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Comparison of Symptom Duration Between Children With SARS-CoV-2 and Peers With Other Viral Illnesses During the COVID-19 Pandemic

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Abstract

Some children and young people (CYP) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience persistent symptoms, commonly called "long COVID." It remains unclear whether symptoms of SARS-CoV-2 persist longer than those of other respiratory viruses, particularly in young children. This cross-sectional study involved 372 CYP (0-15 years) tested for SARS-CoV-2. Character and duration of symptoms (cough, runny nose, sore throat, rash, diarrhea, vomiting, sore muscles, fatigue, fever, loss of smell) were compared between CYP with a positive test (n = 100) and those with a negative test (n = 272), while controlling for medical/demographic covariates. The average duration of symptoms for CYP with a positive SARS-CoV-2 test (8.5 ± 10 days) did not differ from that of CYP with a negative test (7.2 ± 5 days, $P = .71$, d = 0.046). A positive SARS-CoV-2 test did not increase the risk (36/372, 10%) of symptoms persisting for ≥3 weeks (odds ratio = 0.96, 95% confidence interval = 0.45-2.0). These results suggest CYP with non-SARS-CoV-2 infections experience a similar duration of symptoms as peers with SARS-CoV-2 infection.

Keywords

general pediatrics, infectious diseases

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to severe symptoms. However, most children and young people (CYP) with SARS-CoV-2 experience asymptomatic disease or mild symptoms.[1] Emerging evidence suggests that a subset of individuals with coronavirus disease 2019 (COVID-19) may also be at risk of prolonged aftereffects, commonly referred to as "long COVID."[2] Long COVID is defined by the Department of Health and Human Services and the Centers for Disease Control and Prevention as

> signs, symptoms, and conditions that continue or develop after initial COVID-19 or SARS-CoV-2 infection. The signs, symptoms, and conditions are present four weeks or more after the initial phase of infection; may be multisystemic; and may present with a relapsing-remitting pattern and progression or worsening over time, with the possibility of severe and life-threatening events even months or years after infection.

The etiology of long COVID is poorly understood, particularly among CYP.[3]

Several comprehensive systematic reviews have helped to define the current state of knowledge regarding long COVID in CYP.[3-6] The prevalence of long COVID varies widely across studies (4%-66%). Headache, fatigue, sleep difficulties, myalgias, and persistent upper respiratory symptoms comprise the most commonly reported long COVID symptoms. Persistent COVID symptoms may be more common among older children, females, and those with baseline physical and mental health conditions.[7-11] The severity of initial SARS-CoV-2 symptoms may also impact the risk of long COVID, with hospitalized CYP reporting more persistent symptoms.[12]

Several critical limitations have prevented a clear understanding of the epidemiology of pediatric long COVID.[5] These limitations include selection bias, misclassification bias, recall bias, and nonresponse

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bias.[4] One of the most important limitations has been a lack of appropriate controls. Many studies of long COVID in CYP have included no control group or a seronegative control group that includes peers with no symptoms of upper respiratory infection (URI).[13-16] Comparing the duration of symptoms between CYP with SARS-CoV-2 infection and CYP infected with non-SARS-CoV-2 viruses could enhance our understanding of long COVID, while controlling for pandemic-related effects. This may be particularly important in outpatient settings, where anticipatory guidance regarding symptom duration and management can have beneficial impacts on clinical outcomes.[17,18]

The goal of this study was to assess the average symptom duration among CYP with SARS-CoV-2 infection and peers with a non-SARS-CoV-2 infection. The study specifically included infants and toddlers tested for SARS-CoV-2 due to the lack of information regarding symptom duration in this age group. Based on prior literature, we hypothesized that symptom duration would not differ between the two groups. To test this hypothesis, we examined symptom reports from 372 CYP and used regression analyses to control for medical and demographic factors implicated in long COVID, such as age, sex, and baseline medical conditions.

Methods

Ethics Statement

Approval of this study's protocol was obtained from the institutional review board at the Penn State College of Medicine. Written informed consent was obtained for all participants, and written assent was obtained as appropriate.

