, and critical. The authors reported that the prevalence of vitamin D deficiency in these groups was 10.3, 58.6, 24.1, and 6.9%, respectively (p=0.097) (Table 1).

The categories "asymptomatic" and "mild" are found similar to the study by Bayramoglu et al.[10], as well as the study by Alpcan et al.[9] in relation to patient complaints.

Alpcan et al.[9] classified patients with cough, fever, hypoxemia, and no dyspnea as having only "pneumonia." The authors considered respiratory distress as a picture of tachypnea that requires oxygen therapy. Alpcan et al.[9] did not include patients with low 25(OH)D in such groups.

DISCUSSION

Bayramoglu et al.[10] concluded that the more severe the infection, the higher the 25(OH)D deficiency in the patient and found the prevalence of vitamin D deficiency of 17.2% in the asymptomatic group (p=NS), 35.2% in the mild group (p=NS), and 79.6% in the moderate-to-severe group (p=NS). In contrast, Yılmaz and Şen[11] showed no relationship of the prevalence of 25(OH)D deficiency with a worse disease prognosis, with 10.3% in the asymptomatic group (p<0.097), 58.6% in the mild group (p<0.097), 24.1% in the moderate group (p<0.097), and 6.9% in the severe group (p<0.097). However, Alpcan et al.[9] did not report this prevalence in each group (Table 1).

Table 1. Prevalence of 25(OH) D deficiency in coronavirus disease 2019 and relationship of its levels to the clinical course of the disease.

Author, year	Prevalence of low 25(OH)D levels (<12 ng/dL) according to the clinical course of the disease	Classification of the clinical course of the disease	Vitamin D levels in COVID-19 patients
Alpcan et al, 2021[9]		Asymptomatic Mild Pneumonia	21.510; p<0.001
Bayramoğlu et al., 2021[10]	5 (17.2%); p=NS 14 (35.2%); p=NS 24 (70.6%); p=NS	Asymptomatic Mild Moderate-to-severe	16.3 (12.6–19.1); p=NS 13.95 (10–17.2); p<0.001 9.95 (17.9–12.9); p<0.001
Yilmaz and Şen, 2020[11]	3 (10.3%); p<0.097 17 (58.6%); p<0.097 7 (24.1%); p<0.097 2 (6.9%); p<0.097	Asymptomatic Mild Moderate Severe Critical	13.14 (4.19–69.28); p<0.001

NS: not statistically significant.

This review has some limitations. This study analyzed only few articles. The relationship between the age and serum 25(OH) D levels, as explained in all three studies mentioned previously, showed patients with older ages, i.e., adolescents, had the lowest 25(OH)D levels. Knowing the close relationship between the severity of COVID-19 cases and age, with older ages being considered risk factors, there is a need to compare serum 25(OH) D levels and the severity of clinical course by age groups in future similar studies[10]. Another possible limitation for interpretation of the results is the discrepancy between the values established as sufficient, insufficient, and deficient according to each study (Table 1).

To establish a possible relation of the immunomodulatory action of 25(OH)D, a double-blind interventional study based on empirical vitamin D supplementation in hospitalized patients with COVID-19 could offer answers about its role in the clinical outcome in patients.

Pediatric patients who were supplemented with vitamin D during the COVID-19 pandemic showed reduced risk of developing severe pulmonary forms of the disease[10]; however, there is no retrospective study that correlates correct supplementation (75–125 nmol/L) with outcome in COVID-19 sufferers[7], but there are positive evaluations of the relationship between vitamin D and other respiratory pathogens[11].

Studies on association between vitamin D levels and COVID-19 in children are scarce and therefore further studies on this subject are needed.

CONCLUSION

Through the review of studies, it was not possible to establish a relationship between serum levels of 25(OH)D and clinical prognosis by COVID-19. Since this is a recent theme and still little explored in the literature, more studies are needed to prove a possible cause-and-effect relationship of 25(OH)D levels and severity of the clinical picture.

AUTHORS' CONTRIBUTIONS

MAA: Conceptualization, Formal Analysis, Resources, Software, Supervision, Visualization. **BHBR**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **GBM**: Conceptualization, Data curation, Investigation, Project administration, Writing – original draft, Writing – review & editing. **RBM**: Formal Analysis, Validation, Visualization. **EMCGN**: Conceptualization, Investigation. **ISD'A**: Conceptualization, Investigation. **VEVR**: Resources, Software, Supervision, Visualization.

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