Post-COVID-19 syndrome in children (Review)

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Abstract. The persistence of symptoms for a long time after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is now familiar as post-COVID syndrome (PCS). To the best of our knowledge, the risk of long-term clinical outcomes in children after SARS-CoV-2 infection is still unclear. Unlike in adults, current evidence suggests a lower prevalence of persistent symptoms in children. However, since several studies are characterized by great heterogeneity, it is difficult to accurately estimate the exact incidence of PCS in children. The presence and course of recovery depend on risk factors that are more common in adults than children. Proposed pathophysiological mechanisms in PCS in children include age-dependent immune responses, angiotensin-converting enzyme 2 expression, blood-brain barrier development or social issues affecting children behavior, such as school closure and social isolation. However, further longitudinal studies are required for unanswered issues to be clarified. The aim of the present review is to describe the long-term symptoms per biological system in children, potential risk factors and the role of the immune system in the presence of PCS.

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1. Introduction

The number of patients recovering from severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) infection is continuously increasing (1,2). Some patients of all ages require a clinical re-evaluation for persistent symptoms (3). This post-infection syndrome, which lasts ≥4 weeks and cannot be explained by an alternative diagnosis, was named as 'Long COVID-19 syndrome', 'post-COVID syndrome (PCS)', 'post-acute COVID-19 syndrome', 'chronic COVID-19' or 'post-acute sequelae of SARS-CoV-2 infection (PASC)' (4).

Similar postinfectious sequelae were also observed among patients recovering from other epidemic coronavirus diseases, severe acute respiratory syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome (MERS), which included respiratory, mental and cognitive disorders (5). Post COVID-19 symptoms could be physical or psychological and typically include fatigue, cough, shortness of breath, chest pain, olfactory (dysosmia/anosmia) and gustatory (dysgeusia/ageusia) disturbances, depression, anxiety, post-traumatic stress disorder and concentration disturbances (6,7). Children appear to be less susceptible to PCS, but the reasons for this have not yet been fully understood.

The purpose of this review is to describe the reported long-term symptoms per biological system in children, the potential risk factors as well as the role of immune system in the presence of PCS.

2. Incidence of PCS in children

There are three definitions for PCS, according to US Centers for Disease Control and Prevention (CDC), the UK National Institute for Health and Care Excellence (NICE) and World Health Organization (WHO). CDC describes a wide range of ongoing, resolved or returning symptoms that occur in people at least four or more weeks after the onset of the infection, regardless of the presence, combination, duration, severity, or individuals' underlying conditions (8). NICE defines PCS as a cluster of signs and symptoms that develop during or after an

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infection consistent with COVID-19, continue for more than 12 weeks, are not explained by an alternative diagnosis and can fluctuate or change over time (9). According to NICE recommendations, PCS can also be considered before 12 weeks and clinical investigation for PCS is suggested simultaneously with the assessment of an alternative underlying disease (9).

In WHO definition, PCS occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months after the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction, but also others, and generally have an impact on everyday functioning. Symptoms may be new onset after initial recovery from an acute episode of COVID-19 or persist from the initial illness. Symptoms may also fluctuate or relapse over time (10). According to the WHO, adults and children can experience PCS without knowing when they initially had their first infection. This phenomenon is suggestive of describing symptoms long after the recovery from acute disease and directly affects PCS surveillance especially in pediatric population, in which the exact disease onset is frequently unknown.

PCS in children has always been a diagnostic challenge, especially in distinguishing the symptoms related to SARS-CoV-2 infection from those related to the pandemic. The collection of data and analysis methods regarding PCS in children varies greatly among studies. Studies investigating PCS in children are characterized by a wide variety of COVID-19 diagnostic confirmation, since some are based on molecular testing (PCR) (11,12) or serological assays (13,14) or both (15,16), while others do not clearly define the diagnostic methods on which they relied to evaluate PCS in children (17,18). The collection of PCS information also significantly varies and some may be questioned as there is no clinical examination by a physician, but data were collected through questionnaires (19,20), telephone (21,22) or electronic applications (18,23).

