Clinical Features and Follow-up of Referred Children and Young People With Long COVID

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Background: Patient-level data on the clinical features and outcomes of children and young people referred for possible long coronavirus disease (COVID) can guide clinicians on what to expect in managing patients and advising families.

Methods: A Post-Acute COVID Clinic for persons <21 years of age was established in October 2020. Intake was standardized and management was tailored to presenting symptoms. Data were abstracted from the charts of all patients evaluated through December 2021, and the study cohort consisted of patients who had a history of confirmed severe acute respiratory syndrome coronavirus 2 infection, had ≥1 symptom persisting for ≥12 weeks and had no pre-existing diagnosis that explained the symptoms. A structured follow-up interview was conducted in early 2022.

Results: A total of 104 patients were referred, 81 of whom met inclusion criteria. The median age was 14 years (interquartile range, 13–16), and most were female, White/Caucasian and had commercial health insurance. Patients reported previously good health but over half reported moderate-to-severe disability at their first visit. Two clusters of presenting symptoms—fatigue with multiple symptoms, and fatigue and headache with cardiopulmonary symptoms—were identified. Extensive routine testing did not affirm alternative diagnoses. Incident conditions—most commonly anxiety, depression and/or panic disorder; migraines; and autonomic dysfunction—were diagnosed on clinical grounds. Telephone interviews (N = 55) revealed that 78% of patients were improved by about 6 months.

Conclusions: Within the limits of a single-center, referral-based, observational cohort, this study provides reassurance to patients and parents in that most cases of long COVID were self-limited. Extensive evaluations may be more useful in ruling out alternative diagnoses than in affirming specific physiologic disturbances.

Key Words: children and young people, post-acute sequelae of SARS-CoV-2 infection, long COVID

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Adults[1–3] and children and young people[4–12] may have persistent or new, associated symptoms after acute coronavirus disease 2019 (COVID-19), referred to as post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or long COVID.[13]

A survey in the United States showed that as of June 2022, approximately one-third of adults experienced symptoms that lasted ≥3 months after acute COVID-19, and about a quarter of those reported significant limitations in day-to-day activities.[14] Persistent or new symptoms reported by adults after acute COVID-19 include fatigue, headache, shortness of breath, loss of taste or smell, cognitive disturbance and anxiety or depression,[3,15] and risk factors include increased severity of the acute illness, older age, female sex and pre-existing medical conditions.[16] A cross-sectional study conducted in France showed that 10% of adults who had COVID-19 were experiencing persistent symptoms 1 year later.[17]

Children and adolescents also may experience new or persistent symptoms after acute COVID-19,[4–12] and these can follow mild or even asymptomatic acute infection.[1,2,8,10,15,18] Given that >75% of US children and adolescents have serological evidence of prior SARS-CoV-2 infection,[19] the public health burden of post-COVID morbidity in children and adolescents is potentially large. However, several factors make a complete understanding of long COVID in this age group difficult. For example, epidemiologic studies use different definitions of long COVID, some of which may not be specific to children, and typically rely on surveys rather than direct clinical assessments; as a result, estimates of prevalence are highly variable.[20–22] In addition, the occurrence of symptoms in control subjects[6,7,23] and lack of an association between seropositivity and symptoms[9,24] casts some doubt on a causal association between antecedent SARS-CoV-2 infection and long COVID.

These things aside, patients experiencing new or persistent symptoms after acute COVID will be referred to primary care providers or specialists for evaluation. In this context, having patient-level clinical data on referred patients is important. Our academic medical center established one of the first referral-based pediatric Post-Acute COVID Clinics (PACCs) in the United States. Herein, we present clinical data and outcomes on patients seen between October 2020 and December 2021 who, in retrospect, met a recently published research case definition of long COVID in children and adolescents. Only a few substantial series have been published regarding children and adolescents referred for new or persistent symptoms after acute COVID,[8,10,12] and even fewer have used the most stringent and specific definition of long COVID in this age group.[12,25]

