‘Long COVID’: Symptom persistence in children hospitalised for COVID-19

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Aim: We aimed to describe the long-term outcome with respect to symptom persistence amongst children hospitalised for COVID-19.

Methods: This was a follow-up study of 58 children and adolescents hospitalised with COVID-19. For all patients, the data were collected in a phone call to the family in December 2021 (9 months after the initial study and more than 13 months after their admission to hospital). We inquired about their current health status and obtained information, if the responding parent consented orally to participate and answer the questions.

Results: Fifty-one children and adolescents were studied. Only five patients (10%) had persistent symptoms compatible with long-COVID; the reported symptoms include fatigue in four (8%), weakness in three (6%), exercise intolerance in two (4%) and shortness of breath in two (4%) patients. Four patients (7.8%), who did not have any symptoms of long-COVID in phase 1 of the study, reported new-onset symptoms or complaints that are potentially compatible with the diagnosis of long-COVID (weakness, myalgia, excess sputum, cough, fatigue) in the current phase.

Conclusions: Symptom persistence of long-COVID is infrequent amongst children hospitalised for COVID-19. Most of the symptoms of long-COVID will resolve with the passage of time and the residual symptoms are often mild and tolerable. The scientific community should carefully and clearly define long-COVID and its natural course in order to facilitate and harmonise future studies.

Key words: chronic; coronavirus; COVID-19; paediatrics.

What is already known on this topic
1 In a previous study, we observed that 45% of children and adolescents, who were hospitalized with COVID-19, reported symptoms of long-COVID.
2 These symptoms included fatigue, shortness of breath, exercise intolerance, weakness, and walking intolerance.

What this paper adds
1 Most symptoms of long-COVID in children and adolescents will resolve with the passage of time.
2 Symptom persistence of long-COVID is not a common condition in children and adolescents.
3 Scientific community should carefully and clearly define long-COVID.

Long-COVID has been characterised by chronic symptoms (lasting longer than 12 weeks) of fatigue, weakness, headache, dyspnea, cough, exercise intolerance and so forth in previous studies of adult populations with COVID-19; long-COVID has been reported in about half of the adults with COVID-19.1–5 In a previous study, we observed that 45% of children and adolescents with COVID-19 (i.e. requiring hospitalisation) reported symptoms/complaints of long-COVID. These symptoms included fatigue in 21%, shortness of breath in 12%, exercise intolerance in 12%, weakness in 10% and walking intolerance in 9% of the individuals. Older age, muscle pain on admission and intensive care unit (ICU) admission were significantly associated with long-COVID in children and adolescents.6

The pathophysiology of long-COVID is not entirely clear yet. SARS-CoV-2 (the aetiology of COVID-19) invades many tissues and has multi-organ and multi-system impacts.7 Furthermore, psychological factors may also contribute to the development of long-COVID.8 One study showed that the immunological dysfunction may persist for months following the initial SARS-CoV-2 infection.9

Therefore, it is plausible to assume that symptoms compatible with long-COVID may persist for an extended period of time in some patients. A study of post-acute COVID-19 outcomes in children requiring hospitalisation (n = 71) showed that most (n = 60; 85%) children made a full recovery following SARS-CoV-2 infection. The symptoms in the remaining 11 patients (15%) had resolved in 1–3 months in 5 persons.10

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In the current longitudinal study, we aimed to describe the long-term outcome with respect to symptom persistence amongst children hospitalised for COVID-19. In addition, we investigated the risk factors associated with the persistent symptoms compatible with long-COVID in children and adolescents.

Methods
Participants
This was a follow-up study of 58 children with COVID-19 from our previous study (here called phase 1) (DOI: 10.1007/s12519-021-00457-6). In this longitudinal study, children and adolescents who were referred to and admitted at hospitals anywhere in Fars province, Iran, from 19 February 2020 until 20 November 2020, were included. All patients had a confirmed COVID-19 diagnosis if they were symptomatic and had a positive test result on real-time polymerase chain reaction of nasopharyngeal and oropharyngeal samples.

Data collection
For all the children and adolescents, the data (Appendix 1 that was adopted from phase 1 of the study) were collected in a phone call to the patients in December 2021 (9 months after the initial study and more than 13 months after their admission at the hospital). We inquired about their current health status and obtained information, if the responding parent agreed to participate and answer the questions (consented orally). In case of adolescents (age range: 16 to <18 years), we talked to the patient if their parents allowed us (in 4 out of 13 adolescent patients).

