A Systematic Review of Persistent Clinical Features After SARS-CoV-2 in the Pediatric Population

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abstract

CONTEXT: Long-term health effects after coronavirus disease 2019 (COVID-19) have been increasingly reported but their prevalence and significance in the pediatric population remains uncertain.

OBJECTIVE: To present the prevalence and characteristics of the long-term clinical features of COVID-19 (long COVID) in the global pediatric population.

DATA SOURCES: PubMed, Embase, Web of Science, Cochrane Library, WHO COVID-19 database, google scholar, medRxiv, bioRxiv, and multiple national public health databases.

STUDY SELECTION: Published articles and preprints from December, 2019 to December, 2022 investigating the epidemiology and characteristics of persistent clinical features at least 3 months after COVID-19 in children and adolescents (0–19 years old) were included.

DATA EXTRACTION: Study characteristics and detailed description of long COVID were extracted into a predefined form.

RESULTS: Twenty seven cohorts and 4 cross-sectional studies met the inclusion criteria and involved over 15 000 pediatric participants. A total of more than 20 persistent symptoms and clinical features were reported among children and adolescents. 16.2% (95% confidence interval 8.5% to 28.6%) of the pediatric participants experienced 1 or more persistent symptom(s) at least 3 months post COVID-19. Female gender might be associated with developing certain long COVID symptoms.

LIMITATIONS: Included studies presented with great heterogeneity because of significant variations in the definition of "long COVID," follow up duration, and method. There could be nonresponse and other potential bias.

CONCLUSIONS: Persistent clinical features beyond 3 months among children and adolescents with proven COVID-19 are common and the symptom spectrum is wide. High-quality, prospective studies with proper controls are necessary in the future.

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Drs Bhutta and Tang conceptualized the study, supervised the whole process including its design, and critically reviewed and revised the manuscript for important intellectual content; Dr Jiang designed the study, conducted the systematic literature search, designed the data collection, extracted data from literature, and drafted the initial manuscript; BSc Li and Ms Nie also conducted the literature search, extracted data from literature, conducted the data analysis, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Given that more than 758 million coronavirus disease 2019 (COVID-19) cases have been confirmed worldwide with rates still escalating,[1] increasing attention is being paid to the long-term effects of COVID-19 on population health. Several long-term clinical features post-COVID-19 have been observed, mainly in the adult population,[2] involving multiple organs and systems.[3,4] A clinical case definition for post-COVID-19 condition (long COVID) was developed by the World Health Organization (WHO) with multiple stakeholders in October 2021 that can be applied to all settings.[5]

During the early stages of the COVID-19 pandemic, neonates, children, and adolescents aged less than 19 years occupied a small proportion (1% to 10%) of the total reported COVID-19 cases.[6,7] They were also more likely to present with a milder clinical course and more favorable short-term outcomes compared with adults.[6–10] However, with the subsequent surge of cases caused by the Δ and *o* variants, and the fact that a large proportion of children under 12 years old still remain unvaccinated globally, the number of neonates, children, and adolescents infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been increasing significantly.[11–13] With the increased epidemiologic burden of COVID-19, the long-term health effects of SARS-CoV-2 infection on this vulnerable group requires greater attention. It was thought at first that the pediatric population was relatively spared from the long-term effects of COVID-19 after infection,[14] but this changed rapidly with increasing reports and studies of pediatric patients not fully recovering from acute COVID-19.[15–20] Furthermore, since it was first reported in April 2020, multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19,[21–24] also called pediatric inflammatory multisystem syndrome,[22] has become increasingly recognized and widely studied worldwide. Not only can MIS-C lead to serious clinical acute presentation in the short term, it can also impact pediatric patients' long-term health. For example, MIS-C can cause the formation of coronary artery aneurysm that can negatively impact cardiac function.[25] However, long-term health data on neonates, children, and adolescents infected with SARS-CoV-2 (including MIS-C patients) are limited and of varying quality.

Our objective for this review was to synthesize and evaluate current evidence on the characteristics of the long-term clinical features of SARS-CoV-2 infection, defined as persistent or new onset clinical features and laboratory findings at least 3 months after the index infection, in the global pediatric population (0–19 years old) so as to inform clinical practice and public health policy making.

METHODS

We evaluated the long-term clinical features of SARS-CoV-2 infection in neonates, children, and adolescents defined as new, recurring, or persistent signs, symptoms, and laboratory findings that occur 3 or more months after a confirmed infection with SARS-CoV-2 in neonates, children, and adolescents 19 years old or younger. We also evaluated other factors associated with the development of long-term symptoms and/or laboratory findings in children and adolescents' postinfection.

Literature Search

A systematic and comprehensive search of published papers was conducted in PubMed, Embase, Web of Science, Cochrane Library, WHO COVID-19 Database, China National Knowledge Infrastructure Database, WanFang Database, Latin American and Caribbean Health Sciences Literature, and Google Scholar, covering a timeline from December 1, 2019 to February 16, 2022. Then, we did a supplementary search in December, 2022 for the most updated literature. Although the WHO criteria for "long COVID" was not established until October 2021, there might be earlier studies reporting post-COVID signs and symptoms that met the later-established WHO criteria. Therefore, we decided to search the databases since December 2019, the beginning of the COVID-19 pandemic, so as to ensure capturing all qualified studies. Preprints from medRxiv (https://www.medrxiv.org), bioRxiv (https://www.biorxiv.org), and ChinaXiv (http://www.chinaxiv.org/home.htm) were also covered. Complementary searches were conducted manually through the search of national public health websites, the United States Centers for Disease Control and Prevention, and news of World Health Organization (WHO). All reference lists of retrieved articles were examined for relevant papers. There was no language restriction.

Search strategies were developed for each database with a combination of controlled vocabulary and free text (ie, MeSH terms, Emtree terms). The following search terms were included: "severe acute respiratory syndrome coronavirus 2," "novel coronavirus 2019," "2019 nCoV," "COVID-19," combined with "children," "neonates," "infants," "adolescents," "pregnancy," "pregnant women," "long," "long-term," "post," "post-acute," "chronic," "persistent," "prolonged," "follow-up," "outcome," "consequence," "sequalae," and "complication." An information specialist with extensive experience in systematic reviews was consulted. Specific search queries for each database are provided in Supplemental Tables 4–7.

All search results were uploaded into Covidence Systematic Review Software (Veritas Health Innovation, 2016) for the screening process.

Inclusion and Exclusion Criteria

In this systematic review, we included cross-sectional and cohort studies investigating the prevalence and/or presentations of the long-term effects of SARS-CoV-2 infection in the general population of neonates, children, and adolescents (0–19 years old) postinfection. Studies that included participants beyond the age group and those did not report on age-disaggregated data were excluded. Studies only focusing on a subgroup of the pediatric population, eg, MIS-C, immunodeficiency children, were excluded. SARS-CoV-2 infection status should be confirmed by laboratory testing, ie, polymerase chain reaction (PCR) test, serology antibody test. Long-term effects and outcomes were defined in this review as persistent clinical features ≥3 months after the COVID-19 diagnosis. We included all studies reporting long COVID signs and symptoms at least 1 month from SARS-CoV-2 infection at the very beginning, and then further screened these studies' follow-up details. For studies with participants followed less than 3 months, if they reported disaggregated data for those with a follow-up duration ≥ 3months, they were included. Their subgroup data for those with ≥ 3 months follow-up were extracted and analyzed.

Case series, review articles, opinion articles, communications not presenting on data or description of long-term outcome of COVID-19 in neonates, children, and adolescents, as well as interventional, quasi-experimental and modeling papers were excluded. Studies with possible duplication of cases demonstrated by overlapping time periods and same institutions, cities, and countries from where reported cases are from were also excluded unless they reported the results of different lengths of follow-up.

Study Selection

After search results had been uploaded into Covidence, duplicates were identified with Covidence's automatic deduplication function. A team member (L.J.) then manually reviewed identified records to confirm duplication. The final deduplicated library was used for title-abstract screening. Two review authors (L.J. and X.L.) independently reviewed each title and abstract. A decision whether to obtain the full text of the abstract based on the inclusion and exclusion criteria specified above was made using designations of "include," "exclude," or "unclear." The full text article was obtained if at least 1 reviewer marked the study as "include" or "unclear." For studies not written in English (French, Spanish, Portuguese, Italian, and German), if a decision could not be made by reading the English abstract, our colleagues who could read Chinese (L.J. and X.L.) and French (L.J.) and Google Translate helped with translating them into English.

In reference to the criteria specified in the earlier section, the decision was made by the same reviewers to include or exclude the study. Disagreement between the 2 reviewers were discussed, and if no consensus was reached, a third reviewer (J.N. or K.T.) casted the deciding vote to resolve the conflict.

Data Extraction

Two reviewers (L.J. and X.L.) independently reviewed and extracted study data using a predefined form after selection of eligible studies by the full-text screening process. Data extracted included: study title, authors, year and month of publication, country, language of the study, study design, study period, setting, population (general population, neonates, children and adolescents specific), sample size, race, age, gender, comorbidities, SARS-CoV-2 infection confirmation method, severity of acute SARS-CoV-2 infection (eg, asymptomatic, mild, moderate, or severe symptoms, MIS-C or pediatric inflammatory multisystem syndrome diagnosis; hospitalization, ICU admission), duration of follow-up, follow-up method, persistent or new symptoms reported at follow-up, physical examination or laboratory findings at follow-up, and other clinical conditions related to post-COVID-19 infection (eg, readmission, quality of life score, etc).

Data Synthesis

For each dichotomous outcome, the weighted mean prevalence (in proportion) and the 95% confidence interval (CI) were calculated. If multiple measures are reported for an outcome, the measure most commonly reported across all studies was used. Only self- and caregiver-reported symptoms reported by 2 or more studies were included in the meta-analyses to generate a pooled estimate. Descriptive analyses and meta-analyses were performed using SPSS Statistics 22 and Comprehensive Meta-analysis version 2.2.027, respectively. A random-effect model was used for the meta-analyses as it best accommodated the moderate to high level of variation among included studies.

The characteristics, biases, and results of the included studies were summarized using a narrative approach. Statistical heterogeneity across studies was evaluated using the I^2 statistic. I^2 values equal to or above 50% signified "significant" heterogeneity. In addition, heterogeneity was tested using the χ-square test and visual inspection of the forest plot. Meta regression using the metagen and metareg functions of the meta package in R (Version 4.0.3) was used to identify the linear relationship between demographics and medical history with long COVID symptoms.[26] The results are presented as point estimates of coefficient and 95% CIs. The level of statistical significance is set at 5% ($P < .05$) for all statistical analyses.

Assessment of Methodological Quality and Risk of Bias

We consider cross-sectional studies and studies collecting long COVID symptoms in a retrospective fashion are predisposed to a higher risk of recall bias on this topic, given that their participants needed to recall the nature, duration, and intensity of any new, persistent, or recurring symptom they had experienced after SARS-CoV-2 infection. Therefore, we only assessed cohort studies that prospectively identified or collected participants' persistent clinical features after SARS-CoV-2 infection for their methodological quality.