METHODS

Post-acute COVID Clinic

Regional providers were notified about the clinic through e-mails, televised news interviews and the medical center website. Patients were scheduled if they (1) were under 21 years of age, (2) had proven or strongly suspected COVID-19 beginning ≥10 days earlier, (3) were afebrile, (4) had new or lingering symptoms or a sense of not feeling well and (5) were referred by a primary care provider or other pediatric subspecialist (walk-ins

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and self-referred patients were not allowed). Pediatric infectious diseases providers performed intake interviews using a standardized template (see Intake Interview Template, Supplemental Digital Content 1, http://links.lww.com/INF/F218), which included a modified version of the Functional Disability Inventory (mFDI),[26] a measure of functional impairment in pediatric patients with chronic pain that has been widely used in a variety of chronic medical conditions[27] (the items were adapted for use during the pandemic; eg, Item 8—"Being at school all day"—was changed to "Being at school, or doing remote learning, all day"). Subsequent evaluation, subspecialty referral and management were at the discretion of individual providers. Patients received standardized educational material (see Patient Education Material, Supplemental Digital Content 2, http://links.lww.com/INF/F219).

Study Cohort

The charts of all patients evaluated between October 12, 2020 and December 6, 2021 were reviewed. The study cohort consisted of all patients who met a proposed research case definition of long COVID,[25] which includes the following: (1) a history of confirmed SARS-CoV-2 infection (positive PCR, antigen, or serology); (2) ≥1 physical symptom persisting for ≥12 weeks; and (3) no alternative diagnosis that explains the symptoms. For study purposes, new conditions that were diagnosed in PACC or by subspecialists to whom the patients were referred were considered incident and potentially related to the antecedent COVID-19 illness. It is important to point out that the case definition applied here is inclusive of those from the US Department of Health and Human Services,[28] the UK National Institute for Health and Care Excellence,[29] and the World Health Organization.[30]

Patients with acute SARS-CoV-2 infection or multisystem inflammatory syndrome in children were excluded. The results of diagnostic tests performed before referral, in the PACC, or during subspecialty evaluations were interpreted (ie, explanatory or not explanatory with respect to the patient's symptoms) in real time by the ordering providers, and those interpretations were used in this analysis. This portion of the study was approved by the University of Louisville and Norton Children's Institutional Review Boards under a waiver of consent.

Follow-up Telephone Interview

A structured interview (see Structured Telephone Interview, Supplemental Digital Content 3, http://links.lww.com/INF/F220) was conducted by one of the 4 investigators with available and willing patients between January 2022 and March 2022. When possible, both parent/guardian and patient were included. This portion of the study was approved by the University of Louisville and Norton Children's Institutional Review Boards, with verbal consent from the parent/guardian and assent by the patient (if present at the interview).

Statistics

Medians, with interquartile range (IQR), were used as measures of central tendency. Proportions were compared using Fisher exact test or the Mann-Whitney *U* test. The Hopkins statistic[31] was used to determine clustering tendency for presenting symptoms, and the optimum number of clusters was determined based on the silhouette coefficient, which estimates the average distance between clusters.[32] Exploratory cluster analysis was performed for presenting symptoms using a dissimilarity matrix calculated using the Jaccard Distance between observations, and each patient was assigned to a cluster using the divisive analysis clustering algorithm.[33,34] Clusters were described by the proportion of patients with each symptom, and associations with demographic variables and outcomes were sought.

RESULTS

Referrals to PACC occurred ≈2 months after each wave of COVID-19 in the community (see Figure, Supplemental Digital Content 4, http://links.lww.com/INF/F221, which shows the timing of new patient visits to PACC in relation to cases of COVID-19 in the community). A total of 104 patients were evaluated between October 12, 2020 and December 6, 2021, of which 81 met inclusion criteria (Fig. 1). Demographic characteristics of referred patients and those among them meeting the case definition are given in Table 1, which also gives demographic data for children referred

