

Post-COVID syndrome in children compared with adults (Review)

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Abstract. Post-COVID-19 syndrome (or long-COVID) was recognized as a clinical entity as early as in the spring of 2020, when it was documented that a non-negligible number of patients with COVID-19 continued to exhibit symptoms several weeks following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Although in the beginning of the COVID-19 pandemic it was considered that almost all SARS-CoV-2 infections in children and adolescents were either asymptomatic or mildly symptomatic, it was duly noted that children and adolescents may also experience prolonged symptoms and may therefore also manifest post-COVID syndrome. It was subsequently noted that post-COVID syndrome in children may involve multiple organs and systems and persist, in the majority of cases, for several months; however, in some cases symptoms persisted even following 1 year of follow-up. There is also evidence to indicate that children with post-COVID syndrome are at an increased risk of developing anxiety, depression or loss of appetite, while the overall impact of post-COVID syndrome on the developmental and psychological domain and overall well-being of children remains largely unknown. The present review discusses the current state of knowledge on post-COVID syndrome in children and compares it with that of adults. Issues of pathogenesis, prognosis, the role of vaccination and implications for future research are also discussed.

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1. Introduction

Post-COVID syndrome (or long-COVID) was recognized as a clinical entity as early as in the first COVID-19 pandemic wave in the spring of 2020, when it was documented that a non-negligible number of patients with COVID-19 continued to have symptoms several weeks following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). At that time, post-COVID syndrome was defined as the persistence of symptoms for >3 weeks following the acute infection, while chronic COVID-19 was defined as a symptomatic illness extending for a period >12 weeks following the acute infection (1). However, to the best of our knowledge, the first aggregation of data on post-COVID syndrome is attributed to a report entitled 'What does COVID-19 recovery actually look like' that was released by the Patient-Led Research Collaborative on May 11, 2020 (2). This patient-centric survey was conducted by patients themselves and captured first-time data on prolonged COVID-19-associated symptoms (defined as symptoms for >2 weeks) through the experience of 640 patients affected by COVID-19 (2). Since then, several original studies were published, revealing the burden of this novel clinical entity, in terms of prevalence rate and spectrum of manifestations, while risk factors and prognosis were largely unknown at that time (1). The present review summarizes the current state of knowledge on post-COVID syndrome in children compared with adults. Issues of pathogenesis, prognosis and implications for future research are also discussed.

2. Post-COVID in adults

In spring 2021, the author's research team published a comprehensive review of all original studies on post-COVID syndrome published as of March 15, 2021 (1). At that time, it was estimated that 10 to 35% of non-hospitalized patients tested positive for SARS-CoV-2 infection develop post-COVID symptoms; however, among hospitalized cases, rates as high as 80% of post-COVID symptoms were reported (1). That comprehensive review of original studies demonstrated that fatigue, shortness of breath (SOB), anxiety or depression, and sleep disorders were prominent symptoms among patients with

post-COVID, with reported rates of up to 72, 65.6, 37.5 and 26%, respectively (1). Moreover, dyspnea, chest pain, and olfactory and gustatory dysfunction were reported by up to 40%, up to 22%, and up to 11% of patients with post-COVID syndrome, respectively (1). The management of post-COVID-19 cases was based on a symptomatic approach. That previous review also revealed notable methodological limitations among the original studies reviewed (1). For instance, there were studies reporting symptoms from 37 to 180 days following acute COVID-19 infection, while others presented symptoms 48-120 days following discharge from the hospital (1). The main obstacles for assessing the prognosis of patients with post-COVID syndrome in the early phases of the COVID-19 pandemic included the fact that a number of infections were not laboratory-confirmed and that almost all surveillance systems did not capture and record long-term post-COVID complications (1). That review also pointed out, for the first time, to the best of our knowledge, the need for well-described criteria for the diagnosis, follow-up and management of patients with post-COVID syndrome. It also predicted the excess of health-care demand due to post-COVID syndrome, in the frame of the continuing COVID-19 pandemic (1).

