Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study

Rosa Morello,[a] Francesco Mariani,[a] Luca Mastrantoni,[b] Cristina De Rose,[a] Giuseppe Zampino,[a] Daniel Munblit,[c,f] Louise Sigfrid,[d] Piero Valentini,[a] and Danilo Buonsenso[a,e,*]

[a]Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[b]Medical Oncology, Università Cattolica del Sacro Cuore, Rome, Italy
[c]Department of Paediatrics and Paediatric Infectious Diseases, Institute of Child's Health, I.M. Sechenov First Moscow State Medical University, Sechenov University, Moscow, Russia
[d]ISARIC Global Support Centre, GloPID-R Research and Policy Team, Pandemic Sciences Institute, University of Oxford, Oxford, UK
[e]Centro di Salute Globale, Università Cattolica del Sacro Cuore, Roma, Italy
[f]Care for Long Term Conditions Division, Florence Nightingale Faculty of Nursing, Midwifery and Palliative Care, King's College London, London, United Kingdom

eClinicalMedicine 2023;59: 101961
Published Online 14 April 2023
https://doi.org/10.1016/j.eclinm.2023.101961

Summary

Background Adults and children can develop post-Covid-19 condition (PCC) (also referred to as Long Covid). However, existing evidence is scarce, partly due to a lack of a standardised case definition, short follow up duration, and heterogenous study designs, resulting in wide variation of reported outcomes. The primary aim of this study was to characterise risk factors for PCC and longitudinal rates of recovery in a cohort of children and young people using a standardised protocol.

Methods We performed a prospective "disease-based" cohort study between 01/02/2020 to 31/10/2022 including children aged 0–18 years old, with a previous diagnosis of Covid-19. Children with microbiologically confirmed SARS-CoV-2 infection, were invited for an in-clinic follow-up assessment at a paediatric post-covid clinic in Rome, Italy, at serial intervals (3-, 6-, 12- and 18-months post-onset). PCC was defined as persistence of otherwise unexplained symptoms for at least three months after initial infection. The statistical association between categorical variables was obtained by Chi-squared tests or Fisher's exact tests. Multivariable logistic regressions are presented using odds ratios (OR) and 95% confidence interval (CI). Survival analysis was conducted using the Kaplan–Meier method.

Findings 1243 children were included, median age: 7.5 (4–10.3) years old; 575 (46.3%) were females. Of these, 23% (294/1243) were diagnosed with PCC at three months post-onset. Among the study population, 143 patients remained symptomatic at six months, 38 at 12 months, and 15 at 18 months follow up evaluation. The following risk factors were associated with PCC: >10 years of age (OR 1.23; 95% CI 1.18–1.28), comorbidities (OR 1.68; 95% CI 1.14–2.50), and hospitalisation during the acute phase (OR 4.80; 95%CI 1.91–12.1). Using multivariable logistic regression, compared to the Omicron variant, all other variants were significantly associated with PCC at 3 and 6 months. At least one dose of vaccine was associated with a reduced, but not statistically significant risk of developing PCC.

Interpretation In our study, acute-phase hospitalisation, pre-existing comorbidity, being infected with pre-Omicron variants and older age were associated with a higher risk of developing PCC. Most children recovered over time, but one-in-twenty of those with PCC at three months reported persistent symptoms 18 months post-Sars-CoV-2 infection. Omicron infection was associated with shorter recovery times. We did not find a strong protective effect of vaccination on PCC development. Although our cohort cannot be translated to all Italian children with PCC as more nationwide studies are needed, our findings highlight the need of new strategies to prevent and treat pediatric PCC are needed.

Funding This study has been funded by Pfizer non-competitive grant, granted to DB (# 65925795).

*Corresponding author. Largo A. Gemelli 8, 00168, Rome, Italy.
E-mail address: danilobuonsenso@gmail.com (D. Buonsenso).
@danilo.buonsenso_surf4children (D. Buonsenso).

Translation: For the Spanish, Portuguese, Arabic, Chinese, and Japanese translations of the abstract see Supplementary Materials section.

Keywords: Sars-Cov-2 infection; Children; Long covid; Post-covid condition; Risk factors; Sars-CoV-2 variants; COVID-19 vaccination

Research in context

Evidence before this study

A systematic search was conducted from 1st November 2022 to 7th December 2022 on Pubmed; the search terms used were: "COVID19, "children", "adolescents", "long-COVID", "sequelae" and "persistent symptom" (combined with the Boolean logic operation "OR"/"AND"). The title and abstract of 5520 publications were screened; after screening, 36 studies including patients with Post Covid Condition (PCC) were identified. All available studies included children whose persisting symptoms were assessed via online self-completed surveys or by phone and/or used different definitions of PCC (4 8 or ≥ 12 weeks of symptoms persistence). None of the studies assessed patients in clinical settings using standardised medical assessments and exclusion of other alternative diagnoses, to inform the PCC diagnosis and definition. No studies defined the relationship with different SARS-CoV-2 strains and vaccination status on the risk of developing PCC.

Added value of this study

To the best of our knowledge, this is the first study to have prospectively assessed a prospective cohort of children with microbiologically confirmed SARS-CoV-2 infection for up to 18 months post-Sars-CoV-2 infection. Children were assessed by physicians in clinics using a standardised Covid-19 follow-up protocol and in-clinical medical assessments to define PCC, identify risk factors for PCC and recovery rates. PCC was defined as persistence of symptoms for 12 weeks or more, with a negative impact on daily activities, after exclusion of alternative conditions.

Implications of all the available evidence

In this study, using a rigorous approach and objective medical assessments, we identified that pre-existing comorbidities, being of older age, hospitalised during the acute infection and being infected with pre-Omicron variants were risk factors for developing PCC. Most children improved over time (12–18 months), particularly those infected during Omicron waves. We did not identify a strong protective effect of partial or complete vaccination on the risk of developing PCC. These findings highlight important risk factors for developing PCC in children, and the need for investments into research to inform prevention and treatment of PCC in children, to reduce morbidity and improve long term recovery rates and outcomes.