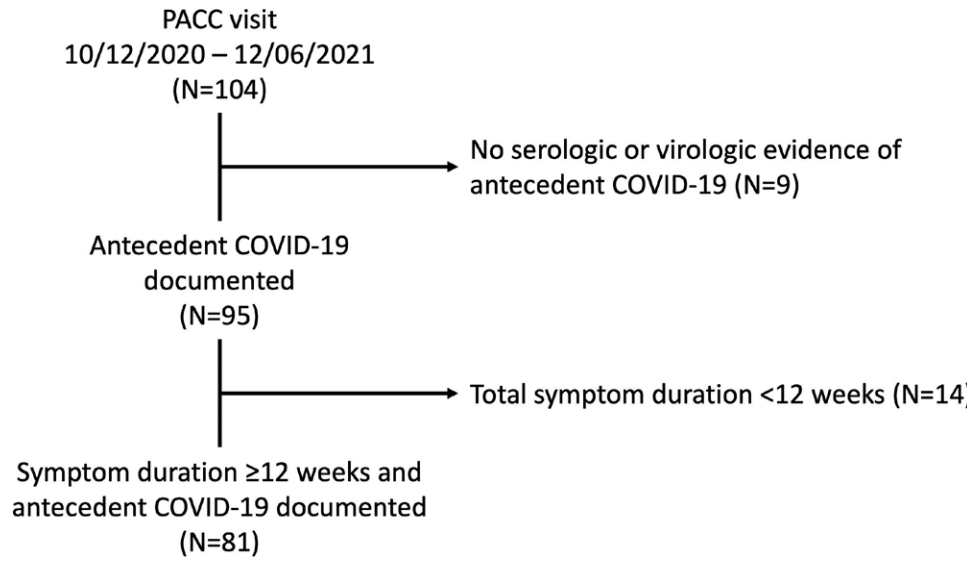

FIGURE 1. Study cohort.
This shows the derivation of the study cohort.

TABLE 1. Demographic Characteristics

Characteristic	Pediatric Infectious Diseases Clinic	Patients Evaluated for Persistent Symptoms After Acute COVID-19	Patients Meeting the Case Definition for Long COVID
Number	533	104	81
Age (y)			
<10	46.4% (N = 248)	11.5% (N = 12)	8.6% (N = 7)
10–11	2.8 (15)	10.6 (11)	11.1 (9)
12–13	9.0 (48)	18.3 (19)	17.3 (14)
14–15	15.0 (80)	31.7 (33)	34.6 (28)
16–17	18 (96)	21.1 (22)	22.2 (18)
18–21	8.8 (47)	6.7 (7)	6.2 (5)
Gender			
Female	49.8 (266)	52.9 (55)	58.0 (47)
Male	50.1 (267)	47.1 (49)	42.0 (34)
Race			
White/Caucasian	66.1 (353)	74.0 (77)	74.1 (60)
Black/African American	13.9 (74)	6.7 (7)	8.6 (7)
Hispanic/Latino	3.6 (19)	5.8 (6)	4.9 (4)
Asian	1.0 (5)	1.0 (1)	1.2 (1)
Biracial	5.4 (29)	1.0 (1)	1.2 (1)
Other or unknown	9.9 (53)	11.5 (12)	10.0 (8)
Insurance			
Commercial	50.1 (267)	67.3 (70)	69.1 (56)
Noncommercial	49.8 (266)	32.7 (34)	30.9 (25)

to the outpatient infectious diseases service for other reasons. Note that patients referred for possible long COVID, and those meeting the case definition, were generally older than other infectious diseases patients and more often had commercial health insurance.

The median age of case patients was 14 years (range 3–19); 91% of patients were ≥10 years of age, 58% were female, 74.1% were White/Caucasian and 69.1% had commercial health insurance (Table 1). Only 13 patients had been vaccinated before their first clinic visit, 9 of them before having developed COVID-19. The median interval from onset of COVID-19 symptoms to the first PACC visit was 3.0 months (IQR, 2.1–5.1). Three patients had been asymptomatic with COVID-19 and 3 had been hospitalized; the remaining patients had mild acute symptoms. Ninety-five percent (N = 79) reported good health before contracting COVID-19, although some had premorbid conditions including asthma and obesity (data were not available for 2 patients).