Participants

This cross-sectional study involved a convenience sample of 1072 CYP, enrolled at the time of a clinical visit to outpatient general pediatrics clinics affiliated with an academic medical center in Central Pennsylvania between October 19, 2020, and July 29, 2022. A simple random sampling technique was used to enroll a probability sample of established clinic patients (n = ~12 500) presenting for regularly scheduled well visits during normal clinic hours (Monday through Friday, 8 AM-5 PM). CYP (ages 0 months-15 years) who received a SARS-CoV-2 test for upper respiratory symptoms were included (n = 372), whereas those who had not been tested for SARS-CoV-2 were excluded (n = 700). Throughout the study period, the clinic followed Centers for Disease Control and Prevention guidelines for SARS-CoV-2 testing procedures, including (1) CYP with symptoms suggestive of COVID-19; (2) CYP who had close contact with an individual with suspected or confirmed COVID-19; and (3) CYP who required screening tests for return-to-school or other public health requirements. Exclusion criteria were wards of the state, non-English-speaking parent/guardian, or parent/guardian with decisional impairment. The primary medical outcome was a positive SARS-CoV-2 antigen or polymerase chain reaction test result. One hundred CYP who received a positive test result were compared with 272 CYP who received a negative test result. This sample size was supported by a power analysis which determined that 100 CYP per group would provide ≥80% power to detect a small-to-moderate effect (Cohen's $d = 0.25$ on 2-tailed Student's t test) of SARS-CoV-2 status on symptom duration (in days) with α set at 0.05.

Data Collection

Data were collected via electronic survey, administered by trained research staff at the time of enrollment to prevent dropouts and eliminate nonresponse bias. Survey questions were adapted, in part, from the Household Pulse Survey, developed by the National Center for Health Statistics.[19] On average, families completed the survey 4 (±3) months after the diagnosis. The primary research outcome was duration of any symptom related to URI. The following symptoms were assessed for presence/absence and duration (in days): cough, runny nose, sore throat, rash, diarrhea, vomiting, sore muscles, fatigue, fever, and loss of smell. These symptoms were selected based on studies of common SARS-CoV-2 symptoms in children.[20] Subjective, unobservable symptoms (ie, headache, loss of taste, dyspnea) were not included because they are difficult to accurately assess in infants and young children. Persistent symptoms (defined as any symptom lasting for ≥3 weeks) were also compared between groups. This definition was chosen based on the observation that few (7/372, 1.8%) CYP in the study met the criteria for the traditional definition of "long COVID" (symptoms lasting for >4 weeks) and because anticipatory guidance regarding URIs typically involves resolution of symptoms within 3 weeks.[21] Families self-reported the following medical and demographic information: CYP age, sex, race, ethnicity, asthma history, mental health history (including anxiety or depression), health insurance status, parent/guardian education, marital status, household income, and household size. Body mass index data were extracted from the electronic medical record.

Table 1. Participant Characteristics.

	All (n = 372)	SARS-CoV-2 positive (n = 100)	SARS-CoV-2 negative (n = 272)
Age, y, mean (SD)	5.9 (4)	6.5 (4)	5.6 (4)
Female sex, n (%)	183 (49)	49 (49)	134 (49)
White race, n (%)	277 (74)	73 (73)	204 (75)
Non-Hispanic ethnicity, n (%)	308 (82)	87 (87)	221 (81)
Asthma, n (%)	31 (8)	9 (9)	22 (8)
Anxiety, n (%)	30 (8)	9 (9)	21 (7)
Depression, n (%)	10 (2)	4 (4)	6 (2)
Marital status, n (%)			
Married	241 (64)	67 (67)	174 (63)
Divorced	30 (8)	6 (6)	24 (8)
Single	42 (11)	16 (16)*	26 (9)
Cohabitating	39 (10)	4 (4)	35 (12)
Other	20 (5)	7 (7)	13 (4)
Parent with college degree, n (%)	219 (58)	61 (61)	158 (58)
Household income, median	$75 000-$99 999	$75 000-$99 999	$75 000-$99 999
Persons in household, median (IQR)	4 (1)	4 (1)	4 (1)

χ^2, Fisher exact, Mann-Whitney, and Student *t* tests were performed to compare medical and demographic variables between groups.
Abbreviations: SARS-CoV-2, acute respiratory syndrome coronavirus 2; IQR, interquartile range.
*$P < .05$ (2-tailed *t* test).

