



Submitted on: 03/24/2021

Approved on: 05/30/2021

REVIEW ARTICLE

Epidemiological and clinical analysis of infection with the new coronavirus in the pediatric population: a systematic review

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Keywords:

Coronavirus Infections,
Severe Acute
Respiratory Syndrome,
Systemic Inflammatory
Response Syndrome,
Coronavirus,
Child,
Systematic Review.

Abstract

Objective : The main objective of this study is to collection review the literature in order to analyze epidemiologically and clinically the infection by the new Coronavirus in the pediatric public. **Methods :** To carry out such an analysis , articles were selected through a structured search strategy in the databases of Pubmed , Cochrane and Scielo . The articles were selected according to the recommendations of the preferred reporting Items for Systematic Reviews and Meta- analysis Protocol (PRISMA-P). and the review protocol (Prospero) was registered at York University under the following identification number : CRD CRD42020197304. **Results :** The literature search identified 985 articles . After methodological screening , 6 studies were eligible for this systematic review. The number of participants ranged from 10 to 43 children aged between 1 month and 16 years old with a predominance of the male population . The clinical presentation was variable , and it can show from asymptomatic forms , which represent the vast majority , to severe cases that result in death. In symptomatic cases, the disease usually manifests itself through mild symptoms of the respiratory tract . In more severe cases, patients may have respiratory failure and multisystemic inflammatory syndrome . **Conclusions :** Studies have shown that children have milder clinical presentations when compared to adults , in addition to faster recovery and better prognosis . The cause for the difference in the manifestation of the disease is not completely elucidated with several hypotheses being studied . In terms of treatment , the care offered is only supportive , aiming at patient comfort and management of comorbidities.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by the novel coronavirus (SARS-CoV-2)¹. In December 2019 the first cases of COVID-19 were reported in Wuhan, China, since then, the numbers have grown rapidly, reaching all continents². In a report, the World Health Organization reported more than 122 million cases worldwide and 2.7 million deaths from the beginning of the pandemic until March 21, 2021³.

The incubation period of the etiologic agent varies between 1 and 14 days. In symptomatic cases, the disease usually manifests itself through symptoms of respiratory infection such as cough, fever and fatigue. However, the clinical presentation is variable, and can range from asymptomatic forms to severe cases that result in death⁴. In the pediatric population, the disease can also manifest itself through rhinorrhea, nasal congestion, myalgia and gastrointestinal symptoms such as vomiting, nausea, diarrhea and abdominal pain, which can progress to severe conditions with respiratory failure and multisystem inflammatory syndrome⁵.

Studies have shown that children have milder clinical presentations when compared to adults, in addition to faster recovery and better prognosis, less laboratory alterations and less radiological alterations⁵⁻⁷. The cause for the difference in the manifestation of the disease is not completely elucidated, with several hypotheses being studied, such as a greater innate immune response, a lower response of inflammatory cytokines. About 83% of children who had the disease had a positive history of contact with people with COVID-19, the majority being family contact⁷. It is still uncertain whether asymptomatic cases are transmitters of the disease, however it is known that even asymptomatic children can have a high viral load in the body⁸.

In terms of treatment, the disease does not yet have specific medication, and the care offered is supportive with invasive and non-invasive mechanical ventilation, aiming at patient comfort and management of comorbidities⁵. However, data in the literature with greater scientific evidence on the topic are scarce and further studies are needed to clarify the issue. Thus, this study sought to systematize the clinical and epidemiological manifestations of COVID-19 present in the pediatric population.

METHODS

The articles were selected according to the recommendations of Preferred reporting Items for Systematic Reviews and Meta-analysis Protocol (PRISMA-P) responsible for coordinating the process of performing meta-analyses and systematic reviews^{9,10}. The review protocol (Prospero) was registered with York University under the following identification number: CRD CRD42020197304.

Population, exposure and outcomes

This systematic review included studies with pediatric patients, who were defined as children under the age of 18 years, diagnosed with COVID-19, which evaluated clinical manifestations, diagnosis, prevalent outcomes, and outcomes of COVID-19 infection in pediatric patients.

The articles were selected through a structured search strategy in the databases: Pubmed, Cochrane and Scielo. Were used the following Medical Subjects Heading (MeSH) terms: Child, Children, childhood, preschool, infant, babies, baby, neonates, pediatrics, pediatrics, pediatrics, pediatric, coronavirus, COVID-19, COVID, severe acute respiratory syndrome, SARS. These terms have been adapted for use in other bibliographic databases in combination with specific database filters for clinical trials, clinical trial, controlled clinical trial, observational studies, and randomized controlled trials. Searches in these databases were performed between June and July 2020, with no language restrictions.

