

Research Article

Clinical Manifestations of Pediatric Patients Hospitalized With COVID-19: A Systematic Review

Edilene Araújo Pamplona*, Beatriz Nayanne Machado da Silva Ferreira, Raquel Ferreira Sá, Renan Alex Fernandes de Oliveira, Milena Lins da Cunha Dias, Rossana Karla Gois Ferreira, Sheva Castro Dantas de Sousa, Ana Carolina Miranda de Luna, and Chiara Svendsen de Menezes

Residência Multiprofissional em Saúde da Criança, Secretaria Estadual de Saúde, Paraíba, Brazil

***Corresponding author**

Edilene Araújo Pamplona, R. Doutor Aristides Vilar, 87 – Oitizeiro, João Pessoa, Paraíba, Brazil, Tel: 55 83 99875-5553; Email: edileneapamplona@gmail.com

Submitted: 24 February 2021

Accepted: 15 March 2021

Published: 18 March 2021

ISSN: 2373-9312

Copyright

© 2021 Pamplona EA, et al.

OPEN ACCESS**Keywords**

- COVID-19
- Hospitalized child
- Signs and symptoms

Abstract

Introduction: COVID-19 mainly affects the respiratory system and leads to flu-like symptoms, which can rapidly evolve to more severe conditions and death. The pediatric age group is susceptible to COVID-19, although the rate of affected patients is lower and most are asymptomatic.

Objective: Analyze the scientific literature regarding COVID-19 clinical manifestations in the pediatric age group.

Method: A systematic review was carried out by searching for articles published between December 1, 2019 and July 28, 2020 in the PubMed®, Scopus, ScienceDirect, Lilacs, MEDLINE® and Cochrane Library databases using the terms “COVID-19”, “Child”, “Clinical characteristics” and “Hospitalized” and their correlates. Data extraction was done with the use of a standardized form and a descriptive analysis was performed with frequencies and percentages calculations to verify the prevalence of clinical manifestations.

Results: Thirty-two studies were included, and it was observed that fever was the predominant symptom, followed by coughing and diarrhea. Among the other symptoms, sore throat, fatigue, headache, dyspnea/difficulty breathing, runny nose, nasal congestion, pneumonia, expectoration and tachypnea, in addition to gastrointestinal symptoms, stood out. However, the presence of asymptomatic patients was noted in most of the studies analyzed.

Conclusion: The symptoms of COVID-19 in children, although hospitalized, are mild to moderate in the vast majority. Serious cases and those that need intensive care have been observed in few studies, which may be associated with the favorable outcome of COVID-19 in pediatrics.

INTRODUCTION

In December 2019, the World Health Organization (WHO), was informed about a disease, then of unknown cause, that coursed with severe pneumonia and could lead to death. The disease originated in Wuhan, China, and among the initial cases, it was observed that there was one factor in common: exposure to city's seafood, fish and live animals market [1]. The cases increased considerably, and, in January 2020, it was declared an international public health emergency, for its seriousness and rapid spread throughout the world. Studies have found that the causative agent of the disease belonged to the coronavirus family, but it was a new presentation of the virus, named SARS-CoV-2 [1,2].

The novel coronavirus mainly affects the respiratory system, and the symptoms course like flu, however, some cases evolve rapidly into acute respiratory distress syndrome (ARDS) and cause death. The most vulnerable age groups, such as children and

the elderly, are generally a priority for health services, however, the rate of pediatric patients at the beginning of pandemic was low and most were asymptomatic, which does not mean that children are less susceptible to the virus and that this rate cannot increase in the future [3,4]. Understanding the pathophysiology of the disease, its different clinical manifestations, complications and evolution is essential, especially in an age group that has a vast clinical variation, so that there is better understanding and management of infant morbidity and mortality [5,6]. Therefore, given the current reality and within this perspective, the present systematic review aimed to analyze the scientific literature regarding the clinical manifestations in the pediatric age group.

METHODOLOGY

This is a systematic review of literature, using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement [7]. The review was registered in the International Prospective Register of Systematic Reviews

(PROSPERO), for prior disclosure of the protocol of this study, to reduce the risk of publication bias. The research was carried out through the search of studies published between December 1, 2019 and July 28, 2020, on the PubMed®, Scopus, ScienceDirect, Latin American and Caribbean Literature MEDLINE® and Cochrane Library databases using the MeSH terms “COVID-19”, “Child”, “Clinical characteristics” and “Hospitalized”, as well as their correlates in English and no language filter was used. For association of descriptors the search strategy with the Boolean term AND was used.

Study eligibility

In the search for literature, the PECO 8 strategy was applied in order to guide the formulation of the research question, whereby each letter represents a component of the issue, as shown in Table 1. The following inclusion criteria was used: publications of original articles (cohort studies, case control studies, case reports, case series and cross-sectional studies), studies with individuals hospitalized patients who tested positive for COVID-19 under the age of 18 years and who described the clinical characteristics in pediatrics. In this stage, the selection of studies was done by four readers reading titles and abstracts and two more reviewers overseeing that the choice of articles adopted the criteria. The exclusion criteria corresponded to: reports and studies of single clinical case, studies with mixed samples (adult and pediatric), and studies that only addressed the clinical characteristics of non-hospitalized children. In addition, duplicate studies were removed. Subsequently, the articles selected were put through the verification of eligibility criteria by two groups, each containing two readers and an independent reviewer responsible for resolving discrepancies between these readers in any of the steps. Articles that presented insufficient information in the abstracts were also previously selected for reading in full. The titles and abstracts of the articles included in the research were recorded in the Mendeley® reference management software.

Methodological Quality Assessment

The methodological quality of the selected observational studies was assessed through the New Castle-Ottawa Scale (NOS) 8, which consists of an instrument of evaluation for cohort and case control studies, composed of 9 items and subdivided into 3 categories: selection of groups (0 to 4 points), comparability (0 to 2 points) and analysis of study exposure or outcome (0 to 3 points), totaling 9 points, which represents high methodological quality. Prospective studies were analyzed by the tool for cohort studies and retrospectives through the tool for case-control studies.

Data Extraction and Analysis

The data extraction was carried out independently by the researchers, through a standardized form prepared by them. Subsequently, the data was inserted into a digital spreadsheet containing information regarding authors, location of study, sample, type of study, aim, data collection instrument and clinical manifestations. To verify the prevalence of clinical manifestations found in the studies included in the sample, a descriptive analysis was performed with calculation of frequencies and percentages.