We asked if the patient (parent) has noticed any problems (e.g. muscle or joint pain, weakness etc.) during the past week, compared with their pre-COVID-19 condition. We specifically asked their symptoms and complaints during the past 7 days in order to minimise the risk of recall bias. We also asked the severity of their symptoms and complaints (i) mild and tolerable; (ii) moderate; (iii) severe and disabling. We defined potential long-COVID in two ways for exploratory purposes, in the current study: (i) any patient, who had reported any symptom and complaint in phase 1 of the study, who also had any symptom and complaint in the current follow-up study; and (ii) any patient, who had reported any symptom and complaint in phase 1 of the study, who also had the same symptom and complaint in the current follow-up study.

Statistical analyses
Values were presented as mean ± standard deviation for continuous variables and as number (percent) of subjects for categorical variables. Fisher's exact test and z-test were used for statistical analyses. A P value (2-sided) less than 0.05 was considered significant.

Standard protocol approvals
The Shiraz University of Medical Sciences Institutional Review Board approved this study (IR.SUMS.Rec.1399.022). Informed consent to participate in the study was obtained from the participants and their parents or legal guardians.

Results
General characteristic of the patients
All 58 patients from our previous study were contacted; 7 people (12%) were not available (did not answer our repeated phone calls) and did not participate in this study (5 males and 2 females; mean age: 13.2 years, standard deviation: 3.5 years; they were not significantly different compared with the studied patients). Fifty-one children and adolescents were studied. The patients included 23 male (45%) and 28 female (55%) individuals. The mean age of the patients was 13.2 years (median: 13.4, minimum: 6.9, maximum: 17.9, interquartile range: 6, standard deviation: 3.3 years). All patients received COVID-19 directed treatments (based on the guidelines at the time of their illness and hospital admission). Ten patients (19.6%) had ICU admission during their initial hospitalisation.

Persistent symptoms compatible with long-COVID
With the first method of looking at the problem (i.e. any patient, who had reported any symptom and complaint in phase 1 of the study...
study, who also had any symptom and complaint in the current follow-up study), 11 (22%) children and adolescents reported symptoms and complaints of long-COVID. These symptoms include fatigue in eight (16%), weakness in seven (14%), exercise intolerance in five (10%), shortness of breath in three (6%), myalgia in two (4%), excess sputum in two (4%) and chronic coughs in one (2%) patient (some patients had multiple complaints). Table 1 shows the severity of the reported persistent symptoms compatible with long-COVID in children and adolescents. Almost all symptoms and complaints were rated as mild and tolerable by the participants.

With the second method of looking at the problem that is considered as a more appropriate methodology to investigate the persistence of symptoms of long-COVID (i.e. any patient, who had reported any symptom and complaint in phase 1 of the study, who also had the same symptom and complaints in the current follow-up study), only five patients (10%) had persistent symptoms compatible with long-COVID. The reported symptoms include fatigue in four (8%), weakness in three (6%), exercise intolerance in two (4%) and shortness of breath in two (4%) patients. In three patients, the follow-up call happened 16 months after the initial hospital admission; in one person it was 15 months and in another patient it was 18 months after the initial hospital admission. None of the patients persistently had muscle pain, excess sputum and chronic coughs. Furthermore, none of the patients in the current follow-up study reported suffering from joint pain (in three patients in phase 1), sleep difficulty (in three), headache (in three) and walking intolerance (in five).

It is important to mention that four patients (7.8%), who did not have any symptoms of long-COVID in phase 1 of the study, reported new-onset symptoms or complaints that are potentially compatible with the diagnosis of long-COVID (weakness, myalgia, excess sputum, cough, fatigue) (in the current phase).

Factors associated with persistent symptoms compatible with long-COVID

In phase 1 of the study, age, muscle pain on admission and ICU admission were significantly associated with long-COVID in children and adolescents. In the current study, none of these variables were significantly associated with persistent symptoms compatible with long-COVID in children and adolescents (age \(P = 0.336\), muscle pain on admission \(P = 0.526\) and ICU admission \(P = 0.669\)). However, the numbers were small in all the statistical cells. We could not identify any other variable with a significant association with persistent symptoms compatible with long-COVID in children and adolescents either.

Discussion

In the current longitudinal study of children and adolescents with COVID-19 (requiring hospitalisation), we observed that most of the symptoms of long-COVID will not last more than 1 year after the initial infection. It seems that many symptoms of long-COVID (e.g. joint pain, sleep difficulty, headache, walking intolerance, muscle pain, excess sputum and chronic coughs) would resolve with the passage of time and in less than 1 year. In addition, the residual symptoms of long-COVID (e.g. fatigue, weakness, exercise intolerance and shortness of breath) are usually mild and tolerable for patients who are suffering from persistent symptoms compatible with long-COVID. We could not identify any risk factor associated with persistent symptoms compatible with long-COVID in this study (probably, due to the small sample size).