The study quality assessment tool for observational studies developed by the National Heart Lung and Brain Institute and the Research Triangle Institute International was used (Supplemental Table 8).[27] Quality was assessed according to the study question (ie, was the objective and study population clearly defined), methods (ie, study population selection, sample size, measurement of exposure and outcome), and results (eg, length and loss of follow-up). Two reviewers (L.J. and K.T.) independently assessed each included study for methodological quality and assigned an overall quality rating for each study (ie, low, moderate, high risk of bias). A final rating for each study was decided by comparing the rating of both reviewers. A third reviewer (X.L. or J.N.) was consulted to resolve any disagreements.

RESULTS

Our preliminary and updated systemic literature search yielded 4660 results, of which, 243 passed initial screening; full articles were then obtained and reviewed. An additional 6 articles were identified via manual searching and reference-checking. Twenty seven cohort studies (19 prospective cohorts[18,20,28–44] and 8 retrospective cohort studies[45–52]) along with 4 cross-sectional studies[53–56] on the pediatric population with a post-COVID-19 follow-up duration of at least 3 months or disaggregated data for participants followed-up for ≥3 months were included in our final systematic review (Fig 1). Studies' characteristics are summarized in Table 1.

Characteristics of Included Studies

Nineteen cohort studies prospectively collected information related to any persistent clinical features or laboratory findings in participants with a laboratory-confirmed SARS-CoV-2 infection. The majority of selected studies were from Europe (13 in total). One study was conducted in multiple countries.[37] The remaining were from Iran (2), Australia (1), China (1), and the United States (1) (Table 1). The total number of children and adolescents (0–19 years old) with confirmed COVID-19 diagnosis and were followed-up for long COVID for at least 3 months was over 15 000, ranging from 15 to 11 950 in each study. The follow-up time varied from 3 to over 12 months. Four studies[20,34,38,40] mainly reported results from participants with a follow-up duration of greater than 12 months. Eight studies exclusively included children and adolescents who were hospitalized because of SARS-CoV-2 infection[29,32,33,38,39,41,43,44]; however, in 1 study from China,[33] hospitalized COVID-19 children were either asymptomatic or only with mild symptoms. The participants of remaining studies were either mainly outpatients during their acute infection stage or recruited from the community. Two studies included a mixed adult and children or adolescent population and reported their results separately.[30,36] Two studies had an overlapping study population[34,42]: they were part of the Children and Young People with Long COVID Study (the CLoCk study), a national, matched, longitudinal cohort study describing the clinical phenotype and rate of post-COVID physical and mental problems in children and adolescents in England, and reported the 3-month and up to 12-month follow up results for adolescents aged 11 to 17 years, respectively. Five studies included a matched control group of SARS-CoV-2 tested negative counterparts to compare the prevalence and/or clinical features of persistent symptoms and signs between groups.[33,34,36,37,42] Two studies collected information from routine data from the health insurance system.[36,43] Four studies collected data via questionnaires or data collection forms[18,34,35,42] and 6 studies via telephone interview.[20,29,32,37,38,40] The remaining 7 studies collected data through clinical assessment and evaluation.[28,30,31,33,39,41,44]

For included cohort studies identifying persistent symptoms after acute SARS-CoV-2 retrospectively, 3 studies[47,49,50] used telephone interview to collect data from pediatric patients with a previous SARS-CoV-2 infection, mainly about the existence, nature, and duration of persistent symptoms after recovering from acute COVID-19. The remaining 5 studies recruited children and adolescents who already presented with persistent symptoms after SARS-CoV-2 infection as the study initiated and evaluated and/or followed these participants afterward.[45,46,48,51,52] Information such as the time elapsed from COVID-19 diagnosis to the emergence of new, persistent symptoms was collected retrospectively in these studies. The majority of included cross-sectional and retrospective cohort studies used questionnaires, surveys, and telephone interviews to identify long-term clinical features of COVID-19.

Risk of Bias of Included Studies

Six prospective cohort studies were evaluated to have potentially high risk of bias, 8 with moderate risk, and 5 with low risk of bias (Supplemental Fig 4). However, certain items were unachievable. For example, assessors were typically not blinded to the SARS-CoV-2 infection status of participants. Furthermore, the recruitment process, response rate, sample size justification, and power descriptions were not clearly described in the majority of studies. Some items cannot effectively distinguish studies with different levels of quality. For instance, all included studies had a follow-up duration of at least 3 months and were rated as "low risk of bias" on "sufficient follow-up frame."

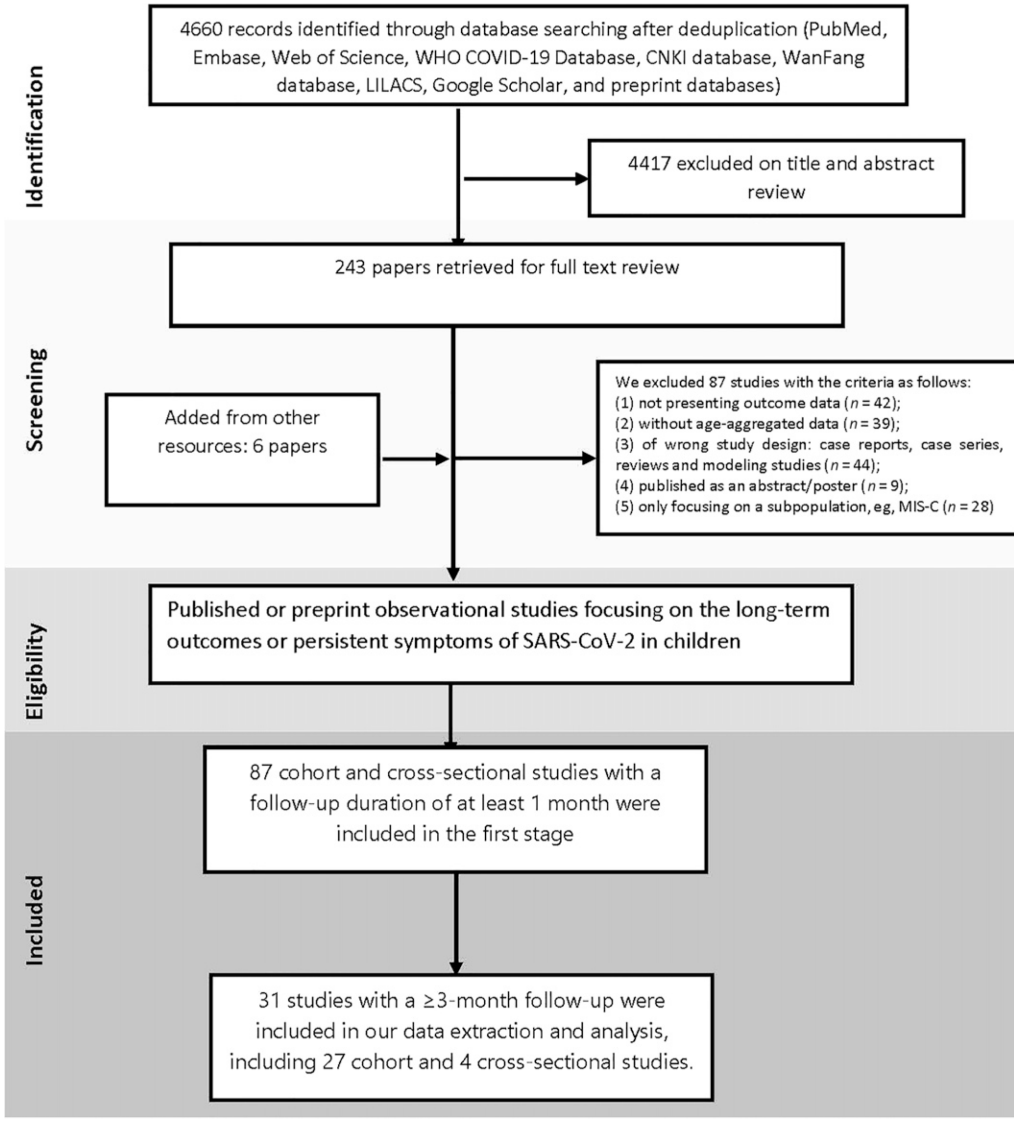

FIGURE 1
PRISMA flow diagram of the study selection process.

Persistent Clinical Features of COVID-19 in the Pediatric Population

More than 20 persistent or new onset symptoms after the acute infection of SARS-CoV-2 were reported in children and adolescents, including fatigue, depression, sleep disturbance, cough, throat pain, gastrointestinal symptoms, etc.

The vast majority of included studies described these self- or caregiver-reported symptoms as "persistent" or "long-term" symptoms after COVID-19. Among them, some specified these symptoms did not exist before the index SARS-CoV-2 infection (ie, described as "new," "novel"), whereas others did not. Therefore, we used the term "persistent symptoms" in our review to represent them. There was a very limited number of studies that had reported signs and laboratory findings after COVID-19 in the general pediatric population and their findings were very diverse. (Table 2)

We were able to perform a meta-analysis on 12 cohort studies prospectively identifying and collecting information related to the persistent clinical features 3 months after acute SARS-CoV-2 infection in a general pediatric COVID-19 population, including more than 6000 children and adolescents. The other 7 cohort studies were not included in the meta-analysis mainly because they only provided quantitative results for laboratory findings only or they reported the incidence rate of persistent symptoms instead of their absolute numbers. The pooled proportion of postacute COVID-19 symptoms in children and adolescents recovered from COVID-19 are presented in Fig 2. There were 16.2% (95% CI 8.5%–28.6%) of children and

TABLE 1 Characteristics of Included Studies ($n = 31$)

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
Prospective cohort studies ($n = 19$)									
1	Asadi-Pooya AA, et al[29]	Iran	Feb to Nov 2020	58	Hospitalized patients	Children and adolescents (6–17y) admitted to any hospitals with PCR-confirmed COVID-19. The participants' duration of hospital-stay for COVID-19 ranged from 1 d to 56 d (mean±SD 7±9 d), whereas 10 patients needed ICU admission.	Researchers randomly selected and contacted every other patient who were at least 3 mo after the acute COVID-19 phase in the database.	In the telephone interview, the researchers inquired about the participants' current health status and symptoms or complaints during the past 7 d.	26 participants reported long COVID symptoms at least 3 mo after the acute COVID-19 phase, including: fatigue, shortness of breath, exercise intolerance, weakness, walking intolerance, cough, sleep difficulty, muscle pain, joint pain, headache, and excess sputum. The majority of these symptoms were mild and tolerable, but a minority of them were rated as severe and disabling (eg, exercise and walking intolerance, sleep difficulty).
2	Blomberg B, et al[30]	Norway	Feb 2020 to Apr 2020	16	Community and hospital	Adults and children or adolescents (0–15 y) who were diagnosed with COVID-19 at the city's centralized testing facility and those admitted to the city's 2 hospitals with COVID-19 were consecutively recruited.	They were prospectively followed till 6 mo after the acute COVID-19 phase. Data related to children and adolescents were presented separately.	Clinical assessment for persistent symptoms were performed at 6-mo follow-up.	Among the 16 children and adolescents participated in this study: any symptoms: 2 (13%); stomach upset: 1 (6%); disturbed taste or smell: 2 (13%).
3	Bogusławski S, et al[41]	Poland	Mar 2020 to Mar 2021	41	Hospitalized patients	Consecutive children (0–18 y old) diagnosed with COVID-19 pneumonia and hospitalized.	Children admitted and diagnosed with COVID-19 pneumonia were included and underwent follow-up visits postdischarge to assess the pulmonary sequelae of COVID-19.	Follow-up assessment included medical history, physical examination, lung ultrasound, and pulmonary function tests. The first follow-up visit was performed 3 mo after initial hospital discharge. Patients with abnormal findings were invited for a second follow-up visit after the next 3 mo.	Persistent symptoms were reported by 7 (17.1%) children, the most common was decreased exercise tolerance (57.1%), dyspnea (42.9%), and cough (42.9%). The most prevalent abnormalities in LUS were coalescent B-lines (37%) and small subpleural consolidations (29%). The extent of LUS abnormalities was significantly greater at the first than at the second follow-up visit ($P = .03$). There were no significant differences in PFTs results neither between the study group and healthy children nor between the 2 follow-up visits in the study group.

