

SYNOPSIS

Review of “Post–COVID-19 Conditions among Children 90 Days after SARS-CoV-2 Infection”

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One-minute summary

- The authors conducted a cohort study of 1,884 children (age 18 and younger) who tested positive for severe acute respiratory syndrome 2 (SARS-CoV-2) at participating emergency departments (ED) between March 7, 2020 and January 20, 2021. The median age of the participants was three years (IQR, 0-10 years) and 994 (52.8%) were male. Participants were enrolled in eight countries: Argentina, Canada, Costa Rica, Italy, Paraguay, Singapore, Spain, and the United States.
- A total of 110 SARS-CoV-2 positive children (5.8% [95% CI, 4.8%-7.0%]) had a post-COVID-19 condition reported at the 90-day follow-up. The rate of post-COVID-19 conditions at 90-day follow-up was higher among hospitalized children (44 of 447 [9.8%; 95% CI, 7.2%-13.0%]) compared with those discharged from the ED (66 of 1437 [4.6%; 95% CI, 3.6%-5.8%]; difference 5.3% [95% CI, 2.5%-8.5%]).
- The authors also compared SARS-CoV-2 positive and SARS-CoV-2 negative children using frequency matching. Rates of post-COVID-19 conditions were greater among SARS-CoV-2 positive children in several demographic and clinical strata. Among children discharged from the ED, post-COVID-19 conditions were reported at 90 days by 55 of 1,295 SARS-CoV-2 positive children (4.2% [95% CI, 3.2%-5.5%]) and 35 of 1,321 SARS-CoV-2 negative children (2.7% [95% CI, 1.9%-3.7%]; difference 1.6% (95% CI 0.2%-3.0%). Among hospitalized children, post-COVID-19 conditions were reported at 90 days in 40 of 391 SARS-CoV-2 positive children (10.2% [95% CI, 7.4%-13.7%]) and 19 of 380 SARS-CoV-2 negative children (5.0% [95% CI, 3.0%-7.7%]; difference 5.2% (95% CI 1.5%-9.1%).
- Most participants reporting post-COVID-19 conditions at 90 day follow-up had one persistent, new, or recurring health problem (59.1% [65 of 110]). The most common symptoms were respiratory (38 of 1,884 [2.0%; 95% CI, 1.4%-2.8%]) and systemic (33 of 1,884 [1.8%; 95% CI, 1.2%-2.5%]). Fatigue or weakness was the most reported individual symptom (21 of 1,884 [1.1%]).

- Risk factors associated with post-COVID-19 conditions present at 90-day follow-up included being hospitalized 48 hours or more compared with no hospitalization (aOR, 2.67 [95% CI, 1.63-4.38]), having 4 or more symptoms reported at the index ED visit compared with 1 to 3 symptoms (4-6 symptoms: aOR, 2.35 [95% CI, 1.28-4.31]; ≥ 7 symptoms: aOR, 4.59 [95% CI, 2.50-8.44]), and being 14 years of age or older compared with the reference age group of those under the age of 1 (aOR, 2.67 [95% CI, 1.43-4.99]).
- Among hospitalized children, those who experienced severe outcomes within 14 days of infection were more likely to report post-COVID-19 conditions at 90 day follow-up than those who did not (13 of 70 [18.6%; 95% CI, 10.3%-29.7%], compared to 31 of 377 [8.2%; 95% CI, 5.7%-11.5%]; difference 10.4% [95% CI, 2.3%-21.3%]). Among hospitalized and non-hospitalized children, the proportion of children reporting post-COVID-19 conditions was higher among children with a greater number of index ED visit symptoms.
- This cohort study found that, although 10% of hospitalized children with acute COVID-19 and 5% of those discharged from the emergency department reported post-COVID-19 conditions at 90 days, these rates were only slightly higher than those observed among SARS-CoV-2 negative controls.

