Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review

Yong-Bo Zheng [a,b,1], Na Zeng [c,d,e,1], Kai Yuan [a,1], Shan-Shan Tian [a], Ying-Bo Yang [f], Nan Gao [f], Xuan Chen [f], An-Yi Zhang [a], Alexandra L. Kondratiuk [g], Pei-Pei Shi [h], Fang Zhang [i], Jie Sun [j], Jing-Li Yue [a], Xiao Lin [a], Le Shi [a], Ajit Lalvani [g], Jie Shi [c], Yan-Ping Bao [c,d,*], Lin Lu [a,b,c,**]

[a] Peking University Sixth Hospital, Peking University Institute of Mental Health, NHC Key Laboratory of Mental Health (Peking University), National Clinical Research Center for Mental Disorders (Peking University Sixth Hospital), Peking University, Beijing, China
[b] Peking-Tsinghua Centre for Life Sciences and PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing, China
[c] National Institute on Drug Dependence and Beijing Key Laboratory of Drug Dependence, Peking University, Beijing, China
[d] School of Public Health, Peking University, Beijing, China
[e] Beijing Friendship Hospital, Capital Medical University, Beijing, China
[f] The First Affiliated Hospital of Xinxiang Medical University, Henan, China
[g] NIHR Health Protection Research Unit in Respiratory Infections, National Heart and Lung Institute, Imperial College, London W2 1NY, UK
[h] Department of Neurology, Taiyuan Central Hospital of Shanxi Medical University, Taiyuan, China
[i] Department of Endocrinology and Metabolism, Peking University People's Hospital, Beijing, China
[j] Pain Medicine Center, Peking University Third Hospital, Beijing, China

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ABSTRACT

Background: Millions of COVID-19 pediatric survivors are facing the risk of long COVID after recovery from acute COVID-19. The primary objective of this study was to systematically review the available literature and determine the pooled prevalence of, and risk factors for long COVID among the pediatric survivors.
Methods: Studies that assessed the prevalence of, or risk factors associated with long COVID among pediatric COVID-19 survivors were systematically searched in PubMed, Embase, and Cochrane Library up to December 11th, 2022. Random effects model was performed to estimate the pooled prevalence of long COVID among pediatric COVID-19 patients. Subgroup analyses and meta-regression on the estimated prevalence of long COVID were performed by stratification with follow-up duration, mean age, sex ratio, percentage of multisystem inflammatory syndrome, hospitalization rate at baseline, and percentage of severe illness.
Results: Based on 40 studies with 12,424 individuals, the pooled prevalence of any long COVID was 23.36 % ([95 % CI 15.27–32.53]). The generalized symptom (19.57 %, [95 % CI 9.85–31.52]) was reported most commonly, followed by respiratory (14.76 %, [95 % CI 7.22–24.27]), neurologic (13.51 %, [95 % CI 6.52–22.40]), and psychiatric (12.30 %, [95% CI 5.38–21.37]). Dyspnea (22.75 %, [95% CI 9.38–39.54]), fatigue (20.22 %, [95% CI 9.19–34.09]), and headache (15.88 %, [95 % CI 6.85–27.57]) were most widely reported specific symptoms. The prevalence of any symptom during 3–6, 6–12, and > 12 months were 26.41 % ([95 % CI 14.33–40.59]), 20.64 % ([95 % CI 17.06–24.46]), and 14.89 % ([95 % CI 6.09–26.51]), respectively. Individuals with aged over ten years, multisystem inflammatory syndrome, or had severe clinical symptoms exhibited higher prevalence of long COVID in multisystems. Factors such as older age, female, poor physical or mental health, or had severe infection or more symptoms were more likely to have long COVID in pediatric survivors.
Conclusions: Nearly one quarter of pediatric survivors suffered multisystem long COVID, even at 1 year after infection. Ongoing monitoring, comprehensive prevention and intervention is warranted for pediatric survivors, especially for individuals with high risk factors.

* Correspondence to: National Institute on Drug Dependence, School of Public Health, Peking University, 38 Xueyuan Road, Beijing 100191, China.
** Correspondence to: Peking University Sixth Hospital, Peking University Institute of Mental Health, National Clinical Research Centre for Mental Disorders, 51 Huayuan Bei Road, Beijing 100191, China.
E-mail addresses: baoyp@bjmu.edu.cn (Y.-P. Bao), linlu@bjmu.edu.cn (L. Lu).
[1] These authors contributed equally to the manuscript.

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Contents

Introduction

The COVID-19 pandemic continues to spread, with the global case count and number of deaths estimated at 657.4 million and 6.7 million, respectively, as of January 5th, 2023 [1]. COVID-19 survivors have reported ongoing persistent symptoms in many organ systems, long after recovery from the acute phase of COVID-19 infection [2,3]. World Health Organization creates a final consensus definition for long COVID: usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis [4]. Several published epidemiological studies [5,6] and reviews [7–10] mostly focused on the long COVID or persistent symptoms of COVID-19 infection amongst adults, due to the large number and often severe symptoms in adult survivors [11,12]. However, long COVID symptoms in children has not been systematically illustrated. Understanding the long COVID burden is essential to allow timely identification and intervention of affected children and appropriate allocation of pediatric healthcare resources.

Children and adolescents are at a critical stage of physical and mental development. COVID-19 infection during this period may have important implications for their functional and social wellbeing in adulthood. Compared with the clinical features and treatment outcomes observed in adult COVID-19 patients, pediatric COVID-19 patients usually presented with milder clinical features at the acute phase [13,14]. However, children are seeing a surge of COVID-19 infections in many countries, coinciding with much lower rates of vaccination amongst children as compared to adults. Higher prevalence of COVID-19 cases in children promotes increases the number of long-COVID cases, and contributes to further spread of disease among vulnerable populations [15]. Recently, a few epidemiological studies reported the prevalence of long COVID among pediatric COVID-19 cases with the follow-up duration ranging from three months to one year [16–18]. The long COVID in pediatric COVID-19 patients generally covered multiple systems, including respiratory, neurological, and cardiovascular systems, and so on [18].

Several factors, including clinical characteristics and demographic information have been found to be associated with long COVID. Multisystem inflammatory syndrome (MIS) was identified in some pediatric COVID-19 cases, and was suspected to have a wide spectrum of presenting signs and symptoms and disease severity [19]. Hospitalization and severe acute initial infection were also suggested to have more potential of long COVID [20,21]. Moreover, evidence supports that sex and age are associated with prevalence of long COVID. Specifically, a few studies pointed out that older age, and female in pediatric survivors may be associated with high risk of long COVID [20,22].