Symptoms at the time of presentation are shown in Figure 2; the most common were fatigue (74%), headache (63%), shortness of breath (53%) and exercise intolerance (53%). Approximately half of the patients were experiencing moderate-to-severe disability at the time of the initial visit as judged by their mFDI scores (see Figure, Supplemental Digital Content 5, http://links.lww.com/INF/F222, which shows the mFDI scores in a box and whisker plot). Note that there was no association between premorbid asthma and obesity and mFDI score (data not shown). Clusterability of presenting symptoms was suggested (Hopkins statistic = 0.7596) and the optimum number of clusters was determined to be 2. Patients in cluster 1 (fatigue with multiple complaints; N = 34) experienced a variety of symptoms [median number of symptoms = 8 (IQR, 7–11)], but the only symptom present in >50% of patients was fatigue (Table 2). Patients in cluster 2 (fatigue with headache and cardiopulmonary symptoms; N = 47) experienced a less diverse array of symptoms [median = 5 (IQR 3–6); $P < 0.001$ (Mann-Whitney)], and >75% of patients in this cluster had fatigue, shortness of breath, exercise intolerance and headache. Clusters were similar in terms of age and race, but females and patients with commercial health insurance were more commonly found in cluster 1 (Table 2).

Patients underwent extensive, albeit not prescribed or standardized, evaluations (see Figure, Supplemental Digital Content 6, http://links.lww.com/INF/F223, which shows a heat map of the studies that were done). Most had a complete blood count, acute phase reactants and routine chemistry panel; more than half had cardiac imaging or a cardiac procedure and pulmonary imaging or a pulmonary procedure (see the Supplemental Digital Content 6, http://links.lww.com/INF/F223, figure legend for details). The most common subspecialty referrals were to Neurology (N = 41 patients), Cardiology (38), Physical Therapy/Physical Medicine and Rehabilitation (38) and Pulmonology (36) (see Figure, Supplemental Digital Content 7, http://links.lww.com/INF/F224, which shows a heat map of the referrals that were made).

In general, the results of routine tests did not affirm alternative diagnoses that would explain the presenting symptoms. The most common incident conditions that were diagnosed between the intake visit and the latest follow-up encounter were anxiety, depression and/or panic disorder (N = 23 patients); migraine headache (21) and autonomic instability (18) (see Figure, Supplemental Digital Content 8, http://links.lww.com/INF/F225, which shows a heat map of the incident conditions that were diagnosed). These conditions were largely diagnosed on clinical grounds rather than the results of specific tests. No patients were diagnosed with myocarditis, heart failure or any electrographic cardiac abnormality. Only 1 child was diagnosed with an autoimmune condition; this patient had antibodies suggesting Hashimoto thyroiditis, but thyroid function was normal.

Information regarding the trajectory of individual symptoms over ≈6 months (IQR, 3.37–10.2) was available for 66 patients (55 via telephone survey and 11 via follow-up clinic visit). The prevalence of 7 symptoms—fatigue, headache, exercise intolerance, shortness of breath, chest pain, myalgia or arthralgia and loss of taste/smell—decreased over time; most patients who had these symptoms at the latest follow-up encounter had them since initial presentation (Fig. 3, persistent symptoms). Four other symptoms that were present at the latest encounter—gastrointestinal disturbance, difficulty concentrating, psychological disturbance and sleep disturbance—were not present at intake in in the majority of patients (Fig. 3, incident symptoms).