Introduction

Since the beginning of the pandemic, the World Health Organization (WHO) has reported over 650 million confirmed cases of COVID-19 globally (as of 13 January 2023).[1] Although most people have recovered fully following SARS-CoV2 infection, a subgroup of adults and children experience unexplained persistent residual or new-onset symptoms. This condition is known as long COVID, post-COVID-19 condition (PCC) and post-acute sequelae of SARS-CoV-2 infection (PASC).[2]

In 2021, the WHO developed a definition of PCC.[3] Subsequently, the US Centres for Disease Control and Prevention (CDC), The National Institute for Health and Care Excellence (NICE), and the National Institutes of Health (NIH) have proposed similar clinical case definitions for PCC in adults.[4–6] The first definition of pediatric PCC was not developed until 2022. It was defined for research purposes, "*Post-COVID-19 condition occurs in young people with a history of confirmed SARS-CoV-2 infection, with at least one persisting physical symptom for a minimum duration of 12 weeks after initial testing that cannot be explained by an alternative diagnosis. The symptoms have an impact on everyday functioning, may continue or develop after COVID infection, and may fluctuate or relapse over time*".[7]

Several signs and symptoms have been associated to PCC in studies in adults and children, including neuropsychiatric, cardiovascular, pulmonary, hematological, gastrointestinal, renal, endocrine, dermatological, and musculoskeletal sequelae.[8] In both populations, chronic fatigue, post-exertional malaise, headache, and other neurocognitive problems are the most frequently reported symptoms.[9–12]

Although PCC is now generally accepted by the medical community as a condition affecting both adults and children,[13] several uncertainties remain. Due to different study designs, symptoms investigated, inclusion case definitions including symptom persistence (4 vs. 8 vs. 12 weeks), the study population (hospitalised vs. outpatient), and the data collection process (self-reported vs. medical records vs. in-clinic assessments), existing studies provides heterogeneous data, preventing meta-analysis. The real incidence of PCC, the underlying pathophysiology, risk factors and long-term outcomes remain unknown. Data from reviews of adult studies have shown a prevalence of PCC ranging from 7.5% to 41%.[5,9,10] A recent systematic review of PCC in

children similarly reported high variability in terms of prevalence ranging from 1.6 to 70%,[11] with variability explained by variations in definitions used, time of follow-up and the presence or not of a controlled group.

So far, all pediatric studies have focused on self-reported symptoms collected by parents via phone calls or online surveys. Two studies have used a different approach comparing healthcare resources in children and adolescents that had or not Covid-19. One multicentre study in the United States used healthcare records to identify the excess need of care in children with previous evidence of SARS-CoV-2 infection and negative controls.[14] Similar results have been obtained from Germany.[15] However, both these approaches have intrinsic limitations. Self-completed surveys can overestimate symptoms, and use of healthcare records is limited to the codes and symptoms recorded. This can miss subtle and difficult to classify symptoms like brain fog or post-exertional malaise. Importantly, none of the available studies used a prospective, in-clinic medical assessment or a standardised PCC definition. In addition, most studies in children included small sample sizes, with short and retrospective follow-up (up to 3 or 6 months only) No study explored the role of different SARs-CoV-2 variants and vaccination and the risk of developing PCC.

In this prospective follow-up study, we aimed to investigate the long-term duration of persisting symptoms and risk factors for developing of PCC in a large cohort of children using in-clinic assessments. This is the first study to explore the impact of SARS-CoV-2 variants and vaccination on the risk of developing PCC in children.

Methods

Study population and setting

This is a prospective follow-up study of children with microbiologically confirmed SARS-CoV-2 infection evaluated in person at a referral pediatric post-covid clinic in Rome, Italy.

The study population is a cohort of paediatric patients younger than 19 years old with laboratory Sars-Cov-2 infection (between 01/02/2020 to 31/10/2022), referred to our public post-Covid outpatient unit from our Emergency Department, admission ward or family pediatricians in the region/in Rome. This is a "disease-based" cohort which invited children previously diagnosed with Covid-19 who were hospitalised or not hospitalised during the acute infection, and children with asymptomatic infection recognised during active case findings due to close contact with a case, or children diagnosed with suspected PCC. The clinic was to all referrals requested by hospital or family pediatricians, Exclusion criteria included patients aged 19 years or more, children that had more than one microbiologically confirmed SARS-CoV-2 infection, individuals with suspected but not lab-confirmed infection, and individuals with ongoing acute infection.

All participants were assessed at 3, 6, 12, and 18 months post-acute Sars-CoV-2 infection. The evaluations were conducted by a paediatrician. Data on demographics (age, gender, and pre-existing conditions) were collected, together with data on severity of acute infection (as previously defined[16]), hospitalisation and medication utilisation, symptoms experienced during acute COVID-19, the outcome of the acute SARS-CoV-2 infection, Covid-19 vaccination status (mRNA vaccines licensed in Italy), and any medication used for post-COVID-19 symptoms. Acute phase severity was defined as mild, moderate or severe.[16] Detailed symptom recording included fever (presence and duration), rhinitis, pharyngitis, smell and taste disturbances (including both complete loss or alterations), cough, dyspnea/exertional dyspnea, chest pain, muscle and joint pain, fatigue, headache, rash/skin lesions, gastrointestinal symptoms (diarrhea, vomiting, abdominal pain, loss of appetite, fever), weakness, neurological symptoms, other symptoms, including cognitive problems. Data on the dominant circulating variant at the time of infection was collected from the report coordinated by the Italian Superior Health Institute,[17] following the method outlined in the supplementary Fig. S2.

Outcome definition

PCC was defined as the persistence of symptoms for at least three months after initial infection, which had a negative impact on daily life, and other possible diagnoses excluded according to the definition provided by *Stephenson T et al.*[7] All patients with possible PCC underwent tests to exclude the following conditions: anaemia, hematologic conditions, coeliac disease, blood glucose, liver and renal function, thyroid problems, autoimmune disease, other infections including intestinal parasites. Patients identified with alternative diagnoses were not classified as PCC and excluded from the analysis. Recovery was defined as the resolution of symptoms or the presence of mild symptoms that did not impede daily activities, school, or sports (Supplementary Fig. S1).

Statistical analysis

The normality of continuous variables was evaluated using visual inspection of Q–Q plots and P–P plots. Categorical variables were reported as count and percentage. Continuous variables with normal distribution were expressed as mean with standard deviation; non-normal data were expressed as median with interquartile range (IQR 25%–75%). Association between PCC development and vaccination status were analysed separately for two groups of children, differentiated by age in relation to differing vaccination eligibility (5–11 years and 12–18 years), both at three- and six-months follow-up. The 11 years cut-off was only used for the vaccination analyses,

and was based on the eligibility of different cohorts for covid vaccines in children (5–11yrs and 12–18yrs, which also received different doses of vaccination but also accessed to vaccination in different periods).

The statistical association between categorical variables was obtained by Chi-squared tests or Fisher's exact tests. Mann–Whitney U-test was used to assess differences in two groups for continuous variables if not normally distributed. A p-value of less than 0.05 was considered statistically significant.

Multiple univariate logistic regressions were performed to investigate potential prognostic factors of symptom persistence at different time points. The results were expressed using Odds Ratios (OR) and a 95% confidence interval (CI). No multiplicity adjustments were performed in the univariate analysis.

To examine the persistence of symptoms at three and six months, two multivariable regression logistic models were conducted. The variables included in these models were selected based on their clinical relevance and statistical significance as determined through univariate analysis. The first model focused on the persistence of symptoms at three months, while the second model focused on the persistence of symptoms at six months. The percentage of heterogeneity explained by the different models was evaluated using Nagelkerke R2.

The multicollinearity diagnostic for the multivariable models is presented in the supplementary material. Survival analysis was conducted in patients still symptomatic at three months. The probability of being symptomatic at further time points was assessed using the Kaplan–Meier method.

Statistical analysis was performed using IBM SPSS Statistics 25.0 software (IBM Corporation, Armonk, NY, USA).

