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REVIEW ARTICLE

Determinant factors of serious and critical covid-19 progress in children: systematic review and metanalysis

Fatores determinantes de evolução grave e crítica da COVID-19 em crianças: revisão sistemática e metanálise

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Palavras-chave:
Infecções por Coronavírus,
Pandemias,
Revisão Sistemática,
Criança,
Lactente,
Fatores de Risco.

Resumo

Objetivos: Realizar revisão sistemática de fatores associados à evolução da infecção pelo SARS-CoV-2 para casos graves e críticos e hospitalização em Unidades de Terapia Intensiva (UTI) na população pediátrica. **Métodos:** Pesquisa de artigos publicados em português, espanhol e inglês nas bases de dados SCOPUS em 2019/2020 e no Portal Regional da Biblioteca Virtual de Saúde (BVS) em 2020 até quatro e seis de julho de 2020, respectivamente. Utilizou-se os termos "COVID-19" and ("*child*" or "*infant*" or "*newborns*" or "*preschool*"). Para avaliar a qualidade dos estudos utilizou-se a escala de New Castle-Otawa e na análise estatística, o cálculo da *Odds Ratio* para os artigos e do valor médio pelos métodos de Mantel-Haenszel e de DerSimonian e Laird. **Resultados:** Dos 1.141 artigos iniciais, 13 foram selecionados para revisão sistemática e três para metanálise. O sexo masculino foi predominante. Prematuridade, doenças congênitas, comorbidades e predisposição genética foram descritas na evolução para quadros graves/críticos e internação em UTI e a idade inferior a um ano considerada fator de risco significante (OR=4,324 e IC=2,160; 8,656). **Conclusão:** A evolução da COVID-19 para casos graves/críticos e a necessidade de internação em UTI é pouco frequente em crianças e em geral está associada à prematuridade, comorbidades, idade inferior a um ano e condições presentes ao nascimento.

Keywords:
Coronavirus Infections,
Pandemics,
Systematic Review,
Child,
Infant,
Risk Factors.

Abstract

Objectives: To carry out a systematic review of factors associated with the evolution of SARS-CoV-2 infection to severe and critical cases and to hospitalization in Intensive Care Units (ICU) in the pediatric population. **Methods:** The search was conducted for articles published in Portuguese, Spanish and English in the SCOPUS databases during 2019/2020 and in the Regional Portal of the Virtual Health Library (VHL) in 2020 until July 4 and 6, 2020, respectively. The terms "COVID-19" and ("*child*" or "*infant*" or "*newborns*" or "*preschool*") were used. To assess the quality of the studies, the New Castle-Ottawa scale was used and in the statistical analysis, the Odds Ratio calculation for articles was performed and it average value by the Mantel-Haenszel and DerSimonian and Laird methods. **Results:** Of the 1,141 initial articles, 13 were selected for systematic review and three for meta-analysis. Male gender was predominant. Prematurity, congenital diseases, comorbidities and genetic predisposition were described in the evolution to severe/critical conditions and admission to the ICU and the age under one year was considered a significant risk factor (OR=4.324 and CI=2.160; 8.656). **Conclusion:** The COVID-19 evolution for severe/critical cases and the need for admission to the ICU is uncommon in children and is generally associated with prematurity, comorbidities, age under one year and conditions present at birth.

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INTRODUCTION

Human infection caused by SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2), known as coronavirus disease 2019 (COVID-19), was first diagnosed in Wuhan, China, in late 2019. On January 30 2020, the World Health Organization (WHO) declared the outbreak as a global health emergency and in March as a pandemic, with catastrophic proportions and unprecedented in the globalized world[1].