In a systematic review including 14 studies on persistent symptoms in children and adolescents, the PCS prevalence in children had a surprisingly wide range between 4-66%, since few studies were settled in the absence of a control group (24). From these studies, only 3 included a control group of children and were able to justify a higher prevalence of persistent symptoms in children with COVID-19 than in healthy ones (24).

Recently, Molteni *et al* (23) recruited 1,334 children aged 5-17 years positive for SARS-CoV-2 and a matched group of children negative for SARS-CoV-2 in a prospective study based on a mobile application. Although the median duration of the disease varied significantly between the two groups (6 and 3 days, respectively), no significant differences in hospitalization or presentation in the emergency department were observed (approximately 2% of each group) (23). A limited but unignorable percentage of those children had persistent symptoms for at least 1 month and 2 months (4 and 2%, respectively) (23).

The prevalence of persistent symptoms for ≥3 months was initially shown to range from 0-27% (25,26). This variability is mainly attributed to the fluctuation in SARS-CoV-2 severity, the undetermined suspected or confirmed cases, the inconsistent methodological assessment and the transient follow-up times (25,26). Unlike PCS rates in adults (may surprisingly extend to one third of hospitalized patients), the estimated prevalence of PCS in children at least three months after the onset of the disease does not exceed 4% (13,14,27). Regarding age groups differences in PCS, children aged 6-11 years may even reach 60% of the pediatric population with PCS (14,28).

During the first two years of COVID-19 pandemic, it become evident that children represent only a minority of all confirmed COVID-19 cases worldwide which rarely exceed 20% according to Centers for Disease Control and Prevention (CDC) (29).

It is important to state that children <5 years are unable to describe symptoms, such as anosmia, ageusia or headache, that represent 'classic' acute phase symptoms, but also persistent COVID-19 manifestations. This leads to a significant restriction in COVID-19 diagnosis in children. Children exposed to SARS-CoV-2 who have not been diagnosed may require hospitalization in the future to relieve symptoms, such as cough or shortness of breath, that could constitute PCS manifestations (30). Hence, a major reason why PCS in children may be underdiagnosed can be justified as a result of the limited diagnostic tests performed on them during the acute phase of infection (31).

The incidence of PCS is difficult to estimate, as several studies indicate that the prevalence of commonly reported PCS symptoms, such as fatigue or headache, does not differ between children with positive and negative SARS-CoV-2 tests (31-33). However, Kikkenborg *et al* (34) showed that the incidence of persistent symptoms 2 months after COVID-19 was higher in convalescent adolescent patients than healthy controls.

Despite the subjective nature of the symptoms frequently described in children with PCS, Buonsenso *et al* (35) support that mental, muscoskeletal, and cardiovascular manifestations are considered the most PCS characteristic conditions of PCS in children. A recent meta-analysis showed that the incidence of PCS can approximately reach 30% of hospitalized COVID-19 children (36).

3. PCS symptoms in children

In contrast to the relatively early recognition of long-term impact of COVID-19 in older patients, there are limited data regarding the risk of persistent symptoms in children following COVID-19. The most common PCS symptoms in children and adults were depicted in Table I. Persistent symptoms commonly reported in children do not differ significantly compared to adults, including fatigue, respiratory distress, headache, myalgias, arthralgias, olfactory and gustatory disturbances, heart palpitations, concentration, and sleep disturbances (23,36,37). Therefore, 7% of children with COVID-19 and persistent symptoms had a reported poor quality of health (14). PCS can also be reported in asymptomatic children, while some manifestations can be misdiagnosed with Multisystem Inflammatory Syndrome in Children (MIS-C) (38).

Symptoms of musculoskeletal system. Fatigue is one of the most common persistent physical symptoms regardless of the disease or hospitalization status and is commonly reported in adult females (6). The exact incidence of fatigue is difficult to be

Table I. Comparison of post-COVID-19 syndrome symptoms reported from pediatric and adult studies (6,13,14,23,24,27,31,32,36,38,40-43,45,47,60,61,63,64).