Selection criteria

Inclusion criteria reflect those noted above for participants/populations, as well as the following study types: randomized controlled trials and observational studies. There were no restrictions on ethnicity, language, country, sex, age (as long as they were under 18 years old) and year of publication. Research with insufficient or non-extractable data, no text available, overlapping datasets, and in vitro or animal study models were not included.

Exclusion criteria were: duplicate publications, age group not consistent with the proposal of the systematic review (adults and elderly), articles dealing with other viruses or just mentioning coronavirus, pediatric cancer patients, studies still in progress and without definitive results, research inaccessible, themes and study designs not suitable for the review proposal.

Data analysis and synthesis

The titles of all articles found were independently evaluated by two reviewers in order to identify and remove possible duplicate articles or studies that did not answer the central question of this review. Those potentially eligible for inclusion were submitted to the reading of abstracts and, subsequently, a comprehensive reading of the full text. The decision on the final selection was made during a consensus meeting. Data were extracted regarding the title of the article, name of the first author, study design, country, journal in which it was published, performing institution, year of publication, level of evidence, age of the sample, gender, comorbidities, clinical characteristics (signs, symptoms and duration), diagnostic tests, major laboratory tests, imaging tests, treatments, severity rating, statistically significant outcome and conclusion. The

analysis was performed according to the *Preferred approach. reporting Items for Systematic Reviews and Meta-Analyses* (Prisma). The number of studies analyzed at each assessment level was shown in the included Prism diagram (fig. 1). Excluded articles were classified as follows: group 1, duplicates; group 2, age group not consistent with the review proposal (adults or elderly); group 3, articles dealing with other viruses or just mentioning coronaviruses; group 4, pediatric oncology patients; group 5, studies still in progress (no definitive results); group 6, inaccessible articles; group 7, topic not suitable for the purpose of this review; group 8, study designs not suited to the review proposal. Studies were evaluated to assess the quality of evidence and to provide a summary of the findings of included studies using the *Oxford Center for Evidence - based Medicine approach*¹¹ as recommended by the National Commission for the Incorporation of Technologies in the Unified Health System (CONITEC). In this approach, studies are classified into evidence levels 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B, C (4) and D (5), with C and D being of low quality and A, B and 1C studies high-quality. Methodological limitations, inconsistencies, inaccuracies,

indirect evidence, and publication bias can reduce the level of evidence, while effect magnitude, dose response, and controlling for all plausible confounders can increase the quality of evidence.

RESULTS

The literature search identified 985 articles. After methodological screening, 6 studies were eligible for this systematic review. Figure 1 describes the inclusion and exclusion stages of the study.

The 6 included studies were published in the year 2020. Among the 6 studies evaluated, 2 were retrospective cohorts, 2 were prospective cohorts and 2 were case-control. The countries of implementation were: 4 studies carried out in China, 1 in Italy and 1 in France. Table 1 summarizes the study characteristics of all publications included.

As observed in table 1, the number of participants ranged from 10 to 43 children aged between 1 month and 16 years, with a predominance of the male population. The most common