Table 1: PECO search strategy.

Acronym	Definition	Description
P	Population of interest	Pediatric patients hospitalized with COVID-19
E	Exposure	Sars-Cov-2 with positive test for COVID-19 (PCR or serological test)
C	Comparison	Not applicable
O	Outcome	Main clinical manifestations presented

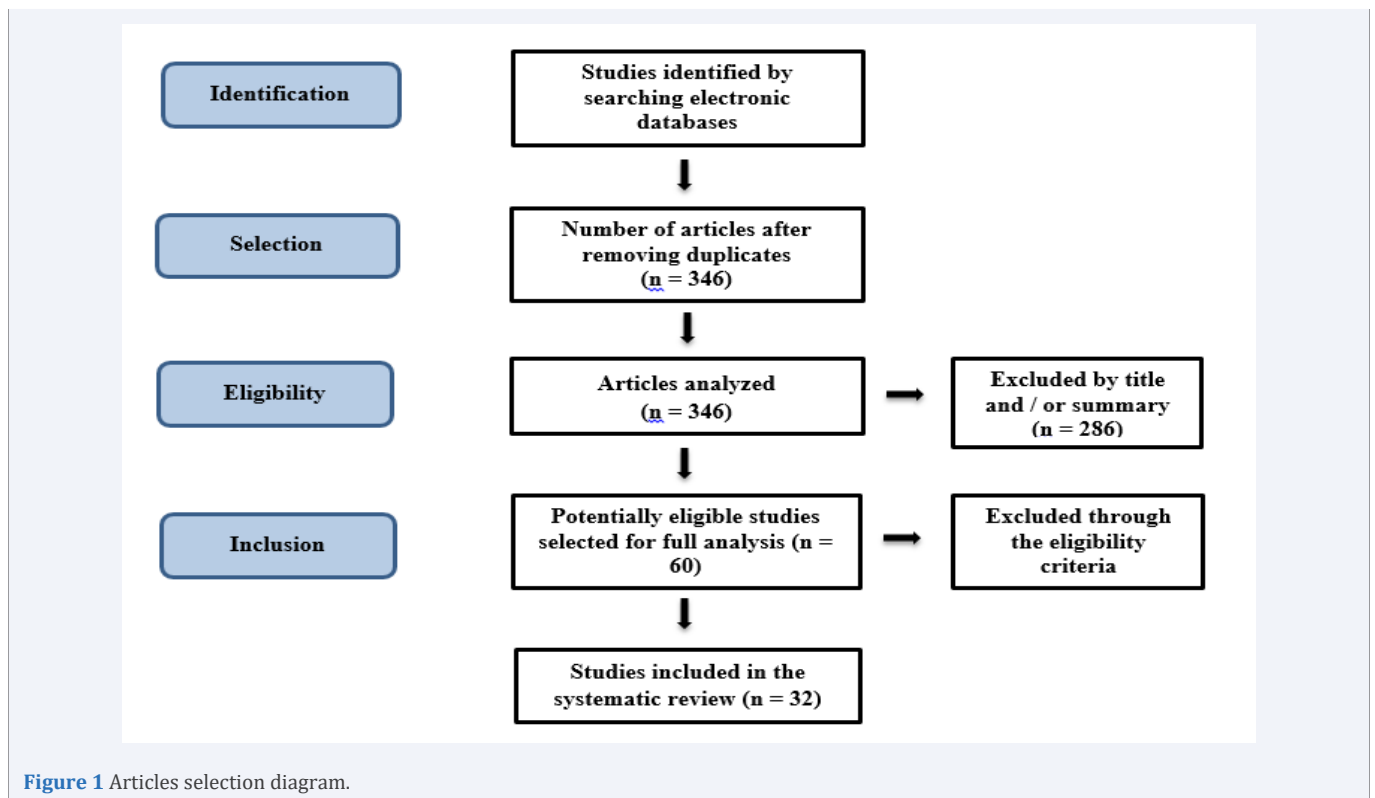
Table 2: Evaluation of the methodological quality of the studies according to the Newcastle Ottawa scale.

Study	Selection	Comparability	Outcome	Total
Bai et al. (2020) ⁹	***		***	6
Cai et al. (2020) ¹⁰	**	*	***	7
Chen et al. (2020) ¹¹	***		***	6
Chen et al. (2020) ¹²	***		**	6
Du et al. (2020) ¹³	***	*	**	6
Du et al. (2020) ¹⁴	***		***	6
Du et al. (2020) ¹⁵	***	*	***	7
Gaborieau et al. (2020) ¹⁶	**	**	**	7
García et al. (2020) ¹⁷	***		***	6
Korkmaz et al. (2020) ¹⁸	***	**	***	8
Li et al. (2020) ¹⁹	***	**	***	8
Lu et al. (2020) ²⁰	**		**	4
Lu et al. (2020) ²¹	****	**	***	9
Mithal et al. (2020) ²²	***		***	6
Oualha et al. (2020) ²³	***		***	6
Peng et al. (2020) ²⁴	***		***	6
Romani et al. (2020) ²⁵	**	*	***	6
Shen et al. (2020) ²⁶	***		***	6
Song et al. (2020) ²⁷	***		***	6
Su et al. (2020) ²⁸	***	**	**	7
Sun et al. (2020) ²⁹	***		***	6
Tan et al. (2020) ³⁰	***	*	***	7
Valente et al. (2020) ³¹	**		**	4
Wei et al. (2020) ³²	***		***	6
Wu et al. (2020) ³³	***		***	6
Wu et al. (2020) ³⁴	***		***	6
Xiong et al. (2020) ³⁵	***	**	***	8
Zhang et al. (2020) ³⁶	***	**	***	8
Zheng et al. (2020) ³⁷	***		***	6
Zheng et al. (2020) ³⁸	***	**	***	8
Zhong et al. (2020) ³⁹	**		**	4
Zhu et al. (2020) ⁴⁰	***	*	***	7

RESULTS

Initially, 363 articles were identified in the selected databases. Of these, 17 were excluded for being in duplicate. Another 286 were excluded for title and/or abstract, leaving 60 to be analyzed by reading in full where 28 more articles were excluded for not fitting the eligibility criteria. Thus, the sample for the final analysis of this review was composed of 32 articles. The flowchart according to PRISMA 7 can be seen in (Figure 1).