Fifty-five patients participated in the telephone survey. mFDI scores for these patients were like the entire cohort (50% in the moderate-to-severe category; data not available for 3 patients). Seventy-eight percent of the 55 patients [median time since intake visit 6.6 months (IQR, 3.83–10.53)] reported that they were improved, and 29% endorsed feeling back to normal. There was no association between functional disability category and outcome ($P = 0.7285$, Fisher exact test; data not available for 3 patients),

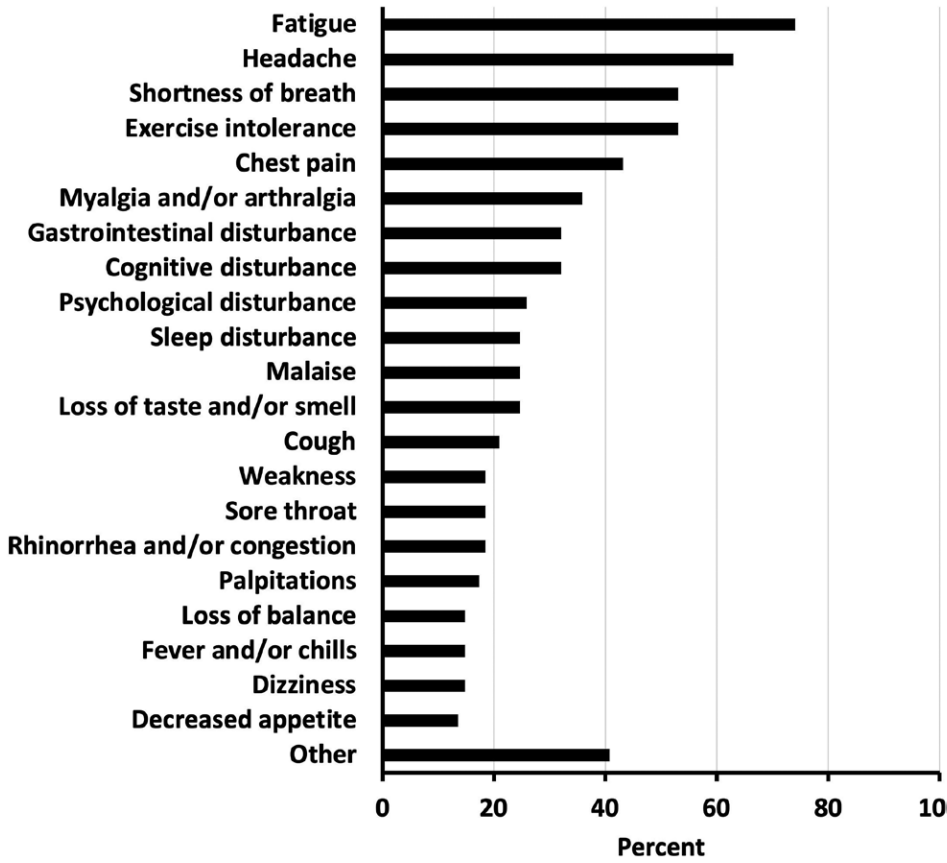

FIGURE 2. Symptoms at the time of presentation to Post-Acute COVID Clinic.
This shows the symptoms reported by patients (N = 81) at the time of the first visit to the Post-Acute COVID Clinic. Shortness of breath includes chest tightness and difficulty breathing. Gastrointestinal disturbance includes abdominal pain, nausea, vomiting, constipation and diarrhea. Cognitive disturbance includes difficulty concentrating, confusion, dream-like sensation, word-finding difficulty, memory loss and brain fog. Psychological disturbance includes anxiety, depressed mood, psychiatric distress and behavior problem. Dizziness includes syncope, orthostasis with visual changes and tachycardia, lightheadedness.

TABLE 2. Presenting Symptom Clusters

	Cluster 1	Cluster 2	*P*-value
Designation	Fatigue with multiple symptoms	Fatigue with headache and cardiopulmonary symptoms	
Number of symptoms [median (IQR)]	8 (7–11)	5 (3–6)	<0.001*
Symptoms present in >75% of patients	None†	Fatigue Shortness of breath Exercise intolerance Headache	
Age (y; median [IQR])	14 (13–16)	14 (12–16)	0.544*
Gender (%)	0.001‡		
Female	79.4	42.6	
Male	20.6	57.4	
Race (%)			0.68‡
White	76.5	68.1	
Non-White	11.8	19.1	
Unknown	11.8	12.8	
Insurance (%)			0.029‡
Commercial	82.4	57.4	
Noncommercial	17.6	42.6	

*Mann-Whitney *U* test.
†The only symptom present in >50% of patients was fatigue (62%).
‡Fisher exact test.