Epidemiological data have shown that COVID-19 affects less the pediatric age group and, in general, is milder than in adults. In children, the disease can be classified according to severity into: (1) Asymptomatic infection: without clinical signs and symptoms or radiological changes, but with positive laboratory tests for the virus; (2) Mild: symptoms of acute upper airway infection, including fever, fatigue, cough, sore throat, sneezing and runny nose with pharyngeal congestion, but normal lung auscultation. The patient may have digestive symptoms (nausea, vomiting, abdominal pain or diarrhea) or be afebrile; (3) Moderate: pneumonia, initially with dry cough evolving to productive, auscultation with wheezing and crackles. It may be asymptomatic and present pulmonary changes on computed tomography (CT); (4) Severe: early onset of respiratory symptoms with dyspnea, central cyanosis and other signs of hypoxia (SatO2 <92%). Gastrointestinal symptoms may be present; (5) Critical: rapid progression to severe respiratory distress syndrome (SRDS), respiratory failure, with shock, encephalopathy, myocardial injury, heart failure, coagulation disorders and acute renal failure[2].

Although the evolution to severe forms and complications in the pediatric population are infrequent, they can occur and cause important social and economic losses, making it imperative to identify their causes. Therefore, the objective of this study is to carry out a systematic review and meta-analysis of the factors associated with the evolution to severe/critical forms and hospitalization in Intensive Care Units (ICU), severity and complications in children infected with SarsCov2.

METHODOLOGY

Search strategy:

The search for articles was carried out in the SCOPUS databases (https://www.scopus.com/) and in the Regional Portal of the Virtual Health Library (VHL, https://bvsalud.org/) that brings together the MEDLINE databases , LILACS, IBECS, Multimedia Resources, Health Information Locator (LIS), Collect SUS, WHO IRIS, PAHO-IRIS, CONASS, SES-GO, BISSAL, BINACIS, ARGMSAL, UNISALUD and LIPECS.

We asked the question based on the PICO strategy (Population, Interest, Comparison, Outcome): "In children, what are the determining factors for Covid-19's severe and critical evolution?" Then, to search the databases, we used the following Boolean operators: "covid-19" AND ("child" OR "infant" OR "newborns" OR "Preschool"). We also used the language filter, selecting articles published in English, Spanish and Portuguese. In the SCOPUS database, we also selected filters for publications from 2020 with the subjects "medicine", "Immunology and Microbiology", "Biochemistry", "Genetics and Molecular Biology", "Nursing", "Pharmacology, Toxicology and Pharmaceutics" and "Neuroscience". In both the VHL and SCOPUS, we set the search date for articles that had been included up 04 and 06 of July 2020, respectively.

The researchers selected the studies independently, and the permanence or withdrawal of the articles selected for the final analysis was decided in a meeting with all the authors of the present review.

Eligibility criteria:

We included articles published in the years 2019 and 2020 in the VHL database and the year 2020 in Scopus that referred (1) to cases of COVID-19 classified as serious and/or critical in the pediatric population, and (2) as to the design, cohort studies (retrospective and prospective), case-control, cross-sectional, case reports, case series clinical trials and reference articles from selected systematic reviews.

We excluded publications in which there was no agreement with the topic, other than scientific articles; (2) those who did not have severe and/or critical cases or factors associated with severity and critical conditions in children; (3) studies with cases of severity without diagnostic confirmation of COVID-19; (4) articles retained from the network (withdrawn from circulation); and (5) studies with non-pediatric populations.

Data extraction:

We used a spreadsheet prepared in Microsoft Excel software version 2019 (Microsoft Office 365 ProPlus, Redmond-WA, USA) to extract the following data: name of the article, database, author, date of publication, study design, size of sample, mean age/age, study location/population, prevalence period, prevalence of COVID-19, prevalence of hospitalizations and complications related to COVID-19, hospitalization criteria and severity classification, other important data found and article link.

In addition, the references from the basic articles of the systematic review were checked to avoid data duplication biases. We assessed the methodological quality of the selected cross-sectional articles using the New Castle-Ottawa scale modified for cross-sectional studies by two of the authors of the present review, and then we ran the meta-analysis.

Statistical analysis:

From the cross-sectional studies included in the analysis, we extracted data and a categorical exposure variable

was created based on the dichotomized classification in individuals with co-morbidities and/or factors associated or not, with the outcomes considered "ICU stay" or "Severe/critical illness". After evaluating the articles, we found that "age <1 year" as a factor associated with the outcome was the data described with the highest quality, which is why it was the only one that received statistical treatment. After the appropriate classifications, we calculated the Odds Ratio association measure for each study and meta-analysis using the combination of data under fixed effect by the Mantel-Haenszel method and the DerSimonian and Laird random effect method. We ran the calculation of the inconsistency measure (I2) to assess the results' heterogeneity. We performed the tabulation using the Microsoft Excel © software and the statistical analyzes using the MedCalc © software, at a significance level of 5%[3].