Ethical approval

The study was approved by the local ethics committee (Ethic approval ID4518, Prot0040139/21) and informed consent was provided. Written and informed consent was obtained from parents/caregivers and from children older than 5 years of age, according to local guidance of the ethic committees.

Role of the funding source

The funders had no role in the development of the project nor in the no role in study design, data collection, data analysis, interpretation of results or writing of the report. DB has full access to dataset and had final decision to submit for publication. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Results

A total of 1243 patients were included (Fig. 1), the median age was 7.25 (4.0–10.2) years, 46.3% were females

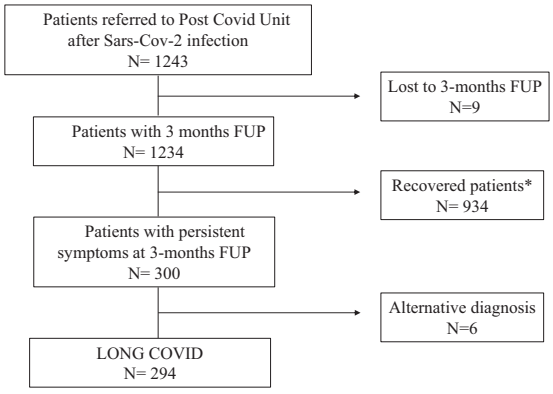

Fig. 1: **Patients flow diagram and number of children with persisting symptoms at each follow-up evaluations.**

(Table 1) and 13.2% (164/1243) had pre-existing comorbidities (Supplementary Table S1), 8.8% (109/1123) were asymptomatic, 89.4% (1111/1243) had a mild, and 1.8% (23/1243) a moderate acute infection.

The Sars-CoV-2 variant analysis assessed that 3.3% were infected with the wild virus, 6.0% (74) with the Alpha, 19.9% (247) with the Delta, and 70.8% (880) with the Omicron variant.

80.5% (1001) were not vaccinated, while 19.5% (242) had received at least one dose of vaccination: in particular 6.4% (79), 11.7% (146), and 1.4% (17) had received one, two, and three doses of Covid-19 vaccine, respectively.

Acute phase and follow-up clinic characteristics

During the acute phase of infection, fever was the most frequently reported symptom, present in 66.6% of patients. Other commonly reported symptoms included rhinitis (46.1%) and cough (36.5%) (Table 2). Most had mild acute infection, 2.2% (28) required hospitalization during the acute phase. Of the 1234 patients who underwent a 3-month follow-up assessment, 76.2% (940) had recovered, while 23.8% (294) reported persistent or new symptoms with a negative impact on daily activities, meeting the criteria for PCC. Among the study population, 143 patients remained symptomatic at six months, 38 at 12 months, and 15 at 18 months follow up evaluation.

The most reported persisting symptoms were fatigue (13.1%), exertional dyspnea (6.2%), headache (5.6%), and gastrointestinal symptoms (4.5%) (Table 2).

The presence of symptoms during infection ($p < 0.002$), their severity ($p < 0.001$), increasing age ($p < 0.001$), the presence of comorbidity ($p < 0.002$), and pre-Omicron virus variants ($p < 0.001$) were associated with greater likelihood of PCC (Table 3).

Survival analysis

294 patients were defined as long-covid patients and 268 of them had a 6-month follow-up assessment and were included in the time-to-event analysis (Fig. 2).

Variables	Entire cohort (n = 1243)
Age (years), median (IQR)	7.25 (4.00–10.25)
Female, n (%)	575 (46.3%)
Pre-existing comorbidities, n (%)	164 (13.2%)
Acute phase severity, n (%)	
Asymptomatic	109 (8.8%)
Mild	1111 (89.4%)
Moderate	23 (1.8%)
COVID variant, n (%)	
Original	42 (3.3%)
Alpha	74 (6.0%)
Delta	247 (19.9%)
Omicron	880 (70.8%)
Covid-19 vaccine doses, n (%)	
0 doses	1001 (80.5%)
1 dose	79 (6.4%)
2 doses	146 (11.7%)
3 doses	17 (1.4%)
Three months follow-up, n (%)[a]	1234 (99.3%)
Six months follow-up, n (%)[a]	1171 (94.2%)
Twelve months follow-up, n (%)[a]	167 (13.4%)
Eighteen months follow-up, n (%)[a]	77 (6.2%)

[a]This represents the number of children that have reached 3, 6, 12 or 18 months of follow-up since the date of initial infection.

Table 1: **Clinical and demographics of the study population.**

Clinical characteristics	Acute phase (n = 1243)	Three months follow-up (n = 1234)
Hospitalization, n (%)	27 (2.2%)	–
Intensive Care, n (%)	1 (0.08%)	–
Fever, n (%)	828 (66.6%)	10 (0.8%)
Days of fever, median (IQR)	1.0 (0.0–2.0)	–
Rhinitis/Nasal Congestion, n (%)	573 (46.1%)	8 (0.6%)
Lost or altered smell, n (%)	64 (5.1%)	11 (0.9%)
Lost or altered taste, n (%)	53 (4.3%)	11 (0.9%)
Cough, n (%)	454 (36.5%)	16 (1.3%)
Dyspnea at rest, n (%)	19 (1.5%)	7 (0.6%)
Dyspnea after exercise, n (%)	18 (1.4%)	77 (6.2%)
Asthma, n (%)	10 (0.8%)	10 (0.8%)
Chest pain, n (%)	31 (2.5%)	29 (2.4%)
Joint pain, n (%)	77 (6.2%)	31 (2.5%)
Tachycardia, n (%)	–	20 (1.6%)
Muscle Pain, n (%)	109 (8.8%)	53 (4.3%)
Weakness, n (%)	278 (22.4%)	162 (13.1%)
Headache, n (%)	278 (22.4%)	69 (5.6%)
Diarrhea and/or other gastrointestinal symptoms, n (%)	179 (14.4%)	56 (4.5%)
Pharyngodynia, n (%)	86 (6.9%)	–
Rash, n (%)	24 (1.9%)	14 (1.1%)
Fatigue under exertion, n (%)	–	15 (1.2%)
Concentration/memory problems, n (%)	–	31 (2.5%)
Other symptoms, n (%)	99 (8.0%)	48 (3.9%)
Number of symptoms, median (IQR)	2.0 (1.0–3.0)	–

Table 2: **Characteristics of acute phase infection and three months follow-up evaluation.**

Overall, 159 events of symptom regression were observed. At the landmark analysis the probability of remaining symptomatic was 53% at six months, 33% at twelve months and 20% at eighteen months.