Symptom	Children, %	Adults, %
Fatigue	3-87	28-87
Myalgias/arthralgias	1-61	3-25
Rhinorrhea	20-52	1-10
Headache	5-26	5-20
Depression	1-25	18-25
Sore throat	19-25	4-10
Anosmia	17-23	11-20
Anxiety	1-20	20-23
Dyspnea	6-15	12-30
Chest pain	5-12	5-22
Concentration problem	4-10	16-34
Sleep disorders	1-7	17-25

precisely estimated, given the large number of existing studies and the increased risk of recall bias from the participants (36).

Although the incidence of fatigue in children can range between 3-87% (Fig. 1) (13,23,24), it is more common in children of older ages (23%). It is also regularly reported in 30% of adolescents before the pandemic (31,38,39). Although fatigue is well tolerable and resolves soon after the acute phase, it is possible to persist for 3 months or longer, especially in intensive care unit adult convalescent individuals (40). Notably, the prevalence of exercise intolerance has been estimated to reach 5% in children with PCS (36).

Regarding myalgias and arthralgias, which may often accompany fatigue, the incidence can range between 1-61% (24). Aiyegbusi et al (41) support the idea that both are included in the most common PCS symptoms as well (25 and 20%, respectively) described by adult convalescent adult patients.

Symptoms of respiratory system. Approximately 30% of patients with severe COVID-19 hospitalized experience at least one persistent respiratory complication that often has a negative impact on individuals' daily activities (14,27,41). Many patients may experience persistent cough at least 2 weeks after the disease which resolved within 3 months, without excluding its persistence until 12 months (7,42-44). Chest pain due to respiratory complications, exertional or positional, is shown to not to be resolved soon after disease and can be persistent in up to 22% of adult patients for at least 3 months (45).

In children, sore throat and hoarseness are the most common PCS symptoms on the upper respiratory tract (23 and 5% of adolescents, respectively), while in another study rhinorrhea was included among the most common symptoms (52%) (Fig. 1) (23,31). Cough and shortness of breath are described in approximately 16 and 12% of adolescents, respectively, and are the most common respiratory symptoms of PCS (32). Persistent cough is characterized by a resolution potential of 4-8 weeks after disease onset and is prevalent in at least 1% of convalescent COVID-19 children, while shortness of breath is

rare but not unignorable (13,45). The risk of persistent dyspnea was significantly higher in children exposed to SARS-CoV-2 than in healthy controls (46,47). In adults, a study including approximately 1700 hospitalized COVID-19 patients previously hospitalized with COVID-19 in Wuhan, China, showed that the prevalence of dyspnea remains consistent six and twelve months after the onset of the disease (26 and 30%, respectively) (43).

Symptoms of the gastrointestinal and cardiovascular systems. Gastrointestinal symptoms (GI), including abdominal pain, nausea, vomiting, poor appetite, and diarrhea, are common in children and adults with COVID-19 (48,49). Abdominal pain was the only persistent GI symptom that has been well described for more than 1 month in <5% of children and its incidence in adolescents reaches approximately 5% (13,31). In contrast diarrhea is considered a relatively common persistent symptom of COVID-19, encountered in approximately 6% of both convalescent adolescents and adult patients (31,40). Poor appetite, nausea, and vomiting are even rarely present within the first 2 weeks after acute phase, since they are reported in 2.3, 1.5, and 0.8%, respectively, but in adolescents the incidence of poor appetite, as reflected by the daily meal intake, can surprisingly reach 12% (31,48) (Fig. 1). In a 6-month surveillance study for persistent COVID-19 symptomatology, the prevalence of poor appetite, diarrhea and vomiting was higher (8, 5 and 5%, respectively) (7). In children, prolonged clinical manifestations from the GI tract due to PCS should not be confused with GI symptoms frequently present in MIS-C several weeks after exposure to SARS-CoV-2. According to a recent meta-analysis, the estimated prevalence of constipation, a symptom that presents in both physical and psychological disturbances, can even reach 2% of children with PCS (36).

Except for MIS-C, the cardiovascular risk for long-term clinical outcomes is generally lower in children compared to adults. Chest discomfort rarely exceeds 6 and 9% of convalescent COVID-19 children and adolescents, respectively, while palpitations and other heart rate abnormalities range between 1-2% (31,45) (Fig. 1).