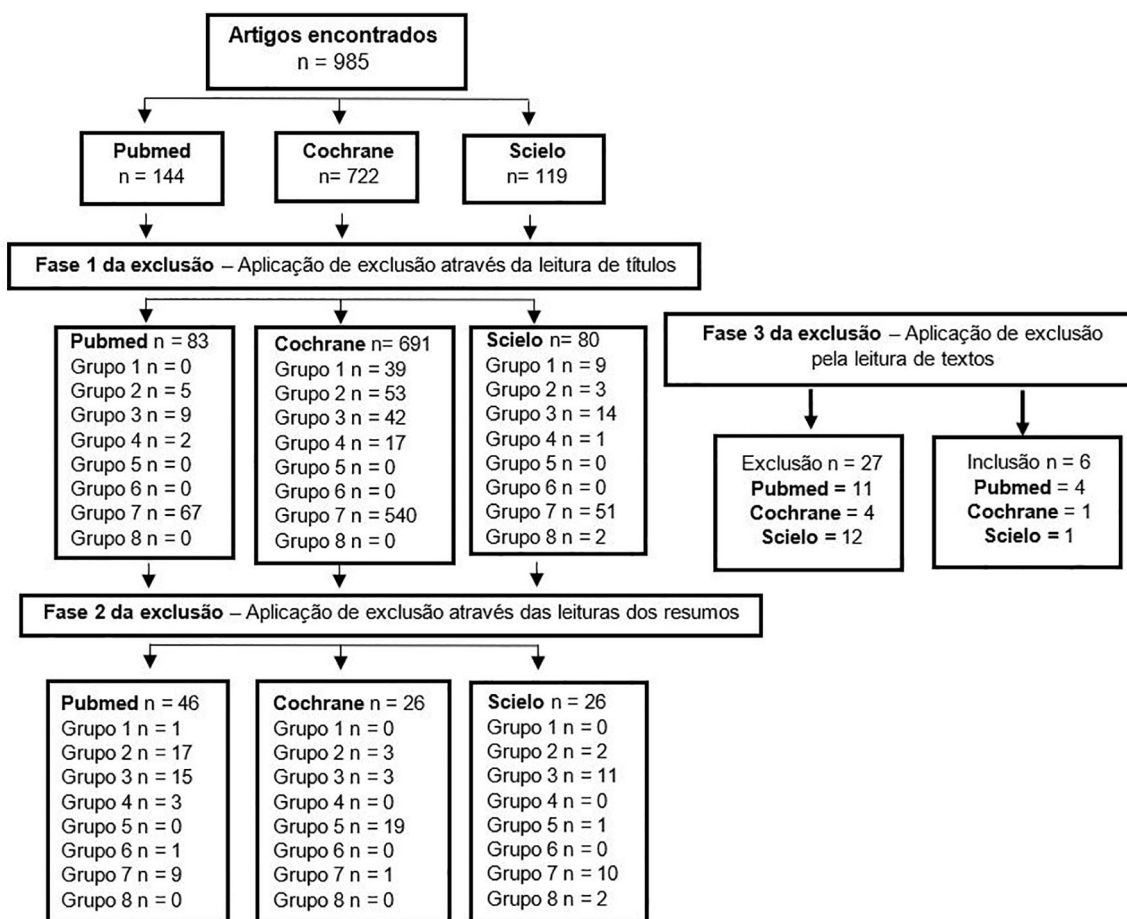


Figure 1. Steps of the selection process for inclusion of articles in the systematic review.

Table 1. Collected and synthesized data from selected studies.

TITLE OF THE ARTICLE	children hospitalized with Severe COVID-19 in Wuhan	Clinical and epidemiological Features of 36 Children with coronavirus Disease 2019 (COVID-19) in Zhejiang, China: Na Observational cohort study	Characteristics of Pediatric SARS-CoV-2 Infection and Potential Evidence for Persistent Fecal Viral Shedding	At Outbreak of Severe Kawasaki-like Disease at the Italian Epicentre of the SARS-CoV-2 Epidemic : At Observational cohort study	Kawasaki-like Multisystem inflammatory Syndrome in Children during the covid-19 Pandemic in Paris, France: Prospective Observational study	Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series
FIRST AUTHOR	Wang, Yanli	Qiu, Haiyan	Xu, Yi	Verdoni, Lucio	Toubiana, Julie	Zhang, Che
STUDY DESIGN	Retrospective control case	Retrospective Cohort	Prospective Cohort	Retrospective control case	prospective cohort	case series
COUNTRY	China	China	China	Itália	França	China
PERIÓDICO	Pediatric infectious disease journal	The Lancet	Nature Medicine	The Lancet	The BMJ	PLoS Medicine
INSTITUTION	Wuhan Children's Hospital	Ningbo Children's Hospital , Third Affiliated Hospital of Medical University and Wenzhou Central Hospital .	Guangzhou Women's and Children's Medical Center	General Pediatrics Unit of the Papa Giovanni XXIII Hospital	Department of General Pediatrics at a University Hospital in Paris	Hubei University of Medicine
YEAR OF PUBLICATION	2020	2020	2020	2020	2020	2020
LEVEL OF EVIDENCE OF THE STUDY	3B	2B	2B	3B	2B	4C
No	43	36	10	*Group 1: 19 **Group 2: 10	21	34