Risk factor analysis – univariate logistic regression

Several factors were significantly associated with PCC at three months. These factors include age greater than 10 years (OR 3.79; CI 2.87–5.01), pre-existing comorbidities (OR 1.73; CI 1.21–2.48), and hospitalization during the acute phase (OR 2.62; CI 1.21–5.67). Among the acute symptoms, chest pain (OR 5.84; 2.74–12.41), dyspnea at rest (OR 5.67; CI 2.21–14.54), and dyspnea during exercise (OR 5.18; CI 1.99–13.49), lost or altered smell (OR 4.55; CI 2.72–7.59), and lost or altered taste (OR 4.53; CI 2.59–7.93) were found to be most strongly associated with persistence of symptoms. Being asymptomatic during the acute phase was found to be a protective factor for the development of persistent symptoms (OR 0.40; CI 0.22–0.73). Similar factors were identified as being associated with increased risk of persistence of symptoms at 6-months and 12-months post-onset. Whereas at the 18 months assessment, only older age and articular pain during the acute infection remained significant risk factors (Supplementary Tables S2–S4).

Risk factor analysis - multivariable logistic regression

Using multivariable regression model, the following variables were associated with persistence of symptoms at the three months follow-up assessment, including age (OR 1.23, CI 1.18–1.28), acute phase hospitalization (OR 4.80, CI 1.91–12.1), asymptomatic during the acute phase (0.46, CI 0.24–0.85), Omicron variant (OR 0.60, CI 0.45–0.81) and comorbidities (OR 1.68, CI 1.14–2.50) (Table 4, Fig. 3).

The second model, exploring risk factors for PCC at 6 months post-onset (Fig. 3 and Supplementary Table S2), identified age (OR 1.23, CI 1.17–1.29) and acute-phase hospitalization (OR 5.20, CI 1.80–14.99), as significant risk factors for PCC, while infection with Omicron was associated with a reduced risk of developing PCC (OR 0.36, CI 0.24–0.53). The Nagelkerke R2 for this model was 0.22, indicating the amount of heterogeneity explained by the model.

Association between vaccination status and PCC

At the three-month follow-up assessment, among children aged 5–11 years with persistent symptoms, 32/149 (21.5%) received at least one vaccination dose, and 14/149 (9.4%) two or more doses. In children older than 11 years with persistent symptoms, 49/112 (43.8%) had received at least one dose and 40/112 (35.7%) at least two doses. At six-month follow-up among children aged 5–11 with persistent symptoms, 10/68 (14.7%) of patients received at least one dose of vaccination, and 5/68

3-months assessment	Recovered patients (n = 940)	PCC patients (n = 294)	p-value
Female, n (%)	422 (44.9%)	148 (50.3%)	0.102
Age (years), median (IQR)	6.33 (3.50–9.42)	9.83 (7.40–12.85)	<0.001
Age older than 10 years, n (%)	192 (20.4%)	145 (49.3%)	<0.001
Comorbidities, n (%)	108 (11.5%)	54 (18.4%)	0.002
Acute phase severity, n (%)			<0.001
Asymptomatic	96 (10.2%)	13 (4.4%)	
Mild	837 (89%)	265 (90.1%)	
Moderate	7 (0.7%)	16 (5.4%)	
COVID variant, n (%)			<0.001
Original	21 (2.2%)	21 (7.1%)	
Alpha	36 (3.8%)	38 (12.9%)	
Delta	182 (19.4%)	65 (22.1%)	
Omicron	701 (74.6%)	170 (57.8%)	
Hospitalization during the acute phase, n (%)	15 (1.6%)	12 (4.1%)	0.011
Acute phase symptoms			
Fever, n (%)	608 (64.7%)	214 (72.8%)	0.01
Days of fever, median (IQR)	1.0 (0.0–2.0)	2.0 (0.0–3.0)	<0.001
Rhinitis/Nasal Congestion n (%)	444 (47.2%)	127 (43.2%)	0.226
Lost or altered smell, n (%)	28 (3%)	36 (12.2%)	<0.001
Lost or altered taste, n (%)	23 (2.4%)	30 (10.2%)	<0.001
Cough during the acute phase, n (%)	348 (37%)	104 (35.4%)	0.609
Dyspnea at rest during the acute phase, n (%)	7 (0.7%)	12 (4.1%)	<0.001
Dyspnea after exercise during the acute phase, n (%)	7 (0.7%)	11 (3.7%)	<0.001
Asthma during the acute phase, n (%)	6 (0.6%)	4 (1.4%)	0.26
Chest pain during the acute phase, n (%)	11 (1.2%)	19 (6.5%)	<0.001
Articular pain during the acute phase, n (%)	36 (3.8%)	40 (13.6%)	<0.001
Muscle Pain during the acute phase, n (%)	52 (5.5%)	57 (19.4%)	<0.001
Weakness during the acute phase, n (%)	152 (16.2%)	120 (40.8%)	<0.001
Headache during the acute phase, n (%)	158 (16.8%)	117 (39.8%)	<0.001
Diarrhea and/or other gastrointestinal symptoms, n (%)	114 (12.1%)	60 (20.4%)	<0.001
Pharyngodynia, n (%)	45 (4.8%)	39 (13.3%)	<0.001
Rash, n (%)	14 (1.5%)	10 (3.4%)	0.038
Other symptoms, n (%)	70 (7.4%)	28 (9.5%)	0.25
Number of symptoms median (IQR)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	0.001

Table 3: **Comparison between PCC patients and patients without persistence of symptoms at three months follow-up evaluation (analysis performed for 1234 patients).**

(7.4%) completed the entire vaccination cycle. A similar analysis was conducted for children older than 11 years with persistent symptoms, where 19/63 (30.2%) received at least one dose of vaccination and 14/63 (22.2%) were fully vaccinated. Fig. 4 and supplementary Tables S5–S8 illustrates the prevalence of persistent symptoms in different age groups based on vaccination status. Although vaccinated children had a reduced risk of PCC, no statistical significance was found in these differences.

Discussion

To our knowledge, this is the first and largest prospective follow-up study of children post SARS-CoV-2 infection, assessed in clinical settings using a standardised PCC definition and protocol. The most commonly persisting symptoms identified were fatigue, post-exertional dyspnea, headache, and gastrointestinal symptoms. In this study, we identified important risk factors for developing PCC. We found that children older than 10 years were at a higher risk, and those with specific pre-existing comorbidities, similar to what has been described in previous studies.[18] However, female gender was not identified as a risk factor, as has been described in previous studies in adults[19,20] and children.[2] We identified an association between hospitalization during the acute-phase and specific acute symptoms (including muscle-skeletal and gastrointestinal) and development of PCC. It is of particular interest the link between gastrointestinal symptoms and PCC, as the gastrointestinal tract has been found to be a possible reservoir of SARS-CoV-2 and has also been linked with the development of Multisystem Inflammatory Syndrome.[21] Whereas many children recovered over time, a proportion where still affected by PCC up to 18-months

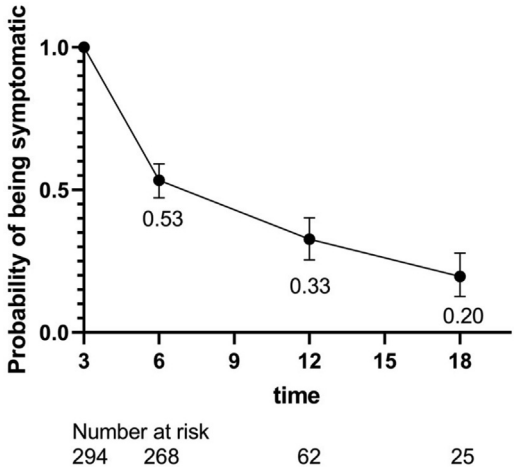

Fig. 2: **Time-to-event analysis for patients with PCC**. 294 patients were symptomatic at 3 months and 268 had a subsequent follow-up visit and were included in the analysis. 159 events of symptom regression were observed.

post-infection. Older age and acute hospitalization remained the main risk factors identified for prolonged recovery up to 18 months post-infection.