RESULTS

Initially, we found 1,141 articles, of which 693 in the VHL database and 448 in SCOPUS. After removing duplicate articles that did not meet the eligibility criteria and including a base article, we selected ten publications for the systematic review process: one article that was in the Medline and Scopus databases simultaneously, five in the VHL and Medline and four in Scopus. As for the design, there were four cross-sectional studies, two case reports, three case series and one report (figure 1).

As per depicted in Table 1, in the selected publications the number of participants ranged from one to 2,572 children. Five studies were conducted in China, two in the United States (USA), one in England, one in Italy and one with a population in the USA and Canada. The male population was predominant in case reports[4,5] and in the two case series it represented 80% of the sample in one study[5] and 56% in another[7]. In cross-sectional studies, the proportion of male participants ranged from 75% to 52%[2,8,9,10]. In turn, the largest share of critically ill patients with comorbidities were female in the study by Ng et. al.11 (2%) and Garazzino et. al.,(59.9%)[12].

Children under one year of age had more frequent comorbidities and complications. As for case reports, one refers to an eight-month-old child[3] and the other to a six-week-old child[4]. In a series of cases, age ranged from three months to 14 years[7] and another from two months to 5.6 years[5]. In the weekly report, from zero to 17 years[9]. In the study by Garazzino et al. The participants were aged between one day and 17.7 years[12], by Shekerdemian et al. between 4.2 to 16.6 years[10], by Sun et. al. two months to 15 years[8], by Ng et. al. five days to 12 months[11] and Dong et. al. between one day and 18 years[2].

Analyzing complications, hospitalizations in the ICU and/or severe and critical cases, we found that in the study by Garazzino et al, 33 (19.6%) developed complications and two required admission to the ICU[11]. The study by Shekerdemian et al., carried out only with children who received treatment

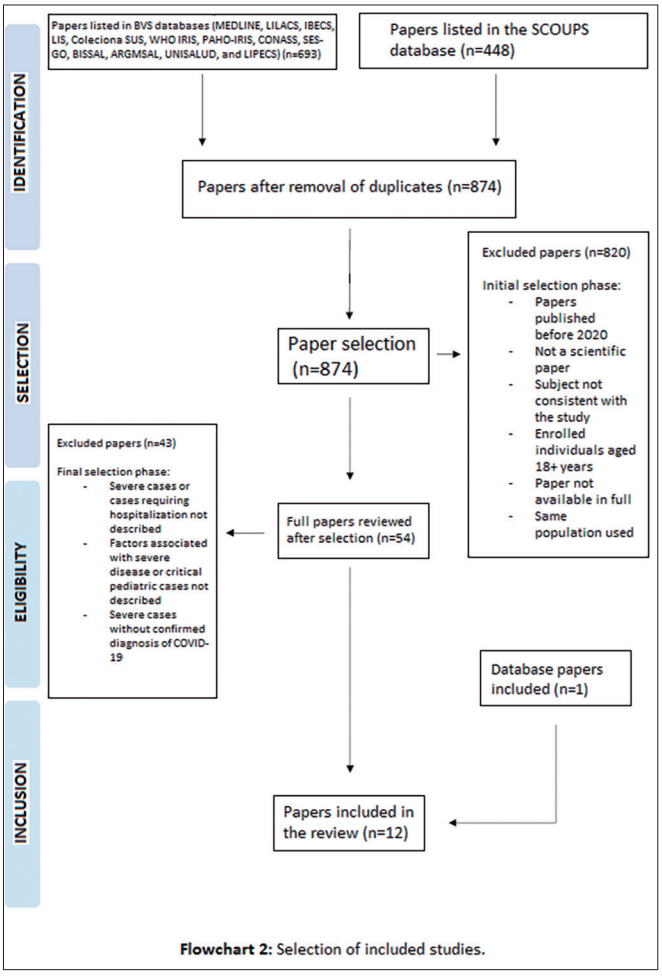


Figura 1. Selection of articles for analysis.

in the ICU, reported 33 (68.75%) severe/critical cases[10] and Sun et. al. presented data on eight children admitted to the ICU, of which five were severe and three were critical[8].

