

# COVID-19 in children; A systematic review

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## Abstract

**Background:** COVID-19 is a type of Coronavirus that has been discovered for the first time in Wuhan, China. The virus resulted in an outbreak and spread rapidly between individuals. Symptoms of COVID-19 among adults are similar to those of common cold and suspected cases undergo testing for confirmation. However, children may not fulfill the criteria of testing and they still have role in the transmission of infection. It is necessary to identify the symptoms of COVID-19 among infected children.

**Aim:** To assess the clinical symptoms of COVID-19 among children based on previous original articles conducted on the subject.

**Methods:** PubMed and Google scholar databases were used for searching process to obtain articles concerned with our subject. Keywords were used for the searching process, including "COVID-19, Presentation, Clinical manifestation, Symptoms, Signs, Clinical features, Paediatrics, Children." The inclusion criteria were original articles focused on COVID-19 symptoms reported among children.

**Results:** A total of 4601 articles were obtained, only six articles were eligible for the inclusion criteria. The total number of COVID-19 children included in the studies was 911. Only one study was from Saudi Arabia and the remaining studies were from China. COVID-19 symptoms reported among children included fever, respiratory and gastrointestinal symptoms as well as other various symptoms.

**Conclusion:** Children are susceptible to COVID-19 infection; fever is the major symptoms of COVID-19 infection among children, followed by respiratory symptoms, especially cough. Clinical presentation of children is generally more favorable and this may lead to better prognosis.

**Keywords:** COVID-19, Children, Pediatric, Clinical manifestations, Symptoms, Presentation.

## Introduction:

In late December 2019, an outbreak of unknown cause was declared by the Chinese authorities; the outbreak was pneumonia emerged in Wuhan, China. The isolation of a new type of Coronavirus (severe acute respiratory syndrome coronavirus 2[SARS-CoV-2]) was done on 7<sup>th</sup> January 2020. This virus was later named coronavirus disease 2019 (COVID-19) [1]. Elderly patients affected with COVID-19 are at increased risk to develop complications, severe acute respiratory syndrome and progression to death [2].

In the early stage of the pandemic, the majority of affected cases were those with middle-aged and older individuals, but with the ongoing pandemic situation, the pediatric population showed an increased trend in many countries in the world [3]. In 6<sup>th</sup> April 2020, it was estimated that there were 176190 children infected with COVID-19 [4].

The children may play a major role in the spread of COVID-19 in the communities [1]. The World Health Organization (WHO) recommended testing all suspected cases; however, pediatrics infected with COVID-19 may cannot underwent this testing as they may not meet all the criteria required in the suspected case definition [5]. Therefore, the identification of COVID-19 symptoms among the pediatric population is necessary. So, this systematic review was performed to identify the symptoms of COVID-19 among the pediatric population based on the previous studies reported this subject.

## Method & Search strategy:

The method of this systematic review follows the PRISMA checklist guidance for systematic review and meta-analysis [6]. Two electronic databases were explored to search for articles concerned with our subjects; these databases were PubMed and Google scholar databases.