AGE	Average: 6.89	1–16 years, average: 8.3 years.	2 months to 15 years	Average: Group 1: 3 years. Group 2: 7.5 years.	Average: 7.9 years.	1 to 144 (median 33.00) months.
SEX	male: 27 (62%) Female: 16 (38%)	Female: 13 (36%) Male: 23 (54%)	Male: 6 Female: 4	Group 1: male: 7 female: 12 Group 2: male: 7 female: 3	Male: 12 Female: 9	Male: 14 (41%) Female: 20 (59%)
Comorbidities	Boy 8 years old: acute lymphoblastic leukemia in remission. And boy 15 years old: primary obesity (BMI: 33.1)	NR	NR	NR	5 patients: BMI > p 97	6 patients (18%): 2 Infectious mononucleosis***, 1 nephroblastoma , 1 atrial septal defect, 1 febrile seizure and 1 asthma.
CLINICAL CHARACTERISTICS (SIGNS, SYMPTOMS AND DURATION)	Severe: dyspnea 7 (87.5%), fever 5 (62.5%), cough 5 (62.5%), GI 3 (37.5%). Not severe: fever 31 (88.6%), cough 31 (88.6%), GI 8 (22.9%).	Asymptomatic 10 (28%); fever 13 (36%); cough 7 (19%); odynophagia 2 (6%); pharyngeal congestion 1 (3%); dyspnea 1 (3%); GI 2 (6%). PNM + fever/cough 11 (30%); Isolated PNM 8 (22%). Without PNM 10 (28%): 5 (14%) only fever and 2 (5%) only cough.	Fever 7 (%), cough 5 (%), sore throat 4 (%), nasal congestion and rhinorrhea 2 (%) and diarrhea 3 (%), asymptomatic 1 (%).	Group 2**: 5 (50%) classical form and 5 (50%) incomplete form. 4 (40%) oropharyngeal alterations, 1 (10%) cervical lymphadenopathy. 2 (20%) conjunctivitis, oropharyngeal changes and rash. 1 (10%) conjunctivitis and polymorphic rash.	GI 20 (95%); headache, cough, runny nose, fever 9 (42%); irritability 12 (57%); meningeal confusion/irritation 6 (29%); pericardial effusion 10 (48%); pleural effusion 3 (14%), myocarditis 16 (76%); 2 ↑ QT interval and arrhythmia. Peritoneal effusion 4 (19%); AACx in 2 of 4 (50%); aseptic peritonitis 1 (5%); anosmia 1 (5%).	Fever (76%), cough (62%), sputum (21%), vomiting (12%) and diarrhea (12%). Moderate condition in 23 (96%) with less than 72 months.