The studies included in the final sample were evaluated for



quality methodology according to the Newcastle-Ottawa Scale 8, where there was a variation of score with a minimum of 4 (four) and a maximum of (9) stars, as described in Table 2. The data related to the analysis categories used to characterize the articles selected for this systematic review are presented on (Table 3).

Fever was the most prevalent symptom, being present in 100% of the studies, followed by cough (90.6%) and diarrhea (43.8%). Among the other symptoms, there was sore throat, fatigue and headache. With regard to respiratory symptoms, there was a prevalence of dyspnea/difficulty breathing, runny nose, nasal congestion, pneumonia, sputum and tachypnea. In addition to diarrhea, vomiting, abdominal pain, nausea, constipation and feeding difficulties were also cited. Five articles comprehensively described the presence of gastrointestinal symptoms, not specifically reporting what such symptoms was (Table 4).

Other nonspecific symptoms have been reported: arthralgia, liver dysfunction, kidney dysfunction, myocardial dysfunction, loss of taste, malaise, chills, paroxysmal crying, muscle symptoms, CNS symptoms, refractory hypoxia and hypotensive shock, with each of them cited only once among the total number of articles selected. Finally, the occurrence of pediatric patients infected by SARS-CoV-2, but presenting asymptomatic infection, was observed in 13 of the included studies in this review. These asymptomatic patients represented 40.6% of the sample of studies.

DISCUSSION & CONCLUSION

The patients in the articles analyzed in this review were hospitalized due to the symptoms of COVID-19, although the

vast majority presented mild symptoms. The literature shows that pediatric hospitalization rate remains low in comparison to adult patients [41-44], this circumstance is due to the fact that children and young people are less susceptible to infection by the virus in question [45]. In addition, studies show that clinical manifestations are milder in children compared to adults [46-49] and that they have a lower incidence of cardiovascular disease and cerebrovascular disease, suggesting a better prognosis compared to adult patients [50].

In the study developed by Leung et al. [51], with 451 individuals, containing a pediatric and adult population, a significant difference was observed between the groups with regard to the number of symptoms, with a lower incidence in children. In a study with 9 children and 14 adults, the authors suggested that there is a lower number of children infected with SARS-CoV-2 and, when they develop the disease, their general symptoms are significantly milder [52].

Current literature demonstrates that the proportion of severe cases of COVID-19 in neonatal and pediatric population is approximately 6%, with the majority of cases included in the asymptomatic, mild and moderate categories [46]. Towards this finding, in this review, only two studies, Garcia-Salido et al. [17], and Oualha et al [23], aimed to analyze the serious and lethal cases of COVID-19 in pediatrics, totaling 6.25% of featured items. The others found a preponderance of mild clinical manifestations and moderate, in addition to the proportion of asymptomatic individuals discussed above.

Regarding the characterization of the lethal cases of COVID-19 in pediatrics, the study of Oualha et al. [23], which was included in the result of this review, showed that 60% of cases of

Table 3: Characterization of the selected studies

Authors	Study site	Sample	Type of Study	Goal	Data collection	Clinical Manifestations
Bai et al. (2020) ⁹	4 hospitals in Chongqing, China	25 children with a mean age of 11 years (0.6–17 years)	Retrospective documentary	To analyze clinical characteristics of children with COVID-19.	Medical records	Fever (24%), Cough (52%), Sore throat (12%), Runny Nose (12%), Diarrhoea (4%) and fatigue (4%).
Cai et al. (2020) ¹⁰	Wuhan Children's Hospital, Wuhan - China.	5 Children (Age range: 2 months - 5 years)	Case Series	Describe the common clinical characteristics among cases	No description	Vomiting (40%), Restlessness (20%), Paroxysmal Crying (20%), Fever (80%), Apathy (20%), Sleepiness (40%), Food Difficulty (20%), Dyspnea (20%), Diarrhea (20%), Lethargy (20%), Renal Dysfunction (20%), Liver Dysfunction (20%), Myocardial Dysfunction (20%), Appendicitis (20%).
Chen et al (2020) ¹¹	3 hospitals of Chongqing - China.	Twelve patients under the age of 18 years diagnosed with COVID-19.	Retrospective	Delineate the epidemiology and clinical characteristics of children infected with SARS-CoV2.	Electronic medical records	Cough (75%), fever (58.3%), diarrhea (33.3%); runny nose and sore throat (16.7%); tonturas (16.7%); fatigue (8.3%).
Chen et al. (2020) ¹²	7 hospitals in Zhejiang - East China.	32 children with a mean age of 9.5 years (3 months - 18 years)	Retrospective	Investigate the clinical and epidemiological characteristics of pediatric patients with COVID-19.	No description	Fever (62.5%), Cough (31.25%), Fatigue (12.5%), Diarrhea (9.37%), Pneumonia (43.75%).
Du et al. (2020) ¹³	Wuhan Children's Hospital, Wuhan - China.	182 Children and adolescents under 16 years (mean age of six years)	Retrospective	Investigate the clinical and laboratory characteristics of children hospitalized with COVID-19	Medical records	Fever (43.3%), dry cough (44.5%), gastrointestinal symptoms (11%), vomiting (3.8%), diarrhea (4.8%), abdominal pain (3.8%), fatigue (2.8%), shortness of breath (1.1%), chest pain (1.6%)
Du et al. (2020) ¹⁴	Jinan Infectious Diseases Hospital and Rizhao People's Hospital - China.	14 Children (Age range: 0-16 years)	Retrospective Descriptive	Analyze and compare clinical and epidemiological characteristics in children with COVID-19	Information record	Fever (35.7%), dry cough (21.4%); Phlegm ((7.1%), Headache (7.1%), Fatigue (7.1%), Sore throat (7.1%), Myalgia (7.1%).
Du et al. (2020) ¹⁵	Jinan Infectious Disease Hospital, Shandong - China.	Ten children with a mean age of 5.08 (9 months - 14 years).	Descriptive-retrospective	Determine how long SARS-CoV-2 virus RNA persists in fecal samples in children with COVID-19.	Electronic medical records and forms for collection	Fever (40%); dry cough (20%); secretion (10%).
Gaborieau et al. (2020) ¹⁶	23 Paediatric hospitals belonging to the "COPHI" network - Paris.	192 children with an average age of 1 year (0 - 18 years)	Prospective multicenter observational	Describe the clinical expression of COVID-19 in pediatric hospitalized patients	No description	Fever (73.9%), Coriza (36.3%), Respiratory distress (24.2%), Diarrhea (15.3%), Vomiting (7.6%), Difficulty eating (10.2%), Absence of smell and taste (4.5%), Chest pain (2.5%).
Garcia-Salido et al. (2020) ¹⁷	Tertiary hospital in Madrid, Spain.	7 children admitted to the PICU (0.5 - 162 months)	Prospective Observational	Clinical features of critically injured patients with COVID-19	Charts	Asymptomatic (14.3%), Fever (71.4%); nausea (28.6%), vomiting (42.8%), diarrhea (28.6%); dyspnea (28.6%); respiratory symptoms (14.3%); and headache (14.3%).