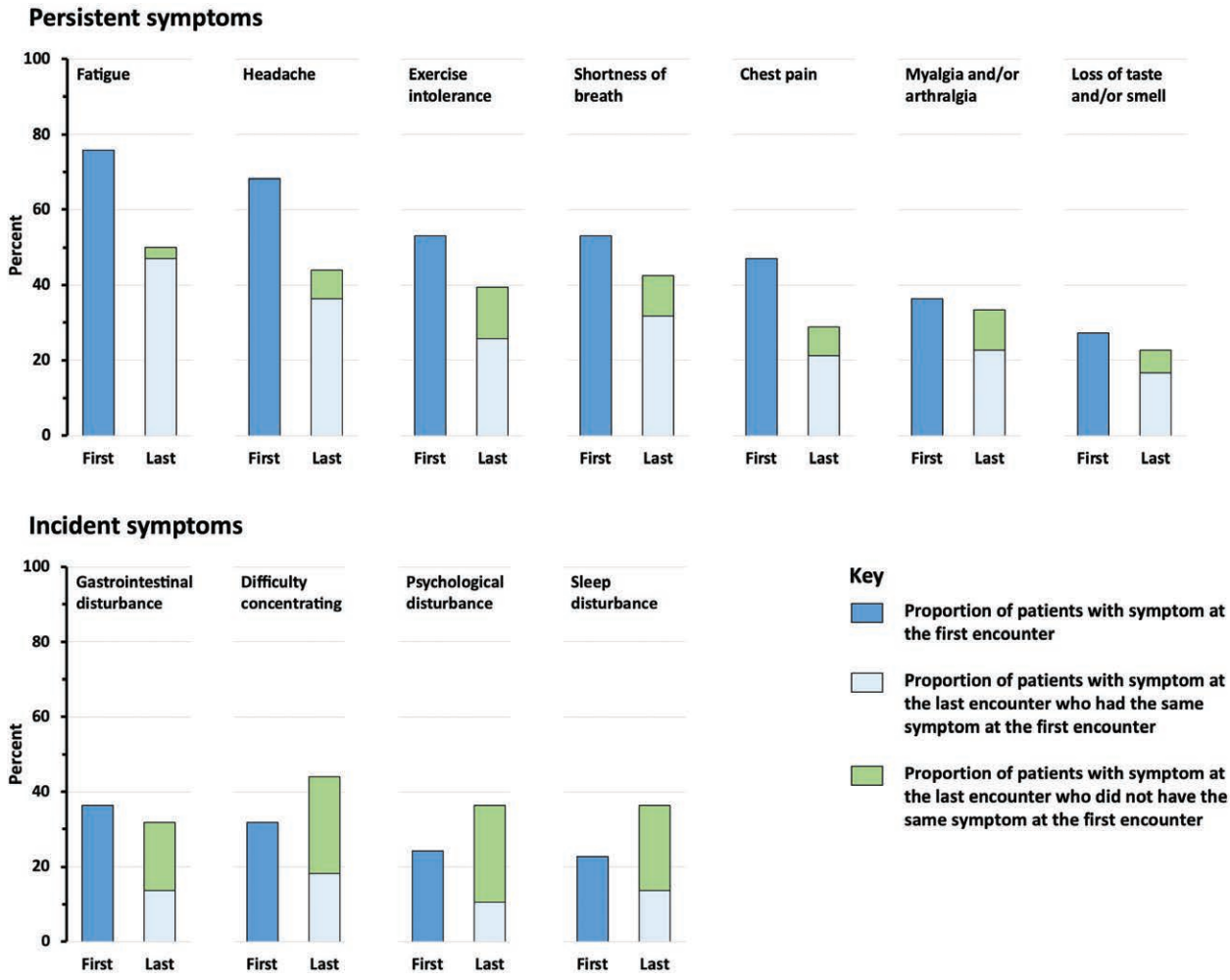

FIGURE 3. Trajectory of symptoms during follow-up.
This shows the evolution of symptoms experienced by individual patients (N = 66) from their first Post-Acute COVID Clinic visit to their last encounter [either the telephone follow-up interview (N = 55) or a clinic visit (N=11)]. The top panel (persistent symptoms) shows symptoms that tended to persist over time (>50% of those with the symptom at the last encounter had the same symptom at the first encounter). The bottom panel (incident symptoms) shows symptoms that developed over time (>50% of those with the symptom at the last encounter did not have that symptom at the first encounter). The median time from the first visit to the last encounter was ≈6 months [IQR, 3.37–10.2]. Shortness of breath includes chest tightness and difficulty breathing. Gastrointestinal disturbance includes abdominal pain, nausea, vomiting, constipation or diarrhea. Difficulty concentrating includes brain fog. Psychological disturbance includes anxiety, depressed mood, psychiatric distress and behavior problem.

nor between the presence of premorbid asthma or obesity and outcome, as compared with no premorbid conditions (P = 0.6362, Fisher exact test). In addition, the proportion of surveyed patients who were improved or back to normal was similar in those who presented with symptom cluster 1 (73.9%) and symptom cluster 2 (81.3%) (P = 0.5296, Fisher exact test).

DISCUSSION

This study provides important insights into the clinical picture of children and adolescents who are referred for persistent symptoms after acute COVID-19 and who meet a stringent definition of long COVID. Several observations are worth highlighting. First, patients tended to be in the adolescent age range, consistent with other studies.[4,35,36] In our cohort, this is not likely to be explained by more severe acute illness because most patients had mild disease. Likewise, poor baseline health status is an unlikely explanation, because most patients reported previously good health. It is possible that biologic effects[37] of the virus last longer in older children; alternatively, older children may articulate symptoms better and may be more readily referred.