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
4	Buonsenso D, et al[40]	Italy	Apr 2020 to Apr 2021	138	Both children hospitalized and community patients assessed in the outpatient unit	Children (≤18 y old) diagnosed with SARS-CoV-2 infection using RT-PCR.	A prospective cohort study including children (≤18 y old) with PCR-confirmed SARS-CoV-2 infection and their household members. Mixed adult and pediatric population.	Participants were assessed via telephone and face-to-face visits up to 12 mo (every 3 mo) post-SARS-CoV-2 diagnosis of household index case, using the ISARIC COVID-19 follow-up survey.	During the acute infection, 2.4% (6 of 249) of children were admitted to hospital, of these 33.3% (2 of 6) required PICU admission. 138 in 249 children were interviewed after 6–9 mo post-SARS-CoV-2 testing, with the following persistent symptoms the most commonly reported: insomnia, asthenia, feverish, constipation, cough, wt loss, and rash. In the pediatric group, there was a significant difference in persisting symptoms between those with confirmed SARS-CoV-2 infection compared with controls at 1–3 mo follow up, but not at 6–9 mo.
5	Doshi JA, et al[43]	USA	Mar 2020 to Feb 2021	372	Hospitalized patients	The final study sample included 372 children hospitalized with COVID-19 and 183 children hospitalized with MIS-C.	The data contain medical (emergency, inpatient, outpatient) and pharmacy claims submitted by health care providers for third party reimbursement after delivery of services to insurance enrollees and have been used in prior studies of COVID-19. From this data source, they identified 2 mutually exclusive groups of children 0–17 y old hospitalized with a primary diagnosis of COVID-19 or a primary or secondary diagnosis of MIS-C.	Participants were required to have continuous enrollment in the 5 mo postdischarge to assess diagnoses for sequelae of SARS-CoV-2 and 5-mo preadmission to assess whether sequelae were new diagnoses. The median time from discharge to the last visit related to SARS-CoV-2 sequelae during follow-up was 18.4 wk and 15.4 wk in the COVID-19 and MIS-C group, respectively.	Over 90% of children in both groups had at least 1 SARS-CoV-2 sequelae related health care visits with a median of 6 visits in the 5 mo postdischarge. Nearly one-quarter (23.7%) of the children hospitalized with COVID-19 had 15 or more visits related to SARS-CoV-2 sequelae over the 5-mo follow-up. At least 25% of the children in both groups continued to have a SARS-CoV-2 sequelae related health care visit in month 5 after discharge. Among the COVID-19 group, 20.4% were readmitted and 18.0% had an emergency department visit related to SARS-CoV-2 sequelae in the 5 mo after their index hospitalization; corresponding rates were lower in the MIS-C group. The overwhelming majority of postdischarge outpatient visits in both groups were related to SARS-CoV-2 sequelae. The median number of outpatient visits in the 5-mo postdischarge period were

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
									substantially higher than in the 5-mo preadmission period in both groups.
6	Esmaeilzadeh H, et al[39]	Iran	Feb 2020 to Jan 2021	69	Hospitalized pediatric patients	Aged $<$ 18 y and having received the diagnosis code of COVID-19 (U07.1) according to ICD-10. Presumed COVID-19 patients, whom PCR did not confirm SARS-CoV-2 infection were excluded.	This prospective study was carried out in a tertiary referral center. During the COVID-19 pandemic, 69 hospitalized pediatric patients admitted with COVID-19 were observed during the study period. Clinical and laboratory data were recorded.	After discharge, patients were followed and visited for cough and asthma evaluation by clinic visit at 1, 2, and 6 mo and by phone in other monthly follow-up (the patients would be asked to come to the clinic if necessary).	Patients with asthma-like diagnoses in follow up defined as asthma-like groups, and patients without any sign of asthma were categorized as the nonasthma group. In follow-up, most of the COVID-19 hospitalized patients (n = 42) (58.5%) were not affected by asthma-like symptoms. 60.9% of the COVID-19 patients were male. The asthma-like group cases had a significantly familial history of asthma (63.0%), past medical history of asthma (33.3%), and allergic rhinitis (85.2%). Rates of signs and symptoms during hospitalization were significantly higher in patients with COVID-19 and past medical history of asthma.
7	Funk AL, et al[37]	Multinational study	Mar 2020 to Jan 2021	1884	Community	Children and adolescents (younger than 18 y) who underwent testing for SARS-CoV-2 at participating ED departments and completed 90-d follow-up.	The study included 8 countries: Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the United States. Participants were recruited in 39 pediatric EDs in the Pediatric Emergency Research Network, including a SARS-CoV-2 positive and a testing negative cohort.	Follow-up telephone (or e-mail or text) surveys were completed 14 d after the index ED visit. Between 90 and 120 d after the index ED visit, caregivers were contacted and asked about any persistent, new, or returning symptoms or health problems of their child that may have been associated with the illness prompting the initial ED evaluation.	A total of 110 SARS-CoV-2-positive children (5.8%, 95% CI 4.8% to 7.0%) reported post-COVID -19 conditions. SARS-CoV-2-positive children were more likely to report these conditions compared with those who tested negative, both among those who were not hospitalized and those who were hospitalized. The most common symptom was fatigue or weakness (n = 21, 1.1%) among SARS-CoV-2 positive children. Characteristics associated with reporting at least 1 post-COVID-19 condition at 90 d included being hospitalized 48 h or more, having 4 or more symptoms reported at the index emergency department visit, ≥7 symptoms, and being 14 y of age or older.
8	Isoldi S, et al[28]	Italy	Apr to Jun 2020	15	All were outpatients	Pediatric patients admitted to the emergency department and tested positive with SARS-CoV-2.	All participants were followed prospectively.	The participants received clinical assessment, blood tests (including COVID-19 serology), ECG evaluation and comprehensive	All asymptomatic at 6-mo follow-up. 2 patients had persistent nocturnal systolic prehypertension; no significant hematologic alterations.

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
								ultrasound assessment at 1- and 6-mo follow-up.	
9	Matteudi T, et al[20]	France	Feb to May 2020	201	Most were outpatients	Patients under 16 y old that were tested positive for SARS-CoV-2 during the first COVID-19 wave in France. Most had mild symptoms. 53 were asymptomatic and diagnosed through close contact screening.	The study population were prospectively followed. Data at diagnosis were available for 194 children, whereas follow-up data were available for 137 children 10–13 mo after the diagnosis.	The participants were followed by the pediatric team via telephone interview 1, 2, 7, 14, and 30 d after the first positive sample and 10–13 mo after the acute phase.	Among 137 participants with the 10–13 month follow-up data: 21 out of 99 children who were symptomatic at baseline had persistent symptoms at follow-up; 2 out of 38 children who were asymptomatic at baseline had persistent symptoms at follow-up. Among these 23 children with long COVID symptoms at 10–13 mo' follow-up,10 had persistent symptoms, and 13 had new late-onset symptoms (occurred at a mean of 180 d after diagnosis, range 36–345 d). The most common long COVID-19 symptoms were: asthenia (9.5%), learning difficulties (8.0%), and headache (5.8%). Those who were symptomatic during the acute phase were statistically significant more susceptible to develop long-term symptoms.
10	Osmanov IM, et al[35]	Russia	Jan to Feb 2021	518	Community	Children $\leq$ 18y who were admitted with RT-PCR confirmed SARS-CoV-2 infection between Apr to Aug 2020.	The study population was contacted during the study period for a follow-up survey.	Questionnaires were used to collect information like any persistent symptoms present at the time of the follow-up interview and lasting for $>$5 mo. Median follow-up duration 268 d (IQR 233–284 d).	At the time of the follow-up interviews, parents of 128 (24.7%) children reported at least 1 persistent symptom, with fatigue, sleep disturbance, disturbed smell, and headache the most common. 44 (8.4%) participants reported persistent symptoms from more than 1 category at the time of the follow-up assessment. The most commonly cooccurring categories were fatigue and sleep problems, and fatigue and sensory problems. 14 (2.7%) children had persistent symptoms from 3 or more different categories. The prevalence of the symptoms presented at the time of discharge declined over time. Risk factors for persistent symptoms

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
									were older age and a history of allergic disease.
11	Öztürk GK, et al[44]	Germany	May to Aug 2020	50	Hospitalized patients	Patients aged 5–18 y who were hospitalized with a confirmed SARS-CoV-2 infection between May 15 and August 1, 2020, and followed up at the clinic were included in the study.	In this study, persistent respiratory symptoms and pulmonary function tests were investigated in children with COVID-19.	Patients were evaluated for ongoing respiratory symptoms and pulmonary function tests 3 mo after infection.	3 months after infection, persistent respiratory symptoms were found to be present in 28% of patients; cough, chest pain and tightness, dyspnea, and exertional dyspnea were the most common symptoms. 3 patients had an obstructive deficit, and 1 had a restrictive deficit. 4 patients had impaired DLCO. A significant decrease in FEV1/FVC and an increase in lung clearance index were found in the patients with persistent respiratory symptoms. Persistent respiratory symptoms were present in 50% of patients who had severe disease and 12.5% with nonsevere disease. DLCO was also significantly lower in the severe disease group.
12	Pazukhina E, et al[38]	Russia	April to Aug, 2020	360	Hospitalized patients	Children admitted to a major pediatric hospital with PCR confirmed SARS-CoV-2 infection.	Prospective cohort: the acute phase data were extracted from the electronic medical records. Then follow-up was conducted to collect long COVID data. PCC were defined according to the WHO case definition. Reported persistent symptoms were categorized into 9 manifestations.	2 follow-up telephone interviews were conducted at 6 and 12 months after discharge., using the International Severe Acute Respiratory and Emerging Infection Consortium survey.	360 of 849 (42%) of children discharged participated in both the 6- and 12-mo follow-ups. PCC prevalence was 50% (95% CI 47% to 53%) in adults and 20% (95% CI 16% to 24%) in children at 6 mo, with decline to 34% (95% CI 31% to 37%) and 11% (95% CI 8–14), respectively, at 12 mo. In children, neurologic comorbidities were associated with PCC both at 6 mo (OR 4.38, 1.36 to 15.67) and 12 mo (OR 8.96, 2.55 to 34.82) whereas allergic respiratory diseases were associated at 12 mo (OR 2.66, 1.04 to 6.47).
13	Pinto Pereira SM, et al[34]	England	Sep 2020 to Mar 2021	2909	Community	The CLoCk study is a cohort study of SARS-CoV-2 PCR-positive CYP aged 11–17 y, matched by month of test, age, sex, and geographical area to SARS-CoV-2 test-negative CYP using	The study has recruited >30 000 CYP in total with a goal of collecting data for 24-mo after a SARS-CoV-2 PCR test taken between September 2020 and March 2021.	The CLoCk study, described in detail elsewhere, 11 is a cohort study of SARS-CoV-2 PCR-positive CYP aged 11–17 y, matched by month of test, age, sex, and geographical area to SARS-CoV-2 test-	Among the test-positives, 10.9% reported fatigue, 4.4% reported shortness of breath, 3.3% loss of smell or taste, 1.7% dizziness or light-headedness, and 1.1% described skipping meals at all 3 time points. The other 16 symptoms affected less than 1% of test-positive.