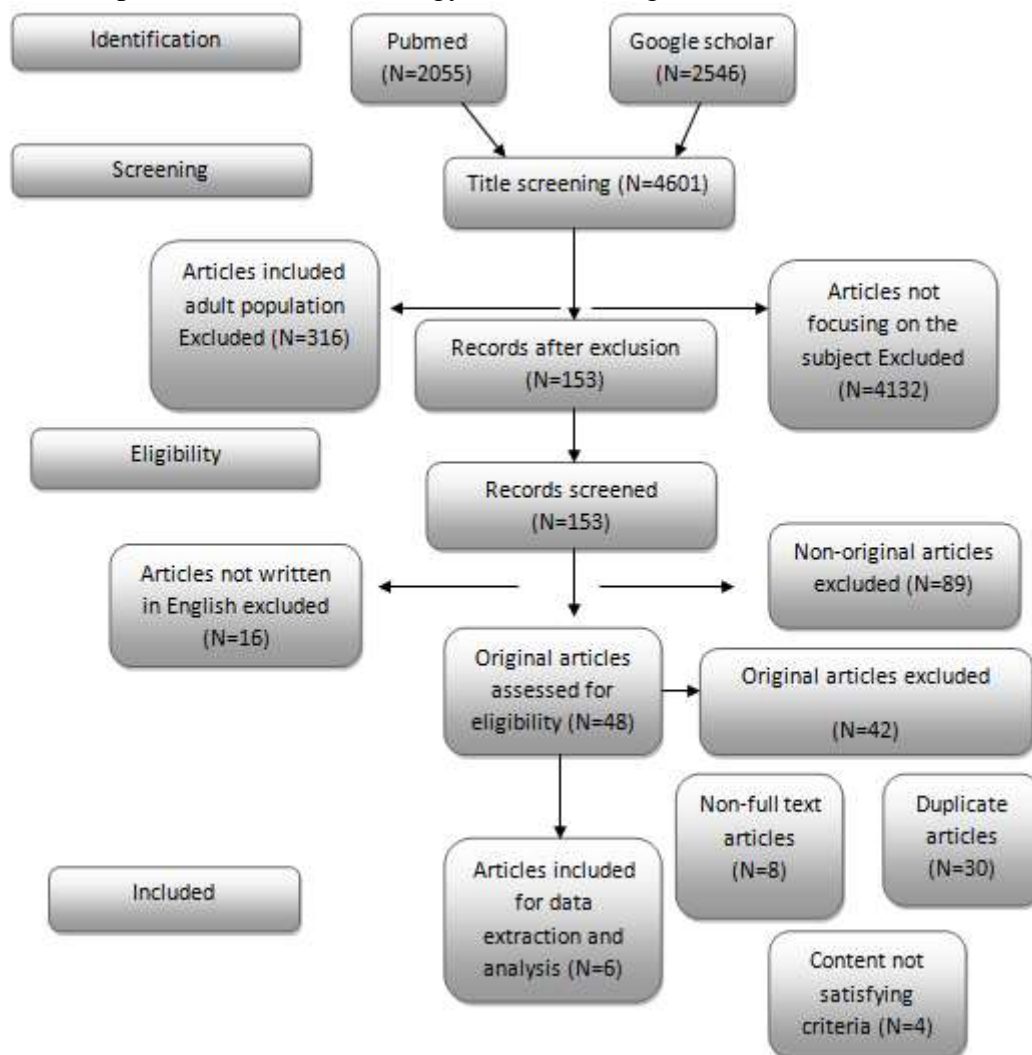
Various terms and keywords were used in the searching process, including "COVID-19, Presentation, Clinical manifestation, Symptoms, Signs, Clinical features, Paediatrics,

Children;" these words were used in various combinations to obtain all possible articles conducted on this subject.

### Eligibility criteria:

All the titles resulted from this primary exploration were revised to exclude articles not focusing on our subject or conducted on adults or conducted on both adult and pediatric population. The abstracts of the remaining articles were scanned to include articles written in English language and original articles, and to exclude articles written in non-English language and non-original articles such as review articles, systematic reviews, case reports, and letters to the editor. Therefore, the remaining articles were original studies focusing on our subject, conducted on children and written in English language.

The second stage involved reviewing abstracts precisely of the included articles, then all duplicate articles, articles not available for full-text, and articles with unsatisfying criteria such as incomplete, or overlapped data and articles included less than five patients were excluded. The full description of the search strategy is shown in figure 1.



**Fig1: Planning of Eligible criteria**

### Data review and analysis:

After reviewing the abstracts of the included studies, the full-text articles were reviewed and data of interest were extracted in an excel sheet. The data of interest included, author and publication year, study design, sample size and participants' characteristics, country of study, results and main findings. The extracted data were then revised and then transferred in to one table to summarize the collected data.

### Results:

The current systematic review included six articles that met the determined criteria [7-12] (table1). Only one study was published in 2021[7], whereas the remaining five studies were published in 2020[8-12]. There were three studies were retrospective[7, 9, 10], two studies were observational[8, 11], and one study was cross-sectional. The total number of children 1409

included in the studies was 911 children infected with COVID-19, with an age range of 1 month to 16 years old, whereas one study didn't state the age range of children and stated the median age (6.25 years). Male patients were dominant in four studies[7, 8,9, 11, 12], whereas females were more dominant in only one study[10]. Five studies were from China[8-12], whereas only one study was from Saudi Arabia[7].

There were three studies reported the rate of symptomatic patients [9, 10, 11]; with a rate of 60.81%, 65%, and 28%, respectively, being symptomatic patients. The remaining studies reported symptoms among all patients[7,8, 12]. The most common symptoms reported was fever that was reported in all studies with a range of 27.03% [9] to 75%[8], followed by respiratory symptoms [21%], with cough being the major respiratory symptom with a range of 19%[11] to 75%[8]. One study reported polypnea as the major symptom [8]. Other respiratory symptoms included chest congestion (5.41%)[9], and dyspnea (2.7%)[9], (3%)[11], (8%)[12]. Gastrointestinal symptoms also were reported in all studies; one study reported that they were prevalent among 10.3%[7], other studies reported more details on the gastrointestinal symptoms[8-12].