In September 2020, a case of Postural Orthostatic Tachycardia Syndrome (POTS) three weeks after COVID-19 was described (50). Despite the resolution of acute phase symptomatology, POTS persisted for over 5 months and could not be explained by any other alternative medical condition (50). Autonomic impairment is a rare but notable immune-related condition often associated with many pathogens, including SARS, but with insufficient pathophysiological clarification (51). However, it still remains questionable whether there is a direct association of autonomic impairment with SARS-CoV-2 pediatric patients and continuous surveillance will assist in the elucidation of all possible underlying mechanisms.

Symptoms of central and peripheral nervous systems. Neurological complications of PCS in children are of major significance and might take years to present and evaluated. This has already been shown by other respiratory pathogens, such as pertussis, in which preschool children after natural infection were associated with an increased risk of epilepsy in adolescence (52). The most common prolonged neurological

Post-COVID-19 long-term symptoms

Psychological and cognitive disorders 0.44–100%

* Bad mood - depression
* Sleep disorder
* Concentration problems
* Memory problems

Respiratory system 5–52%

* Cough
* Shortness of breath
* Chest pain
* Sore throat
* Rhinorrhea-nasal congestion

Gastrointestinal system 0.8–12%

* Poor appetite
* Nausea
* Vomiting
* Diarrhea
* Abdominal pain

Nervous system 15–26%

* Headache
* Dizziness
* Olfactory and gustatory dysfunctions
* Dysfonia
* Dysphagia
* Photosensitivity

Cardiovascular system 1–9%

* Chest discomfort
* Palpitations
* Postural orthostatic tachycardia syndrome

Musculoskeletal system 1–87%

* Fatigue
* Myalgias
* Arthalgias

Rare symptoms:

Dermatologic manifestations 1.2–2.7%
* Hair loss

Otorhinolaryngological and ophthalmologic manifestations 3%

* Pain
* Vertigo
* Conjunctivitis

Urogenital manifestations 1%
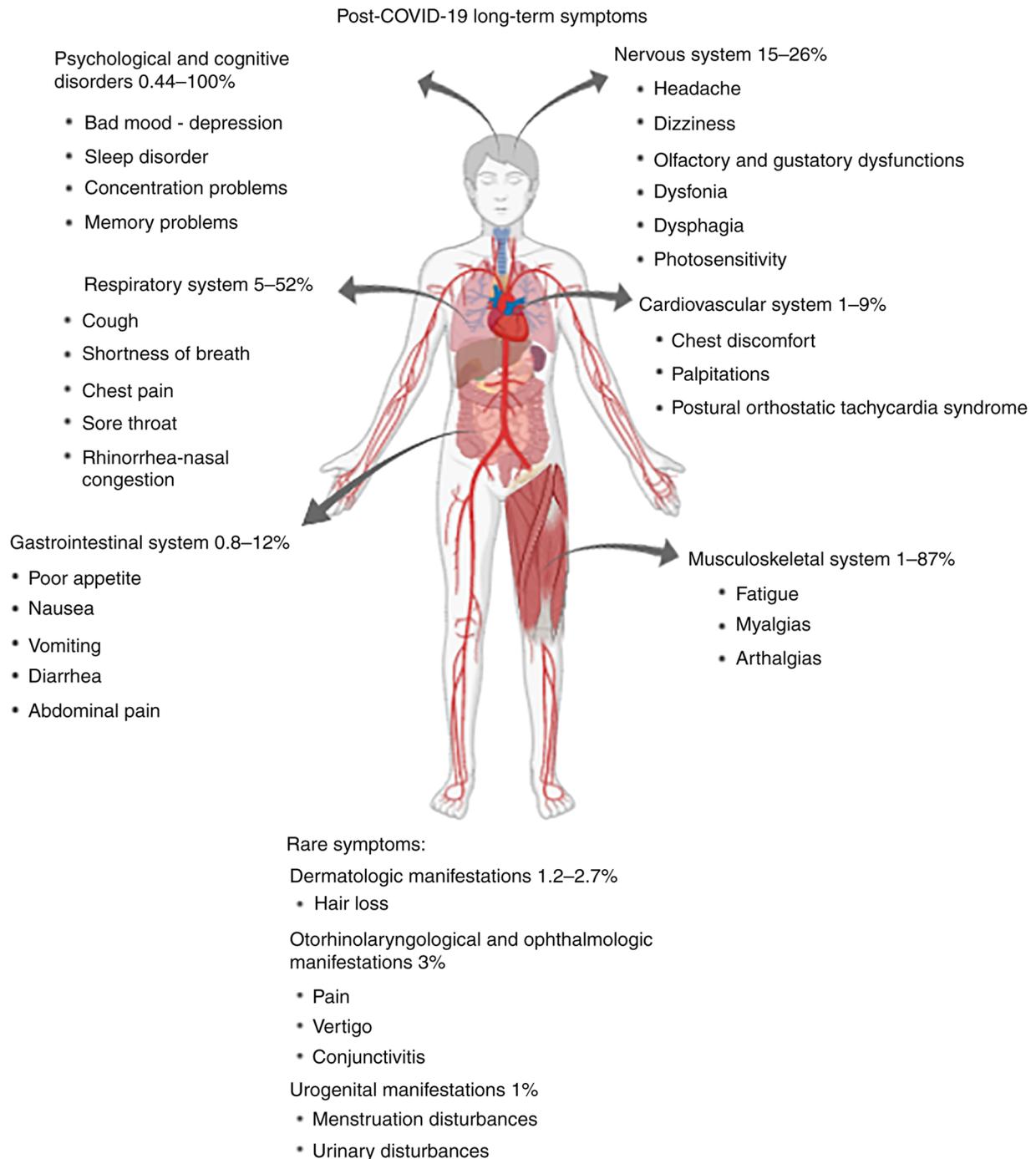* Menstruation disturbances
* Urinary disturbances