Second, the symptoms reported in these patients (Fig. 2) are like those reported in other studies,[4–12,22] a few of which[8,10,12] included referred patients who met prespecified criteria. However, they stand in contrast to the findings of a study showing that the most common syndromic condition 1 to 6 months after testing positive for SARS-CoV-2 was loss of taste and smell, and the most common systemic condition (excluding multisystem inflammatory syndrome in children) was myocarditis.[11] This underscores the differences between (1) clinic-based studies, which report patient-level data in individuals who seek care for their symptoms (current study and others[8,10,12]) and are subject to referral bias and lack of controls; (2) survey studies, which

collect self-reported symptoms in individuals known to have had or not had SARS-CoV-2 infection[6,7,9] and are subject to response and recall biases (note that in these studies, subjects may not be blinded to their SARS-CoV-2 status); and (3) claims database[5] or aggregated electronic health record[11] studies of individuals known to have had or not had SARS-CoV-2 infection, which are subject to misclassification bias, among others.

Exploratory cluster analysis suggested 2 symptom phenotypes: one characterized by many symptoms, with fatigue being the most prominent (cluster 1), and the other dominated by fatigue, headache and cardiopulmonary complaints (shortness of breath and exercise intolerance) (cluster 2). Six distinct symptom clusters were found in a study of the electronic health care records of 6469 adults;[38] while direct comparisons cannot be made, it is interesting that some clusters in that study were dominated by cardiovascular or pulmonary complaints, like cluster 2 here.