In the study by Ng et al., out of eight children, two required admission to the ICU,[11] while Dong et al. reported that among 728 confirmed cases, 18 (2.5%) were classified as severe, and three (0.4%) as critical[2]. In the case series by Zheng et al. two (8%) were considered critical[7] and in Cai et al., there were two (40%) severe cases and two critical (40%)[6]. In the weekly report by Bialek et al. of the 15 admitted to the ICU, five were children under one year old[9]. One report presented a case of critical illness[4] and another of severe atypical evolution[5].

Garazzino et al. found prematurity and congenital heart disease[12] as factors associated with ICU admission. Shekerdemian et al. found that 41 (85%) participants with previous comorbidities had a history of long-term dependence on technological life support and genetic anomalies/developmental delays (40%), immunosuppression/malignancy (23%), obesity (7%), diabetes (8%), seizures (6%) and congenital heart diseases (6%), among others[10].

Table 1. Papers selected according to the eligibility criteria.

Bibliographic reference	Place	Design	Description of participants	N	Age/Mean age	Sex Male (%)	Disease prevalence	Complications
Qiu L, Jiao R, Zhang A, et al. (2020)	China	Case report	Patient with no previous contact with positive SARS-CoV-2 with cough and getting worse	1	8 months	1 (100%)	Not applicable	Recurrent apnea, septic shock, kidney injury and persistent CD4/CD8/CD3cell drop
Dugue R, Cay--Martínez KC, Thakur KT et al. (2020)	United States	Case report	Hospitalized for brief periods with sustained gaze elevation associated with bilateral leg stiffening with irregular appearance	1	6 weeks	1 (100%)	Not applicable	Neurological signs and symptoms
Cai X, Ma Y, Li S et al. (2020)	China	Case series	Wuhan Children's Hospital	5	2 months to 5.5 years	4 (80%)	All the participants	Case 1: child referred to the PICU because of intermittent seizures. 2 severe cases and 2 critical cases Septic shock, MOD1, acute respiratory failure, heart injury. 1 death. Cases without initial respiratory issues (onset with gastrointestinal tract symptoms)
Zheng F, Liao C, Fan Q Hong, et al. (2020)	China	Case series	Hospitalized patients from 10 public hospitals from the urban and periurban areas of Wuhan	25	3 months to 14 years	14 (56%)	All the participants	2 (8%) critical cases
Bialek S, Gierke R, Hughes M, et al. (2020)	United States	Weekly report	Patients tests positive	2,572	0 to 17 years	1,408 (57%)	All the participants	147 hospitalized / 15 admitted to the ICU
Sun D, Li H, Lu XX, et al. (2020)	China	Cross--sectional study	Wuhan Children's Hospital ICU	8	2 months to 15 years	6 (75%)	Entire sample; 5 severe cases and 3 critical cases1	Septic shock, MOD1; hypoglobulinemia, gastroenteritis in severe cases; intussusception, toxic encephalopathy, status epilepticus, kidney stones, hydronephrosis, heart failure, coagulopathy.
Dong Y, Mo X, Hu Y, et al. (2020)	China	Cross--sectional study	China's CDC	2,135	1 day to 18 years	1,208 (56.6%)	728 (34.1%) confirmed cases	18 severe cases and 3 critical cases (2.9% of the confirmed cases)
Shekerdemian LS, Mahmood NR, Wolfe KK, et al.(2020)	USA/ Canada	Cross--sectional study	46 pediatric ICUs	48	4.2 to 16.6 years	25 (52%)	Complete sample	16 (33%) severe cases/ 17 (35%) critical cases
Ng KF, Bandi S, Bird PW et al.(2020)	England	Cross--sectional study	Leicester hospital	70	5 days and 12 months	2 (25%)	8/70 (11.4%) SARS-CoV positive	4/8 (50%) treated with broad-spectrum antibiotics for suspecting of sepsis and 2/8 (25%) admitted to the ICU (1 severe case)
Garazzino S, Montagnani C, Donà D, et al. (2020)	Italy	Cross--sectional study	11 of 13 exclusively pediatric hospitals and 51 of 390 pediatric units	168	1 day to 17.7 years	74 (40.1%)	All the samples	33 (19.6%) complications; 2 admitted to the ICU
Jones VG, Mills M, Suarez D, et al. (2020)	USA, California	Case report	Previously healthy female patient and with complete immunization	1	6 months	0	Not applicable	Kawasaki's disease
Toubiana J, Poirault C, Corsia A, et al. (2020)	Paris, France	Case series	17 children admitted with a diagnosis of KD4 at the Necker Hospital for Sick Children	17	3.7 to 16.6 years	7 (41%)	7/17 (41%) PCR positives and 14/16 (88%) IgG detected	Kawasaki disease; 13 (76%) were admitted to the ICU because of hemodynamic instability; 11 (65%) had shock syndrome associated with KD