Korkmaz et al. (2020) ¹⁸	Department of Pediatrics at Bursa - Turkey.	81 patients with a mean age of 9.50 years (3.16–15.08). Of these, 41 were hospitalized.	Retrospective	Collect data and treatment for SARS-CoV-2 and contribute to the knowledge base according to evidence, evaluating characteristics in children.	Electronic data	Fever (77%), cough (55%), fatigue or myalgia (23%); headache (18%); sore throat (9%); vomiting or diarrhea (7%); dyspnea (5%) and runny nose (5%).
Li et al. (2020) ¹⁹	Wuhan Children's Hospital, Wuhan - China.	57 Hospitalized children (Mean age in covid-19 group 18.7 months)	Retrospective Control Case	Compare the different clinical presentations between COVID-19 and Influenza A pneumonia.	Data extraction form	Cough (70.2%), fever (54.4%), gastrointestinal symptoms (14.1%), seizure (1%), Severe pneumonia (3.5%)
Lu et al. (2020) ²⁰	Women and Children's Medical Center in Guangzhou - China	9 children with a mean age of 7.8 ± 5.3 years (Range: 2 months - 15 years)	Retrospective case series, double blind.	Identify and summarize the most common findings in covid-infected children-19.	No description	Fever only (44.4%), Cough only (11.1%) Fever and Cough (22.2%), Coriza and nasal congestion (11.1%), Asymptomatic (11.1%).
Lu et al. (2020) ²¹	Wuhan Children's Hospital, Wuhan - China	110 Children with a mean age of 6 years (Range 2 months - 15 years).	Retrospective	Assess the symptoms of COVID-19 in children with mild and common symptoms	Medical records in electronic environment	Cough (51.8%), Dyspnea (51.8%), Fever (50.9%), Digestive Symptoms (23.6%), Coriza (9.1%). Symptoms of the Central Nervous System (5.5%), Fatigue (3.6%), Muscle Symptoms (2.7%). Asymptomatic (29%).
Mithal et al. (2020) ²²	Bambino Gesù Children's Hospital, Chicago - United States.	9 babies under 90 days in hospital.	Retrospective	Present a series of cases of American children <90 days of age with COVID-19.	Electronic medical records	Fever (88.9%) Cough or aquipnea (44.4%), inadequate feeding (44.4%) vomiting (33.3%) diarrhoea (11.1%).
Oualha et al. (2020) ²³	Necker Hospital on ile de France - Paris	27 included, 16 hospitalized children and only 5 severe cases reported at the age of 1 month - 18 years.	Observational, retrospective, unicentric case series	Describe the serious forms of COVID-19 in children.	De-identified electronic medical records	Fever (60%), cough (40%), respiratory distress (80%), refractory hypoxia (60%), hypotensive shock (20%).
Peng et al. (2020) ²⁴	Wuhan Children's Hospital - China	75 patients with a mean age of 6 years (1 month - 15 years change)	Retrospective documentary	To analyze the characteristics, treatment and evolution of CASES of COVID-19 in pediatrics.	Medical record	Fever (53.3%), dry cough (61.3%), mild pneumonia (67%), severe pneumonia (20%), asymptomatic (9.3%).
Romani et al. (2020) ²⁵	Bambino Gesù Children's Hospital - Italy	43 Children with an average age of Seven years old.	Case Series	Describe characteristics, clinical, demographic, radiological and laboratory of children with COVID-19	No description	Fever (63%), Cough (42%), Diarrhea/Vomiting (23%), Headache (16%), Dyspnea (12%), Nasal Congestion (12%), Arthralgia (9%), Myalgia (7%), Febrile Convulsion (5%), Sore Throat (5%), Anosmia (5%), Abdominal Pain (2%), Convulsion (2%).

Shen et al. (2020) ²⁶	Public Health Clinic Center of Changsha, Hunan, China.	9 children aged between 1 and 12 years.	Retrospective	Describe the clinical characteristics and outcomes of COVID-19 in children of ChangSha	Electronic medical records data collection form	Asymptomatic (22.2%); Fever (33.3%); Diarrhea (22.2%); Cough (11.1%); and Sore throat (11.1%)
Song et al. (2020) ²⁷	Xiangyang Central Hospital, Hubei - China.	16 children with a mean age of 8.5 years (1 month to 14 years)	Retrospective	Evaluate the clinical profile of pediatric COVID-19.	Electronic medical records	Asymptomatic (25%), Fever (31.25%) and Cough (37.5%).
Su et al. (2020) ²⁸	The Jinan Infectious Diseases Hospital, Shandong - China.	9 children (Age range 11 months - 9 years)	Retrospective	To analyze the different clinical characteristics among children and their families with severe SARS-CoV-2 infection.	Information records and epidemiological history	Asymptomatic (66.7%) Cough (11.1%); Low fever (22.2%).
Sun et al. (2020) ²⁹	Wuhan Children's Hospital - China	36 babies with a mean age of 6.43 months (2 - 12 months change)	Retrospective	Describe the characteristics of children under 1 year of age (excluding newborns) with COVID-19	Electronic medical records	Cough (77.78%), Fever (47.22%), Diarrhea (25%), Expectoration (22.22%), Nasal congestion (16.67%), Nausea/vomiting (11.11%), Aquipnea (5.56%), Constipation (2.78%), Bilateral pneumonia (61.11%), unilateral (36.11%).
Tan et al. (2020) ³⁰	First Affiliated Hospital of Hunan Normal University, Changsha - China	10 Children, average age of seven years	Case Report, Retrospective	Clinical and epidemiological features of COVID-19	Medical records	Fever (40%), Cough (30%), Abdominal pain (10%), Vomiting (10%), Constipation (10%), Convulsion (10%).
Valente et al. (2020) ³¹	Bambino Gesu Children's Hospital - Italy.	27 patients with a mean age of 84 months (8 days to 210 months).	Retrospective	To evaluate the ocular manifestations and prevalence of Sars-CoV-2 in tears of children with COVID-19.	Medical records	Asymptomatic (14.9%), Respiratory symptoms (cough or dyspnea with or without fever) (56%); Gastrointestinal symptoms (vomiting and/or diarrhea with or without fever): (30%); Ocular manifestations consistent with viral conjunctivitis: (15%).
Wei et al. (2020) ³²	Wuhan Children's Hospital - China	20 pediatric patients with a mean age of 2 years (1 day - 14 years and 7 months)	Retrospective documentary	Discuss the differences in computed tomography of the chest, clinical and laboratory aspects of pediatric and adult patients with COVID-19.	Clinical records	Fever (60%), cough (65%), diarrhea (15%), nasal secretion (15%), sore throat (5%), vomiting (10%), aquipnea (10%) and fatigue (5%).
Wu et al. (2020) ³³	Wuhan Children's Hospital, China.	148 pediatric patients (18-123 months)	Retrospective in Medical Records	Describe the clinical characteristics of hospitalized children, with COVID-19	Medical records	Asymptomatic (30.4%), fever (40.5%), dry cough (44.6%), vomiting or diarrhea (21.6%), headache (3.4%).
Wu et al. (2020) ³⁴	Qingdao Women's and Children's Hospital	74 children (< 3 months up to >10 years)	Retrospective	Determine the spectrum of the disease in children	Standardized data collection forms	Cough (32.4%), Fever (27.0%); asymptomatic (40.5%); respiratory symptoms (21.6%).