A few studies assessed the persistent symptoms among the pediatric COVID-19 survivors. By combining data from 22 studies with over 20 thousand individuals, Behnood et al. [23] found that pooled prevalence of persistent symptoms in post-COVID participants ranged from 15 % (diarrhea) to 47 % (fatigue) after one month. In addition, a meta-analysis [24] showed that the prevalence of ongoing (4–12 weeks) and post-COVID-19 (≥ 12 weeks) symptoms was 25.24 % in children and adolescents. However, the burden and risk factor of long COVID still remained unclear in children and adolescents after infection over three months. Moreover, as the effect of important clinical characteristics including MIS, severe infection, hospitalized survivors needed to be furtherly discovered.

The primary objective of this study was to systematically review the available literature and determine the pooled prevalence of long COVID in pediatric survivors. In addition, we intended to explore the estimate of the pooled prevalence of long COVID in child and adolescent survivors with stratified demographic or clinical characteristics. Finally, we aimed to systematically review possible risk factors associated long COVID among pediatric patients.

Methods

This systematic review was performed in accordance with the Meta-Analyses of Observational Studies in Epidemiology (MOOSE; Supplement Table 1) guidelines [25] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Supplement Table 2) guidelines [26]. The PROSPERO registration number for this systematic review is CRD42021293614.

Table 1
Characteristics of the included paper.

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Akçay et al., 2022	Turkey	2021.2.20–2021.3.2	retrospective cohort	7.12 ± 2.34 months	74	14.8 (11–17)	44.59	NA	NA	100.00	psychiatric system	NA
Asadi-Pooya et al., 2022	Iran	2020.2.19–2020.11.20	cross-sectional	> 13 months	51	13.2 ± 3.3	45.10	19.60	NA	100.00	any, generalized, musculoskeletal, psychiatric, and respiratory systems	NA
Ashkenazi-Hoffnun et al., 2021	Israel	2020.11–2021.4	prospective cohort	112 (33–410) days	90	12 ± 5	58.33	2.22	1.11	12.20	cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Bartoszek et al., 2021	Poland	2020.11–2021.1	retrospective cohort	99 (89–104) days	19	8–17	73.68	NA	100.00	100.00	cardiovascular system, and imaging findings	NA
Blankenburg et al., 2022	Germany	2020.5–2020.6	cross-sectional	11 months	178	15	NA	NA	NA	NA	digestive, generalized, musculoskeletal, neurologic, and psychiatric systems	NA
Blomberg et al., 2021	Norway	2020.2.28–2020.4.4	prospective cohort	6 months	16	8 (6–12)	43.75	NA	NA	0	any, cardiovascular, digestive, generalized, neurologic, psychiatric, and respiratory systems	NA
Bode et al., 2022	Germany	2021.2–2021.5	cross-sectional	12 months	25	9.4 ± 3.9	47.17	0	0	0	generalized, and respiratory systems	NA
Brackel et al., 2021	Netherlands	2020.12.18–2021.2.6	cross-sectional	12 weeks	89	2–18	66.67	NA	NA	100.00	cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, and respiratory systems	NA
Buonsenso et al., (a) 2021	Italy	2020.3–2020.10	cross-sectional	120 days	68	11 ± 4.4	51.90	2.33	2.33	4.70	any, cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Buonsenso et al., (b) 2022	Italy	2020.9.30–2022.4.31	prospective cohort	6–9 months, > 12 months	311	< 18	49.00	0.74	NA	2.65	dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Buonsenso et al., (c) 2022	Italy	2020.1–2021.1	cohort	3–6month, > 7 month	428	10.3 ± 3.8	43.70	NA	NA	4.30	cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, ophthalmological, and respiratory systems	NA
Denina et al., 2021	Italy	2020.3.1–2020.6.1	prospective cohort	130 (106–148) days from discharge	25	7.75 (0.4–15)	52.00	16.00	0	100.00	imaging and laboratory findings	NA

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Table 1 (*continued*)

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Doležalová et al., 2022	Czech Republic	2021.1.6–2021.6.30	cohort	> 12 weeks	39	13.5 (8–15)	43.59	NA	NA	100.00	respiratory system, and imaging and laboratory findings	NA
Enner et al., 2022	US	2020.3–2020.8	cross-sectional	23 weeks	47	9 (5–13)	55.32	63.83	100.00	100.00	generalized, neurologic, and psychiatric systems	NA
Erol et al., 2022	Turkey	2021.3.17–2021.6.10	cohort	5.6 months	121	9.16 (10.88–17.92)	53.72	NA	NA	22.31	dermatological, digestive, generalized, neurologic, ophthalmological, and respiratory systems	NA
Esmaeilzadeh et al., 2022	Iran	2020.2–2021.1	cohort	6 months	69	< 18	60.87	NA	NA	100.00	respiratory system	NA
Fink et al., 2021	Brazil	2020.4.11–2021.8.10	cohort	4.4 months	53	14.65 (8–18)	41.51	11.32	5.66	33.96	any, dermatological, digestive, generalized, musculoskeletal, neurologic, ophthalmological, psychiatric, and respiratory systems	NA
Funk et al., 2022	8 countries	2020.3.7–2021.1.20	prospective cohort	90 days	1884	3 (0–10)	52.80	NA	NA	9.80	any, cardiovascular, digestive, generalized, musculoskeletal, neurologic, ophthalmological, psychiatric, and respiratory systems	older age, hospitalized 48 h or more, having 4 or more symptoms reported at the index emergency department visit
Gennaro et al., 2022	Italy	2021.10.1–2022.3.31	prospective cohort	12 weeks	75	10.5 ± 6.7	47.80	NA	NA	9.33	any symptom	NA
Guido et al., 2022	Italy	2021.2–2021.11	cross-sectional	3–5 months	322	9.53 ± 3.73	51.90	NA	NA	NA	any, generalized, musculoskeletal, neurologic, ophthalmological, psychiatric, and respiratory systems	NA
Heiss et al., 2022	Germany	2021.8–2021.12	cross-sectional	> 12 weeks	54	12 ± 3	56.00	0	NA	0	any, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	NA
Matteudi et al., 2021	France	2020.2.27–2020.5.15	cohort	180 (36–345) days	137	9.1	49.49	1.03	0	13.87	any, generalized, and neurologic systems	symptomatic during the acute phase
Méndez-Echevarría et al., 2021	Spain	2020.3–2020.5	prospective cohort	186 (176–192) days	58	8.3 (2.8–13.5)	50.00	NA	12.07	36.21	laboratory findings	NA
Messiah et al., 2022	USA	2021.3–2022.1	retrospective cohort	> 120 days	240	6.65 ± 5.91	52.88	NA	8.33	85.26	any, cardiovascular, dermatological, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	older age, female, private insurance
Mitchell et al., 2022	USA	2020.3.26–2020.7.20	retrospective cohort	6 months	25	8.3 (0.75–17)	56.00	NA	100.00	100.00	cardiovascular, and laboratory findings	NA