Figure 1. Post-COVID-19 long-term symptoms per biological system in children and their reported frequencies.

manifestations in adolescents are headache (26%) and dizziness with photosensitivity (15%) (32) (Fig. 1).

In a multicenter study based on neuroimaging and neurologic symptoms by Lindan *et al* (53), rare incidents of encephalomyelitis, myelitis, hypotonia, ataxia, ophthalmoplegia, and cranial nerve complications were observed in children with PCS. Guillain-Barre syndrome (GBS) with upper and lower extremities involvement is another rare but significant complication of the disease that often requires vigorous rehabilitation with motor physiotherapy in cases with sphincter disturbances or spastic quadriparesis (54). Continuous surveillance is essential for the evaluation of these complications.

Olfactory and gustatory dysfunctions are two of the most characteristic clinical manifestations of COVID-19 in both acute and convalescent phase and are significantly more common in children with COVID-19 than healthy controls (47). The majority of COVID-19 survivors describe a complete loss of smell within the first week of the convalescent phase (55). Therefore, more than 70% of adults describe a complete recovery from smell and taste disturbances within 10 days after their onset (56). Compared to women, male patients may have faster recovery rates during convalescence (57). The loss of smell has been described as one of the most common symptoms in children and adolescents (21%) with PCS and can

remain unresolved for at least 5 months after the onset of the disease in 4.7% of them (31,45) (Fig. 1). Although anosmia can present as the only clinical manifestation in approximately 15% of children with acute COVID-19, it can be detected later in the clinical evaluation of the patient, since manifestations of the respiratory tract often proceed (23,45).

Dysphonia and dysphagia have been reported as a rare complication in 9 children after MIS-C that required 1-6 months to resolve after voice therapy or invasive procedures (58). According to a recent meta-analysis, the estimated prevalence of dysphonia and dysphagia has been evaluated in 0.5-2% of children with PCS (36).

Other physical clinical manifestations. A recent meta-analysis by Lopez-Leon *et al* (36) has evaluated the prevalence of some rare prolonged clinical manifestations of children with COVID-19. Dermatological manifestations, including hair loss, are prevalent in approximately 1.2-2.7% of children with PCS, while otorhinolaryngological symptoms (such as ear pain or vertigo) and ophthalmologic manifestations such as conjunctivitis and pain are estimated at approximately 3% of children after COVID-19 (36). Urogenital symptoms, including menstruation disturbances or manifestations from the urinary tract, are notable but are rarely encountered (approximately 1%) (36).

