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Long-Term Effects of COVID-19 in Hospitalized and Non-Hospitalized Pediatric Patients: A Prospective Study

Hastanede Yatan ve Yatmayan Çocuk Hastalarda COVID-19'un Uzun Dönemli Etkileri: Prospektif Bir Çalışma

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Abstract

Aim: The global COVID-19 pandemic caused by SARS-CoV-2 has led to both acute and long-term health consequences worldwide. Long COVID, characterized by persistent symptoms lasting weeks or months after recovery from the acute infection, has been increasingly reported. We aimed to evaluate long-term (i.e., symptoms persisting ≥12 weeks) effects of COVID-19 in hospitalized and non-hospitalized children in line with WHO criteria.

Material and Method: This prospective study was conducted between June 2020 and June 2021 at Sancaktepe Training and Research Hospital. A total of 60 children with PCR-confirmed COVID-19 were included. The study participants were divided into three groups: Group 1 (30 children followed up in the outpatient clinic), Group 2 (30 children hospitalized in the pediatric intensive care unit (PICU)), and Group 3 (30 children without a prior COVID-19 infection as the control group). Parents completed a questionnaire assessing symptoms persisting for ≥12 weeks after diagnosis.

Results: Group 2 experienced more symptoms both in the acute and post-acute periods. In the post-acute period, the most common symptoms were fatigue (57.9%), sleep disorders (75%), headache (60%) and anxiety (70%) which were statistically significant (p=0.001, p=0.002, p=0.043).

Conclusions: Long COVID is a significant concern for pediatric patients. Fatigue, anxiety, sleep disorders, and headache were the most frequent persistent symptoms. These findings emphasize the need for continued surveillance and targeted rehabilitation strategies to address the long-term effects of COVID-19 on children's physical and mental health.

Keywords: Child, long COVID, post-acute period, SARS-CoV-2

Öz

Amaç: SARS-CoV-2 'nin neden olduğu küresel COVID-19 pandemisi akut ve uzun vadeli sağlık sorunlarına yol açmıştır. Akut enfeksiyondan iyileştikten sonra semptomların haftalar veya aylarca devam etmesi ile karakterize olan Uzun COVID, artan şekilde bildirilmektedir. Çalışmamızda DSÖ kriterleri doğrultusunda hastaneye yatırılan ve yatırılmayan çocuklarda COVID-19'un uzun dönem (yani semptomların ≥12 hafta devam etmesi) etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu prospektif çalışma, Haziran 2020-Haziran 2021 tarihleri arasında Sancaktepe Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. PCR ile doğrulanan COVID-19 tanısı konmuş toplam 60 çocuk dahil edildi. Çalışma katılımcıları üç gruba ayrıldı: 1. Grup (poliklinikten takip edilen 30 çocuk), 2. Grup (çocuk yoğun bakım ünitesinde yatan 30 çocuk) ve 3. Grup (kontrol grubu olarak COVID-19 enfeksiyonu geçirmemiş 30 çocuk). Ebeveynler, tanıdan sonra 12 hafta boyunca devam eden semptomları değerlendiren bir anketi doldurdular.

Bulgular: Grup 2 hem akut hem de post-akut dönemlerde daha fazla semptom yaşadı. Post-akut dönemde en sık görülen semptomlar yorgunluk (%57,9), uyku bozuklukları (%75), baş ağrısı (%60) ve anksiyete (%70) idi ve bunlar istatistiksel olarak anlamlıydı (p=0,001, p=0,002, p=0,043).

Sonuçlar: Uzun COVID pediyatrik hastalar için önemli bir kaynağıdır. Yorgunluk, anksiyete, uyku bozuklukları ve baş ağrısı en sık devam eden semptomlar arasındaydı. Bu bulgular, COVID-19'un çocukların fiziksel ve zihinsel sağlıkları üzerindeki uzun vadeli etkileri ile başa çıkmak için devam eden gözetim ve hedeflenmiş rehabilitasyon stratejilerinin gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Çocuk, uzun COVID, post-akut dönem, SARS-CoV-2

INTRODUCTION

In late 2019 and early 2020, the world faced a fatal global pandemic caused by SARS-CoV-2, which profoundly impacted and constricted our daily lives. [1] Initially, the focus was primarily on the acute symptoms of the disease. However, as time passed, it became evident that COVID-19 had long-term effects on those who contracted the disease at any age, leading to persistent symptoms following the infection. As a result, attention shifted to studying its long-term effects. [2] A broad range of persistent symptoms can significantly impair people's quality of life. [3] Recently, interest has grown in long-COVID syndrome, its pathophysiology, risk factors, consequences, and the available treatment and rehabilitation options, all of which have significant effects on daily activities, work, healthcare costs, and quality of life. [4]