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Table 1 (*continued*)

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Namazova-Baranova et al., 2022	Russia	NA	cross-sectional	1 year	21	11.4 ± 3.5	61.30	NA	NA	NA	neurologic system	NA
Nugawela et al., 2022	UK	2021.1–2021.3	cohort	3 months	3246	11–17	37.00	NA	NA	NA	any, generalized, musculoskeletal, and psychiatric systems	older age, female, poor physical health, poor mental health, more symptoms at testing
Osmanov et al., 2022	Russia	2020.4.2–2020.8.26	prospective cohort	256 (223–271) days	518	10.4 (3–15.2)	47.90	2.72	NA	100.00	any, cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, ophthalmological, respiratory and urological systems	older age, allergic diseases
Öztürk et al., 2022	Turkey	2020.5.15–2020.8.1	retrospective cohort	3 months	50	15 (8–18)	56.00	20	NA	NA	respiratory system, and laboratory findings	NA
Palacios et al., 2022	USA	2021.2–2021.12	retrospective cohort	3.5 months	82	15.2 ± 2.3	41.50	NA	1.20	100.00	respiratory system	NA
Patnaik et al., 2021	India	NA	prospective cohort	3–4 months	16	8.4 ± 4.3	61.54	50	100.00	100.00	cardiovascular, and musculoskeletal systems	NA
Pazukhina et al., 2022	Russia	2020.4–2020.8	prospective cohort	255 (223–270) days	360	9.5	48.00	NA	NA	100.00	any, cardiovascular, dermatological, digestive, generalized, musculoskeletal, neurologic, psychiatric, and respiratory systems	neurological comorbidities, allergic respiratory diseases
Penner et al., 2021	UK	2020.4.4–2020.9.1	retrospective cohort	6 months	46	10.2 (8.8–13.3)	65.00	35.00	100.00	100.00	cardiovascular, digestive, musculoskeletal, neurological, psychiatric, and urological systems, and imaging and laboratory findings	NA
Radtke et al., 2021	Switzerland	2020.6–2021.4	prospective cohort	> 12 weeks	109	6–16	53.21	NA	NA	NA	any, digestive, generalized, neurological, psychiatric, and respiratory systems	NA
Say et al., 2021	Australia	2020.3.21–2020.10.28	cohort	3–6months	151	3 (1–8)	52.63	5.85	0.66	100.00	any, generalized, and respiratory systems	NA
Sezer et al., 2022	Turkey	2020.7–2021.7	retrospective cohort	7.8 months	123	9.6	63.40	NA	100.00	100.00	cardiovascular, digestive, generalized, and respiratory systems	NA
Sirico et al., 2022	Italy	2020.4.26–2021.10.2	retrospective cohort	207 days	23	8.25 ± 4	65.60	NA	100.00	100.00	cardiovascular system, and imaging findings	NA
Stephenson et al., 2021	UK	2021.1–2021.4	cohort	3 months	3065	11–17	36.54	NA	NA	0	any, dermatological, digestive, generalized, musculoskeletal, neurological, ophthalmological, and respiratory systems	older age, female, with lower pretest physical and mental health, positive PCR

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Table 1 (*continued*)

Authors	Investigating Site	Investigating period	Study design	Follow-up duration	Sample size	Age (Mean / Median/ Range)	Male (%)	Severe illness (%)[a]	MIS (%)	Hospitalization rate at baseline (%)	Affected systems	Factors associated with outcomes
Sterky et al., 2021	Sweden	2020.12–2021.1	cohort	219 (123–324) days	55	0–18	58.18	NA	3.64	100.00	any, cardiovascular, digestive, generalized, musculoskeletal, neurological, psychiatric, and respiratory systems	NA
Zhang et al., 2021	China	2020.7–2020.9	cohort	4 months	61	7–18	78.69	NA	NA	100.00	psychiatric system	NA

Abbreviations: MIS, multisystem inflammatory syndrome; NA, not available; PCR, polymerase chain reaction.
[a] Definition of severe COVID-19 infection was based on the National Institute of Health symptom severity criteria, guideline for scoring pediatric patients with COVID-19, the requirement of ventilation or admission to pediatric intensive care unit, or directly reported in the study.

Search strategy

Studies that assessed the prevalence of long COVID amongst pediatric COVID-19 survivors were systematically searched in PubMed, Embase, and Cochrane Library databases up to December 11th, 2022 (Supplement 1). The following search terms were used: (COVID-19 OR SARS-CoV-2 OR coronavirus OR 2019-nCoV) AND (long COVID OR post acute COVID syndrome OR PASC OR long-term OR "long term" OR "long haul*" OR "after recovery" OR prolong* OR persist* OR convalescent) AND (cohort OR follow-up OR longitudinal OR cross sectional) AND (child* OR infant*). The full search strategy is provided in the Supplement 1. The reference lists of retrieved papers and recent reviews were manually searched for additional studies that met the inclusion criteria.

All retrieved records were imported into an EndNote library. Two investigators (Zheng Y and Gao N) independently screened all articles for their eligibility. If consensus could not be reached, the third investigator (Zeng N) reviewed the full text article and resolved disagreements.

Selection criteria

To be eligible for inclusion, studies had to: (1) contain original research; (2) include pediatric COVID-19 survivors aged less than 18 years old; (3) measure long COVID symptoms, relevant laboratory or examination result (such as imaging, lung function tests or blood tests) of post-acute COVID-19; (4) assess symptoms at least 3 months after initial COVID-19 infection, as introduced elsewhere [10]; (5) provide raw data that allowed the calculation of the estimates. Exclusion criteria were as follows: (1) the study was a review article or a case report; (2) not pediatric patients; (3) the long COVID did not meet the follow-up duration. The detailed process of the literature search for the systematic review is shown in Fig. 1.