Psychological and cognitive disorders. Psychological disorders are also common during recovery from COVID-19 and were described from the first months of the pandemic (45). In a longitudinal study of COVID-19 convalescent individuals from China, approximately 25% of participants reported at least one persistent psychological symptom 3 months after the onset of the disease (6). Among 142 ICU survivors, anxiety, depression and post-traumatic symptoms were reported in 23, 18, and 7%, respectively (59). Interestingly, COVID-19 patients with a free prior psychiatric history were associated with a higher risk of developing a 1st psychiatric episode at least 3 months following COVID-19 compared with those recovering from other medical illnesses, such as influenza and other respiratory infections (60). Depression was reported in approximately 15% of hospitalized patients with COVID-19, while sleep difficulties were encountered in approximately 25% of COVID-19 patients six months after discharge (9,60,61).

Cognitive disorders, such as concentration and memory problems, have also been reported in patients in the ICU and non-ICU. In a study from the United Kingdom that included 100 hospitalized and ICU-admitted COVID-19 patients after hospital discharge, approximately 16 and 34% of them reported a new-onset or worsened concentration problem, while a temporary memory impairment was reported in 18 and 19%, respectively (40). Logistic regression models in SARS-CoV-2 individuals without prior documented neurological symptoms have verified that even mild SARS-CoV-2 infection was associated with 18 times greater odds of cognitive decline, as defined by a 4-point decrease in Montreal Cognitive Assessment (MoCA) scores (62).

In addition to persistent physical symptoms, concerns have been raised about the long-term impact of SARS-CoV-2 on the psychological and mental health of convalescent children. A meta-analysis including 29 studies in children and

adolescents from various countries underscores that 25% of children and adolescents recovered by COVID-19 express depressive symptoms, while increased anxiety disorders reached 20% (63). This study also showed that depression and anxiety rates were doubled during the pandemic compared to years before COVID-19 (63). A recent meta-analysis showed that mood and sleep disturbances in children with COVID-19 can exceed 16 and 8% in the convalescent phase, while concentration and learning difficulties can be as common as in 6% of children with COVID-19 (36). In contrast, speech disorders are rarely encountered (0.44%) in children after COVID-19 (36).

The indirect effects of social isolation and school closures during the pandemic period had several consequences. The use of electronic media by children has increased worryingly (100%), they reduced physical activity (80%), increased their BMI (60%), increased learning difficulties (50%) and sleep disorders (45%) (64) (Fig. 1). The prevalence of weight disturbances has been estimated to reach 4% in children with PCS (36).

4. Risk factors associated with PCS in children

Gender plays a dominant role as a predisposing factor to persistent symptoms in children. Compared to men, women are characterized by an increased incidence of symptoms such as joint pain or psychological and cognitive disturbances that may even reach 79% (12,18). As in children, women are more prone to persistent COVID-19 compared to men (33% vs. 47%, respectively) (65). There are some of the studies in which male gender predominates in PCS in children and adolescents, however, these studies do not use a control group (26,65,66).

PCS is positively associated with the number of underlying medical conditions that consist risk factors for severe disease and prolonged hospitalization (65). Risk factors that are associated with PCS in children and adolescents include obesity, impaired medical history of mental health, allergies, prolonged hospitalization and MIS-C (31,45,65,67). Risk factors for PCS in adults include female gender, increased age, obesity, hypertension, asthma and immunosuppression with estimated odds ratios (ORs) ranging from 1.3 to 2.3 (68). Although early published data were indicative of a 2-week recovery schedule in convalescent patients with mild disease and 3 months or longer for those with severe disease, the resolution is characterized by significant heterogeneity (69).