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
						the national SARS-CoV-2 testing dataset.		negative CYP using the national SARS-CoV-2 testing dataset.	
14	Roessler M, et al[72]	Germany	Jan 2019 to Dec 2020	57763	Community	Included a children and adolescent cohort and an adult cohort. The pediatric COVID-19 cohort included children and adolescents (0–11 y) with laboratory-confirmed COVID-19 diagnosis and insured with 1 of the 6 health insurance organizations. The matched control cohort included those without COVID-19 diagnosis in 2020.	Routine data from 6 German statutory health insurance organizations were collected, including COVID-19 status and health outcomes at least 3 mo from the date of the COVID-19 diagnosis. Individual health outcomes were aggregated into diagnosis and symptom complexes. Incidence of documented health outcomes (groups) were calculated.	Routine healthcare data were used to examine the incidence of 96 prespecified diagnoses potentially associated with COVID-19. The average follow-up time since index date of COVID-19 was 236 d (SD 44 d, range 121–339 d) in children and adolescents.	COVID-19 cohort had significantly higher IRs of all post-COVID health outcomes combined than those in the control cohort (not diagnosed with COVID-19 ever) in children and adolescents (IRR = 1.30, 95% CI 1.25–1.35) based on a minimum follow-up time of 3 mo. The relative magnitude of increased documented morbidity was similar for the physical, mental, and physical or mental overlap domain in the COVID-19 cohort. In the COVID-19 cohort, IRs were significantly higher in all 13 diagnosis and symptom complexes in adults and in 10 diagnosis and symptom complexes in children and adolescents. IRR estimates were similar for age groups 0 to 11 and 12 to 17. IRs in children and adolescents were consistently lower than those in adults.
15	Say D, et al[18]	Australia	Mar 2020 to Mar 2021	171	Most were outpatients	Children aged ≤ 18 y who tested positive for SARS-CoV-2; 54 asymptomatic and 97 symptomatic with acute COVID-19.	The study population was referred to this clinic after acute COVID-19 and was followed-up prospectively there.	Follow-up data (collected via standardized clinical information collection form) at 3–6 mo were available for 151 (88%) of 171 children.	12 (8%) children had postacute COVID-19 symptoms, all of whom were symptomatic with acute COVID-19 acute COVID-19. The most common postacute COVID-19 symptoms were mild cough, fatigue, inflammatory conditions. The duration of postviral cough ranged from 3 to 8 wk, and the duration of postviral fatigue ranged from 6 to 8 wk. At the most recent review in March 2021, all 151 children had returned to their baseline health status and postacute COVID-19 symptoms had resolved.
16	Sirico D, et al[31]	Italy	Mar 2020 to Sept 2020	53	Community	Children (0–18 y old) having a history of at least 1 confirmed	Families were enrolled 1–3 mo after COVID-19 infection. For all COVID-	Children recognized as COVID-19 cases underwent a clinical	14 (26%) patients had left ventricular deformation.

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
						intrafamily COVID-19 case and confirmed with COVID-19 themselves by either a positive PCR or a positive serology for SARS-CoV-2.	19 cases, a "baseline time" was defined as the most likely onset of infection, based on either symptom onset or time of first virological positivity at molecular assay. For subjects with an asymptomatic infection and negative or not done NPS but with a serologically confirmed COVID-19, a baseline time was derived by the family outbreak temporal sequence.	assessment and standard cardiac evaluation (including standard transthoracic echocardiogram and speckle tracking echocardiographic study) within 6 mo from baseline time.	
17	Stephenson T, et al[42]	England	Sep 2020 to March 2021	3065	Community	Adolescents aged 11–17 y from the Public Health England database who tested positive for SARS-CoV-2 during the study period with a matched SARS-CoV-2 test negative group.	SARS-CoV-2 test positive and negative CYP were invited to participate in the study. They were contacted 3, 6, 12, and 24 mo after the SARS-CoV-2 test and were given questionnaires to complete.	Questionnaires were collected. The follow-up duration was 3 mo.	3 mo after testing, the presence of physical symptoms had increased in both groups: 2038 (66·5%) of those who tested positive and 1993 (53·3%) of those who tested negative had symptoms of any kind, 928 (30·3%) of those who tested positive and 603 (16·2%) of those who tested negative had at least 3 symptoms, and 411 (13·4%) of those who tested positive and 238 (6·4%) of those who tested negative had at least 5 symptoms (table 4). The most common symptoms among those who tested positive were tiredness, headache, and shortness of breath, and, among those who tested negative, were tiredness, headache, and the unspecified category of other.
18	Sterky E, et al[32]	Sweden	Dec 2020 to Jan 2021	55	Hospitalized patients	Children admitted to hospitals because of SARS-CoV-2 infection (confirmed with a positive nasopharyngeal	Children were followed up after discharge for information on any persistent health issues, including any symptoms that the participants were still	Information was collected during structured telephone interviews. The children were followed up at least 4 mo after being	There were 60 children primarily hospitalized because of COVID-19 during the study period. 9 fulfilled the criteria of MIS-C and 2 of them required intensive care. A total of 55 were interviewed and analyzed. 12 of 55 (22%) patients had

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
						sample RT-PCR for SARS-CoV-2).	experiencing at the time of the follow-up.	admitted (median 219 d range 123–324 d).	persistent symptoms at the time of the follow-up, including: fatigue, gastrointestinal symptoms, cognitive difficulties, reduced smell or taste, myalgia or headache, depression or dysphoria, and respiratory symptoms.
19	Tian X, et al[33]	China	Jan to Nov 2020	31	Hospitalized patients	Asymptomatic or mildly symptomatic children recovered from COVID-19. Serum samples and PBMCs were also isolated from 22 age-matched controls.	The study collected and compared COVID-19 patients' clinical information during the acute phase infection and approximately 6–8 mo after the infection.	All COVID-19 patients completed both pulmonary function tests and chest CT during the follow up after recovering from COVID-19. Serum and PBMCs were collected at 6–8 mo after recovery. The participants were followed up for 6–8 mo (mean 30.77±1.74 wk).	The lung imaging abnormalities gradually improved over 6–8 mo. In most patients, the proportions of ground-glass opacities decreased, and lung lesions were absorbed. The majority of study participants had functional recovery from COVID-19, according to pulmonary functions tests. Representative inflammation signs returned to normal in all age ranges at 6–8 mo after COVID-19. The infants and young children (0–4 y old) had lung lesions that persisted for 6–8 mo and were less responsive for antigen-specific IgG secretion. In the 5-to-14-y-old group, lung imaging abnormalities gradually recovered, and the IgG-specific antibody response was strongest. And there was a robust IgM+ memory B cell response in all age.
Cross-sectional studies (n = 4)									
1	Berg SK, et al[53]	Denmark	Jan 2020 to Jul 2021	6630	Community	Adolescents aged 15–18 y with a positive SARS-CoV-2 test and who responded to the survey.	All Danish adolescents with a positive SARS-CoV-2 test during the study period were identified. Questionnaires were administered to them. 27.3% responded in the COVID-19 group.	Participants were asked to report on the 23 long COVID symptoms going back 3, 6, 9, or 12 mo to match the varying recall times in the case group. They were investigated using ancillary questions and validated questionnaires.	6264 participants in the case group responded to questions about long COVID symptoms, of whom 2997 (47·8%) had long COVID and 2419 (38·6%) suspected that the new symptom was related to COVID-19. 50 (20·7%) of 242 reported at least 1 new symptom lasting 12 mo following SARS-CoV-2 infection. The most frequent symptoms in the long COVID group were headache, fatigue, loss of appetite, trouble

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
									breathing, and trouble remembering or concentrating.
2	Haddad A, et al[54]	Germany	May to Aug 2020	210	Community	Participants were recruited in May–Aug 2020 via local health authorities through traditional and social media information and an in-hospital database of households with at least 1 laboratory-confirmed SARS-CoV-2 infection.	1267 members of 341 households were categorized as having had either a SARS-CoV-2 infection or household exposure to SARS-CoV-2 without infection, based on 3 serological assays and history of laboratory-confirmed infection.	Participants completed questionnaires assessing the presence of long COVID symptoms 11–12 mo after infection in the household using online questionnaires.	The prevalence of moderate or severe persistent symptoms was statistically significantly higher in infected adolescent girls (32.1% 95% CI: 17.2%–50.5%] vs 8.9% [95%CI: 3.1%–19.8%]). However, moderate or severe persistent symptoms were not statistically more common in infected adolescent boys aged 14–18 (9.7% [95% CI: 2.8%–23.6%] or in infected children <14 y (girls: 4.3% [95% CI: 1.2%–11.0%]; boys: 3.7% [95% CI: 1.1%–9.6%]) than in their exposed counterparts (adolescent boys: 0.0% [95% CI: 0.0%–6.7%]; girls < 14 y: 2.3% [95% CI: 0·7–6·1%]; boys < 14 y: 0.0% [95% CI: 0.0%–2.0%]).
3	La Regina DP, et al[55]	Italy	Feb to Nov 2021	607	Community	Children, 0 to 18 y old, infected with SARS-CoV-2 1 to 12 months before enrollment.	This stud enrolled 607 children, 0 to 18 y old, infected with SARS-CoV-2 1 to 12 months before enrollment. Patients were divided into 4 groups according to the distance from the infection (≤3 mo, 4–6 mo, 7–9 mo, and >9 mo).	Medical history was reviewed and clinical data were collected via structured questionnaire. Lung ultrasound was performed on the study population.	This study observed irregular pleural lines in 27.5%, B-lines in 16.9%, and subpleural consolidations in 8.6% of the cases. Some children, even after months of acute infection, have ultrasound artifacts and showed an improvement with the passage of time from the acute episode.
4	Tarantino S, et al[56]	Italy	Jul 2021 to Dec 2021	31	Outpatients	The sample included adolescents aged 12–18 y infected by COVID-19 within 3 to 6 mo before the assessment.	This study is a cross-sectional pilot study documenting the neuropsychological and psychological effects of the SARS-CoV-2 infection in adolescents, using telehealth.	Neuropsychological difficulties, psychological symptoms, and self-reported long-COVID complaints were evaluated using a checklist and a battery of multiple standardized measures, using a telehealth procedure within 3 to 6	58% reported at least 1 long-COVID symptom. The most common symptoms were headache and attention problems (58%). Subjects presenting numbness or weakness, fatigue, brain fog, or attention problems had higher scores in depression, anxiety, and posttraumatic stress symptoms (*P* ≤ .05).