Data extraction

All data were independently extracted from the included studies by two researchers (Zheng YB and Zeng N) who subsequently cross-checked the data. We extracted the following characteristics for each study: authors and year of publication, research site (country), investigating period, study design, follow-up duration, sample size, age and gender of participants, percentage of severe illness, percentage of individuals with MIS, hospitalized rate during acute phase at baseline, the overall whole body symptoms (multiple affected systems mainly including generalized, psychiatric, neurologic, respiratory, digestive, musculoskeletal, cardiovascular, dermatological, ophthalmological, and urological symptoms, etc.), and factors associated with outcomes (Table 1).

Statistical analysis

Meta-analysis was performed to estimate the pooled prevalence of any long COVID and those affecting specific organ systems among pediatric COVID-19 patients. The overall prevalence of symptoms affecting a specific organ system was estimated by pooling the most common symptoms related to that system, if the overall prevalence was not itself reported in the study. Multiple symptoms relating to the same organ system were often reported in the same survivor, therefore the prevalence of the most common symptom was used to estimate the overall prevalence for that system. Additionally, the prevalence of reported symptoms examined in five or more studies was combined [7]. The I^2 index was calculated to assess the between-study heterogeneity and Cochrane Q-test was used to determine statistical significance. An I^2 value > 50 % or a chi-square p value < 0.05 was considered substantial heterogeneity. Pooled rates with 95 % confidence intervals (CIs) were calculated using the

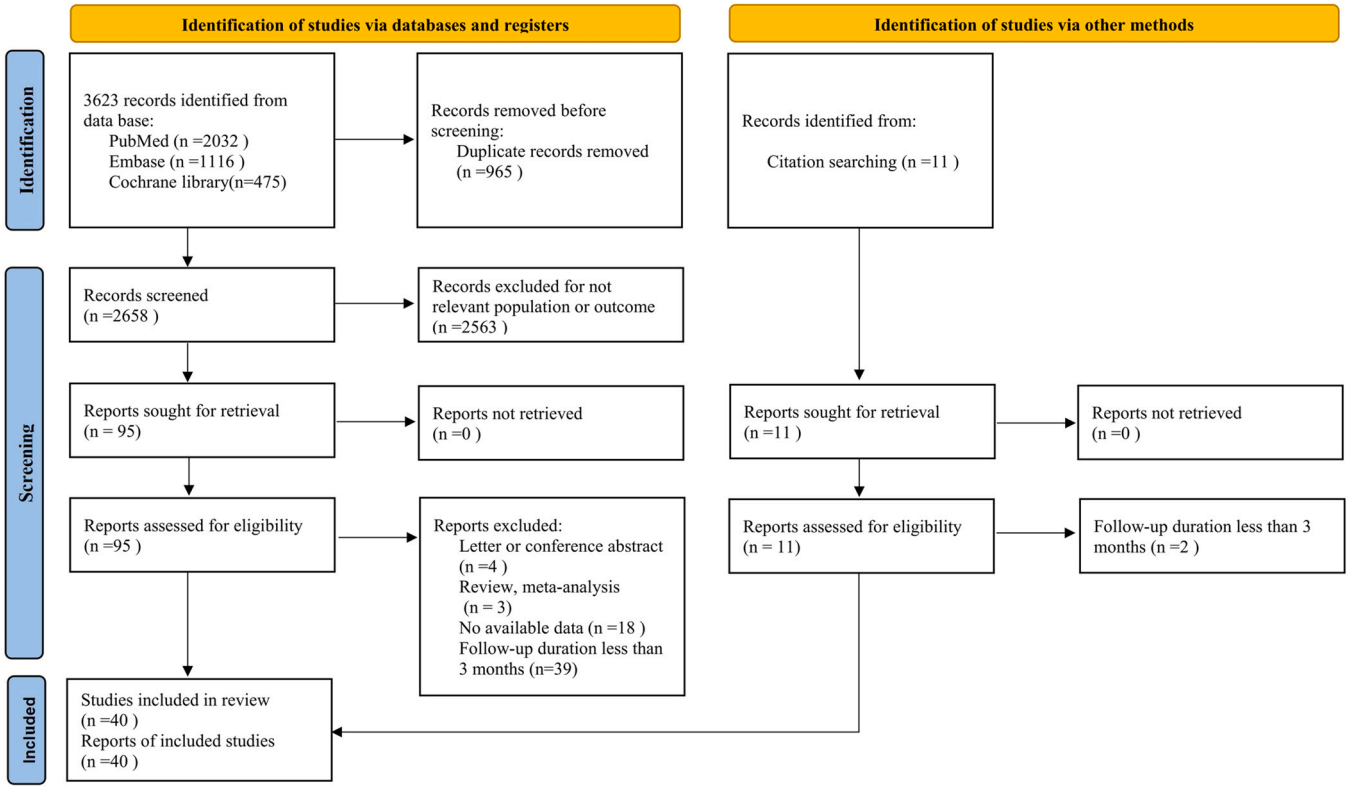


Fig. 1. Flow chart of the selection process.

random-effect model if heterogeneity existed; otherwise the fixed-effect model was used.

Subgroup analyses and meta-regressions on the estimated prevalence of any symptom in each system were performed by stratification with follow-up duration (3–6 months, 6–12 months, > 12 months), mean age of study participants (> 10 years vs. < 10 years), the sex ratio (male proportion > 50 % vs. < 50 %), presence of MIS (yes vs. no), percentage of severe illness (> 50 % vs. < 50 %), and hospitalization rate at baseline (yes vs. no). Leave-one-out sensitivity analysis was conducted to estimate the influence of each study on the pooled results. Funnel plot and the Egger test were used to assess the presence of any publication biases. All analyses were performed with R Software (version 4.0.3).

Quality assessment

The quality of the included studied was assessed using Agency for Healthcare Research and Quality methodology checklist. Two investigators (Yang YB and Chen X) appraised each item of the scale independently. The disagreement was settled by joint review with an experienced methodologist (Zheng YB).