	Princess Margaret Hospital in Hong Kong and Wuhan Children's Hospital - China.	244 paediatric patients with a mean age of Eighty-two months.	Retrospective Comparison	Compare the clinical and laboratory characteristics of severe acute respiratory syndrome of 2003 (SARS) And COVID-19 in 2 Chinese pediatric cohorts.	Electronic medical records	Asymptomatic (21%), Fever (51.3%); Cough (62.2%), Secretion (13%), Runny Nose (12.4%), Nausea (11.9%), Diarrhea (7.8%), Malaise (6.5%); Sore throat (5.2%), Headache (5.2%), Myalgia (4.7%), Poor Nutrition (4.1%), Pain (2.1%), Dizziness (1.6%), Chills (1%).
Xiong et al. (2020) ³⁵	4 Hospitals in Western China	34 children (Age range: 1- 144 months)	Retrospective and Observational	Describe clinic and epidemiology of children with COVID-19	Charts	Fever (76%); cough: (62%); expectoration: (21%); vomiting: (12%); diarrhea: (12%); and aquipnea: (9%).
Zhang et. al. (2020) ³⁶	10 hospitals across Hubei province, China.	25 patients (Age range: 1 month - 14 years)	Case Series - Retrospective	Describe the clinical characteristics of children hospitalized with COVID19.	Hospital records	Fever (52%); nasal congestion (8%); cough (44%); dyspnea (8%); abdominal pain (8%); vomiting (8%); and diarrhea (12%).
Zheng et. al. (2020) ³⁷	11 Hospitals - South China	52 Children with a mean age of 9 years (0-18 years, excluding newborns),	Retrospective	Compare previous data in Wuhan with current data on COVID-19 in children	Medical records	Fever (40.4%), Cough (48.1%), Fatigue (9.6%), Sore throat (9.6%), gastrointestinal (1.9%), Moderate Pneumonia (17.3%), Upper Airway Infection (57.7%); Asymptomatic (23.1%).
Zheng et. al. (2020) ³⁸	Shenzhen Third People's Hospital - China	9 children with an average age of 1 year (Range 7 months - 3 years)	Retrospective documentary	To study the clinical characteristics and chest CT findings of COVID-19 in infants and children.	No description	Asymptomatic (55.5%), Fever (44.4%), Cough (22.2%), Coriza (11.1%).
Zhong et al. (2020) ³⁹	3 hospitals, Jiangsu, CHINA	10 Children (0-18 years)	Case Report	Describe clinical features in children with OVID-19.	Medical records	Fever (40%), Cough (30%), Headache (20%).

pediatric deaths were in adolescents older than 14 years and that the association with some type of comorbidity was also present in 60% of deaths. It is importante to point out that the research carried out by Hillesheim et al. [53], in a Brazilian cohort, observed that the second group most lethally affected by the disease is adolescents over 15 years, second only to the group of neonates, corroborating the results of the study described in the result of this review [23]. Also, as an important finding regarding the age range, Dong et al. [46], demonstrated that 10.6% of severe cases are in the age group of less than one year of age.

In a study by researchers at Harvard University in the USA, children were found to carry a much higher Sars-CoV-2 viral load than previously thought, especially in the first two days of infection, demonstrating a significantly higher level of the virus in airways than adults with COVID-19 hospitalized in ICUs [54].

Dong et al [46], when analyzing 728 children who tested positive for the novel coronavirus, found that when correlating the severity of the disease with the age group, children under one year of age developed more severe and critical conditions. In another study that analyzed the profile of deaths and hospital lethality in children infected with SARS-CoV-2, of the 661 deaths, 198 were in children under one year old, representing 28.9% of

deaths and a lethality of 14.2% leading in relation to other ages [53].

The children's immune systems have distinctions that may explain the different clinical manifestations of COVID-19. The innate response in children is stronger, due to a greater number of natural killer cells (NK cells), which are a type of lymphocytes with an important role in fighting viral infections, being the first line of defense against SARS-CoV-2 [55]. One another study examined serum and cell samples obtained from pediatric patients and adults with COVID-19, where it was observed that children express higher levels of interleukin 17A (IL-17A), that helps increase the immune system response during viral infection, and gamma interferon (INF-γ) that fights viral replication, unraveling why children have less repercussions when infected by SARS-CoV-2 [56].

Regarding the most prevalent symptoms, there is a recurrent presence of fever associated with the clinical manifestations of hospitalized children, being found in all articles included in this research. Similar to this result, a review of the case series of children and adolescents reveals that fever was among the most prevalent symptoms among patients who were hospitalized [57]. Raba et al. [58], in its systematic review of the clinical

Table 4: Prevalence of symptoms in studies.