Our data shows that a high proportion of children can be affected by PCC, especially school-aged children. Although most children improve over time, this can have potential severe implications for education, social activities and psychological wellbeing for those affected. Up to one in twenty children, among those with PCC at three months, were still affected after 18-months. These findings are in line with studies in adults, showing a gradual recovery over a prolonged time. *Martino GP et al*. conducted, in the adult population, using surveys and clinical assessments, where a number of studies documented that many adults recovered after 12 months post-onset.[22,23] However, another study in adults found that certain symptoms such as cognitive problems and dyspnea did not improve.[24] There are few long-term follow-up studies including the paediatric population. A prospective cohort study including children and

	Univariate OR (95% CI)	P	*R2 di Nagelkerke*	Multivariable OR (95% CI)	p
Female[a]	1.24 (0.96–1.62)	0.100	0.003		
Age (years)	1.24 (1.19–1.28)	<0.001	0.176	1.23 (1.18–1.28)	<0.001
Age higher than 10 years	3.79 (2.87–5.01)	<0.001	0.103		
Comorbidities	1.73 (1.21–2.48)	0.003	0.011	1.68 (1.14–2.50)	0.09
Asymptomatic	0.40 (0.22–0.73)	0.003	0.013	0.46 (0.24–0.85)	0.013
Original COVID variant	3.37 (1.81–6.26)	<0.001	0.017		
Alfa COVID variant	3.73 (2.32–6.00)	<0.001	0.034		
Delta COVID variant	1.18 (0.86–1.63)	0.310	0.001		
Omicron COVID variant	0.47 (0.36–0.62)	<0.001	0.035	0.60 (0.45–0.81)	0.001
Vaccination (at least 1 dose)	1.96 (1.44–2.67)	<0.001	0.022		
Vaccination completed (at least 2 doses)	1.87 (1.31–2.67)	0.001	0.014		
Hospitalization during the acute phase	2.62 (1.21–5.67)	0.014	0.007	4.80 (1.91–12.1)	0.001
Symptoms during acute phase					
Fever	1.46 (1.09–1.95)	0.010	0.008		
Days of fever[b]	1.22 (1.13–1.32)	<0.001	0.037		
Rhinitis/Nasal Congestion	0.85 (0.65–1.11)	0.226	0.002		
Lost or altered smell	4.55 (2.72–7.59)	<0.001	0.039		
Lost or altered taste	4.53 (2.59–7.93)	<0.001	0.033		
Cough	0.93 (0.71–1.22)	0.609	<0.001		
Dyspnea at rest	5.67 (2.21–14.54)	<0.001	0.016		
Dyspnea after exercise during the acute phase	5.18 (1.99–13.49)	<0.001	0.014		
Asthma during the acute phase	2.15 (0.6–7.66)	0.239	0.002		
Chest pain during the acute phase	5.84 (2.74–12.41)	<0.001	0.026		
Joint pain during the acute phase	3.96 (2.47–6.34)	<0.001	0.038		
Muscle Pain during the acute phase	4.11 (2.75–6.14)	<0.001	0.055		
Weakness during the acute phase	3.58 (2.68–4.78)	<0.001	0.085		
Headache during the acute phase	3.27 (2.45–4.37)	<0.001	0.074		
Diarrhea and/or other gastrointestinal symptoms during the acute phase	1.86 (1.32–2.62)	<0.001	0.014		
Sore throat during the acute phase	3.04 (1.94–4.77)	<0.001	0.027		
Rash during the acute phase	2.33 (1.02–5.30)	<0.044	0.005		
Other symptoms during the acute phase	1.31 (0.83–2.07)	0.251	0.002		
Number of symptoms during the acute phase	1.55 (1.42–1.68)	<0.001	0.136		

[a]vs male. [b]Performed on 1207 patients.

Table 4: **Risk factor analysis for development of PCC.**

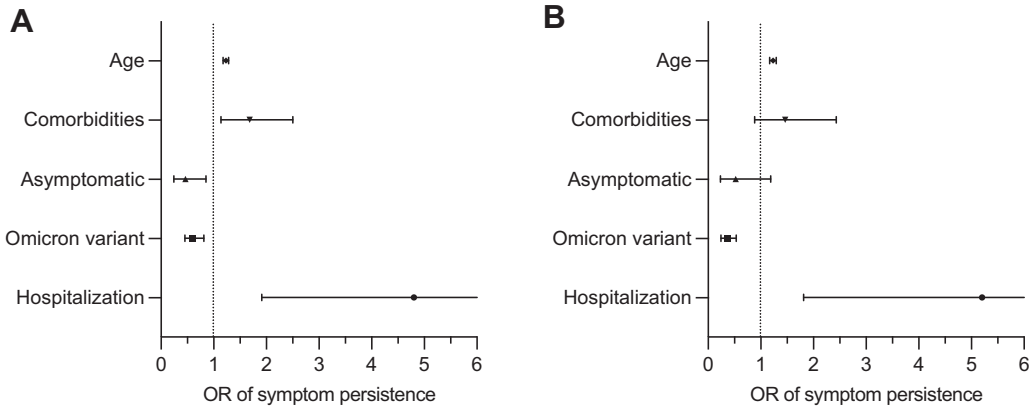

Fig. 3: **Forest plots reporting odds ratio from multivariable analysis performed to investigate the risk factors of persistence of symptoms at three months (Panel A) and 6 months (Panel B) follow-up evaluations**.