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
								mo before to the assessment.	
Retrospective cohort studies (n = 8)									
1	Bergia M, et al[50]	Spain	Mar to Dec 2020	451	Outpatients	Children under 18 y old with a diagnosis of SARS-CoV-2 infection confirmed by polymerase chain reaction, or an antigen test or serology.	This multicentre retrospective study focused on 451 children under 18 y old who were diagnosed with symptomatic COVID-19 between 14 March and December 31, 2020.	Persistent symptoms were analyzed with a telephone questionnaire by the attending physicians from August 1, 2021 to September 30, 2021. The main variable was the presence of at least 1 symptom lasting longer than 12 wk.	There were 14.6% who were symptomatic for longer than 12 wk and the odds risks were higher for children aged 5 y or more (OR 3.0), hospitalized (OR 3.9), admitted to the PICU (OR 4.3) and with relatives who were symptomatic for 12 wk or more (OR 2.8).
2	Bossley CJ, et al[47]	UK	Mar 2020 to Jan 2021	88	Hospitalized patients	The subjects were CYP up to 18 y of age with SARS-CoV-2 RNA positivity who were admitted to a hospital in London.	This study performed clinical assessments on a large cohort of children and young people admitted with a positive SARS-CoV-2 RNA swab.	The telephone review was made by Pediatric Respiratory consultants in March 2021 and therefore from 3–12 mo after the admission.	Most (85%) of children made a full recovery following SARS-CoV-2 infection. A small number had symptoms that lasted for more than 4 wk, most of which had resolved at 3 mo. Symptoms included dry cough, fatigue, and headache. 1 patient suffered from anosmia.
3	Di Gennaro L, et al[52]	Italy	Oct 2021 to Mar 2022	75	Hospital and community	Children (younger than 18 y) with a previous nasopharyngeal swab RT-PCR confirmed SARS-CoV-2 infection that were assessed in post-COVID outpatient clinic. PCC group included those with persistent symptoms at follow-up. A control group included fully recovered children that reported no symptoms after acute SARS-CoV-2 infection at the time of follow-up.	Children can be sent to the post-COVID unit either after discharge from our institution, or directly sent from the family pediatricians, and was assessed prospectively following the ISARIC protocol for PCC.	Children were followed up till 12 wk after COVID-19 for persistent symptoms. Samples were taken at 8 and 12 wk after the SARS-CoV-2 diagnosis and analyzed for coagulation profiling.	46 (61%) of the children had at least 1 persisting symptom at the 8 weeks postonset, (PCC 8); 39 of 75 (52%) had persistent symptoms for more than 12 wk (PCC 12) and 15 of 75(32%) had at least 3 persisting symptoms (PCC $\geq$ 3) at 12 wk. Children with PCC presented more frequently with abnormal D-Dimer levels above the reference range compared with children that had fully recovered at the 8–12 wk (39.1% vs 17.2%, P = .04), and 12 wk follow up or more (41% vs 17.2%, P = .05), and in children with 3 or more symptoms at 12 wk follow up compared with those that

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
									had recovered (64.3% vs. 22.2%, $P = .002$).
4	Doležalová K, et al[75]	Czech Republic	Jan to Jun 2021	39	Inpatient or outpatient settings	11 pediatric pulmonologists enrolled all children aged 2–18 y with persistent respiratory symptoms after COVID-19.	This was a national Czech multicentre study of pediatric post-COVID syndrome, which used a standard protocol to evaluate structural and functional anomalies and exclude alternative diagnoses.	From 6 January to June 30, 2021, 11 pediatric pulmonologists enrolled all pediatric referrals aged 2–18 y with persistent respiratory symptoms more than 12 wk after COVID-19. Medical histories were taken, and physical examinations, lung function testing, chest X-ray, and blood tests were performed.	The dominant symptoms in the 39 children (56.4% girls) were exertional dyspnoea (76.9%) and a chronic cough (48.7%), whereas dyspnoea at rest (30.8%) and chest pain (17.9%) were less prevalent. More than half (53.8%) reported more than 1 symptom, and 38.5% had abnormal results for 1 of the following tests: lung function, chest X-ray, or D-dimers.
5	Gonzalez-Aumatell A, et al[48]	Spain	Dec 2020 to May 2021	50	Outpatients	Eligible participants comprised children and young people < 18 y of age underwent the first outpatient visits at our unit, who presented with 3 or more symptoms lasting longer than 12 wk after SARS-CoV-2 infection.	This study conducted an observational, descriptive, and longitudinal cohort study on CYP who presented COVID-19 symptoms for more than 12 wk after SARS-CoV-2 at the "Pediatric long COVID Multidisciplinary Unit," involving a team of general pediatric practitioners, as well as pediatric specialists.	Data from electronic medical records, physical examinations, and questionnaires to assess fatigue and mental health were collected via data collection forms.	Since the initial infection and up to the first visit, CYP had persisting symptoms for a median of 4.1 mo, and for 18 (36%) CYP these symptoms persisted for more than 6 mo. Fatigue (100%), neurocognitive disorders (74%), muscular weakness (74%), and headache (72%) were the most reported symptoms. A total of 9 (18%) CYP could not attend school, 17 (34%) had a reduced schedule, 33 (66%) showed a decreased school performance, and 68% had stopped extracurricular activities.
6	Horikoshi Y, et al[51]	Japan	Oct 2021 to Jul 2022	24	Outpatients	The inclusion criteria for our study were children aged 15 y or younger who were referred to the clinic for possible post COVID-19 condition by their primary physician.	Children referred to a long COVID-19 clinic were included at Tokyo Metropolitan Children's Medical Center between October 2021 and July 2022.	Post COVID-19 condition was defined by the WHO as a constellation of long-term symptoms lasting more than 8 wk appearing within 3 months of acute COVID-19 onset. Basic blood screening included a complete blood count and tests for electrolytes, renal	All the patients had mild, acute COVID-19. Dysgeusia and brain fog was observed more frequently during the Δ and *o* variant periods, respectively. School absenteeism >4 weeks was observed in 41.6% of the patients. Common symptoms included malaise, headache, dysgeusia, and dysosmia. The median duration of post COVID-19 condition was 4.5 (IQR: 2.8–5.2) months.

TABLE 1 Continued

#	Author	Country	Study Period	Size	Setting	Population	Study Design and Details	Follow Up Duration and Follow Up Method	Reported Symptoms and/or Clinical Findings
								function, liver enzymes, and thyroid function. Additional examination by chest radiography, electrocardiography, and brain MRI was performed depending on the presentation.	
7	Trapani G, et al[49]	Italy	Oct 2020 to Jun 2021	629	Both hospitalized patients and participant from the community	Children and adolescents (0–16 y) diagnosed with COVID-19 by a positive molecular swab and being healed with negative molecular swab from at least 8 wk. The data collected belong to pediatric patients who acquired SARS-CoV-2 infection in the period October 2020–June 2021.	Data concerning primary care patients with previous acute SARS-CoV-2 infection were collected by a questionnaire filled in by PCP during Jun–Aug 2021. Long COVID syndrome was assumed when at least 1 of the predefined manifestations increased in frequency during the 8–36 wk after recovery from SARS-CoV-2 infection, with respect to the previous year.	The PCPs completed the online questionnaire during telephone consultations, or directly in pediatric primary care clinic, collecting data including time elapsed from recovery from COVID-19 and health conditions following clinical recovery from COVID-19. The observation time ranges from 2 to 9 mo after recovery from acute infection.	Cumulative incidence of long COVID-19 resulted to be 24.3% in primary care patients and 58% in hospitalized patients. The most frequently reported symptoms were abnormal fatigue (7%), neurologic (6.8%), and respiratory disorders (6%) for the primary care cohort. Hospitalized patients displayed more frequently psychological symptoms (36.7%), cardiac involvement (23.3%), and respiratory disorders (18.3%).
8	Werner S, et al[45]	Germany	Jan 2021 to May 2022	45	Outpatients	Children and adolescents who presented to the interdisciplinary long COVID outpatient clinic.	This study assessed the sleep behavior of children and adolescents who presented at the outpatient clinic between January 2021 and May 2022 with the CSHQ-DE.	This study compared the sleep behavior at 3 different time points: pre-COVID-19 (retrospectively); post-COVID-19 at the initial presentation; and post-COVID-19 at representation (3 mo later).	The CSHQ-DE score increased significantly from pre-COVID-19 (45.82±8.7 points) to post-COVID-19 (49.40±8.3 points; $P \leq .01$). The score then normalized at representation (46.98±7.8; $P = .1$). The greatest changes were seen in the CSHQ-DE subscale score “daytime sleepiness”.

CYP, children and young people; CSHQ-DE; Children’s Sleep Habits Questionnaire; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG, electrocardiogram; ED, emergency department; IQR, interquartile range; IR, incidence rates; IRR, incidence rate ratio; LUS, lung ultrasound; OR, odds ratio; PCC, post COVID condition; PCP, primary care physician; PFT, pulmonary function tests; PBMC, peripheral blood mononuclear cells; RT-PCR, reverse transcription polymerase chain reaction.