Symptoms	Percentage and Quantitative articles
General	
Fever	100% (32)
Sore throat	25% (8)
Fatigue	25% (8)
Headache	21,9% (7)
Myalgia	12,5% (4)
Seizure	9,37% (3)
Anosmia	6,25% (2)
Dizziness	6,25% (2)
Respiratory	
Cough	90,6% (29)
Dyspnea/ Difficulty breathing	28,1% (9)
Runny	25% (8)
Nasal Congestion	15,6% (5)
Pneumonia	15,6%(5)
Sputum/ Secretion	12,5% (4)
Aquipnea	12,5% (4)
Gastrointestinal	
Diarrhea	43,8% (14)
Vomit	31,25% (10)
Abdominal Pain	15,6% (5)
Gastrointestinal Symptoms	15,6% (5)
Diarrhea or Vomiting	9,37% (3)
Nausea	9,37% (3)
Constipation	6,25% (2)
Feeding difficulties	6,25% (2)

manifestations of COVID-19, also found fever as the main marker symptom of SARS-CoV-2 infection in children and adolescents.

As the pandemic progressed, more cases and evidence emerged of manifestations beyond the respiratory kind; among the most prevalent are gastrointestinal. With an important density in pediatrics, as well as in the studies included in this review, the literature shows that symptoms such as vomiting, diarrhea, constipation, pain and abdominal discomfort are present in hospitalized children and adolescents [62,63]. This fact is due to the angiotensin-converting enzyme (ACE2) being abundantly expressed in glandular cells of the gastric, duodenal, intestinal and rectal epitheliums [64].

A less representative number of pediatric cases with neurological repercussions was observed in this review, corresponding to only 9.3% of those included. This finding corroborates the study by Prata-Barbosa et al. [65], who observed only four cases of children with neural symptoms in a total sample of 79 patients. The potential neurological invasion of SARS-CoV-2 is best perceived in adults, in whom the presence of anosmia and ageusia are likely markers of involvement of the nervous system [67].

According to Carvalho et al. [67], only 6% of the children included in their research presented myalgia, with the age group above fourteen years of age most affected. Such finding is in accordance with that found in this review, where only three articles (9.3%), mentioned myalgia as a symptom associated with pediatric COVID-19, with variation of symptom perception from 4.7% to 7.1% in the sample of these studies. Already in Regarding joint pain (arthralgia), only one study mentions the symptom, consistent with the result of Carvalho et al. [67], with only one case reported. The discussion on the transmissibility of asymptomatic pediatric patients has been perpetuating in recent months and some studies have had similar results when children are tested and infection with the new coronavirus is observed, but without the presence of symptoms. Even when positive and symptomatic family clusters occur as the case described by Silva et al. [68], the pediatric age group proved to be a symptomatic in a sample of seven patients, where two children did not progress with symptomatology and five adults presented the infection and classic symptomatology of COVID-19.

The identification of the total number of asymptomatic patients in the general population is importance for the interpretation of the degree of transmissibility of the disease and its progression, in addition to serving to better outline prevention and control strategies for COVID-19 [69]. In pediatrics this becomes an even greater necessity due to the high number of children who present without symptoms or subclinically, but still with transmission potential that can only be detected from IgG tests (immunoglobulin G) [69].

CONCLUSION

With this review it was analyzed that the symptoms of COVID-19 in children, even when hospitalized, is from mild to moderate in its great majority. The most frequent symptoms found were fever, respiratory and gastrointestinal. Neurological, liver and kidney symptoms were less prevalent. A small amount of studies described patients who needed intensive care, which highlights the favorable prognosis of the disease in the pediatric population.

REFERENCES

1. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *The Lancet Infectious diseases*. 2020; 20: 689-696.
2. Naicker S, Yang CW, Hwang S, Liu B, Chen J, Jha V. The Novel Coronavirus 2019 epidemia e rins. *Kidney international*, mai. 2020; 97: 824-828.
3. Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. As crianças são menos suscetíveis ao COVID-19? *J Microbiol Immunol Infect*. 2020; 53: 371-372.
4. Ramos RT, Silva DCC, Araújo GCB, Riedi CA, Ibiapina CC, Bezerra PGM, et al. Aspectos respiratórios da COVID-19 na infância: o que o pediatra precisa saber?. *Resid Pediatr*. 2020; 10: 1-15.
5. Dias VM, Carneiro M, Vidal CF, Corradi MF, Brandão D, Cunha CA, et al. Orientações sobre Diagnóstico, Tratamento e Isolamento de Pacientes com COVID-19. *J Infection Control*. 2020; 9: 1-20.
6. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus. 2020.