[1]MOD: multiple organ dysfunction; [2]ALL: acute lymphoblastic leukemia; [3]PTNB: Pre-term newborn; [4]KD: Kawasaki Disease.

The study by Sun et al. showed that, among three critical patients, one had acute lymphoid leukemia[8]. Children who required ICU admission had congenital heart disease in the case series of Zheng et al., while in the study by Ng et al.[11] the complication occurred in a preterm newborn. Children under one year of age presented severity in two documents[2,9] and a case report[5].

Intussusception, perforated appendicitis, traumatic brain injury, hydronephrosis, nephrolithiasis and co-infection with rotavirus[7] have been reported in patients who progressed to severe or critical situations[7], history of surgery for congenital heart disease, malnutrition and hereditary metabolic disease6. Bialek et al., described children with chronic lung disease, heart disease and immunosuppression[9]. In the case reported by Qiu et al. the child had a history of cardiac surgery, previous pneumonia, growth restriction and malnutrition (chronic inflammation)[4].

A case report points to an atypical evolution similar to Kawasaki's disease (KD), of a six-month-old girl diagnosed with classical KD and tested positive for COVID-19[13]. In a publication not included in the analysis by the eligibility criteria, the report is about the case of a six-year-old boy who tested positive for coronavirus and who met the clinical criteria of incomplete KD associated with hypotension[14].

An outbreak of KD in France has also been described in the literature with a 13-fold increase in the incidence of KD in eight days, compared to those in the previous 2 years. Of the 17 children with KD, 14 showed positive IgG antibodies to SARS-CoV-2.[15] All had digestive symptoms preceding the condition and only six had a recent history of acute respiratory infection. The authors also point to a possible genetic predisposition, since 60% were from sub-Saharan Africa or the Caribbean, and 12% from Asia.

Other complications seen in children with severe and critical conditions include interstitial pneumonia, SRDS, peripheral vasculitis[12], septic shock[4,6,8], multiple organ dysfunction (MOD)[6,8,10], gastroenteritis[8], recurrent apneas, acute kidney injury[4] , neurological conditions[5], secondary bacterial infection[7], important laboratory changes[4,6,7,8] and death[6,10] (table 1).

We used the New Castle-Ottawa Quality Assessment Scale, adapted for cross-sectional studies. This scale considers participants selection, comparability and result, with each of these criteria receiving a maximum of five, two and three stars, respectively. Among the eligible studies, three were considered to be of good methodological quality[2,10,12] and one had low methodological quality[8] (table 2).

Children under one year of age showed higher percentages of severe/critical conditions or ICU admission (table 3). This age group can be considered a risk factor for these outcomes in the individual analysis of the study by Bialek et. al. (OR = 3.706 and CI = 1.237 - 11.102) and Dong et. al. (OR = 4,324 and CI = 1,689 - 11,069), as well as in the meta-analysis of the three studies evaluated (figure 2) considering the models of fixed effect (OR = 4,324 and CI = 2,160 - 8,656) and variable effect (OR = 4,201 and CI = 2,097 - 8.419), despite the wide CI.

