

## Post COVID-19 Syndrome among Children: Review of the Literature

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| Received: 27.12.2022 | Accepted: 31.01.2023 | Published: 17.02.2023

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### Abstract

### Review Article

Despite the fact that children have a lower risk of contracting COVID-19, a growing number of studies have shown an increase in the incidence of the pandemic among children. Reviewing the previous research on post-COVID-19 syndrome in children was the primary purpose of this study's literature analysis and review. We looked through a large number of research engines, such as PubMed, Google Scholar, ScienceDirect, and ResearchGate. The findings indicated that COVID-19 in children continues to be present for a considerable amount of time after the symptoms have subsided. When considered as a whole, the COVID-19 protocol for children should be adhered to because it does not end when the symptoms are relieved. Following an infection, there is generally a documented potential for the involvement of pathogenesis in multiple organs as a result of the infection.

**Keywords:** COVID-19, children, syndrome, symptoms, infection.

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## 1. INTRODUCTION

A severe form of the acute respiratory distress syndrome 2019 will go down in history as the year that the coronavirus disease that was caused by coronavirus 2, also known as SARS-CoV-2, was first identified (COVID-19). The World Health Organization (WHO) issued a statement in March of 2020 indicating that the number of infections caused by this virus had reached pandemic proportions (WHO, 2020). During the SARS-CoV-2 pandemic, the significant efforts that were made to define the main factors leading to serious illness seemed to focus on the presence of comorbidities, particularly advanced age (O'Driscoll *et al.*, 2021). According to the information that was made available by the Centers for Disease Control and Prevention (CDC) in March 2022, there were a total of more than 970,000 deaths in the United States of America, with a mortality rate for COVID-19 of 1.2%. Children have a lower mortality rate than adults do, and it has been widely reported that the disease is less severe in this population of children, with the majority of cases being mild or asymptomatic (Guo *et al.*, 2020). In addition, the mortality rate of children is lower than that of adults. This is correlated with the decrease in the infant and child mortality rates. It was recently discovered that some people (both adults and children) are unable to recover their previous health after being infected by SARS-CoV-2. These people have long-term symptoms such as a persistent cough, fatigue, altered taste and/or

smell, and memory loss. In addition, they are unable to recover from the SARS-CoV-2 infection. It was just recently discovered that this is the case for some people, despite the fact that the vast majority of people infected with COVID-19, both children and adults, do not experience any changes and continue to live normally after the acute infection. This collection of persistent symptoms is referred to as "long-COVID-19," "post-acute COVID-19 syndrome" (PACS), or "post-COVID-19 condition" within the scientific community. The World Health Organization (WHO) prefers to use the term "post-COVID-19 condition" (WHO, 2021). Despite the fact that some researchers are attempting to understand the mechanisms that are responsible for persistent symptoms in adults, very few studies focus on the post-COVID-19 condition in children. In this study, our goals were to (WHO, 2020) review and summarize the existing knowledge on the post-COVID-19 condition in children, with an emphasis on clinical symptoms and potential pathophysiologic mechanisms; and (O'Driscoll *et al.*, 2021) share the experience of working in the Pediatric Persistent COVID Unit at the Germans Trias Hospital. These goals were broken down as follows: (WHO, 2020) review and summarize the existing knowledge on the post-COVID-19 condition in children, with an emphasis on clinical symptoms and potential pathophysiologic mechanisms (Badalona, Spain).