Continuation **table1.**

EXAMS FOR DIAGNOSIS	RT-PCR of upper nasopharyngeal swabs	RT-PCR upper nasopharynx	IR RT-PCR nasopharyngeal and rectal swab RT-PCR	RT-PCR íru nasofaríngeo e orofaríngeo e IgM e IgG de SARS-CoV-2	RT-PCR and IgG antibodies to SARS-CoV-2	IR RT-PCR nasopharyngeal or oropharyngeal for SARS-CoV-2
OTHER LABORATORY EXAMS	<p>↑ Leukocytes, ↑ PCR-hs, ↑ IL-6, ↑ IL-10 and ↑ D-dimer, ↑ Total Bilirubin, ↑ Uric Acid, ↑ NK Lymphocytes (CD16+/56+) in bass.</p>	<p>↑ CK-MB and ↓ lymphocytes in 11 (31%), ↓ leukocytes in 7 (19%), ↑ procalcitonin in 6 (17%). ↑ ALT and AST in 3(8%).</p>	<p>↑ IL-17F 7(70%) and ↑ IL-22, IL-6 5(50%). ↑ Procalcitonin 5(50%), ↑ ESR 3(30%), ↑ PCR 4(40%), ↓ Leukocyte 3(30%), ↓ neutrophil 4(40%), ↑ leukocyte and ↓ lymphopenia 3(30%), ↑ transaminase 1(10%), ↓ Hb 1(10%). ↑ TTPA 2(20%), ↑ TP 1(10%). ↓ Albumin 2(20%), ↑ LDH 2(20%), ↑ glycemia 2(20%). E ↑ ferritin 1(10%).</p>	<p>↑ proBNP in all (100%). ↑ ESR, ↑ PCR, ↑ ferritin, ↑ leukocytes, ↑ neutrophils, ↓ lymphocytes, thrombocytopenia, ↓ Na in 8 (84.5%). ↑ AST, ↑ ALT, ↑ TGL in 7(87%) of group 2, ↑ fibrinogen in 9(90%), ↑ D-dimer in 8 (80%). ↑ Troponin I in 5 (55%). ↑ IL-6 in 4(40%). ↓ NK in 4. Sterile blood culture in all. Mean CPK 85 IU/L in 1 (10%).</p>	<p>↑ Leukocytes, phyla virus, CRP, procalcitonin and IL-6 in 21 (100%). ↓ Lymphocytes and average Hb 86 g/L in 17 (81%). ↓ Na and ↓ albumin in 20 (95%). ↑ ALT by 62%. ↑ γ-GT by 76%. ↑ Lipase in 10 (63%), ↑ D-Dimer in 19 (95%), ↑ Troponin in 17 (81%) and ↑ BNP in 14 (78%). RT-PCR SARS-CoV-2 (+) in 8 (38%); IgG against SARS-CoV-2 (+) in 19 (90%). median IgG 5.4</p>	<p>↑ Lymphocytes in 17 (50%). ↓ Pre-albumin in 25 (78%), ↑ SAA in 17 of 20 (85%) and ↑ PCR-hs in 17 of 29 (59%), ↑ LDH in 28 of 34 (82%) and ↑ α-HBDH in 25 of 34 (74%).</p>
IMAGE EXAMS	<p>Graves: ground glass 3 (37.5%) and consolidation 2 (25.0%). Non-serious: ground glass (45.7%) and consolidation (20.0%). Average SP: 5.50 in bass and non-bass: 1.50. Lower left lobe (100%). Right lower lobe (75.0% severe and 27.6% non-severe)</p>	<p>CT: 19 (53%) ground-glass opacity.</p>	<p>RX: Coarse pulmonary markings (7). Chest CT: ground-glass opacities (5).</p>	<p>US: depression of left ventricular function, mitral valve regurgitation and pericardial effusion in 2 (20%). RX: minimal mono or bilateral infiltrates in five (50%). Chest CT: bibasilar lung thickening in 2 (20%). 2 (20%) left coronary aneurysm (> 4 mm), EF 48% and 40%; 1 pericardial effusion.</p>	<p>Ground-glass opacities, irregular consolidation, and interstitial abnormalities in eight (44%). Echocardiography: coronary artery abnormalities in eight (38%), dilatations in five (24%) and increased coronary visibility in three (14%) patients.</p>	<p>Chest CT: Changes in 28 (82%): Unilateral (41%) and bilateral (41%). Ground glass opacity (3%). Injury progression in 18 of 28 (64%) during hospitalization. Late onset (4-5 days) on chest CT in 4 of 34 (12%). Absence of lesions in 2 of 34 (6%). Lesions still at discharge in 24 of 32 (75%).</p>
TREATMENTS	<p>Oxygen therapy (100% of severe patients), 5 (13.5%) non-invasive mechanical ventilation, 3 (8.1%) endotracheal intubation and invasive ventilation under progressive hypoxia.</p>	<p>Aerosolization Interferon α 2x/day in 36 (100%), 14 (39%) lopinavir-ritonavir 2x/day and 6 (17%) oxygen therapy.</p>	<p>Interferon α oral spray (8,000 U, 2 sprays, 3x/day) in 10. Azithromycin 10 mg/kg/day for 5 days and IVIG 300 mg/kg/day for 3 days (1).</p>	<p>GI IV 2 g/kg for all. Corticosteroids in 4 (16%) of group 1 and 8 (80%) of group 2. Aspirin 50-80 mg/kg/day (if Kobayashi <5) for 5 days or 30 mg/kg/day + corticosteroid 2 mg/kg/day for 5 days (if Kobayashi ≥5), then corticosteroids for 2 weeks. Aspirin up to 48 hours without fever, then dose 3-5 mg/kg/day for 8 weeks.</p>	<p>IG IV (2 g/kg) for a mean of 5 days and aspirin (3-5 mg/kg/day) in 21 (100%). Corticosteroids (2-10 mg/kg/day) in 7 (33%). 3rd generation cephalosporin in 18 (86%) for an average of 6.5 days. 2nd IG IV infusion (2 g/kg) in 5 (24%) with corticosteroids (2 mg/kg/day) in 4 resistant patients.</p>	<p>Interferon-α nebulization 2x/day (100%). Ribavirin in 15 (44%) 2x/day. Traditional Chinese Medicine in 20 (59%). Antibiotics in 11 before COVID-19 diagnosis and discontinued after confirmation. Azithromycin in 9 (26%) for bacterial infections. Corticosteroid 5 (15%) and oxygen 3 (9%).</p>