Statistical Analysis

Chi-square test or Fisher's exact test was used to compare ordinal and dichotomous medical/demographic variables between CYP with SARS-CoV-2 infection and those with non-SARS-CoV-2 infection. Mann-Whitney tests or Student *t* tests were used, as appropriate, to compare continuous variables. The primary study outcome (duration of any viral symptom) was compared between groups with a Student *t* test. The proportion of CYP with persistent symptoms was compared between groups with a chi-square test. The duration and persistence of individual viral symptoms were also compared between groups. Finally, a linear regression was used to assess the effect of SARS-CoV-2 infection on symptom duration while controlling for medical and demographic factors previously implicated in long COVID (eg, age, sex, race, anxiety and depression, and asthma status).[7-11] Akaike information criterion (AIC) was reported for the overall model, and an analysis of variance omnibus test was used to determine the effect of individual factors (SARS-CoV-2 status and medical/demographic covariates) on symptom duration. Statistical analyses were performed using Jamovi software (v2.3.13).

Results

The average age of the participants CYP was 5.9 (±4) years (Table 1). Approximately half were female (183/372, 49%). The majority were white (277/372, 74%) and non-Hispanic (308/372, 82%). Few had a history of asthma (31/372, 8%), anxiety (30/372, 8%), depression (10/372, 2%), or obesity (29/372, 7.8%). Most parents were married (241/372, 64%), had a college or postgraduate degree (219/372, 58%), and had private health insurance (244/372, 65%). The median household income was $75 000 to $99 999, and the average household size was 4 (±1) persons.

There were 100 CYP with a positive SARS-CoV-2 test result and 272 with a negative test result. CYP with a positive SARS-CoV-2 test were more likely to live in a single-parent household ($\chi^2 = 9.0$, $P = .024$) than peers with a negative SARS-CoV-2 test (26/272). The 2 groups did not differ in sex, race, ethnicity, insurance status, parental education, household size, or household income ($P > .05$).

Children and young people with a positive SARS-CoV-2 test were more likely to experience initial symptoms of diarrhea (10/100, 10%, $\chi^2 = 4.87$, $P = .027$), myalgias (9/100, 9%, $\chi^2 = 4.28$, $P = .039$), fatigue (31/100, 31%, $\chi^2 = 14.8$, $P = .00011$), fever (50/100, 50%, $\chi^2 = 11.1$, $P = .0012$), and anosmia (9/100, 9%, $\chi^2 = 14.6$, $P = .00013$) than those with a negative test (diarrhea, 11/272, 4%; myalgias, 10/272, 3%; fatigue, 37/272, 13%; fever, 85/272, 31%; anosmia, 3/272, 1%) (Table 2). There was no difference between groups in the occurrence of cough, runny nose, sore throat, rash, or emesis ($P > .05$).

Table 2. Initial Symptoms of Upper Respiratory Infection Among Children and Young People Who Tested Positive or Negative for SARS-CoV-2.

Symptom, n (%)	All (n = 372)	SARS-CoV-2 positive (n = 100)	SARS-CoV-2 negative (n = 272)
Cough	161 (43)	47 (47)	114 (41)
Runny nose	167 (44)	49 (49)	118 (31)
Sore throat	78 (20)	24 (24)	54 (19)
Rash	6 (1)	3 (3)	3 (1)
Diarrhea	21 (5)	10 (10)*	11 (4)
Vomiting	27 (7)	11 (11)	16 (5)
Sore muscles	19 (5)	9 (9)*	10 (3)
Fatigue	68 (18)	31 (31)*	37 (13)
Fever	135 (36)	50 (50)*	85 (31)
Loss of smell	12 (3)	9 (9)*	3 (1)

χ^2 test and *t* test were performed to compare the proportion of children and young people experiencing each symptom in SARS-CoV-2 positive and negative groups.
Abbreviation: SARS-CoV-2, acute respiratory syndrome coronavirus 2.
*$P < .05$ (2-tailed *t* test).

The average duration of symptoms for CYP with a positive SARS-CoV-2 test (8.5 ± 10 days) did not differ from that for CYP with a negative SARS-CoV-2 test (7.2 ± 5 days, $P = .71$, d = 0.046) (Figure 1). Approximately 10% of participants (36/372) experienced persistent symptoms. A positive SARS-CoV-2 test did not increase the risk of persistent symptoms (odds ratio = 0.96, 95% confidence interval = 0.45-2.0). Among all CYP with persistent symptoms, the most commonly reported symptoms were cough (25/36, 69%), runny nose (16/36, 44%), and fatigue (6/36, 16%). Among those with a positive SARS-CoV-2 test, loss of smell persisted the longest (18.9 ± 17 days), followed by fatigue (7.6 ± 8 days), and cough (7.0 ± 8 days) (Figure 2). CYP with a positive SARS-CoV-2 test experienced longer duration of fatigue (7.6 ± 8 days) than CYP with a negative SARS-CoV-2 test (4.7 ± 3 days, $P = .030$, d = 0.26). However, the 2 groups did not differ in the duration of cough, runny nose, sore throat, diarrhea, vomiting, fever, or loss of smell ($P > .05$).