## 2. From a severe case of the disease to a post-COVID-19 state

Acute COVID-19 has been extensively studied, and its clinical manifestations and symptoms have been described and reviewed (Huang *et al.*, 2020; Wang *et al.*, 2020). Fever, fatigue, and a dry cough are the three symptoms that adults experience the most frequently. Although infected children experience symptoms that are comparable to those experienced by infected adults, the acute infection in children is not as severe as it is in adults. Multiple studies demonstrate that 5.9% of children do not exhibit any symptoms, in contrast to the 1% of adults who do so, and that the infection is mild in 99.3% of cases affecting children, in contrast to 81% of cases affecting adults (Liu *et al.*, 2020; Lu *et al.*, 2020). According to the findings of a study that was carried out in China with 341 children aged 4–14 years (median age: 7 years), the most common symptoms were fever (77.9%), cough (32.4%), and diarrhea (4.4%) (Guo *et al.*, 2020). Noteworthy is the fact that COVID-19 has been linked to the multisystem inflammatory syndrome (MIS), a condition in which multiple organs and systems within the body (including the heart, lungs, kidneys, brain, skin, eyes, and gastrointestinal organs) can become inflamed. A recent study suggested that MIS in children (MIS-C) is more common than was previously thought. This is in spite of the fact that previous research has shown that acute infections are not as severe in children as they are in adults (Alfredo *et al.*, 2022). The researchers looked at the symptoms of 1,200 hospitalized children with a median age of 4.7 years and found that 10.6% of those children (127/1,200) had MIS-C while they were infected with the infection. Even though they suffered from serious co-morbidities like acute leukemia and bone marrow transplants, being overweight, and malignant neoplasm, the three patients who were diagnosed with MIS-C in this study all ended up passing away in the end. MIS-C because of COVID-19 has been examined in another context (Hoste *et al.*, 2021). Adults are less likely to be affected by MIS, despite the fact that it has been demonstrated and described in patients with severe COVID-19 (Pombo *et al.*, 2021). SARS-CoV-2 has been shown to be able to infect trophoblasts in the placenta and cause fetal death in 2.5% of cases (5 out of 198 placental tissue samples), according to a recently published article (Garrido-Pontnou *et al.*, 2021). Despite the fact that vertical transmission of SARS-CoV-2 in pregnant women has been documented, it appears to be a relatively uncommon occurrence (Kotlyar *et al.*, 202). During the pandemic, an interesting phenomenon that occurred with some children was that they developed chilblains (more common than in adults). An earlier study came to the conclusion that chilblains were not associated with COVID-19 because none of the patients tested positive for SARS-CoV-2 antigens, nucleic acids, or SARS-CoV2 antibodies (Herman *et al.*, 2020).

At the beginning of the COVID-19 pandemic, the percentage of confirmed cases among children was

relatively low, and at that time, it was believed that children were only rarely affected by SARS-CoV-2. However, as the pandemic progressed, the number of confirmed cases increased significantly among children (Ladhani *et al.*, 2020). Because subsequent studies have consistently shown that children and adolescents are susceptible to SARS-CoV-2 infection, despite the fact that a large percentage of children are either asymptomatic or pre-symptomatic, the true incidence of infection is underestimated because of the low rate of testing that is performed on children. This is due to the fact that there is a large percentage of children who are either asymptomatic or pre-symptomatic (Bi *et al.*, 2020). In general, children who have been infected with COVID-19 will exhibit less severe symptoms and have a lower risk of developing life-threatening complications that will call for hospitalization (Dong *et al.*, 2020). Despite this, there have been reports of children developing what is known as the multisystem inflammatory syndrome in children, which is a post-infectious hyperinflammatory multisystem syndrome (MIS-C). These instances of children suffering from severe illness have been described (Biglari *et al.*, 2021). The risk of transmission from an asymptomatic individual who is infected with SARS-CoV-2 is lower when compared to the risk of transmission from an individual who is exhibiting symptoms of the disease (Li *et al.*, 2021). Therefore, preliminary research suggested that children do not significantly contribute to the spread of SARS-CoV-2 due to the fact that the symptoms they experience are less severe than those experienced by adults. However, more recent research has shown that there is reason to be concerned that children may be able to spread the infection to other people (DeBiasi *et al.*, 2021).

## 3. Rate of SARS-CoV-2 Infections in Children

At the very least in the early stages of the COVID-19 pandemic, children typically accounted for up to 2% of laboratory-confirmed cases of SARS-CoV-2 infection. Several different surveillance studies carried out in different nations came to the same conclusion (Ladhani *et al.*, 2020). The Chinese Center for Disease Control and Prevention published a report of 72,314 laboratory-confirmed or suspected (based on history of exposure), symptomatic or asymptomatic SARS-CoV-2-infected cases; children 19 years of age accounted for 2% of the total number of cases; in this study, there was no difference in the rate of infection among children of different ages. Children under the age of 19 accounted for 2% of the total number of cases (Wu *et al.*, 2020). 1.1% of the 129,704 cases of SARS-CoV-2 infection that were reported in England between January 16 and May 3, 2020 were cases involving children. These cases were reported between January 16 and May 3, 2020. (2). By March 2020, only one percent of Italy's total patient population will be comprised of children younger than 18 years old who are infected with SARS-CoV-2. This number is expected to be lower than it is currently (Ladhani *et al.*, 2020). In Ontario, 5.1% of

the total confirmed COVID-19 cases were reported in children between January 15, 2020 and December 29, 2020. To be more specific, the rate of infection among children was significantly lower (60,4 per 100,000 population) than the rate of infection among adults (298.8 per 100,000 population) (Shekerdemian *et al.*, 2020). In the most recent study, it was discovered that the incidence rates of illness were highest among children aged 15–19 years old (109.6 per 100,000 population). This was found to be the case when compared to younger pediatric age groups (Shekerdemian *et al.*, 2020).