Results

Literature search

As shown in Fig. 1, 3623 records were retrieved through the initial database search, and 965 duplicate papers were removed. Of the 2658 records remaining, the majority were excluded after the first screening based on titles or abstracts. The full texts of ninety-five papers and eleven additionally identified studies [27–37] investigating the prevalence of long COVID of pediatric COVID-19 survivors were scanned. Of these articles, four were letters, conference proceedings, abstracts or comments, three was a review or meta-analysis, eighteen had no available data, forty-one (including thirty-nine initial extracted and two additional identified studies) provided outcomes not had the symptom duration less than 3 months, and were hence excluded from analysis. Finally, a total of 40 eligible studies [16–18,20–22,27–30,32,33,35–62] were included in the final analysis.

Characteristics of the included studies

Table 1 presents the primary descriptive characteristics of the 40 eligible studies. All of the included studies were published between 2020 and 2022. A total of 12,424 participants were included in the final analysis, with the study sample sizes ranging from 16 to 3246. Among the included studies, there were nine cross-sectional and thirty-one cohort studies. The follow-up duration ranged from 3 to 13 months. Of all the included studies, 24 were conducted in Europe [17,18,21,28,29,32,33,36,39–46,50–53,55,56,60,62], 9 in Asia [16,27,30,37,38,48,57,59,61], 4 in North America [16,20,22,27,30,37,38,47,48,54,57–59,61], and 1 in Oceania [35], South America [49], and multi continents [20], respectively. The mean or median age of the participants ranged from to 3–15.2 years old, and most of the studies included more than 50% male patients. Fifteen studies [16,17,21,27,32,35,42–45,47,49,52,57,59] reported the percentage of severe COVID-19 infection, with prevalence of severe illness ranging from 0 to 63.86 %. Eighteen studies [16,17,21,27,32,35,39,43–45,47,49,52,54,57,59,61,62] reported percentage of MIS among pediatric survivors, and seven [17,39,47,54,59,61,62] of them solely included those with MIS. Thirty-four studies [16–18,20–22,27–30,32,35–39,41–50,52–54,58–62] reported the percentage of hospitalization rate of survivors, and nineteen [16,17,21,28,35–39,45–48,54,58–62] of them were 100.00 %, while rest of them ranged from 0 % to 85.26 %. In addition, seven studies [18,20–22,32,56,60] provided information on risk factors associated with long COVID symptoms.

The pooled prevalence of long COVID by organ system and specific symptoms

We pooled the prevalence of long COVID of any one symptom and multiple organ systems. Seventeen studies [16,18,20–22,32,33,35,36,41,43,49–52,56,60] reported any symptom amongst their study population during follow-up, with the prevalence of long COVID ranging from 3.67 % to 66.49 %. By combining prevalence of any long COVID, the pooled prevalence was 23.36 % ([95 % CI 15.27–32.53], I^2 = 99 %; N = 17) among the pediatric COVID-19 participants (Fig. 2).

Estimated prevalence of long COVID by organ system is presented in Fig. 2 and Supplement Fig. 1. Overall, generalized system showed the top pooled prevalence (19.57 %, [95 % CI 9.85–31.52], I^2 = 99 %; N = 26) of long COVID among the pediatric survivors, followed by respiratory (14.76 %, [95 % CI 7.22–24.27], I^2 = 99 %; N = 25), neurologic (13.51 %, [95 % CI 6.52–22.40], I^2 = 99 %; N = 22), psychiatric (12.30 %, [95 % CI 5.38–21.37], I^2 =98 %; N = 20), digestive (11.87 %, [95 % CI 4.22–22.46], I^2 = 99 %; N = 16), musculoskeletal (9.38 %, [95 % CI 3.59–17.31], I^2 = 99 %; N = 19), cardiovascular (7.32 %, [95 % CI 2.68–13.66], I^2 = 97 %; N = 16), dermatological (6.42 %, [95 % CI 1.39–14.46], I^2 = 99 %; N = 12), ophthalmological (3.92 %, [95 % CI 0–14.34], I^2 = 99 %; N = 7), and urological systems (0.44 %, [95 % CI 0–4.02], I^2 = 62 %; N = 2).

The pooled prevalence of abnormal imaging was 13.12 % ([95 % CI 7.38–19.90], I^2 = 0; N = 5). In addition, the pooled prevalence of abnormal laboratory findings ranged from 0 (international normalized ratio: [95 % CI 0–2.51]; N = 1) to 86.71 % (IgG positivity: [95 % CI 79.95–92.36], I^2 =0; N = 3). In addition, Penner et al. [63] reported that 8.70 % ([95 % CI 1.95–18.89]; N = 1) of survivors were readmitted to the hospital after discharge. Estimation of prevalence of abnormal imaging and laboratory findings among pediatric patients is presented in Supplement Fig. 2.

The pooled prevalence of reported symptoms

We combined the pooled prevalence of specific reported symptoms examined in five or more studies. Overall, dyspnea (22.75 %, [95 % CI 9.38–39.54], I^2 =94 %; N = 11) was the top specific symptom among the pediatric survivors (Fig. 3), followed by fatigue (20.22 %, [95 % CI 9.19–34.09], I^2 =99 %; N = 21), headache (15.88 %, [95 % CI 6.85–27.57], I^2 =99 %; N = 18), shortness of breath (15.30 %, [95 % CI 3.13–33.85], I^2 =99 %; N = 7), abdominal pain (12.42 %, [95 % CI 2.94–26.81], I^2 =99 %; N = 12), concentration difficulties (11.44 %, [95% CI 1.54–28.04], I^2 =99 %; N = 10), muscle pain (11.42 %, [95 % CI 3.45–22.96], I^2 =99 %; N = 14), sleep disturbances (8.38 %, [95 % CI 1.77–18.57], I^2 =94 %; N = 9), diarrhea (8.01 %, [95 % CI 1.66–18.08], I^2 =98 %; N = 9), skin rashes (7.60 %, [95 % CI 0.38–21.62], I^2 =99 %; N = 7), heart palpitations (6.59 %, [95 % CI 0.72–16.68], I^2 =98 %; N = 8), cough (6.17 %, [95 % CI 2.16–11.78], I^2 =97 %; N = 17), dizziness (6.16 %, [95% CI 0.15–18.22], I^2 =99 %; N = 8), chest pain (5.88 %, [95 % CI 1.27–13.15], I^2 =97 %; N = 12), fever (5.02 %, [95 % CI 0.36–13.47], I^2 =95 %; N = 12), altered or loss of smell/taste (3.97 %, [95 % CI 0–12.72], I^2 =94 %; N = 6), weight loss (3.73 %, [95 % CI 0.07–11.15], I^2 =94 %; N = 5), joint pain or swelling (2.74 %, [95 % CI 0.36–6.74], I^2 =94 %; N = 7), altered or loss of smell (2.47 %, [95 % CI 0.36–5.90], I^2 =97 %; N = 9), and altered or loss of taste (1.71 %, [95 % CI 0.08–4.68], I^2 =89 %; N = 6).