TABLE 2 Laboratory Findings at the Latest Follow-up (at least 3 mo after acute COVID-19) in Children and Adolescents Infected With SARS-CoV-2		
Laboratory Tests	**Studies**	**Findings**
Chest image: (X ray, CT, or ultrasound)	Bogusławski S, et al[41]	At the first follow-up visit, 26 patients had abnormal LUS findings, including: separate B-lines ($n = 16$), coalescent B-lines ($n = 15$), small subpleural consolidations ($n = 12$), irregular pleural line ($n = 6$), and pleural effusion ($n = 1$). All children with abnormal LUS findings at the second follow-up visit had abnormal LUS at the first follow-up visit. The abnormalities included: coalescent B-lines ($n = 10$), separate B-lines ($n = 4$), small subpleural consolidations ($n = 7$), irregular pleural line ($n = 2$), and pleural effusion ($n = 1$).
	Öztürk GK, et al[44]	There was no significant difference between the 2 groups with and without persistent symptoms in terms of frequency of lobe involvement score, total lung severity score, or the rate of bilateral lung disease by CT.
	Tian X, et al[33]	The lung imaging abnormalities gradually improved over 6–8 mo. In most patients, the proportions of ground-glass opacities decreased, and lung lesions were absorbed. However, patchy shadows were still seen in several cases.
	Doležalová K, et al[75]	2 participants presented with basal limited infiltration; 5 with perihilar opacities.
	Gonzalez-Aumatell, et al[48]	1 patient had an abnormal thorax radiograph with infiltrate.
Pulmonary function	Bogusławski S, et al[41]	At the first follow-up visit, 15 patients performed spirometry, body plethysmography, and DLCO, and 17 patients performed IOS. There were no significant differences in spirometry, body plethysmography, and IOS results between the study group and healthy children. In the study group, 1 boy with untreated asthma presented an obstructive ventilatory defect. A restrictive ventilatory defect was present in 3 subjects, 2 with severe COVID-19 pneumonia and 1 with a mild course of the disease. 1 patient had a decreased DLCO. At the second follow-up visit, 12 patients performed spirometry, body plethysmography, DLCO, and 13 patients performed IOS. There were no significant differences in PFTs results between the 2 follow-up visits in the study group. An obstructive ventilatory defect was present in 2 patients, 1 previously mentioned boy with untreated asthma and 1 girl with newly diagnosed asthma. A restrictive ventilatory defect was found again in 3 patients.
	Doležalová K, et al[75]	5 participants had abnormal spirometry findings: 1 with mild reduction and 1 with moderate reduction of vital capacity; 2 with mild obstruction on F-V loop, with positive BDT, and 1 with moderate obstruction on F-V loop, with negative BDT; 3 participants had a decline in oxygen saturation during 6MWT to 83%, 88%, and 92%, respectively; 3 had declined DLCO (68%, 66%, and 60% of predictive value, respectively).
	Öztürk GK, et al[44]	3 patients had an obstructive deficit (FEV1/FVC $< 80\%$), and 1 had a restrictive deficit (FVC $< 80\%$ and TLC $< 80\%$). 4 patients had impaired DLCO). A significant decrease in FEV1/FVC and an increase in lung clearance index were found in the patients with persistent respiratory symptoms. DLCO was also significantly lower in the severe disease group.
	Tian X, et al[33]	At the 6–8 mo follow-up, pulmonary function tests showed no pulmonary dysfunction or mildly restrictive lesions in the 5–9-y-old or 10–14-y-old age group, respectively. In the 0–4-y-old age group, 13% of patients presented mild-to- moderate obstructive disease, and 25% of patients presented moderate obstructive disease.
	Gonzalez-Aumatell, et al[48]	10 of 41 spirometries showed an obstructive pattern (considered as FEV1/FVC < 0.8 or FEV1 $< 80\%$). Among them, 2 CYP, who had previous medication conditions including asthma and allergic rhinitis, had a significant obstructive spirometry pattern. 8 suggested a mild-to-moderate restrictive pattern (however, without performing confirmatory plethysmography), among whom only 2 had a medical condition before (obesity and lupus, respectively).
	La Regina DP, et al[55]	The study followed up the pediatric participants for 12 mo and found irregular pleural lines in 27.5%, B-lines in 16.9%, and subpleural consolidations in 8.6% of the cases. These artifacts were observed more frequently in the lower lobe projections, particularly patterns B1 and B2 in lower lobes were observed in 80% and 69%, respectively. The frequency of artifacts decreases with increasing time since infection. In symptomatic patients during COVID infection, B-lines ($P = .02$) and pattern B1 ($P = .04$) were more frequently found. In some cases, even after months of acute infection, have ultrasound artifacts and showed an improvement with the passage of time from the acute episode.

TABLE 2 Continued		
Laboratory Tests	Studies	Findings
Cardiac assessment (ECG or echocardiography)	Sirico D, et al[31]	Left ventricular ejection fraction was within normal limits but significantly lower in the cases group compared with controls (62.4±4.1% vs 65.2±5.5%; *P* = .012). Tricuspid annular plane systolic excursion and LV global longitudinal strain were comparable between the 2 groups. Regional LV strain analysis showed a significant reduction of the LV midwall segments strain among cases compared with controls. Furthermore, in the cases group, there were 14 subjects (26%) with a regional peak systolic strain below −16% (−2.5 Z score in our healthy cohort) in at least 2 segments.
	Gonzalez-Aumatell, et al[48]	2 patients had abnormal ECG, with alternating atrial rhythm and ectopic atrial rhythm without repolarization disturbances, respectively.
Hematologic tests (immune profile, complete blood count, biochemistry, inflammatory markers, etc.)	Blomberg B, et al[30]	SARS-CoV-2 spike protein specific IgG and microneutralizing antibody titers detected after 2 mo were significantly higher in hospitalized patients than home-isolated patients. Increased antibody titers were independently associated with both persistent fatigue and total number of symptoms at 6 mo.
	Di Gennaro L, et al[52]	Children with PCC presented more frequently with abnormal D-Dimer levels above the reference range compared with children that had fully recovered at the 12 wk follow up or more (41% vs 17.2%, *P* = .05), and in children with 3 or more symptoms at 12 wk follow up compared with those that had recovered (64.3% vs 22.2%, *P* = .002). For the other coagulation profiles, there were abnormal values detected for VWF, FVIII, RC, and fibrinogen but no significant differences between children with PCC compared with controls.
	Esmaeilzadeh H, et al[39]	Complete blood cell count indicated that white blood cell, hemoglobin, platelet, C-reactive protein, alanine aminotransferase, alkaline phosphatase, and eosinophil count were not significantly different between COVID-19 patients with and without posthospitalization asthma-like symptoms.
	Öztürk GK, et al[44]	The Lymphocyte count in the group with respiratory symptoms was significantly lower than among those without persistent symptoms.
	Tian X, et al[33]	Representative inflammation signs returned to normal in all age ranges. The infants and young children (0–4 y old) had lung lesions that persisted for 6–8 mo and were less responsive for antigen-specific IgG secretion. In the 5–14-y-old group, the IgG-specific antibody response was the strongest. A robust IgM+ memory B cell response was found in all age groups. Memory T cells specific for the spike or nucleocapsid protein were generated, with no significant difference in IFN- response among all ages.
	Doležalová K, et al[75]	2 girls had abnormal D-dimers.
	Gonzalez-Aumatell, et al[48]	17 CYP had inadequate levels of vitamin D (<20ng/mL); 16 had folic acid deficiencies (<5.3ng/mL)

BDT, bronchodilator test; CT, computed tomography; CYP, children and young people; DLCO, diffusing capacity of the lungs for carbon monoxide; ECG electrocardiogram; FVIII, coagulation factor VIII; IFN, interferon; IOS, impulse oscillometry; LUS, lung ultrasound; LV, left ventricular; PCC, post COVID condition; PFT, pulmonary function tests; 6MWT, the 6-minute walk test; RC, ristocetin cofactor; VWF, von Willebrand factor; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC, total lung capacity; F-V loop, flow-volume loop.

adolescents with a laboratory-confirmed diagnosis of COVID-19 that experienced 1 or more persistent symptom(s) in their latest follow-up, which was ≥3 months postinfection (the follow-up duration ranged between 3 to 13 months). The 5 most prevalent long-term clinical manifestations after COVID-19 in this pediatric population were sore throat (2 studies, *N* = 3106; pooled estimate = 14.8%, 95% CI 4.8%–37.5%), persistent fever (4 studies, *N* = 5128; pooled estimate = 10.9%, 95% CI 2.4%–38.2%), sleep disturbance (3 studies, *N* = 697; pooled estimate = 10.3%, 95% CI 4.9%–20.4%), fatigue (8 studies, *N* = 6110; pooled estimate = 9.4%, 95% CI 4.1%–20.2%), and muscle weakness (2 studies, *N* = 196; pooled estimated = 8.7%, 95% CI 5.5%–13.6%), followed by cough (8 studies, *N* = 5890; 6.8%, 95% CI 2.4%–17.7%), headache (7 studies, *N* = 5809; 4.6%, 95% CI 1.2%–16.2%), dyspnea (5 studies, *N* = 5560; 95% CI 4.3%, 95% CI 1.1%–15.1%), abdominal pain (4 studies, *N* = 3718; 3.7%, 95% CI 2.3–5.8%) and diarrhea (2 studies, *N* = 3564; 3.5%, 95% CI 1.3%–8.9%). (Figs 2 and 3)

Sensitivity Analysis

We were able to conduct a sensitivity analysis by pooling the data from 2 studies of low risk of bias[37,42] and 5 studies of moderate risk of bias[18,29,30,35,44] together. The 5 most prevalent long-term symptoms reported by these studies included persistent fever (2 studies, *N* = 559; pooled estimate = 7.9%), fatigue (5 studies, *N* = 5654; pooled estimate = 7.4%), altered smell and/or taste (4 studies, *N* = 5433; pooled estimate = 6.1%), dyspnea (5 studies, *N* = 5560; pooled estimate = 4.3%) and headache (4 studies, *N* = 5493; pooled estimate = 3.9%). (Supplemental Fig 5)

Followed–symptoms	Number of studies	Cases	Sample size	I^2
Number of children with persistent symptoms	9	1403	6018	98.4115
Systemic symptoms				
Fatigue	8	824	6110	97.7652
Persistent fever	4	598	5128	98.2441
Sleep disturbance	3	70	697	85.9963
Headache	7	850	5809	97.8394
Weight loss	2	24	2022	98.4017
Dizziness	4	469	5571	96.9358
Neurocognitive symptoms				
Difficulty in concentration	2	5	541	87.7034
Cardiac symptoms				
Chest pain and/or tightness	6	302	5665	93.2100
Palpitation	3	6	969	0.0000
Respiratory symptoms				
Dyspnea	5	386	5560	97.0808
Cough	8	551	5890	97.0939
Nasal congestion	3	30	2430	98.0614
Sore throat	2	690	3106	78.5186
Other respiratory symptoms	3	18	1997	88.9558
Gastrointestinal symptoms				
Abdominal pain	4	155	3718	53.9755
Diarrhea	2	176	3564	89.7739
Neurologic and musculoskeletal symptoms				
Depression	2	9	1939	93.7922
Paresthesia	2	15	609	94.2817
Tinnitus	2	159	4949	97.5185
Altered smell and/or taste	8	691	6027	96.5744
Arthralgia	3	9	688	64.4369
Muscle pain	8	359	6091	94.1990
Muscle weakness	2	17	196	0.0000
Tremor	2	3	638	0.0000
Skin manifestations				
Skin rash	4	71	5584	96.4406

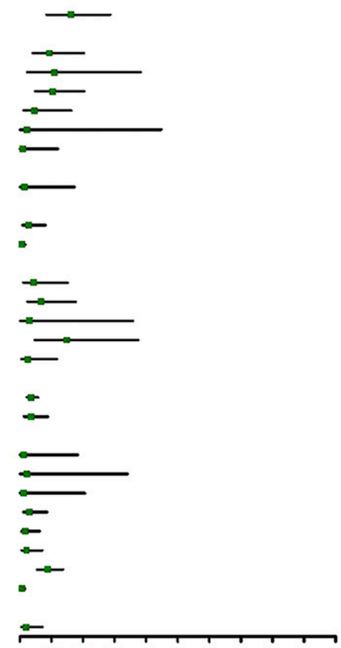

FIGURE 2
Pooled proportion of persistent symptoms of COVID-19 (at least ≥3 months) in children and adolescents (0–19y) recovered from COVID-19.