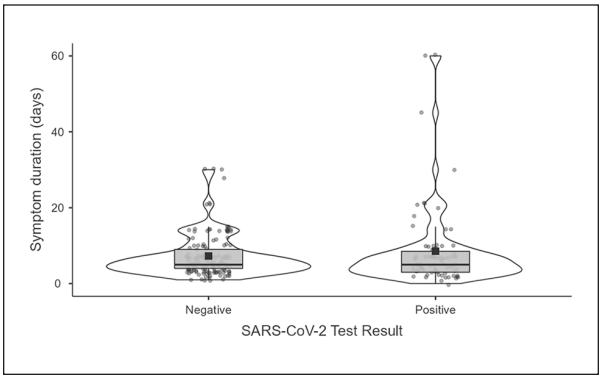

Figure 1. The average duration of symptoms does not differ between CYP with a positive SARS-CoV-2 test and those with a negative test. The violin box plots display the longest duration of any symptom for CYP with positive (n = 100) or negative (n = 272) results on SARS-CoV-2 testing. There was no difference ($P = .71$, d = 0.046) in the duration of symptoms between CYP with a positive test (8.5 ± 10 days) and those with a negative SARS-CoV-2 test (7.2 ± 5 days). Mean (black box), median (black stripe), and standard deviation (vertical bars) are displayed.
Abbreviations: CYP, children and young people; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

A linear regression controlling for the effects of medical and demographic covariates (ie, age, sex, race, asthma status, anxiety, depression, and obesity) found no association between SARS-CoV-2 infection and the duration of symptoms ($F = 0.46$, $P = .49$) or the duration of fatigue ($F = 0.006$, $P = .9326$) (Table 3). No individual factor contributed significantly to the duration of symptoms, but obesity contributed to the duration of fatigue ($F = 8.85$, $P = .004$). The model could not accurately account for the between-group variance in symptom duration ($R^2 = 0.041$, AIC = 1496, $P = .33$), but did account for fatigue duration ($R^2 = 0.30$, AIC = 409, $P = .006$). There was no interaction effect between obesity and SARS-CoV-2 infection on fatigue duration ($F = 0.05$, $P = .98$).