Importantly, we should be careful on how we define and investigate the persistence of symptoms in long-COVID. In the current study, we observed that some patients (more than half of the patients seemingly) with persistent symptoms reported symptoms that could be considered as being compatible with what we expect as the usual manifestations of long-COVID (e.g. fatigue, weakness, exercise intolerance), whilst they had not reported such symptoms before and in the early months after their initial infection with SARS-CoV-2. New-onset symptoms cannot be assumed to be related to COVID-19 and these symptoms should not be considered as persistent symptoms compatible with long-COVID. This observation highlights that long-term COVID-19-associated symptoms may be difficult to investigate. In other words, accurately determining the characteristics of long-COVID is challenging. Existing studies in children and adolescents have considerable limitations and distinguishing long-term COVID-associated symptoms from non-specific symptoms indirectly caused by pandemic circumstances may be difficult.

Previous studies have suggested that symptoms of long-COVID, specifically the non-respiratory symptoms, are due to persistent endothelial dysfunction. Finally, many studies have shown that the current pandemic has had detrimental psychological impacts on all human populations, including those with cured COVID-19. These psychiatric problems have significant associations with some of the subjective symptoms that are reported by patients with long-COVID (e.g. fatigue). Therefore, it is plausible to assume that symptoms compatible with long-COVID may persist for an extended period of time in some patients. Any persistent medical problems in children and adolescents, who are suffering from long-COVID, should be identified after the acute phase of the infection and adequately managed to assure complete resolution.

Limitations

The sample size of the current study was limited. Furthermore, the data were not collected prospectively and we cannot provide any information on the course of the long-COVID based on the current study. Also, there might be information bias, since the parents answered the questions on behalf of their children. In addition, we have not used any standardised measures (e.g. fatigue scales, health-related quality of life etc.) which limits any external comparisons. Furthermore, we did not assess whether the symptoms had any impact on everyday functioning of the children and adolescents in this study. Finally, we did not investigate asymptomatic infections and also those with a mild illness in this study. We did not have access to the data on the infection rates in children in Fars province at around the time of the study.
Conclusions
Symptom persistence of long-COVID is infrequent amongst children hospitalised for COVID-19. Future multicentre and well-designed studies should investigate the prevalence, the spectrum and the natural course of long-COVID in children, adolescents and adults.

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Data availability statement
The data are confidential and will not be shared as per the regulations of Shiraz University of Medical Sciences.

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Appendix
Long COVID-19 study in children, Fars, Iran
Name: Sex: male/female Phone number: 
Responder: patient/immediate family member living with the patient.
Date of the hospitalisation due to COVID-19: …

• Any symptoms or complaints or problems that you did not have before your COVID-19, but have persistently had ever since and during the past 7 days
  1. Muscle weakness Yes/No (mild and tolerable-moderate-severe and incapacitating).
  2. Muscle pain Yes/No (mild and tolerable-moderate-severe and incapacitating).
  3. Joint pain Yes/No (mild and tolerable-moderate-severe and incapacitating). Which joins …
  4. Fatigue Yes/No (mild and tolerable-moderate-severe and incapacitating).
  5. Sleep difficulty Yes/No (mild and tolerable-moderate-severe and incapacitating).
  6. Shortness of breath Yes/No (mild and tolerable-moderate-severe and incapacitating).
  7. Chest pain Yes/No (mild and tolerable-moderate-severe and incapacitating).
  8. Palpitation Yes/No (mild and tolerable-moderate-severe and incapacitating).
  9. Cough Yes/No (mild and tolerable-moderate-severe and incapacitating).
  10. Excess sputum Yes/No (mild and tolerable-moderate-severe and incapacitating).
11 Decreased sense of smell Yes/No (mild and tolerable-moderate-severe and incapacitating).
12 Decreased sense of taste Yes/No (mild and tolerable-moderate-severe and incapacitating).
13 Sore throat Yes/No (mild and tolerable-moderate-severe and incapacitating).
14 Headache Yes/No (mild and tolerable-moderate-severe and incapacitating).
15 Dizziness Yes/No (mild and tolerable-moderate-severe and incapacitating).
16 Concentration difficulty Yes/No (mild and tolerable-moderate-severe and incapacitating).
17 Excess sweating Yes/No (mild and tolerable-moderate-severe and incapacitating).
18 Exercise difficulty Yes/No (mild and tolerable-moderate-severe and incapacitating).
19 Walking difficulty Yes/No (mild and tolerable-moderate-severe and incapacitating).
20 Diarrhoea Yes/No (mild and tolerable-moderate-severe and incapacitating).
21 Abdominal pain/stomach ache Yes/No (mild and tolerable-moderate-severe and incapacitating).
22 Loss of appetite Yes/No (mild and tolerable-moderate-severe and incapacitating).
23 Skin lesions Yes/No (mild and tolerable-moderate-severe and incapacitating).