In 2023, a systematic review and meta-analysis of 194 studies with 735,006 patients with COVID-19 (either self-diagnosed or confirmed by a PCR test) and ongoing symptoms for at least 28 days post-infection and a mean follow-up of 126 days was published (3). This latter review estimated that at least 45% of COVID-19 survivors, regardless of their history of hospitalization, had at least one unresolved symptom (3). The pooled prevalence rates of symptoms among non-hospitalized patients were 34.82% for fatigue/weakness, 20.44% for breathlessness/dyspnea, 17.01% for muscle pain/myalgia, 15.28% for sleep disorders, 12.66% for smell dysfunction, 8.69% for taste dysfunction, 7.65% for gastrointestinal symptoms, 6.5% for cough, 6.04% for headache/migraine, 5.28% for nasal symptoms, 4.47% for chest pain/tightness, 4.11% for joint pain, and 4.08% for sore throat (3). In the mixed (hospitalized and non-hospitalized patients) analysis, the pooled prevalence rates of symptoms were 25.24% for fatigue/weakness, 18.22% for breathlessness/dyspnea, 17.37% for impaired usual activity, 14.93% for taste dysfunction, 14.12% for smell dysfunction, 13.29% for depression, 12.75% for muscle pain/myalgia, 12.39% for joint pain, 11.96% for sleep disorders, 11.73% for gastrointestinal symptoms, 11.20% for dizziness, 10.67% for anxiety, 10.37% for cough, 9.92% for nasal symptoms, 8.92% for headache/migraine, 8.84% for palpitations, 8.60% for hair loss/alopecia, 7.28% for change in appetite, 6.35% for chest pain/tightness, 5.21% for affected hearing, 4.78% for fever, 4.24% for vomiting/nausea, 4.08% for sore throat, 4.00% for diarrhea, 3.82% for abdominal pain, 3.71% for skin changes, and 2.12% for chills (3). The pooled prevalence for at least one symptom was 34.46% among the non-hospitalized patients and 37.8% in the mixed population (hospitalized and non-hospitalized patients) (3). The researchers of that review and meta-analysis still acknowledged the following limitations: The heterogeneous design of the included studies, variations in definitions of post-COVID syndrome and differences in follow-up duration (3). Moreover, it is not clear to the reader whether these findings are based on diagnostic records of physicians or self-reported surveys

by the patients. According to recent estimates, post-COVID syndrome affects 10% of all infected patients, and in particular 10%-30% of non-hospitalized patients, 50%-70% of hospitalized patients, and 10%-12% of vaccinated patients (4). Based on rather conservative estimates, currently, at least 65 million individuals globally have long-COVID, with cases increasing daily; the number of long-COVID cases is likely to be markedly higher given the numerous undiagnosed cases (4).

3. Post-COVID in children and adolescents

In the very early stages of the COVID-19 pandemic, it was considered that children were rarely affected by SARS-CoV-2 and that their contribution to virus transmission was relatively limited (5-7). Subsequent studies consistently revealed that children and adolescents were frequently infected with SARS-CoV-2; however, almost all infections in the pediatric age group were either asymptomatic or mildly symptomatic (5,8). Nevertheless, soon it also became evident that children and adolescents may also experience prolonged symptoms following infection with SARS-CoV-2 and may therefore also manifest post-COVID syndrome.