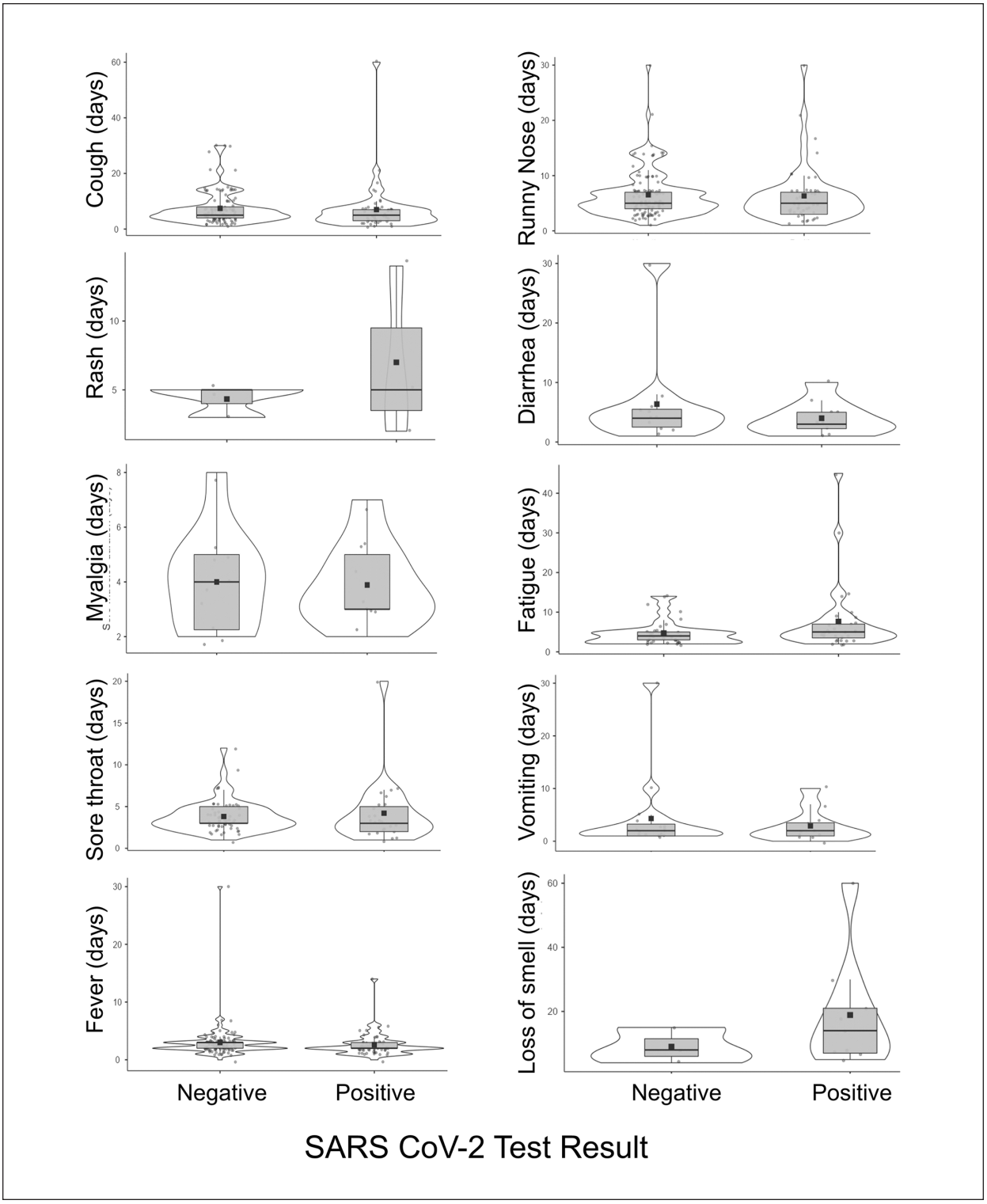

Figure 2. Duration of fatigue is longer in CYP with a positive SARS-CoV-2 test than in peers with a negative test. The violin box plots display the duration (in days) of 10 symptoms (cough, runny nose, sore throat, rash, diarrhea, vomiting, sore muscles, fatigue, fever, and loss of smell), as reported by families of CYP with a positive (n = 100) or negative (n = 272) SARS-CoV-2 test result. CYP with a positive test experienced significantly longer ($P = .030$, d = 0.26) duration of fatigue (7.6 ± 8 days) than CYP with a negative SARS-CoV-2 test (4.7 ± 3 days). There was no difference ($P > .05$) in the duration of other symptoms. Mean (black box), median (black stripe), and standard deviation (vertical bars) are displayed.
Abbreviations: CYP, children and young people; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Linear Regression Reveals No Effect of SARS-CoV-2 Infection on Duration of Symptoms or Duration of Fatigue, When Controlling for Medical and Demographic Covariates.

Symptom, n (%)	Estimate	95% CI	*T*	*P* value
Longest duration of any symptom ($R^2 = 0.041$, $F = 1.15$, $P = .33$)				
Positive SARS-CoV-2 test	0.73	−1.4 to 2.8	0.68	.49
Age, y	0.18	−0.02 to 0.4	1.7	.088
Sex (male)	0.50	−1.4 to 2.4	0.51	.60
Race (white)	0.55	−1.8 to 2.9	0.45	.64
Asthma	1.9	−1.9 to 5.8	0.99	.32
Anxiety	−0.48	−4.2 to 3.2	−0.25	.80
Depression	1.9	−4.1 to 8.0	0.61	.53
Obesity	1.3	−1.6 to 4.3	0.91	.36
Duration of fatigue ($R^2 = 0.55$, $F = 3.11$, $P = .006$)				
Positive SARS-CoV-2 test	−0.12	−3.3 to 3.1	−0.07	.93
Age (years)	0.16	−0.10 to 0.43	1.23	.22
Sex (male)	0.24	−2.4 to 2.9	0.17	.85
Race (white)	−1.27	−5.0 to 2.4	−0.67	.49
Asthma	1.8	−3.4 to 7.2	0.71	.47
Anxiety	1.27	−3.3 to 5.8	0.55	.58
Depression	4.3	−2.1 to 10.8	1.34	.18
Obesity	6.27	2.0 to 10.4	2.97	.004

Results of linear regression analyses are displayed, where duration of any symptom (model 1) and duration of fatigue (model 2) served as the dependent variable. Positive/negative SARS-CoV-2 test served as the primary independent variable, and child/young person age, sex, race, asthma status, anxiety, depression, and obesity served as covariates. Results of the overall model are displayed along with estimates of the contributions of each variable.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; CI, confidence interval.