Additional information

- The authors defined acute symptoms as those present between symptom onset and the time of the index ED visit. Acute SARS-CoV-2 illness hospitalization and illness severity status incorporated events occurring until 14 days after the index ED visit. Illness severity was classified as severe or not severe based on specific interventions (e.g., positive pressure ventilation, inotropic support), the occurrence of specific complications, organ dysfunction, or death.
- The authors defined post-COVID-19 conditions as any persistent, new, or returning symptoms or health problems reported by the caregiver at the 90-day interview. Post-COVID-19 conditions were not present if the caregiver indicated that these symptoms were neither persistent (i.e., recovered completely prior to 90 days) nor novel (i.e., underlying condition without exacerbation). Post-COVID-19 conditions were classified as cardiovascular, dermatologic, ophthalmologic or otolaryngologic, gastrointestinal, neurologic, psychological, respiratory, systemic (e.g., fatigue, weakness, fever, anorexia), or other.
 - The most commonly reported persistent symptom in the study's SARS-CoV-2 positive participants was fatigue. Although other studies have identified that fatigue, headache, and anosmia are common post-acute symptom in children, fatigue is the most common symptom reported in adults.
- Follow-up telephone (or email or text, depending on site) surveys were completed 14 days after the index ED visit to classify outcomes. Medical record reviews were performed to confirm caregiver-reported index ED visit disposition and 14-day outcome data. Between 90 and 120 days after the index ED visit, caregivers were contacted and asked if their child had any persistent, new, or returning symptoms or health problems that may have been associated with the illness prompting the initial ED evaluation.

- Authors note that a strength of this study is that they recruited children in numerous countries and captured repeated SARS-CoV-2 test results within 14 days to appropriately classify children with false-negative index test results. Other strengths noted by the authors include: the presence of a SARS-CoV-2-negative control group for comparison, prospective data collection, and consistent and identical follow-up for all participants.
- Authors note several limitations to the study:
 - Defining the presence of post-COVID-19 conditions through the use of an open-ended questionnaire administered to caregivers may have underestimated the presence of conditions compared with detailed report forms, such as those used in other studies.
 - Authors cannot exclude the possibility that the findings were associated with unmeasured and residual confounding, or that the small number of events for some outcomes limited the ability to detect some associations with SARS-CoV-2 test result status. The survey is susceptible to recall bias as caregiver knowledge of prior infection results may have influenced the findings.
 - 20% of participants were lost to follow-up with substantial demographic differences observed between included children and those lost to follow-up.

PHO reviewer's comments

- Authors found that 5.8% (95% CI, 4.8%-7.0%) of SARS-CoV-2 positive patients developed post-acute conditions at 90 days, and the prevalence of post-COVID-19 conditions increased for children who were hospitalized during initial infection (9.8%; 95% CI, 7.2%-13.0%) compared to those who were not hospitalized (4.6%; 95% CI, 3.6%-5.8%). However, compared to SARS-CoV-2 negative controls the difference in post-COVID-19 conditions for non-hospitalized and hospitalized children was 1.6% (95% CI, 0.2%-3.0%) and 5.2% (95% CI, 1.5%-9.1%), respectively. This study highlights the importance of including control groups for the evaluation of post-COVID-19 conditions due to the frequency of post-infectious symptoms and/or recurrent illnesses.
- Authors noted that the prevalence of post-acute conditions at 90-day follow-up in their study was lower than earlier studies on the topic. The findings in this study were similar to a rapid review conducted by Public Health Ontario (PHO) in June 2022, which found that based on eight controlled studies, the prevalence of post-acute conditions or symptoms among children was below 10%.¹ The review found that sequelae were more frequently reported in children with previous SARS-CoV-2 infection, compared to controls not infected with SARS-CoV-2, although this difference is likely small. However, the authors of the PHO review noted that overall there is inconclusive evidence demonstrating a causal link between SARS-CoV-2 infection and post-acute conditions in children and findings may change as more high quality research is conducted.¹
- Individuals included in this study were those under the age of 18 who were tested for SARS-CoV-2 in pediatric emergency departments. This group may not be representative of the general pediatric population as it does not include children who tested positive for SARS-CoV-2 in the community (i.e., testing facilities, community-based physician), or children with less access to healthcare services. Thus, this may have had an impact on the proportion of children reporting post-acute COVID-19 symptoms.

- This study covers a pandemic period up to January 2021, which is prior to availability of SARS-CoV-2 vaccination for children and before the emergence and circulation of the currently dominant Omicron variant and its subvariants. While the association between vaccination and prevalence of post-acute symptoms requires further study,² it is well documented that vaccines reduce severity of initial infection.³⁻⁵
- A key limitation of this study is the limited description of whether and how symptoms, conditions, and levels of function at baseline or before SARS-CoV-2 infection was assessed. Without validated pre-COVID-19 clinical assessments, it is difficult to attribute post-acute COVID-19 symptoms solely to SARS-CoV-2 infection. It is also not possible to ascertain that symptoms reported as post-acute COVID-19 symptoms on a questionnaire administered to caregivers were in fact not due to other causes. A SARS-CoV-2 diagnosis in their child may have also affected caregivers' recall of symptoms. Further studies should determine baseline, pre-infection comorbidities among case patients and non-case subjects, allowing for separation of sequelae due to COVID-19 or other etiologies.

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