Third, patients in our cohort underwent extensive testing (Supplemental Digital Content 6, http://links.lww.com/INF/F223); for the most part, test results were more helpful in ruling out alternative diagnoses than ruling in specific diagnoses that would explain the symptoms. Studies in adults[15] and children[10] with post-COVID symptoms show a lack of benefit of extensive testing, and guidelines[29] discourage the use of broad, prescribed batteries of laboratory investigations. Some authors have suggested first-tier (including complete blood count, metabolic panel and inflammatory markers) and second-tier (based on presenting symptoms and clinical judgment) screening tests in children who present for evaluation of long COVID.[39] Many of the incident conditions diagnosed in our patients (Supplemental Digital Content 8, http://links.lww.com/INF/F225)—including anxiety, depression and/or panic disorder; migraines; and autonomic dysfunction—were made on clinical grounds. Although it is possible that these conditions were present but unrecognized in some patients before they developed COVID-19, the fact that the majority reported that they were previously healthy suggests that these conditions may have been a consequence of COVID-19. These conditions have been highlighted in other studies of long COVID,[40–45] so it is important that clinicians are aware of common management strategies.[46–48]

Fourth, patients in this cohort experienced significant functional impairment (Supplemental Digital Content 5, http://links.lww.com/INF/F222), consistent with other studies.[12] Similar degrees of dysfunction are seen in other post-acute infection syndromes, including myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[49] Others have drawn attention to the overlap between the symptoms and demographic characteristics of patients with ME/CFS and long COVID.[50] However, while ME/CFS can be triggered by infection, long COVID is epidemiologically unique because of the large number of people affected, all of whom were infected with the same agent over a short period of time, during which drastic measures were implemented to prevent the spread of the virus. This makes comparisons with episodic post-infectious fatigue syndromes difficult and makes it challenging to parse out what is "long COVID syndrome" and what is "long pandemic syndrome,"[9] especially in young people, who may be more profoundly affected by the social isolation and personal stresses brought on by the lockdowns. To this point, a recent study from Norway showed that post-COVID condition was just as common among young people 6 months after testing negative for SARS-CoV-2 infection as it was among those testing positive.[24] The toll that the pandemic has taken on the mental and social well-being of children and adolescents[51] must be included in any understanding of long COVID in pediatric patients.

Finally, most patients in this cohort reported improvement in symptoms and functioning within 6 months, and no associations were found between presenting symptom cluster or functional disability category and outcome. Although this may reflect the natural history of long COVID, some improvement may have been attributable to active management of specific symptoms by PACC providers or referral services (eg, medication for headaches, increased water and salt intake for autonomic instability, etc), physical therapy, education or reassurance from the medical provider.

This study must be interpreted with caution. First, findings from a clinic-based cohort may not be generalizable to the whole population, although we would point out that characteristics of our patients closely parallel those reported in population-based studies. Second, the lack of a control group makes it difficult to distinguish between symptoms due to COVID-19 and symptoms due to other factors. Third, longitudinal data regarding the trajectory of post-COVID symptoms were only available for some of the patients; in this context, it is important to note that serious morbidity or mortality in the remaining patients was not found during chart review. Finally, most patients were seen when ancestral, Alpha, or Delta strains of SARS-CoV-2 predominated, and it remains possible that the epidemiology and clinical features of long COVID are different in the Omicron era. To the latter point, a recent population-based study among adults in Norway showed that the range of complaints was similar following Omicron and Delta infection during the acute (14–29 days) and subacute (30–89 days) phases, but the risk of any complaint in general, and musculoskeletal pain in particular, was lower among those who had had Omicron.[52]

CONCLUSIONS

Most patients referred for evaluation in PACC met criteria for long COVID. Most patients were adolescents, were previously healthy and had a history of mild acute COVID-19. Presenting symptoms were like those reported in adults and other pediatric studies. Extensive routine laboratory evaluations and subspecialty referrals did not affirm alternative diagnoses that would explain the presenting symptoms, and the most common incident post-COVID conditions were anxiety, depression and/or panic disorder; autonomic dysfunction; and migraines. Most patients improved within 6 months.

Within the limits of a single-center, referral-based, observational cohort, this study provides a measure of reassurance to patients and parents that most cases of long COVID are self-limited. In addition, these data may offer guidance to providers regarding the extent of diagnostic testing and referral that should take place, and the symptoms and incident conditions that might need to be managed.

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