A previous systematic review of 11 observational studies (case-control, cross-sectional, cohort, or case series) involving 2,279 children aged <18 years using the WHO case definition estimated that the most frequent symptom was exercise intolerance with a pooled prevalence of 29% [95% confidence interval (CI), 7-57%], followed by non-specific respiratory symptoms (12%; <95% CI, 0-48%) and psychological disorders (10%; 95% CI, 1-25%) (9). The pooled prevalence rates at ≥12 months post-infection were 6% (95% CI, 2-10%) for exercise intolerance and 3% (95% CI, 0-8%) for fatigue (9). Another review and meta-analysis by Zheng *et al* (10) of 40 original studies published from 2020 to 2022 with a total of 12,424 pediatric COVID-19 survivors aged <18 years and at least 3 months of follow-up following SARS-CoV-2 infection, estimated a 23.36% (95% CI, 15.27-32.53%) overall pooled prevalence rate of long-COVID. The authors of that study also estimated the pooled prevalence rate of long-COVID by follow-up duration: 26.41% (95% CI, 14.33-40.59%) in cases with 3-6 months follow-up duration, 20.64% (95% CI, 17.06-24.46%) in cases with 6-12 months follow-up duration, and 14.89% (95% CI, 6.09-26.51%) in cases with >12 months follow-up duration (10). Subsequently, Zheng *et al* (10) estimated the prevalence rate of long-COVID among pediatric and adolescent patients by organ system, as follows: Generalized symptoms: 19.57% (95% CI, 9.85-31.52%); subjective respiratory symptoms: 14.76% (95% CI, 7.22-24.27%); neurological symptoms: 13.51% (95% CI, 6.52-22.40%); psychiatric symptoms: 12.30% (95% CI, 5.38-21.37%); digestive symptoms, 11.87% (95% CI, 4.22-22.46%); musculoskeletal symptoms: 9.38% (95% CI, 3.59-17.31%); cardiovascular symptoms: 7.32% (95% CI, 2.68-13.66%); dermatological symptoms: 6.42% (95% CI, 1.39-14.46%); ophthalmological symptoms: 3.92% (95% CI, 0.00%-14.34%); and urological symptoms: 0.44% (95% CI, 0.00-4.02%) (10). The prevalence rates per organ system varied significantly by follow-up duration as well. For instance, subjective respiratory symptoms were present in 21.50% of patients with 3-6 months follow-up duration, in 13.65% of patients with 6-12 months follow-up duration, and in 1.80% of patients with

>12 months follow-up duration (P-value <0.01) (10). Similarly, psychiatric symptoms occurred in 13.84% of patients with 3-6 months follow-up duration, in 14.51% of patients with 6-12 months of follow-up duration, and in 1.34% of patients with >12 months follow-up duration (P-value <0.001) (10). In terms of isolated symptoms, dyspnea, fatigue, headache, SOB and abdominal pain prevailed in children and adolescents with long-COVID symptoms (reported in 22.75, 20.22, 15.88, 15.30 and 12.42% of children and adolescents with long-COVID symptoms, respectively), followed by concentration difficulties, muscle pain and sleep disturbances (11.44, 11.42 and 8.38% of children and adolescents with long-COVID symptoms, respectively) (10). Less frequently reported symptoms were diarrhea, skin rashes, heart palpitations, cough, dizziness, chest pain, fever, altered or loss of smell/taste, weight loss, and joint pain or swelling (10). These findings indicate that almost one quarter of pediatric and adolescents with COVID-19 develop long-COVID symptoms which involve multiple organs and systems, while the overall prevalence of long-COVID symptoms decreases as follow-up duration increases (10). Indeed, long-COVID symptoms subsided, and most children recovered, although it may take several months. However, in some cases, symptoms persisted even following 1 year of follow-up (10). That meta-analysis also pointed out that being >10 years of age, being a female, having a more severe acute infection (e.g., symptomatic acute infection, more symptoms at acute infection or hospitalization for ≥ 48 h) and multisystem inflammatory syndrome (MIS) were risk factors for long-COVID (10). In particular, compared with younger patients, patients >10 years of age had a higher prevalence of long COVID overall (36.6 vs. 8.6%, P-value=0.04), and in particular of respiratory (28.3 vs. 1.9%; P-value <0.01) and musculoskeletal symptoms (18.9 vs. 0.6%; P-value <0.01) (10). In addition, three studies reported that female patients were more vulnerable for long-COVID (10). Lastly, a poor mental or physical status of the patient at the time of the initial SARS-CoV-2 infection, the presence of neurological comorbidities or a PCR-positive at three months after initial diagnosis also were associated with increased risk for long-COVID among children and adolescents (10). It should be noted that depression, anxiety and sleep disorders are frequently reported by adolescents and were frequently encountered in the context of the COVID-19 pandemic, which underlines the challenges to define and address such symptoms in the context of long-COVID. Moreover, there has been no standardized definition of long-COVID for the pediatric age group and diagnostic criteria for adults have been consistently implemented in pediatric studies. Additional limitations include the heterogenous design of the studies (mostly retrospective cohort and cross-sectional studies), the various study settings (hospital vs. community studies), a wide range of follow-up duration of cases after the acute infection, and the absence of control groups (10). All these limitations render it difficult to compare the prevalence rate and severity of post-COVID syndrome in children and adolescents among studies. Therefore, criteria for diagnosis and follow-up of post-COVID-19 syndrome in children are required, as well as longitudinal studies of pediatric populations.