DISCUSSION

The present study reports that the majority of severe cases and/or those with COVID-19 complications occur in children under one year of age, an age group that also required more hospitalizations and hospitalizations in intensive care units (ICU)[6,7, 11,12,13]. The reason for this is still not clear, although a multicenter study conducted in Italy justified that the high number of children under one year (40%) in its sample could reflect a greater tendency among families to seek medical care for younger children, in addition to a greater propensity for doctors to admit them to hospitals[14].

Corroborating this finding, two case reports described the involvement of children under one year of age[4,5], while in the study by Garazzino S, Montagnani C, Donà D, et al[12] the child was eight months old and had several comorbidities, such as neonatal cardiac surgery, previous pneumonias, growth disorder and malnutrition, contributing factors to a chronic inflammatory state in the patient[4].

A North American cross-sectional study also found that 80% of patients admitted to the ICU had comorbidities, of which two children had MOD and died, one of them had sepsis by gram-negative bacteria prior to infection by SARS-CoV-2[10].

Another risk factor associated with serious pediatric cases of COVID-19 reported was prematurity[11]. In a retrospective study, a 34-week-old preterm born by emergency cesarean delivery due to maternal diagnosis of COVID-19 required admission to the ICU at five days of life. She had decreased breastfeeding, lethargy and jaundice, progressing with apnea and a drop in oxygen saturation, that is, a severe condition resulting from prematurity associated with SARS-CoV-2[11] infection.

In the study by Zheng et al,[7,25] the children were diagnosed with COVID-19, most of whom were previously healthy. However, two children (8%) progressed to a critical condition, being admitted to the ICU, both of whom had a history of surgical correction of congenital heart disease; one of them was also malnourished and suspected of hereditary metabolic disease[7]. While in adults and the elderly, risk factors associated with severity are generally linked to chronic-degenerative diseases in children, in turn; congenital diseases stand out, although obesity can be a risk factor for older children[10].

On the other hand, in a study reporting five pediatric cases of COVID-19, two patients were in critical condition and had underlying conditions: intussusception, rotavirus

Table 2. Assessing the quality of the studies according to the Newcastle scale– Ottawa (Adapted for cross-sectional studies).

	Selection				Comparability		Result	
Studies	**Representativity**	**Sample size**	**unrespondents**	**Exposure determination**	**Comparable subjects**	**Assessment of outcomes**	**Statistical test**	**Total**
Sun et al. (2020)[8]			*	*		*		3
Dong et al. (2020)[2]	*	*	*	**	**	**	*	10
Shekerdemian et al. (2020)[10]	*	*	*	**	**	**		9
Garazzino et al. (2020)[12]	*	*	*	**	**	**	*	10

(Adapted for cross-sectional studies)

Table 3. Number of cases and Odds Ratio (OR) for association between age <1 year, ICU stay and Covid's severe/critical conditions[19] in children, with a 95% Confidence Interval (CI) and p – value.

	Age	**N (%)**	**OR (CI)**	***p*-value**
ICU stay Bialek et al.[9]	< 1 year	5 (5.26)	3.706 (1.237-11.102)	0.023*
	> 1 year	10 (1.54)	-	-
Gazzarino et al.[12]	< 1 year	2 (3.03)	8.200 (0.387-173.608)	0.183
	> 1 year	-	-	-
Severe/critical cases Dong et al.[2]		7 (8.24)	4.324 (1.689-11.069)	0.004*
	< 1 year	-	-	-
	> 1 year	14 (2.18)	-	-
Combined analysis[c]	< 1 year	14 (6.03)	4.324 (2.160-8.656)[a]	< 0.001
			4.201 (2.097-8.419)[b]	< 0.001
	> 1 year	24 (1.75)	-	-

Source: own authorship. * Statistically significant. [a] Fixed effect model. [b] Variable effect model. [c] I^2 = 0,00% X^2 = 0,2448, df = 2.