The pooled prevalence of long COVID during different follow-up durations

The prevalence of any symptom exhibited a decreasing trend with the progress of follow-up (Fig. 4), they were 26.41 % ([95 % CI 14.33–40.59], I^2 =100 %; N = 11), 20.6 4% ([95 % CI 17.06–24.46], I^2 =31 %; N = 5), and 14.89 % ([95 % CI 6.09–26.51], I^2 =75 %; N = 2) during 3–6, 6–12, and > 12 months, respectively. The prevalence of long COVID among the pediatric survivors during different follow-up durations significantly different in the following specific system: respiratory (P < 0.01), psychiatric (P < 0.01), neurologic (P < 0.01), and cardiovascular (P < 0.01) systems. No significant difference of prevalence of long COVID during different follow-up duration was explored in the rest of systems.

Subgroup analysis

Fig. 5 and Supplement Table 3 shows the meta-regression results of estimation of prevalence of long COVID, and detailed prevalence of long COVID in stratified populations is presented in Supplement Fig. 3-7. Compared with patients with age < 10 years, those with age > 10 years had a higher prevalence of long COVID in generalized (36.6 % vs. 8.6 %; P = 0.04), respiratory (28.3 % vs. 1.9 %; P < 0.01), and musculoskeletal (18.9 % vs. 0.6 %; P < 0.01), and systems. MIS patients exhibited a higher prevalence of long COVID in neurologic (29.9 % vs. 5.2 %; P < 0.01), psychiatric (22.6 % vs. 2.9 %; P < 0.01), cardiovascular (9.6 % vs. 3.2 %; P < 0.01), and musculoskeletal (12.2 % vs. 1.4 %; P = 0.04), when compared with those without MIS. In addition, severe patients had a higher prevalence of neurologic (38.3 % vs. 10.5 %; P < 0.01), and psychiatric (42.5 % vs. 7.6 %; P < 0.01) symptoms than non-severe patients. No significant difference was found between prevalence of long COVID of each organ and percentage of hospitalization proportion at baseline, as well as the sex ratio of the studies.

Symtoms	No. of study	No. of events	No. of participants	Prevalence (%) (95% CI)	I^2(%)	P value
Any of the symptoms	17	3421	10426	23.36 (15.27, 32.53)	99.0	<0.01
Generalized symptoms	26	2575	11496	19.57 (9.85, 31.52)	99.0	<0.01
Subjective respiratory symptoms	25	1205	8119	14.76 (7.22, 24.27)	99.0	<0.01
Neurologic symptoms	22	951	7979	13.51 (6.52, 22.40)	99.0	<0.01
Psychiatric symptoms	20	736	7939	12.30 (5.38, 21.37)	98.0	<0.01
Digestive symptoms	16	580	7177	11.87 (4.22, 22.46)	99.0	<0.01
Musculoskeletal symptoms	19	805	10853	9.38 (3.59, 17.31)	99.0	<0.01
Cardiovascular symptoms	16	214	3933	7.32 (2.68, 13.66)	97.0	<0.01
Dermotogical symptoms	12	304	7009	6.42 (1.39, 14.46)	99.0	<0.01
Ophthalmological symptoms	7	332	6244	3.92 (0, 14.34)	99.0	<0.01
Urological symptoms	2	2	540	0.44 (0, 4.02)	62.0	0.10

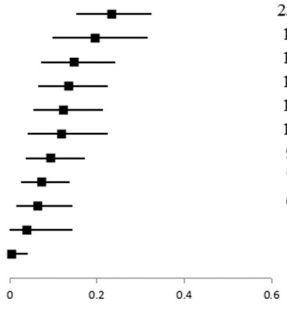


Fig. 2. Estimation of prevalence of long COVID among pediatric patients.

Symtoms	No. of study	No. of events	No. of participants	Prevalence (%) (95% CI)	I^2(%)	P value
Dyspnoea	11	173	545	22.75 (9.38, 39.54)	94.0	<0.01
Fatigue	21	1950	8084	20.22 (9.19, 34.09)	99.0	<0.01
Headache	18	1287	7420	15.88 (6.85, 27.57)	99.0	<0.01
Shortness of breath	7	797	5521	15.30 (3.13, 33.85)	99.0	<0.01
Abdominal pain	12	536	4825	12.42 (2.94, 26.81)	90.0	<0.01
Concentration difficulties	10	226	3318	11.44 (1.54, 28.04)	99.0	<0.01
Muscle pain	14	727	7515	11.42 (3.45, 22.96)	99.0	<0.01
Sleep disturbance	9	113	1304	8.38 (1.77, 18.57)	94.0	<0.01
Diarrhoea	9	287	4415	8.01 (1.66, 18.08)	98.0	<0.01
Skin rashes	7	209	1521	7.60 (0.38, 21.62)	99.0	<0.01
Heart palpitations	8	165	1419	6.59 (0.72, 16.68)	98.0	<0.01
Cough	17	303	7002	6.17 (2.16, 11.78)	97.0	<0.01
Dizziness	8	595	6270	6.16 (0.15, 18.22)	99.0	<0.01
Chest pain	12	304	6598	5.88 (1.27, 13.15)	98.0	<0.01
Fever	12	250	6177	5.02 (0.36, 13.47)	95.0	<0.01
Altered or loss of smell/taste	6	40	2715	3.97 (0, 12.72)	94.0	<0.01
Weight loss	5	24	824	3.73 (0.07, 11.15)	94.0	<0.01
Joint pain or swelling	7	32	1218	2.74 (0.36, 6.74)	99.0	<0.01
Altered or loss of smell	9	433	4294	2.47 (0.36, 5.90)	97.0	<0.01
Altered or loss of taste	6	28	1120	1.71 (0.08, 4.68)	89.0	<0.01

Fig. 3. Estimation of reported long COVID symptoms examined by five or more studies.