Gastrointestinal symptoms included nausea/vomiting as the major reported gastrointestinal symptoms followed by diarrhea. There were other gastrointestinal symptoms and it were less common, including constipation (12.5%)[8], anorexia (4.05%)[9], and abdominal pain (8%)[12]. Headache was reported in four studies[8, 9, 11, 12], with a rate of 2.7%[9] to 12.5%[8], whereas fatigue/myalgia was reported in two studies; 12.5%, and 6.7%, respectively [8, 9].

The radiological findings were reported in only two studies[8, 12]; one study reported that all patients showed remarkable abnormalities[8], whereas the other study reported that abnormalities were found among 68%, with a major bilateral involvement (48%)[12]. The lab investigations were reported in four studies[8-11]; abnormalities included, increased C-reactive protein[8, 9, 10], procalcitonin[8, 11], lactate dehydrogenase[8, 10], abnormal liver function[8, 10], increased IL-6[8], abnormal white blood cells (WBCs) [9, 10, 11], abnormal PCT[9], abnormal ESR[9, 10], increased lymphocytes (96%) [10], decreased lymphocytes (31%)[11], and abnormal platelets[10].

| Author and Publication year | Study design  | Sample size and characteristics of participants  | Country      | Results and main findings   |
|-----------------------------|---------------|--|--------------|---|
| Alharbi et al 2021 [7]      | Retrospective | -742 COVID-19 patients<br>-Males=53.6%, females=46.4%<br>-Median age=75 m (6.25 y)                       | Saudi Arabia | *The most common symptoms at onset included; Fever (32.5%), respiratory symptoms (21%), gastrointestinal symptoms (10.3%)<br>*7(0.94%) were admitted to PICUS with COVID-19 related symptoms<br>*Children infected with SARS-CoV-2 are less likely to develop symptomatic or serious diseases.<br>*Among symptomatic children, the most common clinical features were fever and respiratory symptoms followed by gastrointestinal manifestations.   |
| Sun et al 2020 [8]          | Observational | -8 severe of critically pediatric children with COVID-19<br>-Males=75%, females=25%<br>-Age range=6m-15y | China        | *The most common symptoms included: Polypnea (100%), fever (75%), cough (75%), expectoration (50%), nausea/vomiting (50%), diarrhea (37.5%), headache (12.5%), constipation (12.5%), fatigue/myalgia (12.5%).<br>*All patients showed remarkable abnormalities in chest through CT or X-ray.<br>*Lab tests revealed increased C-reactive protein, procalcitonin and lactate dehydrogenase (75%), normal or increased whole blood count (87.5%), abnormal liver function (50%), increased IL-6 (25%) |
| Wu et al 2020 [9]           | Retrospective | -74 children with COVID-19<br>-Males=59.4%, females=40.54%<br>-Age≤3m->10 years                          | China        | *The most common symptoms at the onset occurred among (60.81%) and included: Cough (32.43%), fever (27.03%), fatigue (6.76%), chest congestion (5.41%), anorexia (4.05%), diarrhea (4.05%), dyspnea (2.7%), headache (2.7%) and expectoration (2.7%).<br>*Lab tests revealed abnormal WBCs among 31.08%, and it increased among 25.68% and reduced among  |