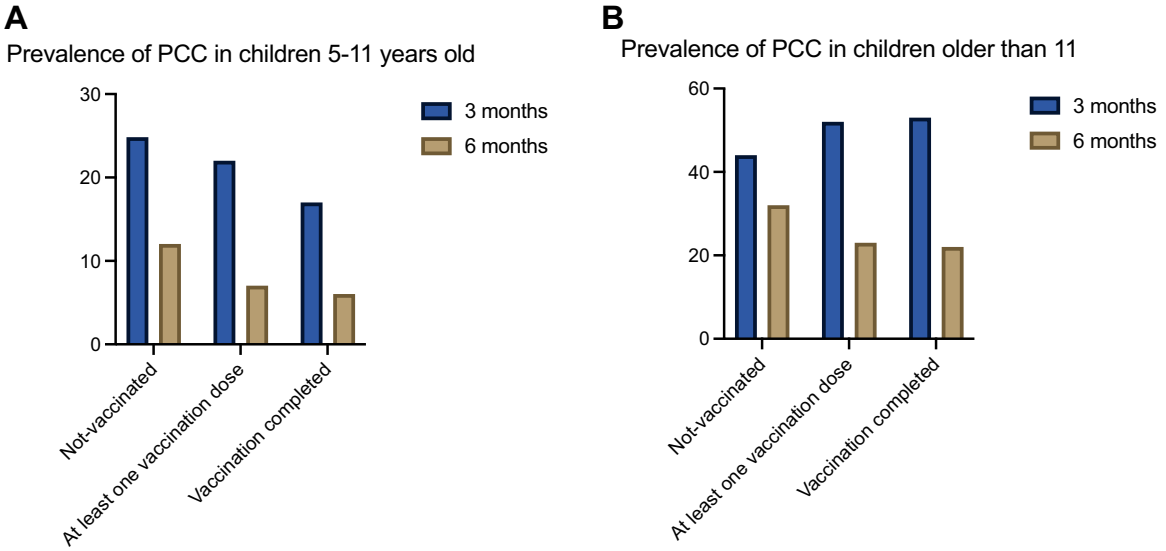

Fig. 4: **Prevalence of PCC at three months (blu) and six months (gold) follow-up in children with zero, one or at least two doses of vaccination before SARS-CoV-2 infection, in children aged 5–11 (A) or >11 years of age (B)**.In both cases, differences among the groups were statistically non-significant (P > 0.05).

adults post-Covid-19 hospitalization, using telephone follow-up assessments, identified a prevalence of 50% (95% CI 47–53) of post-Covid symptom sequelae in adults and 20% (95% CI 16–24) in children at 6-months post-discharge. At 12-months post-discharge, the prevalence was 34% (95% CI 31–37) in adults and 11% (95% CI 8–14), in children.[2] Two paediatric studies including a small number of children followed up to 12-months post-infection, found spontaneous recover of many symptoms within a year.[18,25] Another study found that many symptoms resolved in 54–75% of children within 5 months, depending on age.[26]

Our study is the first one to explore impact of different Sars-CoV-2 variants on risk of developing PCC in children, which is particularly relevant for the paediatric population, since a huge number of children became infected during the omicron waves. We found that children infected during the omicron waves had a significantly lower risk of experience persisting symptoms post-acute infection, compared to children infected by earlier variants at three- and six-months post-infection. This is an important finding for clinical and public health policies and planning, considering the high number of children that have been infected globally during omicron waves.[27] A couple of adult studies have similarly identified a lower risk of developing PCC in adults infected with the Omicron variant compared to the delta variant.[28,29] In contrast, a prospective cohort

study in Norway, found a similar risk of persistent post-Covid symptoms in adults infected with the delta as those infected with the omicron variant.[30] On the opposite, *S. Morikota et al.*,[31] in Japan, did not find significant differences in the prevalence of post- COVID-19 condition between the Omicron and pre-omicron groups. A study set in the UK, conducted a 2-year retrospective study analysing electronic health records of including more than 1 million subjects and 185 748 children, did not identify a difference in persistent neurological and psychiatric outcomes between delta and omicron waves.[32] The varying results may be due to the heterogeneity in case and core outcome definitions, including laboratory confirmations used, and illustrates the need for investments in robust studies to establish the impact of and risk factors for PCC in both adults and children. Despite this it interesting to note that children infected with omicron variants also have a significantly reduced risk of developing Multisystem Inflammatory Syndrome,[33,34] suggesting that omicron may be associated with a general reduced risk of post-acute consequences, including MIS-C and PCC. Of note, it is important to highlight that, at least theoretically, the changing risk of developing PCC can also be related to different treatment options during acute infection. However, while this may be true for the adult population, it is a less plausible hypothesis for children since most of the time they have a mild illness and do not require specific therapies during acute infection. Specifically, in our cohort most children had a mild infection and did not require specific treatments other than supportive ones.

Another key aspect is the role of vaccinations in PCC prevention. Our study identified a small, non-statistically significant protective effect of partial- and full vaccination on preventing PCC after breakthrough infection in children. The protective effect were more pronounced in children who had received two doses of vaccine. Unfortunately, the number of children receiving three doses was too small to be included in separate analyses. There is only one more study that has addressed this issue in children. *Messiah et al.* showed that patients who did not report vaccination information were six-times more likely to develop PCC than those who were vaccinated (RR: 5.76, 95% CI: 1.18–28.06).[29] Studies in adults have shown a stronger protective effect of vaccinations, suggesting that vaccination before SARS-CoV-2 infection could reduce, but not eliminate, the risk of PCC. A literature review and meta-analysis including 18 studies, mostly from USA, UK, and Spain showed that the vaccinated group had a lower risk of developing persistent symptoms after Sars-Cov-2 infection, compared to the unvaccinated group.[35] However, the protective effect was restricted to cognitive symptoms, kidney diseases, myalgia, and sleeping disorders. Similar findings have been reported in other studies in adults.[36] There have been several hypothetical physiologic mechanisms to explain a protective effect proposed, including a less severe illness, with less organ damage following vaccination, and a faster elimination of viral particles, reducing the risk of chronic inflammation.[35,36] A possible explanation for the lack of protective effect of vaccines identified in our study may be due to a low number that were fully vaccinate with three doses. Another hypothesis could be that protection provided by the vaccines wains after 4–6 months.[37] Thus, moving away from vaccination, it's possible protective effect may gradually decrease until it returns to the risk of pre-vaccination status.

A key negative impact of PCC and other post-viral chronic fatigue syndromes is how these conditions negatively affect school attendance, sport and other social activities in a child's daily life. It is reasonable that in PCC, like in Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), there is a spectrum severity of disease which has different negative impact on daily life. Unfortunately, in pediatric PCC there is not yet a classification of severity, nor an agreed set of core outcomes that should be measured, although our team is working on this[38] (details available at www.pc-cos.org/children). For these reasons, our study could not be designed to have other useful outcome measures.

Our study is not without limitations. First, this is a single-centre study although all children with a positive Sars-CoV-2 infection were referred to participate from outpatient family pediatricians and not only from our Institution. Secondly, we did not have access to sequencing of the variants at the time of diagnosis, and this data were estimated from reports on the most prevalence variant circulating in the city at the time. In addition, we were not able to rule out any preceding asymptomatic SARS-CoV-2 infection in children whose symptomatic infection was diagnosed during delta and omicron waves, although it is known that most children have been infected during Omicron, and that multiple reinfections were rare with previous variants.[39] In addition, we have not collected data such as ethnicity and body mass index, therefore we were not able to determine if these factors affect the risk of PCC in children. Also, the incidence of PCC observed in our cohort may be inflated due to our clinic being one of the few pediatric PCC clinics in the country, resulting in a higher proportion of patients with persistent symptoms seeking care at our centre. However, understanding the burden of PCC was not an aim of our study. Last, we have not discussed treatments used in our children. As previously published, our diagnostic protocol for PCC is personalised and based on main symptoms, and as such is our treatment (eg. chronic headache is managed according to current guidance for headache, and so on), since there is so far no formal treatment of PCC being its pathogenesis still unclear).[13,21] Despite these limitations, one of the important strenghts of our paper is

represented by the use of in-clinic specialist assessments (although clinicians where unblinded) based on a rigorous, paediatric clinical case definition of PCC identifying children with persistent symptoms that are so severe that they impact on daily activities (although our study began before the WHO release of a pediatric PCC definition, the one we used is percetly in line with the WHO one released in 2023).[40]