Continuation **table1.**

SEVERITY CLASSIFICATION	severe PNM (min. 1 criterion): RR: ≥ 70 times/min (< 1 year), ≥ 50 times/min (≥ 1 year); SatO ₂ $< 92\%$; hypoxia: assisted breathing, cyanosis, intermittent apnea; consciousness: drowsiness, coma, or seizure; refusal/difficulty eating with signs of dehydration.	Radiographic changes, decreased lymphocytes, elevated body temperature, and elevated levels of procalcitonin, D-dimer, and creatine kinase MB were associated with the severity of COVID-19.	NR	NR	NR	NR
OUTCOME AND FINAL RESULT	Altered CT on day 1, greater number of lung segments affected, bilaterality were associated with the severity of COVID-19 in children. Reduction in lesion size and severity is associated with improvement in hypoxia. Elevation of IL-6 is associated with severity. Hepatobiliary and intravascular coagulation dysfunction may suggest multiple organ dysfunction. Only 1 critically ill patient died.	Older children had lymphocytes $\downarrow$, procalcitonin $\uparrow$, and CK $\downarrow$ compared to younger children. Pneumonia was more frequent in COVID-19 than in H1N1 influenza. Significantly lower prevalence of values indicating disease severity, such as fever, cough, pneumonia, elevated C-reactive protein, and type of severe illness compared to adults.	Viral shedding in the digestive tract may be greater and last longer than in the respiratory tract, however, there is no evidence of viral infectivity in fecal smears. Mild and atypical presentations of the infection in children can make it difficult to detect.	Differences between groups: mean age (3 vs 7.5 years), cardiac involvement (2 of 19 vs 6 of 10), KDSS (0 of 19 vs 5 of 10), MAS (0 of 19 vs 5 of 10), steroids adjuvants (3 out of 19 vs 8 out of 10). Group 1: 19 diagnosed at 5 years, group 2: 10 diagnosed at 1 month (incidence 0.3 per month vs 10 per month). KD incidence: group 1: 0.019% vs 3.5% group 2. Group 2: lower number of leukocytes, lymphocytes and platelets than group 1. Criteria for KDSS and MAS positive in 5 (50%) in group 2 vs. None in group 1. Seven (70%) in group 2 with Kobayashi ≥ 5 points vs. Two (10%) from group 1.	No deaths were recorded. The temporal association between the start of the pandemic in France and test results for SARS-CoV-2 with Kawasaki-like disease suggests a causal relationship. Only one had symptoms of COVID-19, most had positive IgG, suggesting that the DK is due to a post-viral immune reaction. Kawasaki-like syndrome associated with COVID-19 differs from classic KD in having: greater African descent, predominant acute GI symptoms, hemodynamic instability, and myocarditis.	Mixed infection in 13 (62%) patients was more common between 12 and 72 months, and 12 (92%) of these were mild. It is suggested that the mixed infection did not increase protection for COVID-19. 79% of all moderate cases were < 72 months of age, suggesting that preschool age is more susceptible to developing SARS-CoV-2 infection. It is attributed that high prevalence of asymptomatic and milder disease in pediatrics can potentially spread the disease in the outbreak.

symptoms reported by the authors were dyspnea, fever, cough and diarrhea/vomiting¹²⁻¹⁵. Less frequently observed were rhinorrhea and odynophagia, and there were few cases with neurological alterations or signs of heart, kidney or liver failure. The studies by Toubiana et al¹⁶. and Verdoni et al¹⁷. noticed a picture of Kawasaki disease in children with current or previous coronavirus infection. Qiu et al¹³. reports that, compared to cases in adults in the same city, children had a lower prevalence of fever, cough, pneumonia, C-reactive protein (CRP) and the severe form.

The comorbidities reported in the study by Wang et al¹². were acute lymphoblastic leukemia in remission and primary obesity. In another study, 5 were obese¹⁶. Zhang et al¹⁵. reported one child with asthma, one febrile seizure, one with atrial septal defect, one with nephroblastoma and mixed infection in 62% of patients aged 12 to 72 months.

Among the laboratory alterations reported were leukocytosis/leukopenia, lymphopenia, elevation of inflammatory tests (CRP, erythrocyte sedimentation rate (ESR),

ferritin and procalcitonin), increase in hepatic transaminases and decrease in albumin. Wang et al¹². found higher levels of leukocytes, uric acid and inflammatory markers in more severe cases compared to mild cases and while little difference was found in lymphocyte count levels. Xu et al¹⁴. reports that there were few alterations or alterations in a small degree of the laboratory tests in 90% of the patients.

Qiu et al¹³. described significantly different variables between mild and moderate cases, being lower lymphocyte count, higher body temperatures, higher level of procalcitonin , D-dimer and creatine kinase -MB (CKMB) associated with more severe cases. In addition, older children had lower lymphocyte counts, elevated procalcitonin , and lower creatine kinase (CK) than younger children.