Subgroup Analyses

Then, we performed a subgroup analysis of the included prospective cohort studies according to their length of follow-up: 3 to 6 months, 6 to 12 months, and ≥12 months. Studies whose follow-up duration cannot be disaggregated to fit into these 3 subgroups were excluded from this analysis. The clinical spectrum of long COVID symptoms were quite different for these subgroups. Four studies ($N = 5158$) had a follow-up duration of 3 to 6 months, with sore throat, persistent fever, muscle weakness, fatigue and cough the most common persistent symptoms at the time of follow-up. Three studies ($N = 668$) had a follow-up duration of 6 to 12 months, with sleep disturbance, weight loss, persistent fever, fatigue, and muscle weakness as the 5 most commonly reported long-term symptoms after COVID-19. Only 1 study ($N = 360$) followed all its participants for any long COVID symptoms for over 12 months and found fatigue, palpitation, arthralgia, and muscle pain the most frequently reported at that time. (Supplemental Fig 6)

None of the included studies were from low-income countries. Seven studies collected data from 7 upper middle-income countries (Argentina, China, Costa Rica, Czech Republic, Iran, Russia, and Paraguay).[29,33,35,37–39,44] One of these studies was a multinational study also including participants from high-income countries, and it did not provide data for individual countries.[37] Pooled data from 4 studies[29,35,38,44] reported that 33.4% (95% CI 17.3%–54.7%) of their pediatric participants had long COVID. The most commonly reported symptoms in studies from upper middle-income countries were muscle weakness (1 study, $N = 58$; 10.3%, 95% CI 4.7%–21.1%), fatigue (3 studies, $N = 914$; 9.5%, 95% CI 4.0%–20.8%), sleep disturbance (2 studies, $N = 559$; 7.9%, 95% CI 6.0%–10.5%), and dyspnea (3 studies, $N = 611$; 5.6%, 95% CI 1.3%–20.9%). Twenty cohort and 4 cross-sectional studies were from high-income countries (HICs). We were able to pool the data from 7 prospective cohort studies from HICs[18,20,30,32,40–42] together, which reported that 14.4% (95% CI 6.7%–28.2%) of participants had long COVID. The most commonly reported symptoms from HICs were nasal congestion (1 study, $N = 41$; 34.2%, 95% CI 21.4%–49.7%), persistent fever (3 studies, $N = 3244$; 25.6%, 95% CI 10.5%–50.3%), sleep disturbance (1 study, $N = 138$; 18.8%, 95% CI 13.2%–26.2%), cough (4 studies, $N = 3395$; 17.9%, 95% CI 7.4%–37.3%) and fatigue (4 studies, $N = 3312$; 16.2%, 95% CI 7.4%–32.1%). (Supplemental Figs 7 and 8)

Seven studies only recruited the pediatric population for follow-up, whereas 2 studies had a mixed adult and child or adolescent population. The most commonly reported long-term symptoms from studies included exclusively children and adolescents were sore throat, fatigue, persistent fever, muscle weakness, and sleep disturbance. For the 2 studies including a mixed adult and children population, the spectrum of reported persistent symptoms were limited, with sleep disturbance, weight loss, cough, skin rash, and persistent fever as the leading complaints from the pediatric participants. (Supplemental Fig 9)

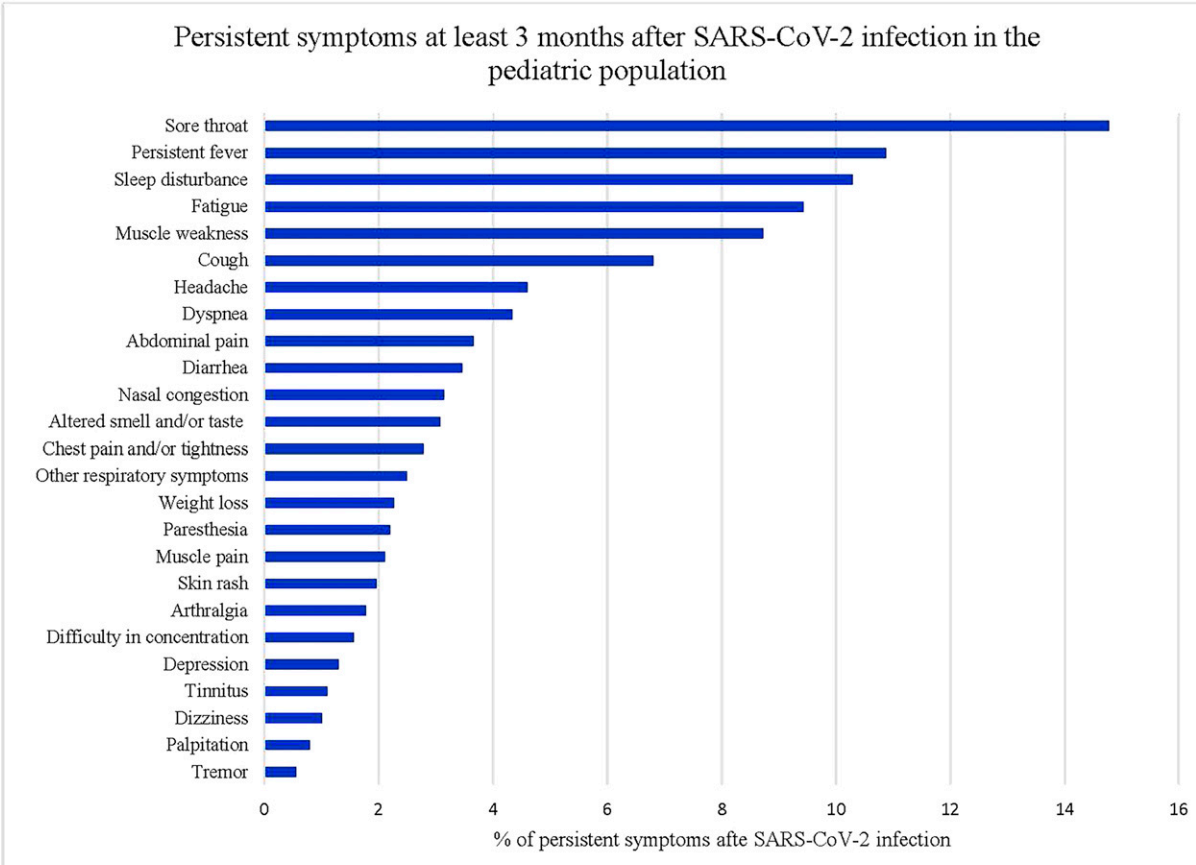

FIGURE 3
Persistent symptoms of COVID-19 (at least 3 months after acute SARS-CoV-2 infection) reported in children and adolescents (0–19y).

Potential Influencing Factors for Developing Persistent Symptoms After COVID-19

We planned to identify potential risk factors associated with long COVID by using meta-regression analysis, which is recommended to contain at least 5 studies per potential risk factor to ensure a reliable result.[57] In our included prospective studies, only gender was presented in 9 studies. Female gender was found to be associated with a higher risk of developing certain long COVID symptoms, ie, sleep disturbance and headache ($P < .01$). (Supplemental Table 7) The other risk factors, such as race, morbidity, and severity of disease during acute SARS-CoV-2 infection, were reported in less than 5 included studies and could not be analyzed by meta-regression for their potential relationship with developing long COVID in the pediatric population.

DISCUSSION

Our findings demonstrate that less than one fifth (16.2%, 95% CI 8.5%–28.6%) of children and adolescents (0–19y) with COVID-19 continue to present with at least 1 persistent symptom(s) beyond 3 months postinfection. A wide spectrum of symptoms, physical, and laboratory findings was reported. Sore throat, persistent fever, sleep disturbance, fatigue, and muscle weakness were among those most commonly reported.

First reported in 2020, long COVID, also known as post-COVID-19 syndrome or condition,[5,58–60]postacute sequelae of SARS-CoV-2,[61] and chronic COVID syndrome,[62] represents a group of symptoms that develop or persist after the acute phase of SARS-CoV-2 infection. Hypotheses for long COVID included persisting reservoirs of SARS-CoV-2 in tissues, immune dysregulation, autoimmunity, dysfunctional signaling in the brainstem and/or vagus nerve, etc.[63] However, many definitions of long COVID exist (Table 3).[5,58–60] Current clinical definitions for long COVID are generally broad and sensitive to ensure that as many patients affected by long COVID are provided access to services and support as possible. However, asymptomatic patients and patients with undetectable levels of antibodies during testing may be left out, leading to an underestimation of the prevalence of long COVID. Furthermore, case definitions also serve other purposes, such as research. Broad definitions of long COVID can also hamper comparison between studies. High heterogeneity was observed in the inclusion criteria of individual studies,

TABLE 3 Definition of Long COVID From Different Organizations			
	WHO[5,58]	US CDC[59]	NICE[60]
Terminology used	Long COVID	Post-COVID conditions	Ongoing symptomatic COVID-19 and post-COVID-19 syndrome
Defined symptoms	New onset or persistent symptoms	New, returning, or ongoing health problems	● Ongoing symptomatic COVID-19—persistent signs and symptoms of COVID-19; ● post-COVID-19 syndrome—signs and symptoms that develop during or after an infection consistent with COVID-19
Acute COVID-19 diagnosis	Probable or confirmed SARS-CoV-2 infection	Being infected with SARS-CoV-2 (not specified whether confirmatory test is needed), no matter symptomatic or not in the days or weeks after they were infected	Signs and symptoms of COVID-19
Duration of signs and/or symptoms	Initially occurred within 3 mo of acute COVID-19 and symptoms lasting for at least 2 mo	4 or more weeks	● Ongoing symptomatic COVID-19—4 to 12 wk; ● post-COVID-19 syndrome—more than 12 wk, but may be considered before 12 wk while the possibility of an alternative underlying disease is also being assessed.
Alternative diagnosis	Exclude alternative diagnosis	Not specified	Not explained by an alternative diagnosis

resulting in varying prevalence of long COVID. Differences mainly include the diagnostic method of acute COVID-19 infection (clinical diagnosis versus laboratory testing), duration of the post-COVID period, and the inclusion or exclusion of symptoms presented before COVID-19.