Risk factors for long COVID

Seven studies [18,20–22,32,56,60] reported risk factors for any long COVID in pediatric patients. Of these studies, five of them [18,20–22,56] pointed out the being older age was associated with higher risk for long COVID. Also, three studies [18,22,56] showed that female were more vulnerable for long COVID. Patients with poor physical or mental health were identified impacting long COVID [18,56]. In addition, those with more severe symptoms (e.g., symptomatic during the acute phase [32], hospitalized 48 h or more [20]), affected in specific organs (e.g., allergic diseases [21], and neurological comorbidities [60], etc.), and had more symptoms at initial infection [20,56], are more likely to develop long COVID. Others factors, such as insurance types [22], and polymerase chain reaction positive 3 months after diagnosis [18] were also mentioned to be associated with long COVID.

Quality control and publication bias

The quality scores of the included articles ranged from 5 to 10 points (Supplement Table 4). We observed no significant study effect when estimating the prevalence of long COVID. Applying the leave-one-out sensitivity analysis did not significantly alter the pooled estimates of prevalence of long COVID, indicating that no individual study influenced the results significantly. For those long COVID reported by over five studies, no significant publication bias was explored. These results are presented in Supplement Table 5 and Supplement Fig. 8.

Discussion

This study is, to our knowledge, the most wide-ranging systematic review to date, comprehensively summarizing current evidence on the long COVID of pediatric COVID-19 survivors. The findings suggest that nearly one quarter of pediatric patients had long COVID symptoms, which widely involved multi-organ systems. Prevalence of long COVID symptoms decreased as time went by. In addition, patients who were aged over 10 years, with MIS, and severe illness exhibited higher prevalence of long COVID. We also summarized the factors associated with long COVID in children, manly included older age, female, poor mental or physical status, as well as severe symptoms at initial infection. These findings have significant clinical implications and suggest that long-term monitoring is warranted for pediatric COVID-19 survivors.

The COVID-19 pandemic is our generation's greatest global challenge to our public health system [64–68], and children and adolescents have been affected both physically and psychologically [69,70]. In this meta-analysis and systematic review, we found that persistent COVID-19 symptoms were common among the pediatric COVID-19 survivors, with nearly one quarter reporting at least one long COVID symptom after recovery from acute illness or hospital discharge. The finding is similar to previous findings that suggesting post-COVID symptoms was 25.24 % in children and adolescents. However, the prevalence of long COVID-19 symptoms among the pediatric survivors was lower compared with adults, with at least half of them was reported having persistent long COVID [7]. These findings implicated the necessity of long-term monitoring for pediatric survivors recovered from COVID-19.

As indicated in this meta-analysis, dysponea, fatigue, and headache, occurred the most frequently, which is similar to adults with fatigue and dyspnea most prevalent [45]. However, symptoms such as myocarditis [28], splenomegaly [63], and appendicitis [71] are presented in pediatric survivors, which are serious long COVID of COVID-19 infection, albeit thankfully less common. The exact mechanism of these less common long COVID, and whether they are due to direct viral pathogenesis, requires further exploration. Apart from the symptoms mentioned above, developmental regression [27], memory impairment [27,28], and cognitive difficulties [36] have been reported in pediatric COVID-19 survivors, which may impair physical and psychological development of children in the future. Aside from the clinical assessment, imaging and laboratory findings also have implications for monitoring persistent COVID-19 symptoms amongst pediatric survivors.

We also found that the long COVID symptoms decreased as the follow-up duration, especially in respiratory, cardiovascular, psychiatric, and neurologic systems. The findings suggest that the long COVID symptoms were reversible, and the patients would be recovered despite it took a long time. However, one thing still should be taken into consideration is that some long COVID symptoms even exist after one-year follow-up duration, longer-term follow-up is

Symptoms	No. of studies	No. of events	No. of participants	Prevalence(%) (95% CI)	I^2(%)	P value
Any symptoms						
3-6 months	11	3205	9289	26.41 (14.33, 40.59)	100.0	0.41
6-12 months	5	237	1086	20.64 (17.06, 24.46)	31.0	
>12 months	2	51	411	14.89 (6.09, 26.51)	75.0	
Subjectively repiratory symptoms						
3-6 months	17	1094	7096	21.50 (9.41, 36.74)	98.0	<0.01
6-12 months	9	234	1645	13.65 (2.29, 31.55)	99.0	
>12 months	4	12	590	1.80 (0.22, 4.38)	49.0	
Psychiatric symptoms						
3-6 months	12	476	6793	13.84 (4.95, 26.08)	98.0	<0.01
6-12 months	9	331	1707	14.51 (3.26, 31.32)	99.0	
>12 months	3	10	565	1.34 (0, 5.26)	82.0	
Neurologic symptoms						
3-6 months	14	664	6784	13.01 (5.66, 22.67)	98.0	<0.01
6-12 months	9	353	1753	17.76 (3.86, 38.22)	99.0	
>12 months	3	13	534	1.89 (0.20, 4.70)	44.0	
Generalized symptoms						
3-6 months	15	2086	10077	19.50 (7.78, 34.75)	99.0	0.31
6-12 months	9	501	1842	19.30 (3.13, 43.97)	99.0	
>12 months	4	46	590	8.90 (2.96, 17.25)	88.0	
Digestive symptoms						
3-6 months	9	289	6033	12.38 (2.10, 29.02)	99.0	0.11
6-12 months	9	381	1754	14.76 (2.77, 33.23)	99.0	
>12 months	2	10	514	2.22 (0, 8.93)	90.0	
Musculoskeletal symptoms						
3-6 months	13	570	9797	8.97 (2.09, 19.52)	98.0	0.26
6-12 months	7	304	1608	13.61 (1.43, 34.52)	99.0	
>12 months	3	12	565	3.03 (0.05, 9.07)	81.0	
Dermotosis symptoms						
3-6 months	10	169	6283	7.10 (1.34, 16.46)	97.0	0.17
6-12 months	4	207	1333	11.17 (0, 40.21)	99.0	
>12 months	2	11	514	2.09 (0.97, 3.57)	0.0	
Cardiovascular symptoms						
3-6 months	9	95	3077	7.71 (1.58, 17.22)	97.0	<0.01
6-12 months	9	168	1457	8.60 (1.53, 19.68)	98.0	
>12 months	1	1	360	0.28 (0, 1.19)	/	
Ophthalmological symptoms						
3-6 months	5	197	5445	1.69 (0, 6.10)	98.0	0.52
6-12 months	2	135	799	12.63 (0, 74.04)	100.0	
Urological symptoms						
3-6 months	1	0	496	0 (0, 0.35)	/	0.11
6-12 months	2	2	540	0.44 (0, 4.02)	62.0	