In the study carried out by Zhang et al¹⁵. 50% of the children had an elevation of lymphocytes, 59% an elevation of CRP, 82% an elevation of lactate dehydrogenase (LDH), 78% a reduction of pre - albumin and 85% a reduction of serum amyloid A protein and none of them showed alterations in CK or CKMB.

in a study image changes were found in all severe cases in contrast to about half of mild cases. The most common radiological imaging changes were ground-glass opacity on computed tomography (CT), gross lung markings and consolidations, and there was a predilection (75%) for the left lower lobe of the lung¹². On the other hand, Qiu et al¹³. reports that half of the children had ground-glass opacity on CT. Xu et al¹⁴. reports that patients had only gross pulmonary markings without signs of pneumonia (PNM) on radiography (XR) and ground-glass opacity on CT in half of the children. Zhang et al¹⁵. reported pulmonary consolidations in 82% of patients on admission, only 3% had ground-glass opacity and 6% had no radiological changes.

Analyzing complications, hospitalizations in the intensive care unit (ICU) and/or severe and critical cases, there was only 1 death reported by Wang et al¹² The study pointed to an increase in *natural killer* (NK) cells, total bilirubin and involvement of more than 3 lung segments as factors associated with more severe conditions. The same author describes as severe PNM if at least 1 criterion is present: respiratory rate (RR): ≥ 70 times/min (<1 year), ≥ 50 times/min (≥ 1 year); capillary oxygen saturation (SatO2) <92%, respiratory distress, cyanosis, intermittent apnea , altered consciousness, drowsiness, coma or convulsion, food refusal with signs of dehydration. Furthermore, Qiu et al¹³. and Wang et al¹². reported longer hospital stays and longer duration of symptoms and longer time to negative real-time Polymerase Chain Reaction (RT-PCR) in severe cases when compared to non-severe cases.

In the study by Wang et al¹². only ventilatory support and oxygen therapy were offered. In another three

studies¹³⁻¹⁵ interferon- α was also used in 100% of the children. There were no studies that included the use of antimalarials. Furthermore, Zhang et al¹⁵. and Qiu et al¹³. also used antivirals such as lopinavir/ritonavir and ribavirin. There were still authors who offered antibiotic treatment with azithromycin or cephalexin and corticosteroids to patients. And, in the two studies that patients had Kawasaki or *Kawasaki-like disease* received intravenous immunoglobulin (IVIG), aspirin, and corticosteroids as needed by comorbidity^{16,17}.

DISCUSSION

The COVID-19 pandemic has brought to light the need for research related to the subject for early recognition of signs and symptoms, adequate treatment and social isolation of those infected or suspected. The speed of publication and amount of information available is such that it became necessary to review this available content, facilitating access and understanding of the disease in the pediatric population.

The high transmissibility of COVID-19 was similar to that found in Severe Acute Respiratory Syndrome (SARS) and Influenza A (H1N1). Comparing the presence of pneumonia due to COVID-19, SARS and H1N1, it is observed that the first two are similar in terms of prevalence, 53% and 65%, respectively. H1N1, on the other hand, was only 11%¹³.

The coronavirus has an estimated average incubation time of 5.2 days¹⁴ and among all the symptoms it can cause, fever and dry cough stand out as the main ones that affect children¹³⁻¹⁵. Gastrointestinal symptoms such as vomiting and diarrhea were observed by Zhang et al.¹⁵ as the first symptoms, contrary to what was seen by Xu et al.¹⁴ who did not observe lethargy, dyspnea, myalgia, headache, nausea, vomiting and disorientation, commonly found in adults.

Most infected children were asymptomatic (94%)^{13,15} and among the small symptomatic portion, most were mild cases¹², with recovery time of around 3 to 4 days¹⁵. The prevalence of fever, cough, pneumonia, elevated CRP and severe illness was significantly lower compared to adults^{13,20,21}. The milder form of COVID-19 in children presupposes a reduced inflammatory response in this population, since their immune system is not yet fully formed compared to adults^{13,15}.

Two studies analyzed disagreed with regard to the hypothesis. The study by Qiu et al.¹³ states that children had a lower RT-PCR than adults, which suggests a lower immune response in the pediatric group. On the other hand, the study by Zhang et al.¹⁵ observed that RT-PCR positivity was

similar to that found in adults, suggesting a similar immune response between adults and children. It was also hypothesized that the repetitive exposure of younger children to various viruses is a strengthening of their immune system, thus causing them to have milder courses¹⁵.

It was observed that activated T cells and elevation of interleukin-6 (IL-6) are related to more severe disease in children, unlike adults, in which neutropenia and lymphopenia are associated¹². On the other hand, NK cells, IL-6 and IL-10 are found in lower expression in mild cases¹², which suggests that cytokines are important predictors of severe disease¹⁷.

The factors that may be related to the severity of the disease are organic dysfunction, hepatobiliary and intravascular coagulation, being seen by the alteration of bilirubin, uric acid, prothrombin and D-dimer activity time. Clinical-demographic variables such as age, sex, high body mass index (BMI) and clinical signs and symptoms did not show a statistically significant association for severe COVID-19 in children^{12,16}.