7. Moher D, Liberati A, Tetzlaff J, Altman DG. Principais itens para relatar Revisões sistemáticas e Meta-análises: A recomendação PRISMA*. *Epidemiol Serv Saúde*. 2015; 24.
8. Brasil. Diretrizes metodológicas: elaboração de revisão sistemática e metanálise de estudos observacionais comparativos sobre fatores de risco e prognóstico. Brasília: Ministério da Saúde. 2014.
9. Bai K, Liu W, Liu C, Fu Y, Hu J, Qin Y, et al. Clinical analysis of 25 COVID-19 infections in children. *Pediatr Infect Dis J*. 2020; 39: E100-103.
10. Cai X, Ma Y, Li S, Chen Y, Rong Z, Li W. Clinical Characteristics of 5 COVID-19 Cases With Non-respiratory Symptoms as the First Manifestation in Children. *Front Pediatr*. 2020; 8: 1-9.
11. Chen J, Zhang ZZ, Chen YK, Long QX, Tian WG, Deng HJ, et al. The clinical and immunological features of pediatric COVID-19 patients in China. *Genes Dis [Internet]*. 2020; 7: 535-541.
12. Chen Z, Tong L, Zhou Y, Hua C, Wang W, Fu J, et al. Childhood COVID-19: a multicentre retrospective study. *Clin Microbiol Infect*. 2020; 26: 1260.e1-1260.e4.
13. Du H, Dong X, Zhang J jin, Cao Y yuan, Akdis M, Huang P qi, et al. Clinical characteristics of 182 pediatric COVID-19 patients with different severities and allergic status. *Allergy Eur J Allergy Clin Immunol*. 2020; 1-23.
14. Du W, Yu J, Wang H, Zhang X, Zhang S, Li Q, et al. Clinical characteristics of COVID-19 in children compared with adults in Shandong Province, China. *Infection*. 2020; 48: 445-452.
15. Du W, Yu J, Liu X, Chen H, Lin L, Li Q. Persistence of SARS-CoV-2 virus RNA in feces: A case series of children. *J Infect Public Health*. 2020; 13: 926-931.
16. Gaborieau L, Delestrain C, Bensaid P, Vizeneux A, Blanc P, Garraffo A, et al. Epidemiology and Clinical Presentation of Children Hospitalized with SARS-CoV-2 Infection in Suburbs of Paris. *J Clin Med*. 2020; 9: 2227.
17. García-Salido A, Leoz-Gordillo I, Martínez De Azagra-Garde A, Nieto-Moro M, Iglesias-Bouzas MI, García-Teresa MÁ, et al. Children in Critical Care Due to Severe Acute Respiratory Syndrome Coronavirus 2 Infection: Experience in a Spanish Hospital. *Pediatr Crit Care Med*. 2020; 21: E576-580.
18. Korkmaz MF, Türe E, Dorum BA, Kiliç ZB. The epidemiological and clinical characteristics of 81 children with COVID-19 in a pandemic hospital in Turkey: An observational cohort study. *J Korean Med Sci*. 2020; 35: 1-11.
19. Li Y, Wang H, Wang F, Du H, Liu X, Chen P, et al. Comparison of hospitalized patients with pneumonia caused by COVID-19 and influenza A in children under 5 years. *Int J Infect Dis*. 2020; 98: 80-83.
20. Lu Y, Wen H, Rong D, Zhou Z, Liu H. Clinical characteristics and radiological features of children infected with the 2019 novel coronavirus. *Clin Radiol*. 2020; 75: 520-525.
21. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, et al. Symptomatic Infection is Associated with Prolonged Duration of Viral Shedding in Mild Coronavirus Disease 2019: A Retrospective Study of 110 Children in Wuhan. *Pediatr Infect Dis J*. 2020; 39: E95-99.
22. Mithal LB, Machut KZ, Muller WJ, Kociolek LK. SARS-CoV-2 Infection in Infants Less than 90 Days Old. *J Pediatr*. 2020; 224: 150-152.
23. Oualha M, Bendavid M, Berteloot L, Corsia A, Lesage F, Vedrenne M, et al. Severe and fatal forms of COVID-19 in children. *Arch Pediatr*. 2020; 27: 235-238.
24. Peng H, Gao P, Xu Q, Liu M, Peng J, Wang Y, et al. Coronavirus disease 2019 in children: Characteristics, antimicrobial treatment, and outcomes. *J Clin Virol*. 2020; 128: 104425.
25. Romani L, Chiurchiù S, Santilli V, Bernardi S, Haywood Lombardi M, Scarselli A, et al. COVID-19 in Italian paediatric patients: The experience of a tertiary children's hospital. *Acta Paediatr Int J Paediatr*. 2020; 109: 2311-2312.
26. Shen Q, Guo W, Guo T, Li J, He W, Ni S, et al. Novel coronavirus infection in children outside of Wuhan, China. *Pediatr Pulmonol*. 2020; 55: 1424-1429.
27. Song W, Li J, Zou N, Guan W, Pan J, Xu W. Clinical features of pediatric patients with coronavirus disease (COVID-19). *J Clin Virol*. 2020; 127: 1-8.
28. Su L, Ma X, Yu H, Zhang Z, Bian P, Han Y, et al. The different clinical characteristics of corona virus disease cases between children and their families in China - the character of children with COVID-19. *Emerg Microbes Infect*. 2020; 9: 707-713.
29. Sun D, Chen X, Li H, Lu XX, Xiao H, Zhang FR, et al. Infecção por SARS-CoV-2 em bebês menores de 1 ano de idade na cidade de Wuhan, China. *World J Pediatr*. 2020; 16: 260-266.
30. Tan YP, Tan BY, Pan J, Wu J, Zeng SZ, Wei HY. Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China. *J Clin Virol*. 2020; 127: 104353.
31. Valente P, Iarossi G, Federici M, Petroni S, Palma P, Cotugno N, et al. Ocular manifestations and viral shedding in tears of pediatric patients with coronavirus disease 2019: a preliminary report. *J Am Association for Pediatr*. 2020; 24: 212-215.
32. Wei X, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: Different points from adults. *Pediatr Pulmonol*. 2020; 55: 1169-1174.
33. Wu H, Zhu H, Yuan C, Yao C, Luo W, Shen X, et al. Características clínicas e imunológicas de pacientes pediátricos hospitalizados com doença por coronavírus 2019 (COVID-19) em Wuhan, China. *JAMA Netw Open*. 2020; 3: 1-10.
34. Wu Q, Xing Y, Shi L, Li W, Gao Y, Pan S, et al. Coinfection and other clinical characteristics of COVID-19 in children. *Pediatrics*. 2020; 146: 1-11.
35. Xiong X, Chua GT, Chi S, Kwan MYW, Sang Wong WH, Zhou A, et al. A Comparison Between Chinese Children Infected with Coronavirus Disease-2019 and with Severe Acute Respiratory Syndrome 2003. *J Pediatr*. 2020; 224: 30-36.
36. Zhang C, Gu J, Chen Q, Deng N, Li J, Huang L, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. *PLoS Med*. 2020; 17: 1-15.
37. Zheng F, Liao C, Fan QH, Chen HB, Zhao XG, Xie ZG. Clinical Characteristics of Children with Coronavirus Disease 2019 in Hubei, China. *Curr Med Sci*. 2020; 40: 275-280.
38. Zheng G, Wang B, Zhang H, Xie C, Zhang Y, Wen Z, et al. Clinical characteristics of acute respiratory syndrome with SARS-CoV-2 infection in children in South China. *Pediatr Pulmonol*. 2020; 55: 2419-2426.
39. Zhong Z, Xie X, Huang W, Zhao W, Yu Q, Liu J. Chest CT findings and clinical features of corona virus disease 2019 in children. *J Cent South Univ (Medical Sci)*. 2020; 45: 236-242.
40. Zhu L, Wang J, Huang R, Liu L, Zhao H, Wu C, et al. Clinical characteristics of a case series of children with coronavirus disease 2019. *Pediatr Pulmonol*. 2020; 55: 1430-1432.
41. Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization Rates and Characteristics of Children Aged < 18 Years Hospitalized with Laboratory-Confirmed COVID-19. *Morb*