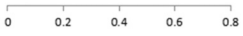
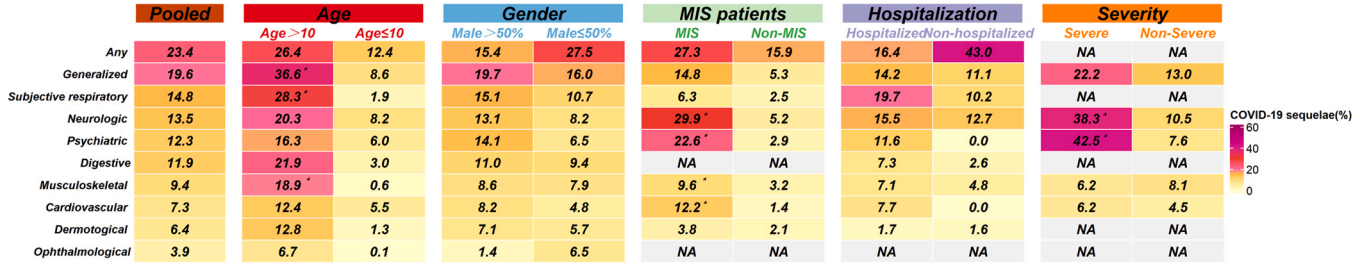


Fig. 4. Subgroup analysis of prevalence of long COVID in pediatric patients during different follow-up duration.

necessary to help define the extended natural history of pediatric survivors, even after one year or longer.

In this study, we also found children and adolescents with MIS, or had severe infection were more vulnerable to having long COVID symptoms. Children and adolescents with MIS generally exhibited serious and life-threatening illness [19,72]. Seven studies in this systematic review independently assessed the long COVID among the pediatric survivors with MIS. Overall, the pediatric survivors



Severe patients is defined as more than 50% of the patients who are seriously ill in acute phase.
* means subgroup difference p<0.05

Fig. 5. Subgroup analysis of prevalence of long COVID in pediatric patients.

with MIS had a higher prevalence of long COVID affecting multiple systems and organs. Participants with severe acute illness was also identified associated with long COVID in multi-systems. Osmanov et al. [73] associated severe acute COVID-19 with a six times greater likelihood of reporting long COVID; suggesting further characterization of which specific organ systems are most likely to be affected in severe cases of COVID-19 is still required. Moreover, by summarizing risk factors associated with long COVID, we also noticed that patients with more symptoms, or affected by specific diseases (e.g., neurologic, or allergic diseases) were more likely to develop long COVID. No statistical difference between the prevalence of long COVID affecting each specific organ system and hospitalization rate at baseline; however, more hospitalization duration was mentioned to associated with long COVID in Funk et al. findings [20]. All these findings implicated the importance of assessing the clinical conditions during the initial infection, and more attention should be paid to pediatric survivors with MIS, severe infection, or had comorbidities.

Some demographic characteristics have been mentioned to be associated with long COVID. Consistent with the findings of Behnood et al. [74], older age was associated with higher prevalence of long COVID symptoms. Despite no significant difference was explored between long COVID symptom and sex ratio in this study, several studies [18,56] implied that female are more risk for long COVID. In addition, patients with poor mental or physical health status also exhibited higher risk for long COVID. Exploring these vulnerable populations further could help policy-makers and physicians establish population-stratified support for patients most in need.

Several limitations should be pointed out in this study. First, the prevalence of long COVID among the pediatric survivors may biased due to the limited included number of studies. To the best of our knowledge, the majority of the studies focused on long COVID among the adults, as the symptoms may be more severe. As there still remained a lot of unknowns about the long COVID in pediatric COVID-19 survivors, more related researches are recommended. Second, the heterogeneity of the study could not be avoided. Many symptoms were not captured using standardized definitions or instruments, and it was difficult to compare frequency and severity. Objective measurement as well as well-designed examinations is suggested to in the near future. Third, the long COVID after COVID-19 infection were merely symptoms among the survivors; therefore, the causal relationship between COVID-19 infection and long COVID should be cautiously read. Many symptoms such as fatigue, muscle pain, and headache are highly prevalent in the general population, and it may be not necessarily caused by COVID-19 infection. Based on this consideration, it is of great necessity to introduce the comparison group to address the issue of long COVID of COVID-19 infection among the pediatric survivors. Disappointingly, few included studies set the control groups to compare the long COVID among the COVID-19 pediatric survivors, which limited us to furtherly clarify the relationship between COVID-19 infection and long COVID. Fourth, the impact of COVID-19 infection on growth and intelligence development after long period seemed to be not clear. Memory impairment, and cognitive difficulties have already been reported in pediatric COVID-19 survivors [28,51], which implied the potential side effects of COVID-19 infection on growth and intelligence development. Thus, the long period monitoring for pediatric COVID-19 survivors is necessary. Fifth, evidence of risk factors associated with long COVID symptoms was limited, which needs further investigation in the future. Patients with MIS, more severe symptoms at initial infection generally presented with higher prevalence of long COVID. Therefore, these vulnerable patients should be cautiously treated with medical service not merely during acute phase, but also be monitored after long duration.

Conclusion

In conclusion, this meta-analysis provides a comprehensive overview of the current state of knowledge of the long COVID among the pediatric COVID-19 survivors and the risk factors associated with it. Our findings suggest that pediatric COVID-19 survivors who have recovered from COVID-19 have a high burden of long COVID after hospital discharge, and the cases with multisystem inflammatory syndrome, and more severe symptoms at initial infection had higher burden. It is important to follow-up these patients and appropriately manage any persistent or emerging long COVID in both physical and psychological domains.

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CRediT authorship contribution statement

LL, and YPB proposed the topic of the systematic review. YBZ, NZ, SST, YBY, NG, and XC performed the literature search, extracted and selected articles. YBZ and NZ performed the primary analysis, and all authors help interpreted the results. YBZ and KY drafted the manuscript, ALK, AL, JS, JLY, XL, LS, JS, YPB and LL were responsible for critical revision of the manuscript, and all authors revised the manuscript, approved the final submitted version of the manuscript, and approved the decision to submit the manuscript.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgments

None.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2023.03.005.

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