As for RT-PCR, the study by Wang et al.¹² reports that the test remained positive for a longer time in critically ill children when compared to non-serious children. On the other hand, the studies by Qiu et al.¹³ and Zhang et al.¹⁵ demonstrate that the time required for negative results is not influenced by the severity of the disease. Therefore, it is advisable to use the gold standard RT-PCR exam only for diagnosis and not for disease follow-up¹⁸.

Coinfections with respiratory viruses and bacteria were not reported in the study by Xu et al.¹⁴, contrasting the study by Zhang et al.¹⁵ who found it in 47% of cases, being more common in children between 12 and 72 months of age. Therefore, there is no evidence of protection against COVID-19 in cases of co-infection¹⁵.

After the beginning of the SARS-CoV-2 pandemic in Bergamo - Italy, there was a 30-fold increase in the monthly incidence of Kawasaki disease compared to the last 5 years ($p < 0.0001$). In this group of patients, for the most part, there is evidence of current or previous infection, which suggests an association between the coronavirus and Kawasaki disease.^{16,17} The immune response to coronavirus infection suggested greater severity in the development of Kawasaki-like syndrome compared to the classic form of Kawasaki disease. However, it is important to note that Kawasaki-like syndrome is still a rare condition, affecting no more than 1 child in every 1,000 children exposed to the virus¹⁷.

The pro-inflammatory state together with organ dysfunction, called Pediatric Multisystem Inflammatory

Syndrome associated with SARS-CoV-2 infection, brings into vogue the strong immune reaction that this virus, in particular, can cause to the host compared to other viruses¹⁶. Therefore, monitoring the condition, even after hospital discharge, is suggested by the studies^{13,15}.

The forms of transmission of the virus found were predominantly through contact with infected people and a history of exposure in endemic areas¹³. Furthermore, Xu et al.¹⁴ suggests the existence of a fecal-oral transmission due to the persistence of positive rectal smears even after the swab is negative. nasopharyngeal _ It is possible to assess the possibility of a negative rectal smear as a parameter in determining the time to end the isolation¹⁴. However, performing a rectal swab is an uncommon practice for the diagnosis of coronavirus and was not addressed in any other article selected in this systematic review, in addition to the fact that the infectivity of the coronavirus by fecal excretion was not proven¹⁴.

In the laboratory alterations of pediatric patients, it was observed, in the study by Zhang et al.¹⁵ that serum amyloid A protein (SAA) levels were present in most patients (85%) and, together with RT-PCR, drastically normalized after 7 days of illness. Cited by Zhang et al.¹⁵, Yip et al.²² found a statistically significant relationship between the elevation of SAA and the extent of SARS-CoV-1 pneumonia, this information makes further studies on the correlation between elevated SAA and the extent of SARS-CoV-2 pneumonia necessary. However, its routine use should be evaluated, since it is not widespread and applied in Brazil, as well as the study's limitation in presenting a low level of scientific evidence (4C)¹¹.

As for the radiographic findings, almost half of the pediatric patients did not present changes suggestive of COVID-19 infection¹³. As there is no correlation between the course of the disease and the image in mild to moderate cases, the use of radiography as a predictor of prognosis is not indicated¹⁵. On the other hand, critically ill patients had CT with positive findings on the first day of hospitalization, with the involvement of more than three lung segments being associated with greater severity of pneumonia ($p = 0.006$)¹². Thus, it is recommended that monitoring with imaging tests be performed in severe cases, because, in addition to the chance of rapid progression of the lesions and late onset pattern, there is a correlation between the improvement of the tomographic pattern and the clinical improvement of the patient^{12,15}.

Even after the collection and careful analysis of these studies, there is great doubt as to why children are still an audience less likely to develop severe conditions

due to the coronavirus. Several studies suggest reasons and raise hypotheses, as seen throughout the article, but studies with strong evidence and good methodologies need time to be carried out in an adequate way according to scientific standards.

The present research provided the gathering and analysis of studies present in the scientific environment with the intention of facilitating access to Brazilian health professionals on the subject. There was also an absence of selection bias by the applied PRISMA-P methodology, being selected, in the end, studies from several countries that had a good level of evidence. It is noteworthy that the sample size obtained by the studies is small and, therefore, there is a higher probability of occurrence of type 2 or β random error. At the time of selection of articles, there were Brazilian studies in the pre-publication stage, which contributed to their not being included. Our research should serve as a stimulus for the realization of new works on the subject, improving knowledge on this subject.

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