- Mortal Wkly Rep. 2020; 69: 1081-1088.
42. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. *MMWR Morb Mortal Wkly Rep.* 2020; 69: 759-765.
43. Hoang A, Chorath K, Moreira A, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: A systematic review. *E ClinicalMedicine.* 2020; 24: 100433.
44. Tezer H, Bedir Demirdağ T. Novel coronavirus disease (Covid-19) in children. *Turkish J Med Sci.* 2020; 50: 592–603.
45. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 Infection among Children and Adolescents Compared with Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr.* 2020.
46. Dong Y, Dong Y, Mo X, Hu Y, Qi X, Jiang F, et al. Epidemiology of COVID-19 among children in China. *Pediatrics.* 2020; 145.
47. Safadi MAP. The intriguing features of COVID-19 in children and its impact on the pandemic. *J Pediatr (Versão em Port.)* 2020; 96: 265-268.
48. Swann O V., Holden KA, Turtle L, Pollock L, Fairfield CJ, Drake TM, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: Prospective multicentre observational cohort study. *BMJ.* 2020; 370.
49. Ciuca IM. COVID-19 in children: An ample review. *Risk Manag Healthc Policy.* 2020; 13: 661-669.
50. Pei Y, Liu W, Bilal Masokano I, Li F, Xie S, Zhou G, et al. COVID-19: Children Comparison with Adults Based on the Latest Data. *SSRN Electron J.* 2020.
51. Leung C. Clinical characteristics of COVID-19 in children: Are they similar to those of SARS?. *Pediatr Pulmonol.* 2020; 55: 1592-1597.
52. Su L, Ma X, Yu H, Zhang Z, Bian P, Han Y, et al. The different clinical characteristics of corona virus disease cases between children and their families in China—the character of children with COVID-19. *Emerg Microbes Infect.* 2020; 9: 707-713.
53. Hillesheim D, Tomasi YT, Figueiró TH, Paiva KM de. Síndrome respiratória aguda grave por COVID-19 em crianças e adolescentes no Brasil: perfil dos óbitos e letalidade hospitalar até a 38ª Semana Epidemiológica de 2020. *Epidemiol e Serv saude Rev do Sist Unico Saude do Bras.* 2020; 29: e2020644.
54. Yonker LM, Neilan AM, Bartsch Y, Alter G, Fasano A, et al. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses. *The J Pediatr.* 2020; 227: 45-52.
55. Simon AK, Hollander GA, Michael A. Evolution of the immune system in humans from infancy to old age. *Proc Biol Sci.* 2015.
56. Pierce CA, Hurlburt PP, Dai Y, Aschner B, Cheshenko N, Galen B, et al. Respostas imunológicas à infecção por SARS-CoV-2 em pacientes pediátricos e adultos hospitalizados. *Sci Transl Med.* 2020.
57. Streng A, Hartmann K, Armann J, Berner R, Liese JG. COVID-19 in hospitalized children and adolescents: A systematic review on published case series (as of 31.03.2020) and first data from Germany. *Monatsschr Kinderheilkd.* 2020; 168: 615-627.
58. Raba AA, Abobaker A, Elgenaidi IS, Daoud A. Novel coronavirus infection (COVID-19) in children younger than one year: A systematic review of symptoms, management and outcomes. *Acta Paediatr Int J Paediatr.* 2020; 109: 1948-1955.
59. Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, et al. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. *World J Pediatr.* 2020; 16: 240-246.
60. Götzinger F, Santiago-García B, Noguera-Julián A, Lanaspá M, Lancelli L, Calò Carducci FI, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Heal.* 2020; 4: 653-661.
61. Palabiyik F, Kokurcan SO, Hatipoglu N, Cebeci SO, Inci E. Imaging of COVID-19 pneumonia in children. *Br J Radiol.* 2020; 93: 20200647.
62. Miller J, Cantor A, Zachariah P, Ahn D, Martinez M, Margolis KG. Gastrointestinal Symptoms as a Major Presentation Component of a Novel Multisystem Inflammatory Syndrome in Children That Is Related to Coronavirus Disease 2019: A Single Center Experience of 44 Cases. *Gastroenterology.* 2020; 159: 1571-1574.e2.
63. Chen TH, Kao WT, Tseng YH. Gastrointestinal involvements in children with COVID-related multisystem inflammatory syndrome. *Gastroenterology.* 2020.
64. Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. *Int J Antimicrob Agents.* 2020; 56: 106024.
65. Prata-Barbosa A, Lima-Setta F, Santos GR dos, Lanziotti VS, Castro REV de, Souza DC de, et al. Pediatric patients with COVID-19 admitted to intensive care units in Brazil: a prospective multicenter study. *J Pediatr (Versão em Port.)* 2020; 96: 582-592.
66. Nunes MJM, Carlos J, Silva S, Oliveira C De, Victor G, et al. Alterações Neurológicas na Covid-19 : uma Revisão Sistemática. *Rev Neurocienc.* 2020; 28: 1-22.
67. Carvalho CP, Castro C, Graça IS, Lorenzo C, Rodrigues AB, Inácio R, et al. Case series of 103 children with SARS-CoV-2 infection in Portugal. *Acta Med Port.* 2020; 33: 795-802.
68. Silva JH da, Oliveira EC de, Hattori TY, Lemos ERS de, Terças-Trettel ACP. Descrição de um cluster da COVID-19: o isolamento e a testagem em assintomáticos como estratégias de prevenção da disseminação local em Mato Grosso, 2020. *Epidemiol e Serv saude Rev do Sist Unico Saude do Bras.* 2020; 29: e2020264.
69. Dias VM de CH, Cunha CA da, Vidal CF de L, Corradi MFD Ben, Michelin L, Muglia V, et al. Orientações sobre Diagnóstico, Tratamento e Isolamento de Pacientes com COVID-19. *J Infect Control [Internet].* 2020; 9: 56-75.

Cite this article

Pamplona EA, da Silva Ferreira BNM, Renan Alex Fernandes de Oliveira RF, da Cunha Dias ML, Gois Ferreira RK, et al. Clinical Manifestations of Pediatric Patients Hospitalized With COVID-19: A Systematic Review. *Ann Pediatr Child Health* 2021; 9(3): 1231.