Role of adaptive immunity in PCS. According to the UK Office for National Statistics, the first dose of any COVID-19 vaccine results in a 13% decrease in self-reported PCS symptoms in individuals with confirmed COVID-19 before vaccination (70). Compared to the first, the second dose was associated with an additional 9% decrease in reported prolonged COVID-19 symptoms, and vaccinees developed long-term complications that significantly prevented daily activities less frequently than unvaccinated individuals (70). Antonelli *et al* (71) found that vaccinated individuals after the second dose have a reduced risk of persistent symptoms for at least 28 days by 50%. However, no significant correlations of prolonged symptoms with antibody titers elicited by vaccination or viral load in COVID-19 breakthrough vaccines have been established (72). Since the absolute frequencies of COVID-19 vaccination in

children are lower compared to adults (73), this could be a reason why children could be more prone to PCS despite the low reported incidence of the syndrome.

According to current evidence, it is possible that certain immunological conditions could predispose to PCS. Increased levels of inflammatory cytokines during the acute phase of the disease in adults, such as interferon-α (IFN-α), granulocyte colony stimulating factor (G-CSF), TNF-α and interleukins IL-1β, IL-6, IL-13 and IL-17 or activation of lymphocyte subpopulations, such as Th9, CD8$^+$ effector T cells or CD4$^+$ effector memory T cells, could predispose to long-term complications of the disease (74). In a multicenter prospective study involving 175 patients who were followed for a year for long-term complications of the disease, a positive association of PCS and lower levels of IgM and IgG3 antibodies was observed (75). The decryption of the immune mechanisms elicited by SARS-CoV-2 infection will contribute to the detection of more prognostic immunobiomarkers related to PCS.

In a large-scale cohort study involving children and young adults with COVID-19, persistent symptoms were reported more frequently 3 months after the disease onset in the age group 11-17 years (32). Since the first trimester coincides with the peak of antibody levels after natural infection (our unpublished data), a possible association between antibody levels and PCS could be implemented. Most studies currently focus on PCS in adults and children aged <6 years (23,31). Since children aged 1-6 years have relatively higher antibody titers compared to other age groups of childhood (30), future studies should illuminate a possible underlying pathophysiological basis that associates immune responses with PCS in children <11 years old.

Based on these results and despite the limited data on the impact of vaccination in PCS in children, it is reasonable to support massive vaccination policies in children not only for critical prevention of COVID-19 and MIS-C, but also for long-term indirect effects.

5. Possible pathophysiological mechanisms for PCS in children

Children have fewer comorbidities and typically have milder clinical manifestations compared to adults who rarely require hospitalization. This mild clinical outcome of acute SARS-CoV-2 infection alongside the decreased hospitalization rates result in diminished follow-up assessment of children in healthcare facilities (46). In an observational study that investigated long-term complications of COVID-19 in children, approximately 40% of the initial population typically responded to follow-up evaluation (46). This is indicative of the underestimation of PCS in children, as it becomes difficult to record physical or psychological symptoms of patients lost to follow-up.

Why children are less likely to develop life-threatening physical complications of the disease is multifactorial and is attributed to the vital early mucosal immune response, the reduced cytokine release syndrome, and limited comorbidities (76). The expression of the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 (TMPRSS2) is quantitatively lower in children compared to adults (77).

The angiotropic nature of the disease has been well described in adults for acute and delayed manifestation and raised the awareness in children with the existence of post-inflammatory condition of MIS-C. Hyperinflammatory and hypercoagulable states alongside cytokine release syndrome can prove harmful to myocardial cells leading to a wide variety of cardiovascular complication including thromboembolic and ischemic events, myopericarditis, arrhythmias and heart failure in both adults and children (37,77,78). Furthermore, an increased expression of the ACE2 receptor has also been found in sustentacular cells of the olfactory epithelium (79). It is reasonable to hypothesize that decreased expression of the ACE2 receptor in the cardiovascular, respiratory, or GI system could be associated with lower proportion of long-term complications involving these systems.

In fatigue, possible pathophysiological mechanisms are multifactorial and range from central nervous system (CNS) implementation to psychological factors (68). Long-term fatigue is usually associated with prolonged hospitalization, CNS inflammation and sarcolemma damage of the skeletal muscles, but although all of these etiologies are relatively rare in children, they may only partially explain the decreased incidence of fatigue compared to adults (68). The impact of the pandemic in children should not be underestimated regarding only psychological, but also physical complications such as fatigue, although more evidence is required for this hypothesis to be enlightened.