In conclusion, using a rigorous definition and a long follow up time, we present important findings relevant to policy makers to inform health service planning, clinical and public health policies. Through in-clinic assessments, we confirm that a significant proportion of children can develop PCC, particularly school-aged children older than 10 years of age. Importantly, although most children recover over time, one-in-twenty of those with PCC at three months were still affected by 18-months post-SARS-CoV-2 infection. In this study we identified a small but not significant protective effect of mRNA vaccines against PCC. Although our cohort cannot be translated to all Italian children with PCC (in terms of demographic and risk factors) as more nationwide studies are needed, it is plausible that main symptoms and long-term outcomes can be generalised to other cohort of pediatric PCC. Importantly, our findings highlight the urgent need of more research to identify underlying pathophysiology to inform treatment strategies and to further explore the longer-term impact of PCC in children on physical health, well-being and education.

Contributors

DB conceptualised the study. DB, RM and CDR were responsible for patient management and data collection. FM and LM were responsible for statistical analyses. DM and LS contributed to the protocol development as international advisors, contributed to the first draft of the manuscript and English editing. PV and GZ were responsible for study and team supervision. DB wrote the initial draft of the manuscript, final version and coordinated the revision process. All authors read and approved final version of the manuscript. DB has full access to dataset and had final decision to submit for publication. DB, FM and RM verified the data. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Data sharing statement

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others after reasonable request to the corresponding author, including the statistical analysis plan and informed consent form. Data will be available as soon the paper is published and shared privately by email. Data will be available for subanalyses, new analyses, confirmatory analyses, with or without investigator support, after approval of a proposal, with a signed data access agreement, for research purposes.

Declaration of interests

DB was been granted a non-competitive grant from Pfizer to study PCC in children, and has won a grant to study mRNA profile in children with PCC from Roche Italia and ESPID. DB has participated in educational peer-to-peer programs on PCC organised by Pfiser and has participated as invited speaker and a sponsored session of Covid-19 vaccines in children at the ESPID conference in 2022. LS was supported by funding via ISARIC from the UK Foreign, Commonwealth & Development Office, Wellcome (215091/Z/18/Z) and the Bill & Melinda Gates Foundation (OPP1209135).

Acknowledgments

This study has been funded by Pfizer Italia non-competitive grant, granted to DB (# 65925795).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101961.

References

1 WHO. Coronavirus (COVID-19) dashboard, 06-December-2022. Available at: https://covid19.who.int/; 2022.
2 Pazukhina E, Andreeva M, Spiridonova E, et al. Prevalence and risk factors of post-COVID-19 condition in adults and children at 6 and 12 months after hospital discharge: a prospective, cohort study in Moscow (StopCOVID). *BMC Med*. 2022;20:244. https://doi.org/10.1186/s12916-022-02448-4.
3 WHO/2019-nCoV/Post_COVID-19_condition/Clinical_case_definition/2021.1, 2021
4 Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021;372:n136. https://doi.org/10.1136/bmj.n136. Erratum in: *BMJ*. 2022J;376:o126. PMID: 33483331.
5 Centres for Disease Control and Prevention. Available at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fhcp%2Fclinical-care%2Fpost-covid-index.html.
6 National Institute of Health, Long Covid, 2021. Available at: https://covid19.nih.gov/covid-19-topics/long-covid#:~:text=Long%20COVID%2C%20long%2Dhaul%20COVID,of%20a%20COVID%2D19%20diagnosis.
7 Stephenson T, Allin B, Nugawela MD, et al. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. *Arch Dis Child*. 2022;107(7):674–680. https://doi.org/10.1136/archdischild-2021-323624. Epub 2022 Apr 1. PMID: 35365499; PMCID: PMC8983414.
8 Desai AD, Lavelle M, Boursiquot BC, Wan EY. Long-term complications of COVID-19. *Am J Physiol Cell Physiol*. 2022;322(1):C1–C11. https://doi.org/10.1152/ajpcell.00375.2021. Epub 2021 Nov 24. PMID: 34817268; PMCID: PMC8721906.
9 Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post-Coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. *J Infect Dis*. 2022;226(9):1593–1607. https://doi.org/10.1093/infdis/jiac136. PMID: 35429399; PMCID: PMC9047189.
10 Nittas V, Gao M, West EA, et al. Long COVID through a public health lens: an umbrella review. *Public Health Rev*. 2022;43:1604501. https://doi.org/10.3389/phrs.2022.1604501. PMID: 35359614; PMCID: PMC8963488.
11 Pellegrino R, Chiappini E, Licari A, Galli L, Marseglia GL. Prevalence and clinical presentation of long COVID in children: a systematic review. *Eur J Pediatr*. 2022:1–15. https://doi.org/10.1007/s00431-022-04600-x. Epub ahead of print. PMID: 36107254; PMCID: PMC9476461.
12 Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep*. 2022;12(1):9950. https://doi.org/10.1038/s41598-022-13495-5. PMID: 35739136; PMCID: PMC9226045.
13 Buonsenso D, Di Gennaro L, De Rose C, et al. Long-term outcomes of pediatric infections: from traditional infectious diseases to long Covid. *Future Microbiol*. 2022;17:551–571. https://doi.org/10.2217/fmb-2022-0031.
14 Rao S, Lee GM, Razzaghi H, et al. Clinical features and burden of postacute sequelae of SARS-CoV-2 infection in children and adolescents. *JAMA Pediatr*. 2022;176(10):1000–1009. https://doi.org/10.1001/jamapediatrics.2022.2800. PMID: 35994282; PMCID: PMC9396470.
15 Roessler M, Tesch F, Batram M, et al. Post-COVID-19-associated morbidity in children, adolescents, and adults: a matched cohort study including more than 157,000 individuals with COVID-19 in Germany. *PLoS Med*. 2022;19(11):e1004122. https://doi.org/