Another recent systematic review and meta-analysis of studies reporting mental health symptoms of long COVID or treatment of anxiety or depression in long-COVID (defined

as persistent symptoms after 4 weeks of acute laboratory-confirmed COVID-19 infection or clinically diagnosed as COVID-19) in children conducted by Mat Hassan *et al* (11), estimated that children with past COVID-19 had a 2-fold greater risk of developing anxiety or depression and a 14% higher risk of developing a loss of appetite. Concentration impairment and cognitive difficulties were also common among children recovering from COVID-19 (11). In the latter review and meta-analysis, the majority of the included studies used parents as proxies or guardians to their children, while only two studies had the adolescents answering the questionnaire (11). Persistent neurological/neuropsychiatric symptoms are frequently reported by children/adolescents following acute SARS-CoV-2 infection (12). Studies should also involve control groups to assess the impact of psychological stressors associated with the COVID-19 pandemic per se (12). The overall impact of COVID-19 on the developmental and psychological domain of children remains largely unknown. Morello *et al* (13) also prompted the attention of healthcare professionals and researchers to the negative impact that persistent symptoms (e.g., fatigue, headache, gastrointestinal symptoms, abdominal pain, and arthralgias) experienced by children with long-COVID may have on their daily life, school attendance, social activities, and overall well-being.

The importance of variations in the duration of symptoms between definitions of post-COVID syndrome in children was also noted by Ha *et al* (14). For instance, the United Kingdom National Institute of Health and Care Excellence applies the persistence of symptoms following acute infection with COVID-19 for ≥ 4 weeks, while the US Centers for Disease Control and Prevention uses the presence of physical and mental health consequences over four weeks after SARS-CoV-2 infection (14). Moreover, as also noted in adult studies, it is not clear to what extent published data on post-COVID syndrome in children and adolescents are based on the records of physicians or the self-reported surveys of patients. In response to the necessity for a standardized definition and following an expert consensus, on February 16, 2023 the WHO posted the definition of a clinical case of post COVID-19 condition in children and adolescents (15). According to the WHO definition, post-COVID-19 condition in children and adolescents is defined as a history of confirmed or probable SARS-CoV-2 infection and experience of symptoms lasting for at least 2 months, initially occurring within 3 months of acute infection (15). The implementation of standardized diagnostic criteria or guidelines for the clinical management of pediatric cases of post-COVID-19 condition is imperative to define its incidence and overall prevalence, as well as its clinical spectrum and prognosis.

4. Pathogenesis and management of post-COVID syndrome

Research has indicated that the pathogenesis of post-COVID syndrome is multifactorial, and that more than one mechanism may be involved in each patient. Prolonged inflammation plays a key role in the pathogenesis of post-COVID syndrome and may account for several symptoms (16). For instance, it is well known that prolonged inflammation may alter neuronal function in the context of a profound increase of circulating cytokines (e.g., IL-6 and IL-4); GABAergic impairment may also be implicated

in neuromotor and cognitive fatigue (16). Lung dysfunction is common in patients with long-COVID and may also contribute to post-COVID fatigue (16). As with other coronaviruses that are neurotropic, SARS-CoV-2 may also invade the blood-borne barrier through periphery or olfactory neurons and therefore directly affect the central nervous system; the later mechanism may be implicated in memory deficit (16). Other possible pathogenetic mechanisms include persistent extra-pulmonary infection (e.g., in heart, liver, kidneys), immune-mediated vascular dysfunction and microvascular injuries which may reduce cerebral blood flow, and episodes of thromboembolism encountered in the post-COVID-19 period (16).