Despite the underestimation of prolonged physical symptoms after COVID-19, the prevalence of psychological symptoms in children and adolescents is considerably higher compared to adults (80). Although school closure and lockdown measures are of great importance in preventing long-term manifestations of the disease, nevertheless they have a negative impact on the psychosocial balance of children (81). During the pandemic, children were forced to distance themselves from their friends, sports, and educational activities (81). The age-dependent vulnerability of the pediatric population to mental health disturbances, including depression and anxiety, requires a longitudinal assessment by specialists to evaluate long-term psychological aspects.

There is insufficient evidence regarding long-term neurologic and cognitive disorders of children. Immunologic response to CNS infections is modulated by astrocytes that act as antigen-presenting cells and by endothelial cells that mediate inflammatory response and cytokine release (81,82). However, the mechanisms by which SARS-CoV-2 traverses the blood-brain barrier and enters the CNS remains poorly understood. Given the neurotropic nature of SARS-CoV-2, chronic inflammation of the brain stem by leukocytes and the age-dependent blood-brain and blood-cerebrospinal fluid barrier of babies <4 months (68,82,83), long-term neurologic and cognitive impairment could not be excluded, but it is still difficult to accurately evaluate.

6. Postinfectious syndromes after other infectious diseases

The question on the existence of prolonged clinical manifestations attributed to different viral and non-viral pathogens has been set for decades (84). Some of the most common pathogens that are associated with post-infectious syndromes include

respiratory tract infections (for example influenzae H1N1), EBV, measles, mumps, rubella, Ebola, *Coxiella burnetti*, *Borrelia*, *Giardia lamblia*, Dengue, West Nile virus, VZV, Coxsackie B, Chikungunya, Polio, *Salmonella, Shigella, Yersinia, Campylobacter,* and *Streptococcus pyogenes* (84,85). Post-Ebola syndrome is characterized by fatigue, myalgias, arthralgias, hearing loss, dysphagia, ophthalmologic manifestations, neurocognitive disorders, and sleep disturbances (86-89). Post-treatment Lyme disease syndrome is characterized by fatigue, myalgia, arthralgia, irritability, neurocognitive disorders, and sleep disturbances (90,91). Post-chikungunya syndrome is characterized by fatigue, myalgias, arthralgias, hearing loss, ophthalmologic manifestations, hair loss, irritability, neurocognitive disorders, sleep disturbances and depression (92-94). Q-fever fatigue syndrome is associated with fatigue, fever, myalgias, arthralgias, shortness of breath, headache, lymphadenopathy, ophthalmologic manifestations, teeth problems, fasciculation, irritability and neurocognitive disorders (95-98). However, most of these studies refer to adults, and there is not enough evidence in the pediatric population.

In contrast to the syndromes mentioned above, post-infectious syndrome after infectious mononucleosis has been well described in the pediatric population and especially in adolescents, with prolonged fatigue being the predominant and most characteristic manifestation that can last for over 6 months (99). Chronic fatigue syndrome has also been associated with other viral pathogens, including pandemic influenzae (H1N1), VZV, polio virus, Coxsackie virus B, West Nile and Dengue (100-105). Arthralgias, another common prolonged post-infectious syndrome, has been associated with mumps, rubella, and GI tract infections, such as *Salmonella, Shigella, Yersinia,* and *Campylobacter*, as reactive arthritis (84,106).

7. Conclusions

COVID-19 pandemic has resulted in a growing population of pediatric and elderly patients with a wide range of persistent symptoms several weeks after acute SARS-CoV-2 infection. The prevalence of persistent symptoms in children is significantly limited compared to adults, but remains considerable. The differences between the three definitions of PCS (WHO, CDC and NICE) alongside the lack of uniformly data collection, analysis methods and control groups among the different studies raise questions about the incidence precision of PCS in children. In order the exact incidence of the syndrome in children to be approached and the underlying pathophysiological mechanisms to be enlightened, future longitudinal studies should include control groups, detailed record of physical and psychological clinical features and frequent follow-up schedules.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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