Discussion

In this cohort, diarrhea, fatigue, fever, and anosmia were more common among CYP with a positive SARS-CoV-2 test. Anosmia, fatigue, and cough were the most persistent symptoms among CYP with a positive SARS-CoV-2 test. However, symptom duration did not differ between CYP with a positive SARS-CoV-2 test and peers with a non-SARS-CoV-2 infection. Duration of fatigue was the only specific symptom that persisted longer among CYP with a positive SARS-CoV-2 test, but this association became insignificant when controlling for medical and demographic factors.

Interestingly, no medical or demographic variable contributed significantly to the duration of symptoms. This finding contrasts with previous studies that have found an association between long COVID and older age, female sex, and baseline physical/mental health.[7-11] This difference may have resulted because the current study treated symptom duration as a continuous measure or because the current cohort included a large number of infants and toddlers with mild symptoms. In contrast, many prior studies have focused on adolescents,[9,22] included hospitalized patients,[23,24] or focused on symptoms persisting beyond 12 weeks.[10,25] The results did display a strong association between duration of fatigue and child obesity, an important medical factor reported in previous studies of SARS-CoV-2.[26]

The rate of persistent symptoms reported here (10%) and the similarity in persistent symptoms between CYP with a positive SARS-CoV-2 test and those with a negative test is consistent with the study by Radtke and colleagues.[16] In addition, both studies found fatigue to be a prominently persistent symptom among CYP. A study by Borsch and colleagues found that uninfected children of the age range 0 to 5 years were more likely to have persistent symptoms than peers with SARS-CoV-2.[27] This may explain why the current study, which included 185 children younger than 5 years, did not detect an effect of SARS-CoV-2 on symptom duration, whereas several studies involving adolescents have reported an effect.[8,9]

The results of this study may aid primary care clinicians in providing anticipatory guidance to families of CYP at the time of SARS-CoV-2 diagnosis. CYP with SARS-CoV-2 may experience a higher burden of certain viral symptoms during their initial infection stages (eg, myalgias, fever, fatigue, anosmia). Based on these results, CYP who experience persistent symptoms from SARS-CoV-2 are most likely to report fatigue; however,

they are unlikely to experience a longer duration of symptoms than would be expected with other viral infections. It remains unclear whether individual medical or demographic factors contribute to the risk of persistent symptoms.

This study has several strengths, including the inclusion of infants and toddlers, the use of seropositive results to avoid misclassification bias, and lack of nonresponse bias. The inclusion of important demographic and health variables also adds to our understanding of social determinants of health on symptom duration. There are several limitations that should be considered. The study focused on outpatients with mild disease, and this convenience sample may introduce elements of selection bias. The study was adequately powered to test the primary hypothesis; however, the sample size (n = 372) may be insufficient to draw conclusions about persistent symptoms as a dichotomous variable (ie, "long COVID" or symptoms beyond 4 weeks). As with any study relying on parental survey, there is a possibility for recall bias. However, we note that both groups completed surveys an average of 4 months after infection. Survey questions were not assessed for validity and reliability. The longitudinal nature of enrollment (October 2020-July 2022), allowed us to capture a wide range of SARS-CoV-2 variants. However, this approach also may have introduced variations related to vaccination status that we cannot control for. The study period also included the introduction of new testing modalities (ie, lateral flow assay), with varying sensitivity and specificity when compared with gold standard tests (ie, polymerase chain reaction). This could contribute to misclassification bias.

In conclusion, this study supports the notion that the duration of symptoms in CYP with SARS-CoV-2 does not differ from that in peers infected with other viruses during the COVID-19 pandemic. A larger, multicenter cohort is necessary to confirm these findings and to tease apart the potential influences of medical and demographic factors on symptom duration.

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Author Contributions

SDH: Contributed to conception and design; contributed to data acquisition; and drafting and critically revised the manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The author serves as a paid consultant and scientific advisory board member for Quadrant Biosciences and Spectrum Solutions, neither of whom played a role in the current study.

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Ethics Statement

This study received ethical approval from the institutional review board at the Penn State College of Medicine (STUDY00014022). All parents/guardians provided written consent, and youths provided written assent when appropriate.

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