Estimates of the prevalence of long COVID vary considerably among studies, as reflected by varying case definitions and follow-up durations, as well as high I^2 and wide 95% CIs, suggesting great heterogeneity among studies. Systematic reviews focusing on the persistent symptoms of COVID-19 in the adult population reported similar issues.[15,64] There are several additional explanations for the high heterogeneity observed between studies. Firstly, the study design of included studies varies greatly. Even though we only included cohort studies prospectively collected information related to long COVID in a general pediatric population in our meta-analysis, there were still large differences among their study details. For instance, some studies only included hospitalized patients,[29,32,33,38,39,41,43,44,47] whereas others had a mixed population recruited from both the community and/or the hospital setting. Some studies recruited participants through the review of medical records, and therefore, only included symptomatic patients who had sought medical help. Some studies recruited participants from the community. Only very few studies were population-based studies[53,65] in which children and adolescents who tested positive in SARS-CoV-2 confirmatory tests were identified for further follow-up via national registry or by contacting households or schools randomly selected in the community. This approach included both asymptomatic and symptomatic cases and may better reflect the true prevalence of long COVID. This is of particular importance as the proportion of asymptomatic infection in neonates, children, and adolescents are higher compared with the adult population.[66] Secondly, various data collection methods were used by individual studies. The majority of studies developed a study specific standardized survey or interview questionnaire, whereas only a number of studies used in-person clinical assessment at the clinic. Thirdly, there exist many definitions of long COVID and methods of describing or reporting these symptoms. For instance, fatigue may be described as fatigue in general in some studies, but others may describe and categorize fatigue as feeling tired after sleep or feeling tired after exercise, etc.

There are a large number of studies on long COVID in the adult population.[2,4,67] They have identified a large number of long-term physical and psychological signs and symptoms after recovering from COVID-19, including weakness, fatigue, concentration impairment, headache, dyspnea, depression, anxiety, etc. From the included studies in our review, we identified more than 20 long COVID clinical features in the pediatric population, relating to multiple organs and systems. Although the specific sequence may differ according to study design and follow-up duration, the symptoms most commonly reported by children and adolescents after at least 3 months recovering from COVID-19 were sore throat, persistent fever, sleep disturbance, fatigue, and muscle weakness. Our finding is not completely consistent with existing systematic reviews on this topic. The most common long COVID symptoms (≥1 months after laboratory-confirmed SARS-CoV-2 infection) found in a systematic review including children and adolescents[63] were mood symptoms, fatigue, sleep disorders, headache, and respiratory symptoms, which are similar with our findings. Such discrepancy can be explained by the different inclusion criteria of studies. From our systematic literature search, we noticed the design and focus of each individual study differed significantly. Some researchers focused on specific post-COVID-19 signs and symptoms (eg, ophthalmology findings,[68] dysphonia, and dysphagia[69]) or a specific population (eg, MIS-C) within children and adolescents recovering from COVID-19. Some studies adopted a broad approach and identified a large number of long-term symptoms in the pediatric COVID-19 population. Therefore, we only included studies focusing on a more general pediatric COVID-19 population in our current analysis. We decided to exclude studies using a self-reporting platform and to include only cohort studies prospectively followed up their participants for any persistent symptoms and/or laboratory findings to minimize selection and recall bias.

There are considerable gaps in terms of evidence on long-term effects of COVID-19 in low and middle income countries (LMICs) because of lack of fundings and resources, as well as limited capacities to diagnose and monitor long COVID. In a systematic review examining the worldwide prevalence of long COVID,[70] only a third of included studies were from LMICs, and they found the pooled estimated prevalence of long COVID in the United States and Europe (most studies from HICs) was lower than that in Asia (most studies were from China and India). Research on long-term effects of COVID-19 in the pediatric population from LMICs is further limited and of varying quality. We were able to pool the data from 4 studies (3 of moderate risk of bias, 1 of high risk of bias) conducted in upper-middle-income countries in this review and found the prevalence of long-COVID in neonates, children, and adolescents were higher comparing to their counterparts in HICs, with quite different clinical presentations as well. However, because of the relatively low quality of these studies, as well as the great heterogeneity observed, we still could not draw a conclusion on the disease burden and clinical spectrum of long COVID in the pediatric population between LMICs and HICs.

Persistent clinical features after recovering from acute COVID-19 have been shown to decline over time both in adults and in children and young people. Pinto Pereira et al[34] examined within-individual change in symptom profile of the CLoCk cohort population and found the prevalence of 11 common symptoms at baseline declined greatly by 12-month follow-up. For children and young people who first described 1 of their symptoms at 6-month follow-up, there was also a decline in prevalence by 12 months. Similarly, it has also been observed in adults that persistent post-COVID-19 symptoms declined with time.[71] Therefore, we conducted a subgroup analysis by different follow-up durations and found the spectrum of persistent, new symptoms after SARS-CoV-2 infection differed for the follow-up duration of 3 to 6 months, 6 to 12 months, and greater than 12 months. But our subgroup analysis by follow-up duration covered different study populations, and the trend we revealed that long COVID symptoms may change with time could be confounded by various factors. Future within-individual studies are needed to investigate the dynamic of persistent clinical features and symptoms in the pediatric population.

Only 6 studies included in our systematic review had a control group without a previous history of COVID, 5 of which collected persistent symptoms after SARS-CoV-2 infection in a prospective manner. The CLoCk study conducted in the United Kingdom found that nearly all symptoms reported by children with a positive SARS-CoV-2 test result were also reported by those who tested negative.[34,42] Certain nonspecific symptoms, such as psychological alterations, appetite, and weight changes may be related to the pandemic, eg, lockdown, school closure, etc, rather than COVID-19 infections. These symptoms may also present after other viral infections. Two recent cohort studies with a large sample size found SARS-CoV-2-positive children were more likely to report long COVID conditions compared with those who tested negative. Roessler et al[72] matched 11 950 children and adolescents with laboratory-confirmed COVID-19 with a control cohort and found a significantly higher incidence rate for all health outcomes combined in the COVID-19 cohorts. Funk et al[37] also matched SARS-CoV-2 positive children and adolescents with those who tested negative and found the positive group were more likely to report post-COVID-19 conditions at 90 days than their SARS-CoV-2 negative counterparts. Behnood et al[73] conducted a meta-analysis of controlled and uncontrolled studies on persistent symptoms following COVID-19 in children and young people and found the majority of reported persistent symptoms was similar in SARS-CoV-2 positive cases and controls. These contradictory findings highlighted the importance of a control group in future studies to adjust for confounders and avoid potential bias. Furthermore, long COVID may be diagnosed subjectively (eg, nonspecific complains), or objectively (eg, laboratory and imaging). It would be ideal to standardize the data collection process by using a structured and validated survey or questionnaire to reduce variability. This will also help to standardize terminologies used and to ensure that validated tools are used.

In mixed studies with an adult-dominant population, female gender, the presence of comorbidities, increasing age, and ethnic minorities were found to be significantly at higher risk of long COVID.[4] However, evidence in children and adolescents are still limited. Merzon et al[74] examined the demographic, clinical, and socioeconomic factors associated with long COVID in children aged 5 to 18 years. They found children with long COVID were more likely to be severely symptomatic, required hospitalization, and experienced recurrent acute infection within 180 days. In our analysis, we used male to female ratio as one of the factors included in the meta-regression to investigate the potential association of certain gender with the development of COVID-19. We found female gender is a potential risk factors for developing certain long COVID symptoms (sleeping disturbance and headache) in children and adolescents at least 3 months after the acute infection phase. To be noteworthy, the number of qualified studies that provided detailed information of potential risk factors is limited in our systematic review; therefore, we were not able to investigate their association with long COVID. In general, little is still known about whether a certain population is more likely to develop long COVID postinfection. Future research should collect detailed information on pre-existing medical conditions and signs and symptoms before, during, and after COVID-19. With such information, researchers may better identify long-term effects attributed to SARS-CoV-2 infection and the risk factors for developing long COVID in the pediatric population.

Limitations

There are various potential biases in included studies. We only included studies that prospectively followed up pediatric participant for their persistent post-COVID symptoms in our analyses to minimize recall bias. However, the majority of these studies conducted their follow-ups by contacting the participants regularly, eg, monthly or quarterly, instead of using a "real-time" reporting system or platform that the participants could report their symptoms actively and reasonably quickly, hence leaving open the potential of some recall bias. A couple of studies conducted follow-ups via telephone interviews or questionnaires with various response rates, which may lead to nonresponse bias. The fact that asymptomatic or mild COVID-19 cases might also not get tested should not be ignored. Particularly, during the early stages of the COVID-19 pandemic when testing was still limited, it was not uncommon for the diagnosis of SARS-CoV-2 infection to be based on reported clinical symptoms and contact or travel history.[15,17] Even after PCR tests are widely applied in diagnosing SARS-CoV-2 infection, its accuracy (ie, false positive and negative rates) may still have an unknow impact on identifying a proper study population and the accuracy of the study's results.

Bias may also exist when investigating the association between various demographic factors and the risk of developing long COVID, eg, race and ethnicity. Although we included studies from multiple countries, most studies with the information of race came from the United States, the United Kingdom, and Italy. Certain races and ethnic groups may be over- or under-reported because of various reasons (eg, over-/under-representative in the study population, different classification system, or terms used in different contexts, etc). A precise and detailed definition and/or description of these factors was missing or unclear in many of the original studies, precluding any firm conclusions as to the contribution of race and ethnicity to persistent symptoms after COVID-19.

Furthermore, the definition of "long COVID" in the pediatric group is still vague. A large number of studies defined long COVID by clinical features persisting for at least 1-month postinfection and lacked follow-up data of a longer duration. Most reported studies also did not systematically collect information on laboratory features among evaluated children, and the latter information was mainly restricted to hospitalized children. While conducting this systematic review, we found that studies of long COVID in the pediatric population with a follow-up of at least 3 months for analysis only accounts for a third of the total studies on this topic. Within our included studies, only some of them clearly described the duration of each symptom during follow-up and they did not report new onset symptoms and persistent symptoms separately. The limited number of studies with sufficient follow-up length and data, as well as the considerable heterogeneity observed among studies, made it challenging to pool these data and estimate the prevalence and symptom spectrum of long COVID in the pediatric population. Therefore, our conclusions should be interpreted with caution.

Recently, recurrent infection of SARS-CoV-2 has become increasingly common because of the emergence of new variants. Other viral infections are also common. The majority of current studies did not collect or provide information related to other concurrent viral infection during follow-up, nor did they take recurrent COVID-19 into consideration. Establishing the relationship between "new, persistent, and/or recurring" symptoms during follow-up and previous SARS-CoV-2 infection remains a big challenge for long COVID studies.

Lessons Learned From Existing Studies

It is not surprising that current studies on long COVID in the pediatric population were subjected to great heterogeneity, biases, and limitations given the rush to getting information out and the thirst for COVID-19 studies among the journals. We feel that it is extremely important that academia better communicate, collaborate, and support each other in designing and conducting high quality studies in such an outbreak situation in the future.

CONCLUSIONS

We found less than one fifth of children and adolescents with a confirmed COVID-19 diagnosis continue presenting with at least 1 persistent clinical feature that cannot be explained by alternative diagnosis beyond 3 months after the acute phase of infection. Long COVID in children and adolescents has been reported with a very wide symptom spectrum and with great heterogeneity among studies included in this review. The presentation of long COVID may change with time. There is the need for high quality, prospective, and well controlled studies to address these issues. In the interim, preventing COVID-19 infection and vaccinations for children and adolescents must remain a priority.

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ABBREVIATIONS

CI: confidence interval
MIS-C: multisystem inflammatory syndrome in children
PCR: polymerase chain reaction
WHO: World Health Organization

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