At the level of affected organs, there is an association between prevalent symptoms and pathogenetic mechanisms (4). For instance, chest pain and palpitations are associated with cardiac impairment and myocardial inflammation, and cough and dyspnea with abnormal gas exchange in lungs (4). Fatigue appears to be associated with coagulopathy, deep vein thrombosis, endothelial dysfunction, microangiopathy, circulating microclots, pulmonary embolism, and stroke (4). Signs and symptoms of neurological involvement and nervous system dysfunction, such as cognitive impairment, sleep disorders, memory loss, and tinnitus may be associated with dysautonomia, myalgic encephalomyelitis/chronic fatigue syndrome, neuroinflammation, reduced cerebral blood flow, and small fiber neuropathy (4).

The pathogenesis of long-COVID in children remains largely unknown and relevant research is very limited (13). The available data indicate that the following mechanisms may be implicated in various organs and systems: direct virus invasion and critical organ damage in the acute phase of infection, latency of SARS-CoV-2, persistent endothelium impairment with circulating microclots, prolonged inflammation, and imbalanced immune responses (13). Intestinal dysbiosis, followed by impaired intestinal permeability which may alter the gut-brain axis, and subcellular metabolism abnormalities in mitochondrial and oxidative pathways, have been also proposed and are under research (13). Currently, the management of children and adolescents with long-COVID is based on a symptomatic approach. The multifactorial pathogenesis of post-COVID syndrome (prolonged inflammation, nervous system dysfunction, endothelial damage, thromboembolism) in the context of a wide spectrum of manifestations indicates the necessity of a personalized healthcare approach (13).

Lastly, there is evidence to indicate that COVID-19 vaccination is associated with a decreased risk of developing post-COVID in children. A US multicenter study enrolled 622 children and adolescents aged from 5-17 years between July 21, 2021 and September 1, 2022 and followed-up the patients by weekly SARS-CoV-2 tests and post-COVID-19 symptoms (defined as more than one new or ongoing symptom lasting for at least 1 month following SARS-CoV-2 infection) (17). Of the 622 enrolled children, 474 children (67%) were fully vaccinated with mRNA COVID-19 vaccines, while 28 children (5%) developed post-COVID-19 symptoms (17). In this latter cohort study, a history of full COVID-19 vaccination with mRNA vaccines was associated with a decreased likelihood of developing at least one post-COVID-19 symptom by an adjusted odds ratio (aOR) of 0.66 (95% CI, 0.43-0.99), more than two post-COVID-19 symptoms by an aOR of