|                             |                      |  |       |  |
|-----------------------------|----------------------|--|-------|--|
| <b>Tang et al 2020 [10]</b> | Retrospective        | -26 children with COVID-19<br>-Males=35%, females=65%<br>-Age=1-13 years | China | <p>5.41%; abnormal CRP among 17.57%, abnormal PCT among 2.7%, abnormal ESR among 35.71%</p> <p>*There were 35% didn't experience symptoms, whereas 65% experienced symptoms including; Fever (42%), cough (46%), rhinorrhea (8%), vomiting (8%), diarrhea (8%), more than one symptoms (38%), discharged (65%)</p> <p>*Lab tests revealed increase in WBCs among 15% and reduction among 50%, increase in lymphocytes among 96%, abnormal PLTs among 31%, increase AST and ALT among 12%, increased lactate dehydrogenase among 46%, increased ESR among 27% increased CRP among 19%.</p> <p>* COVID-19 children showed asymptomatic or mainly respiratory symptoms such as fever and dry cough, some of them have digestive tract symptoms, and their clinical symptoms are mild; the clinical types were mild and common.</p> <p>*The clinical characteristics of COVID-19 infection in children were different from adult as the overall condition among children was mild with good prognosis.</p> |
| <b>Qiu et al 2020 [11]</b>  | Observational cohort | - 36children with COVID-19<br>-Males=64%, females=36%<br>-Age=0-16 years | China | <p>*There were 19(53%) moderate cases and 17 (47.2%) mild cases who were either symptomatic 10(28%), or had acute upper respiratory symptoms 7(19%)</p> <p>*The most common symptoms on admission included: Fever (36%), dry cough (19%), headache (8%), sore throat (6%), vomiting/diarrhea (6%), dyspnea (3%).</p> <p>*Abnormal lab findings included: elevated creatinine kinase (25%), decreased lymphocytes (31%), leucopenia (19%), and elevated procalcitonin (17%)</p>   |

|                              |                 |   |       |  |
|------------------------------|-----------------|---|-------|--|
|                              |                 |   |       | *Decreased lymphocytes, elevated body temperature, and high levels of procalcitonin, d-dimer and creatinine kinase were associated significantly with severity of COVID-19   |
| <b>Zheng et al 2020 [12]</b> | Cross-sectional | -25 children with COVID-19<br>-Males=56%, females=44%<br>-Age=1m-≥6 y | China | *The most common symptoms at onset included: Fever (52%), cough (44%), diarrhea (12%), nasal congestion (8%), dyspnea (8%), abdominal pain (8%), vomiting (8%).<br>*The median values of lab tests were reported with no more information<br>*CT findings showed abnormality among 68% and of those 20% had unilateral involvement and 48% had bilateral involvement<br>*Children were susceptible to COVID-19 like adults, while the clinical presentations were more favorable; however, children less than 3 years old accounted for majority cases and critical cases lied in this age group, which demanded extra attentions during home caring and hospitalization treatment |

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PICU: Primary intensive care unit; ALT: Alanine amino transferase, AST: Aspartate amino transferase; PLT: Platelets; CRP:C-reactive protein, ESR; Estimated sedimentation rate; IL: Interleukin.

**Discussion:**

The lack of criteria to confirmation tests among children [5] prevents suspected children for COVID-19 to underwent testing; hence, children may play a role in the spread of COVID-19 between individuals in the community [1]. As a result, it is necessary to identify COVID-19 symptoms among children, especially it was stated that children infected with COVID-19 tended to experience a milder clinical course compared to adults and reports of death are rare [13,14].

This systematic analysis was conducted to identify COVID-19 symptoms among children based on original articles as previous systematic analysis was based on cases reports and case series [15], mixed studies including reviews and original articles [16] or even systematic analysis involved review articles only [17].

In our analysis we found only six studies met the inclusion criteria; only one study was from Saudi Arabia [7], and the remaining five studies were from China [8-12]. This was similar to a previous systematic review, where a total of 18 studies were included; also, 17 out of 18 studies were from China [18]. This reflects that China is more concerned with the pandemic compared to other countries; however, more reports from other countries should be presented.

Our analysis involved a total of 911 children and this total number was higher compared to previous systematic reviews reported; one included 160 infants [18], and another reported 114 children [19]. It was reported that children of all ages are susceptible to COVID-19 infection, with no significant difference regarding gender [19]. However, in our analysis, male patients were dominant in four studies [7, 8, 9, 11, 12], but there were no differences reported regarding severity of the disease or symptoms regarding gender of patients.

It was demonstrated that most symptomatic cases of COVID-19 occurred among adult population, and they characterized by fever, cough, and malaise [20]. In our analysis, all studies included in our analysis reported symptomatic children, except for two studies reported that there were 39.2% [9], and 35% [10] asymptomatic. Fever was the most commonly reported symptom associated with COVID-19 infection among children; it was reported by all the included studies. Cough was the second most reported symptoms among children infected with COVID-19. Gastrointestinal symptoms were less frequent compared to fever and cough.