A clinical recovery occurred in the vast majority of children who were diagnosed with MIS-C and had severe cardiac manifestations within the first 30 days after receiving treatment. It was discovered that the case fatality rate, which is also referred to as the CFR, was 0% (Toubiana *et al.*, 2020), 1.9% (Feldstein *et al.*, 2021), and 2% in large cohorts (Godfred-Cato *et al.*, 2020). According to the CDC report, one of the risk factors for MIS-C is obesity, and they found that obesity was present in 270 of the 570 patients that they studied (Godfred-Cato *et al.*, 2020).

The criteria that are applied in different countries to decide who is eligible for hospitalization influence the percentage of children who are admitted to hospitals. These criteria vary from country to country. It is anticipated that this pattern will continue, despite the fact that the rate of hospitalization of children in the United States is significantly lower than that of adults (Dong *et al.*, 2020). The cumulative COVID-19-associated hospitalization rate among children younger than 18 years was highest among children younger than 2 years (32.7%); rates were significantly lower in children aged 2–4 years (8.7%) and 5–11 years (16.8%), but higher in ages 12–17 years (41.8%) (Kim *et al.*, 2020).

In another study, 57% of children in Italy who were diagnosed with COVID-19 at one of the country's 28 centers, the vast majority of which were hospitals, were required to be hospitalized as a result of their condition (Parri *et al.*, 2020). In Greece, 26.1% of the children who were diagnosed during the first epidemic wave had to be hospitalized; in this series, being younger than 5 years old was a predictor of hospitalization (Maltezou *et al.*, 2020).

Funk *et al.*, (2022) showed that out of a total of 8642 children who participated in the research, 2368 of them (or 27.4%) tested positive for SARS-CoV-2. There was index ED visit disposition data for 2365 of these patients (99.9%), which were available. The 1884 children, 79.7% of whom completed the follow-up, had a median age of 3 years (interquartile range [IQR], 0-10 years), and 994 of them were boys. There were a total of 110 children who tested positive for SARS-CoV-2, and PCCs were reported by 5.8% of them (the 95%

confidence interval [CI], 4.8%-7.0%) When it came to these children, 44 out of 447 (9.8%; 95% confidence interval [CI], 7.4%-13.0%) were hospitalized during the acute illness, whereas 66 out of 1437 (95% CI, 3.6%-5.8%) were not hospitalized during the acute illness (difference: 5.3%; 95% confidence interval [CI], 2.5%-8.5%). In children who tested positive for SARS-CoV-2, the most frequently observed symptom was fatigue or weakness (21 cases, or 1.1% of all cases). Adjusted odds ratio (aOR) of 2.67 [95% confidence interval (CI): 1.63-4.38]; having 4 or more symptoms reported at the index ED visit compared with 1 to 3 symptoms; 4-6 symptoms: aOR, 2.35 [95% CI, 1.28-4.31]; 7 symptoms: aOR, 4.59 [95% CI, 2.50-8.44]; and being 14 years of age or older. When compared with children who tested negative for the virus, those who reported PCCs at 90 days were more likely to have tested positive for SARS-CoV-2. This was the case for children who were hospitalized as well as children who were not hospitalized (40 of 1295, 4.2%; 95% confidence interval [CI], 3.2%-5.5%] vs 35 of 1321, 2.7%; 95% confidence interval [CI], 1.9%-3.7%]; difference, 1.6% [95% confidence interval [CI], 0.2%-3.0%]). In addition to this, it was discovered that the presence of SARS-CoV-2 was associated with the reporting of PCCs 90 days after the index ED visit (aOR, 1.63 [95% CI, 1.14-2.35]), more specifically, systemic health problems (for example, fatigue, weakness, fever; aOR, 2.44 [95% CI, 1.19-5.00]). The researchers concluded that the children who took part in this cohort study, having SARS-CoV-2 infection was linked to having a report of PCCs at the end of the observation period (90 days). It is of the utmost importance that hospitalized children of a more mature age who are experiencing a greater number of acute symptoms receive direction and care after discharge (Funk *et al.*, 2022).

It is still difficult to adequately describe the conditions that have persisted among children after COVID-19 was implemented. Early reports indicated that the percentage of children who experienced PCCs months after their acute illnesses ranged from 25% to 58%, and the incidence was not correlated with the severity of the disease. This was the case despite the fact that the number of children who experienced PCCs after their illnesses ranged from 25% to 58% (Buonsenso *et al.*, 2021). However, a subsequent study that primarily included children who were not hospitalized and who tested positive for SARS-CoV-2 discovered that only 4% of those children exhibited symptoms 28 days after being tested and only 2% of those children exhibited symptoms 56 days after being tested. This study found that only 4% of those children exhibited symptoms 28 days after being tested (Molteni *et al.*, 2021). In spite of the fact that these risks were higher than those that were reported among participants who had not been infected, other reports (Blankenburg *et al.*, 2021; Chevinsky *et al.*, 2021) described there being no difference in the frequency of PCCs among pediatric COVID-19 patients and controls. [Further citation is required] These reports

are flawed in a number of ways, including having testing criteria that relied on typical adult symptoms, having low follow-up rates, relying on information obtained from health care encounters, having small sample sizes, and classifying exposure based on antibody levels (Blankenburg *et al.*, 2021).