0.52 (95% CI, 0.32-0.83), and particularly any respiratory post-COVID-19 symptom by an aOR of 0.53 (95% CI, 0.33-0.87) (17). These findings indicate the protective effect of mRNA vaccination against post-COVID-19 in children and adolescents during a period dominated by highly transmissible Omicron SARS-CoV-2 variants (17). Moreover, another study on 1,319 children and adolescents aged 0-18 years (median age, 87 months; 88.6% with mild symptomatic SARS-CoV-2 infection) with laboratory-confirmed SARS-CoV-2 infection prospectively assessed at 3, 6, 12, 18 and 24 months post-infection in a pediatric post-COVID clinic in Rome, Italy between February, 2020 and February, 2024, found that 23.2, 13.2, 7.9, 6.1 and 7.1% of the patients were diagnosed with long-COVID implementing the WHO criteria (18). An age >12 years (P-value <0.001; OR, 7.98; CI, 4.2-15.15), the presence of comorbidities (P-value=0.025; OR, 1.61; 95% CI, 1.06-2.44), infection with the ancestral SARS-CoV-2 variants (P-value <0.001; OR, 5.85; 95% CI, 2.46-13.47), and female sex (P-value <0.001; OR, 1.39; 95% CI, 1.02-1.89) were significantly associated risk factors for long-COVID at 3 months post-infection (18). An age >12 years (P-value=0.002; OR, 3.7; 95% CI, 1.58-8.64), and infection with ancestral SARS-CoV-2 variants (P-value=0.012; OR, 3.52; 95% CI, 1.32-9.37), and particularly infection with the alpha variant (P-value <0.001; OR, 4.09; 95% CI, 2.01-8.3) remained significant risk factors for long-COVID for at least 18 months post-infection (18). As regards COVID-19 vaccination, 1,049 (79.6%) children were not vaccinated against COVID-19, 82 (6.2%) children had received one vaccine dose, 166 (12.6%) children had received two vaccine doses, 20 (1.52%) children had received three vaccine doses, while this information was not available in 2 (0.2%) children (18). Overall, that observational study of the largest pediatric cohort to date, demonstrated that COVID-19 vaccination was associated with a significantly lower risk of developing long-COVID at 3, 6 and 12 months, particularly among adolescents, and a lower risk of re-infection (18). They also found that infection with the ancestral SARS-CoV-2 variant was associated with an increased risk of new-onset autoimmune disorders (P-value=0.035; 95% CI, 1.12-2.4) (18). Similarly, a survey-based study among 802 pediatric patients (<18 years old) with COVID-19 confirmed by PCR from Thailand estimated that the prevalence of long-COVID (defined as having symptoms for ≥ 3 months post-infection) was 36.3% during the Delta period compared with 23.9% during the Omicron period (19). These findings underline the need to invest in research on pediatric long-COVID to identify effective diagnostic and therapeutic approaches (18). In light of the acceptable safety profile of COVID-19 vaccines in children and adolescents (20), COVID-19 vaccination should be considered as a key measure for the prevention and management of long-COVID in this age group. The latter may prove critical for the physical and mental health of children and adolescents but also for public health.

Lastly, a retrospective cohort study demonstrated that children aged 12-18 years with COVID-19 treated with nirmatrelvir plus ritonavir had a lower, though non-significant, incidence of post-acute sequelae of SARS-CoV-2 infection (e.g., fatigue, cardiopulmonary symptoms, pain, cognitive impairment, headache, sleep disorders) in the 30-180-day follow-up period compared with the control

group (633 patients in each group) (21). These data appear promising in potentially preventing the onset of post-acute symptoms in adolescents.

5. Conclusions and future perspectives

As in adults, post-COVID syndrome in children and adolescents is a multisystem clinical entity with a multifactorial pathogenesis. The present research revealed that almost one quarter of children and adolescents with COVID-19 develop long-COVID symptoms after recovery from their illness or discharge from hospital. Nevertheless, some symptoms may persist for >1 year, which may impact their social and educational activities and overall well-being. Identified factors associated with an increased risk for long-COVID in children and adolescents include an age >10 years, female sex, poor physical or mental status at the time of initial SARS-CoV-2 infection, neurological comorbidities, severe acute SARS-CoV-2 infection, development of MIS, and a PCR-positive at 3 months following the initial SARS-CoV-2 diagnosis. Published evidence indicates that COVID-19 vaccination is associated with an overall significantly lower risk of developing long-COVID, particularly among adolescents. Knowledge on post-COVID syndrome in children and adolescents and its impact in both physical and psychological domains is evolving. Nevertheless, there are still a number of gaps, particularly regarding the pathogenetic mechanisms involved. These issues need to be resolved by research and translated to a personalized, targeted management approach. The use of standardized criteria for the diagnosis and management of post-COVID-19 syndrome along with longitudinal studies of pediatric populations are warranted.

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Author's contributions

HCM conceptualized the study, performed the review of the literature, synthesized the published data, wrote the first draft of the manuscript, and reviewed and edited the manuscript. Data authentication is not applicable. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The author declares that she has no competing interests.

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