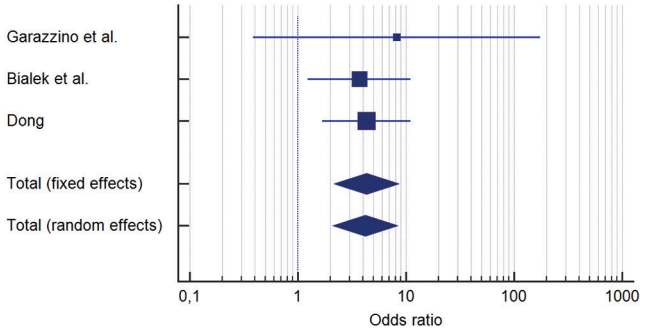


Figura 2. Association between age <1 year and severe/critical forms or admission to the ICU by Covid-19.

infection, hydronephrosis and kidney stones. However, two other patients also had comorbidities (complicated acute appendicitis and subdural hemorrhage because of brain injury) and did not develop a critical condition, and the reason why they did not progress severely[6] is unknown.

As for the clinical picture associated with severity, a case report described typical critical characteristics, including high fever, septic shock, recurrent apnea, severe hematuria, hypofibrinogenemia, lymphopenia and acute kidney injury. The initial clinical manifestation was septic shock, similar to that of adults[4].

However, other studies described clinical characteristics of uncommon severity in adults, such as neurological repercussions (sustained gaze upwards, bilateral dystonic extension of the legs, altered responsiveness and toxic encephalopathy)[5,8]; increased enzyme lactic dehydrogenase (DHL), hyponatremia, secondary bacterial infection[7], septic shock, MOD, intussusception, disseminated intravascular coagulation (DIC), renal calculi, hydronephrosis, heart failure, coagulopathy, hypoglobulinemia and gastroenteritis[8]. In addition, gastrointestinal disorders have been described as initial symptoms, while in severe cases in adults, in general, they are respiratory[6].

Regarding the need for ventilatory support, a cross-sectional study in which 81% of patients admitted to the Pediatric Intensive Care Unit (PICU), 44% were treated non-invasively, 38% required endotracheal ventilation or tracheostomy and 13% adjuvant ventilatory interventions or extracorporeal therapies[10].

There are reports in the literature that suggest that infection with the new coronavirus may trigger an immune response similar to that of KD. The knowledge of the possibility of occurrence of these atypical forms of presentation enables the early referral of affected patients to tertiary care[16].

There are some hypotheses that explain the lower severity of COVID-19 in children, such as low prevalence of comorbidities[17] and immune system differences between children and adults. In addition to having a stronger innate immune response, children do not show an exaggerated release of cytokines in the proinflammatory response, as in adults, an important fact for the development of severe COVID-19 symptoms[19].

Other hypotheses would be the greater contact of children with other coronaviruses, with a cross immune response, and a greater colonization of the nasal mucosa by viruses and bacteria, which could limit the growth of another microorganism, such as SARS-CoV-2[20]. Also, the fact that in children the angiotensin-converting enzyme (ACE2), which acts as a gateway for the virus in the cell and plays a role in the pathogenesis of COVID-19, is more immature. Corroborating for less severe conditions in the pediatric age group[21,22].

It is important to stress that the present study, although presenting relevant data, has some limitations: due to the recent discovery of the disease, despite the large number of publications, there are few studies with primary data on severe/critical cases and of the cohort and case-control cases in the pediatric population. In the vast majority, the studies are cross-sectional and case reports, limiting the establishment of more solid evidence from the meta-analysis regarding the association of the disease with the factors involved.

In addition, despite highlighting the basic characteristics of patients diagnosed with the disease, most studies do not address factors associated with complications and progression to severity, including because they are less frequent events in the pediatric population and what the present study had as objective to assess.

Although the results are significant, we noticed that the confidence intervals are wide, reducing the strength of the association. In this sense, a meta-analysis with a larger number of studies and with larger samples may, in the future, bring better evidence.

Finally, this systematic review showed a greater likelihood of progression to the severe/critical forms of the disease, and for the need of ICU admittance of children with congenital diseases, comorbidities and premature ones, while the metanalysis showed a higher chance of progress to this outcome in children under one year of age. It is paramount to hold new studies assessing these factors, aiming to increase the strength of evidence and expanding scientific knowledge, concerning the Covid-19 in the pediatric population.

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