10.1371/journal.pmed.1004122. PMID: 36355754; PMCID: PMC9648706.
16 Buonsenso D, Parri N, De Rose C, Valentini P. Gemelli-pediatric COVID-19 team. Toward a clinically based classification of disease severity for paediatric COVID-19. *Lancet Infect Dis*. 2021;21(1):22. https://doi.org/10.1016/S1473-3099(20)30396-0. Epub 2020 May 15. PMID: 32422205; PMCID: PMC7228718.
17 https://www.epicentro.iss.it/coronavirus/pdf/sars-cov-2-monitoraggio-varianti-rapporti-periodici-27-maggio-2022.pdf; 2022.
18 Buonsenso D, Pazukhina E, Gentili C, et al. The prevalence, characteristics and risk factors of persistent symptoms in non-hospitalised and hospitalised children with SARS-CoV-2 infection followed-up for up to 12 months: a prospective, cohort study in Rome, Italy. *J Clin Med*. 2022;11:6772. https://doi.org/10.3390/jcm11226772.
19 Fernández-de-Las-Peñas C, Martín-Guerrero JD, Pellicer-Valero Ój, et al. Female sex is a risk factor associated with long-term post-COVID related-symptoms but not with COVID-19 symptoms: the LONG-COVID-EXP-CM multicentre study. *J Clin Med*. 2022;11(2):413. https://doi.org/10.3390/jcm11020413. PMID: 35054108; PMCID: PMC8778106.
20 Bai F, Tomasoni D, Falcinella C, et al. Female gender is associated with long COVID syndrome: a prospective cohort study. *Clin Microbiol Infect*. 2022;28(4):611.e9–611.e16. https://doi.org/10.1016/j.cmi.2021.11.002. Epub 2021 Nov 9. PMID: 34763058; PMCID: PMC8575536.
21 Morello R, Martino L, Buonsenso D. Diagnosis and management of post-COVID (Long COVID) in children: a moving target. *Curr Opin Pediatr*. 2023;35(2):184–192. https://doi.org/10.1097/MOP.0000000000001221. Epub 2023 Jan 23. PMID: 36660968; PMCID: PMC9994801.
22 Martino GP, Benfaremo D, Bitti G, et al. 6 and 12 month outcomes in patients following COVID-19-related hospitalization: a prospective monocentric study. *Intern Emerg Med*. 2022;17(6):1641–1649. https://doi.org/10.1007/s11739-022-02979-x. Epub 2022 Apr 9. PMID: 35397762; PMCID: PMC8994524.
23 Mariani C, Borgonovo F, Capetti AF, et al. Persistence of Long-COVID symptoms in a heterogenous prospective cohort. *J Infect*. 2022;84(5):722–746. https://doi.org/10.1016/j.jinf.2022.01.024. Epub 2022 Jan 22. PMID: 35077770; PMCID: PMC8783396.
24 Tran VT, Porcher R, Pane I, Ravaud P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. *Nat Commun*. 2022;13(1):1812. https://doi.org/10.1038/s41467-022-29513-z. PMID: 35383197; PMCID: PMC8983754.
25 Asadi-Pooya AA, Nemati M, Nemati H. 'Long COVID': Symptom persistence in children hospitalised for COVID-19. *J Paediatr Child Health*. 2022;58(10):1836–1840. https://doi.org/10.1111/jpc.16120. Epub 2022 Jul 19. PMID: 35851732; PMCID: PMC9349535.
26 Borch L, Holm M, Knudsen M, Ellermann-Eriksen S, Hagstroem S. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. *Eur J Pediatr*. 2022;181(4):1597–1607. https://doi.org/10.1007/s00431-021-04345-z. Epub 2022 Jan 9. PMID: 35000003; PMCID: PMC8742700.
27 Buonsenso D, Morello R, Mariani F, De Rose C, Mastrantoni L, Zampino G, Valentini P. Risk of long Covid in children infected with Omicron or pre-Omicron SARS-CoV-2 variants. *Acta Paediatr*. 2023. https://doi.org/10.1111/apa.16764. Epub ahead of print. PMID: 36938946.
28 Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet*. 2022;399(10343):2263–2264. https://doi.org/10.1016/S0140-6736(22)00941-2. PMID: 35717982; PMCID: PMC9212672.
29 Messiah SE, Hao T, DeSantis SM, et al. Comparison of persistent symptoms following SARS-CoV-2 infection by antibody status in nonhospitalised children and adolescents. *Pediatr Infect Dis J*. 2022;41(10):e409–e417. https://doi.org/10.1097/INF.0000000000003653. Epub 2022 Aug 1. PMID: 35939608.
30 Magnusson K, Kristoffersen DT, Dell'Isola A, et al. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants. *Nat Commun*. 2022;13:7363. https://doi.org/10.1038/s41467-022-35240-2.
31 Morioka S, Tsuzuki S, Suzuki M, et al. Post COVID-19 condition of the Omicron variant of SARS-CoV-2. *J Infect Chemother*. 2022;28(11):1546–1551. https://doi.org/10.1016/j.jiac.2022.08.007. Epub 2022 Aug 11. PMID: 35963600; PMCID: PMC9365517.
32 Taquet M, Sillett R, Zhu L, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatr*. 2022;9(10):815–827. https://doi.org/10.1016/S2215-0366(22)00260-7. Epub 2022 Aug 17. PMID: 35987197; PMCID: PMC9385200.
33 Cohen JM, Carter MJ, Ronny Cheung C, Ladhani S, Evelina PIMS-TS Study Group. Lower risk of multisystem inflammatory syndrome in children (MIS-C) with the delta and omicron variants of SARS-CoV-2. *Clin Infect Dis*. 2022:ciac553. https://doi.org/10.1093/cid/ciac553. Epub ahead of print. PMID: 35788276; PMCID: PMC9278259.
34 Buonsenso D, Perramon A, Català M, et al, COPEDI-CAT Research Group. Multisystem inflammatory syndrome in children in western countries? Decreasing incidence as the pandemic progresses?: an observational multicentre international cross-sectional study. *Pediatr Infect Dis J*. 2022;41(12):989–993. https://doi.org/10.1097/INF.0000000000003713. Epub 2022 Oct 21. PMID: 36102705; PMCID: PMC9645445.
35 Gao P, Liu J, Liu M. Effect of COVID-19 vaccines on reducing the risk of long COVID in the RealWorld: a systematic review and meta-analysis. *Int J Environ Res Publ Health*. 2022;19:12422. https://doi.org/10.3390/ijerph191912422.
36 Notarte KI, Catahay JA, Velasco JV, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: a systematic review. *eClinicalMedicine*. 2022;53:101624. https://doi.org/10.1016/j.eclinm.2022.101624. PMID: 36051247; PMCID: PMC9417563.
37 Chemaitelly H, AlMukdad S, Ayoub HH, et al. Covid-19 vaccine protection among children and adolescents in Qatar. *N Engl J Med*. 2022;387(20):1865–1876. https://doi.org/10.1056/NEJMoa2210058. Epub 2022 Nov 2. PMID: 36322837; PMCID: PMC9644642.
38 Munblit D, Buonsenso D, Sigfrid L, Vijverberg SJH, Brackel CLH. Post-COVID-19 condition in children: a COS is urgently needed. *Lancet Respir Med*. 2022;10(7):628–629. https://doi.org/10.1016/S2213-2600(22)00211-9. Epub 2022 Jun 14. PMID: 35714657; PMCID: PMC9197248.
39 Oeser C, Whitaker H, Borrow R, et al. Following the Omicron wave, the majority of children in England have evidence of previous COVID infection. *J Infect*. 2022;(22):S0163–S4453. https://doi.org/10.1016/j.jinf.2022.12.012. Epub ahead of print. PMID: 36543312; PMCID: PMC9759455.
40 https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-Post-COVID-19-condition-CA-Clinical-case-definition-2023-1.