A complete knowledge of pediatric PCCs is necessary in order to provide direction for the treatment of children who are at high risk and to inform policies that govern public health (Fazel *et al.*, 2021).

Garai *et al.*, (2022) conducted a study in the light of the existence of some considerations including the need for further understanding of pediatric long COVID syndrome (LCS) in order to be able to create specific case definitions and guidelines for providing good clinical care. This understanding gap has been brought about by the necessity of further research. Conducting research is one way to bridge this comprehension gap. The researchers collected the medical histories of all LCS patients who requested their records while they were visiting our specially designated LC clinic. Because there is no control group, the researchers conducted descriptive analyses instead. These analyses provided a summary of the clinical presentation, findings, and history of the children who participated in the study. At the same time, the research team conducted a diagnosis of exclusion utilizing a multidisciplinary approach to the patient's medical examinations (physical, laboratory, and radiological examinations, specialist consultations, etc.). Because of this, they were able to arrive at a conclusive diagnosis. The vast majority of the children who participated in the study reported having at least a mild impairment to their quality of life, with 17 (23%) of them having moderate or severe difficulties in their daily lives. On average, 18% of the patients had findings that could be directly connected to the linked complaint category. Respiratory symptoms with objective alterations were the most common complaint category, accounting for 37% of the total. Even though we identified the majority of non-specific conditions, in a smaller number of patients we discovered well-described causes such as autoimmune thyroiditis (7%). This was despite the fact that we identified the majority of non-specific conditions. As a matter of conclusion, the vast majority of the children surveyed reported a decrease in the quality of life they were able to enjoy, but only a minority of the children exhibited symptoms related to medical conditions. This indicates that the majority of the children do not have a medical condition. Controlled studies are necessary if one is to disentangle the effects of the pandemic from those of the time period in which it took place. The list of tests that are recommended to be carried out could be easier to rationalize with the assistance of guidelines for pediatric care that are backed by evidence (Garai *et al.*, 2022).

On the basis of the extensive research that has been carried out over the course of the previous two years, it has been indicated that children have significantly lower rates of severe acute Coronavirus disease 2019 in comparison to adults (Irfan *et al.*, 2021). Despite this, the most recent clinical experience demonstrates that the post-acute consequences of the infection may pose a risk of outcomes that are similarly significant (Ludvigsson, 2020; 2021). The World Health Organization (WHO) developed a clinical case definition of the post-COVID condition in October 2021 by employing the Delphi consensus methodology; however, it is indicated that it might not be suitable for children. This was done in order to improve the quality of care for patients suffering from this condition (Soriano *et al.*, 2021). It is difficult to provide an accurate estimate of the epidemiological and medical characteristics of diseases related to COVID-19 in children because of the complexity of these factors. According to a meta-analysis that was conducted and published in August of 2021, it is anticipated that 35 percent of all cases will remain asymptomatic throughout the duration of the infection. This prediction was made based on previous research (Sah *et al.*, 2021). The prevalence of symptoms that persist 12 weeks after a Coronavirus infection ranges from 3% based on tracking specific symptoms to 12% based on self-classification of long COVID syndrome (LCS) (Garai *et al.*, 2022). LCS is a growing public health concern due to the fact that its persistent and emerging symptoms are widespread, frequently overlapping, variable, and changing over time. This is all due to the fact that LCS has been linked to a number of different conditions. In addition, long-term exposure to LCS has the potential to have an effect on multiple organ systems, which may have a negative impact on one's quality of life (Venkatesan, 2021). There are only a handful of prospective studies that have been conducted in the field of pediatrics that collect systematic data from larger cohorts of children and carry out clinical assessment utilizing an approach that draws from a number of different disciplines. These studies frequently omit alterations to the patient's quality of life, comprehensive clinical characteristics, and confirmation of the acute infection. 8 additional studies that followed up patients who had previously been hospitalized during the acute phase of COVID are reporting responses given to interviews without conducting clinical assessment. These patients had been hospitalized during the acute phase of COVID. There are studies that have been conducted that concentrate on the long-term effects of COVID-19 infection on the neurological system, the cardiovascular system, the pulmonary system, or the mind; however, these studies can only be found in isolation from one another (Garai *et al.*, 2022).

#### 4. CONCLUSIONS

COVID-19 in children should be followed because it does not end as symptoms relieved. In general, the possibility of involvement of pathogenesis of

multiple organs following the infection has been documented.

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