In a previous systematic review included 18 review articles, it was reported that the range of asymptomatic children and young individuals was between 14.6% to 42%. Similar to our analysis, the previous systematic review [17] reported that fever and cough were the major symptoms, where the rate of fever was 46% to 64.2%, and the rate of cough was 32% to 55.9%. Also, it was reported that gastrointestinal symptoms such as diarrhea and vomiting, as well as fatigue were infrequent and they occurred among less than 10%-20% [17], and these findings were similar to ours, except for nausea/vomiting and diarrhea, which was reported in one study to be 50%, and 37.5%, respectively. However, it should be noted that this study that reported this high rate of nausea and diarrhea included only eight patients.

In a systematic review the rate of total asymptomatic cases was lower compared to ours, where there were 14.2% asymptomatic children were reported [1]. In agreement with our findings, the previous systematic analysis [1], revealed that fever and cough also were the major symptoms reported among children, whereas nasal symptoms, gastrointestinal symptoms including diarrhea and nausea/vomiting were 11.2%, 8.1%, and 7.1%, respectively. We found that nasal symptoms were less common and they included rhinorrhea (8%) [10], and nasal congestion (8%) [12].

Similarly, Cui et al in their systematic analysis reported that the major clinical symptoms of COVID-19 children were fever (51%), and cough (41%), where asymptomatic patients represented 33% [3]. Other two systematic analysis also reported that fever and cough were the major symptoms of COVID-19 among pediatric population [15,18].

Our analysis revealed that fever and cough were the most common symptoms of COVID-19 among children patients and this were in agreement with previous systematic

analysis[15,17,18]. However, one systematic analysis revealed that fever and respiratory symptoms shouldn't be considered as the hallmark of COVID-19 infection among children[1]. Radiological examination wasn't common in our study, only two studies reported radiological findings [8, 12]. Abnormalities were either reported for all patient[8], or more than one-half of patients[12]. In a previous systematic review, abnormalities of computed tomography was reported in more than one-half of children cases[1], which was similar to our findings.

Regarding laboratory findings, the major abnormalities reported included abnormalities of C-reactive protein, liver enzymes, white blood cells, estimated sedimentation rate (ESR) and lactate dehydrogenase. Moreover, it was found that some laboratory investigations were significantly associated with the severity of COVID-19 among children, including D-dimer, high levels of procalcitonin, creatine kinase, and decreased lymphocytes [11]. Cui et al showed that the most common laboratory findings included normal white blood cells, lymphopenia, elevated creatine-kinase[3]. In our analysis, white blood cells were either increased or reduced among patients. In contrast to our findings, Liguoro et al in their analysis they reported that laboratory findings weren't specific [16], whereas in our analysis some laboratory findings were associated with the severity of the disease.

It was reported that critical cases of children accounted for 14% and occurred among children under one year of age[3], whereas in our analysis, the majority of critical cases were less than three years old[12].

In our analysis we could conclude that children infected with COVID-19 if not asymptomatic, they develop mild symptoms of COVID-19 with favorable presentation and this may be the reason for good prognosis. In a previous systematic review conducted on children, it was reported that children diagnosed with COVID-19 had an excellent prognosis [20]. Previous analysis also confirmed these findings and reported that children infected with COVID-19 may experience milder disease [3], generally experience less severe illness or even asymptomatic illness [15].

#### **Conclusion:**

Children are susceptible to COVID-19 infection; fever is the major symptoms of COVID-19 infection among children, followed by respiratory symptoms, whereas gastrointestinal symptoms are less common compared to respiratory symptoms. Children generally experience mild COVID-19 symptoms and less serious disease. Some laboratory investigations are predictors for the severity of COVID-19 among children, including D-dimer, and lymphocyte count. Children affected with COVID-19 present with more favorable condition, therefore they experience better prognosis. However, the majority of critical cases among children are those less than three years.

#### **Limitations, strength, and recommendations:**

The small number of the included studies in our analysis was one of the limitations of our analysis; however, this is due to the exclusion of case reports and case series included five patients and less number of patients. Another limitation was including the majority of studies from China; however, this was dependent on the inclusion criteria which met with the Chinese studies. Strength of this systematic analysis is it included original articles only with the exclusion of case reports, and exclusion of adult individuals; the analysis focused on children even those younger than one year. It is recommended to perform further studies on the pediatric population regarding COVID-19 symptoms to report symptoms from all countries in the world and investigate if the symptoms are affected with ethnicities of children or the genes. Also, it is important to investigate if the diagnosis of COVID-19 among children can be performed through clinical manifestations and laboratory investigations only without radiological evaluation or not. These studies are strongly recommended to be performed as the majority of systematic analysis is based on case reports. Retrospective design of the studies can be helpful to gather data of children affected with COVID-19 from each country in the world.

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