According to the World Health Organization (WHO), ongoing, recurrent, or newly developed symptoms or related conditions that appear three months after the initial SARS-CoV-2 infection, with these symptoms lasting at least two months and not explained by an alternative diagnosis, are defined as long COVID or post-COVID-19 condition.[5] It has been reported that symptoms can persist for up to three years. [6] The exact underlying mechanism remains unclear.[7] A meta-analysis involving 21 studies with 80,071 children and adolescents reported the prevalence of long COVID as 25.24%.[8] Nittas et al.[9] reviewed 23 studies and 102 primary studies and found that the prevalence of long COVID in primarily non-hospitalized children was 2-3.5%. In 2023, in Turkey, Demirbuğa et al.[10] conducted a study with 116 pediatric patients and determined that post COVID-19 was 11.2%. The aim of the present study is to evaluate the long-term (≥12 weeks post-infection) symptoms of PCR-positive COVID-19 hospitalized and non-hospitalized children according to WHO

MATERIAL AND METHOD

criteria for long COVID.

Study Design

This prospective study was conducted between June 2020 and June 2021 at a tertiary hospital. The study was approved by the hospital's research and ethics committee (Date: 15.06.2022, Number: E-460596653-020) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents or legal guardians.

Study Population

During the study period, a total of 1.560 children had PCR-confirmed COVID-19 infection. Of these, 1.081 were followed up in our outpatient clinic, and 479 were hospitalized. Among the hospitalized children, 386 were admitted to the pediatric intensive care unit (PICU). The study sample of children with PCR-confirmed COVID-19 infection was divided into two groups: Group 1 consisted of 30 children who were followed up in the outpatient clinic, and Group 2 included 30 children who were followed up in the PICU. Additionally, a third control group (Group 3) was composed of children who had no history of symptomatic or asymptomatic COVID-19 infection with negative PCR and

serology for SARS-CoV-2, no acute or chronic disease that may be confused with COVID signs and symptoms, and presented to the outpatient clinic for reasons unrelated to infection.

Children who were vaccinated for COVID-19, those with mental and/or motor developmental delays, children diagnosed with a mental illness and followed up by a child psychiatrist, and those using drugs or substances that could affect cognitive functions were excluded from the study.

For the signs and symptoms of acute period, medical records of the subjects were tracked through the electronic pediatric patient data registry and reviewed. For post-acute period the information was collected at the 12th week post-diagnosis by contacting the parents of the cases. Parents of the children in Group 3 were also contacted during the same period. The literature on long COVID was reviewed. A structured questionnaire consisting of 14 items across somatic, cognitive, and psychological domains was used, adapted from WHO, and validated for pediatric use (5). Sample size was calculated based on anticipated symptom prevalence, with 80% power and a 5% significance level. The subjects and their parents were invited to the outpatient clinic for a questionnaire, physical examination, and assessment of symptoms 12 weeks after the onset of the disease. Parents completed a questionnaire regarding symptoms experienced by their children over 12 weeks after the diagnosis of COVID-19 infection, including throat pain, shortness of breath, cough, diarrhea, nausea/vomiting, fever, weight loss, fatigue, muscle/ joint pain, loss of taste or smell, anxiety, sleep disorders, and headache. The answers were recorded on a form designed for the present study. All data were collected and analyzed.

Statistical Analysis

Data obtained from the study were analyzed using statistical methods appropriate for the study's purpose. Variations within and between groups were examined over time. SPSS for Mac version 26 software was used to determine the effects. The compliance with normal distribution was assessed using visual methods (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/ Shapiro-Wilk tests). Descriptive statistics such as means and standard deviations were used for numerical data with a normal distribution. For normally distributed numerical data, ANOVA (post hoc Bonferroni) was used to compare groups, while for non-normally distributed data, the Kruskal-Wallis test (post hoc Mann-Whitney U test) was used. Nominal data were presented in cross-tabulations and dependent groups. Differences between independent groups were assessed using the McNemar test, Chi-Square test, and Fisher's exact test. A p-value of <0.05 was considered statistically significant.

RESULTS

In this prospective study, a total of 90 children were included. The study population consisted of 44 (48.9%) girls and 46 (51.1%) boys, with a mean age of 9.8±4.5 years. The characteristics of the groups are shown in **Table 1**.

Table 1. Demographic and Clinical Characteristics of Hospitalized and Non-Hospitalized								
Variables	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value				
Age (year), (mean±SD)	9.47±4.89	10.8±5.08	9.27±3.31	0.361				
Gender (male), n (%)	17 (37)	14 (30.4)	15 (32.6)	0.733				
Weight (kg), (mean±SD)	36.48±20.59	42.28±21.48	35.98±16.10	0.385				
Height (cm), (mean±SD)	133.2±26.2	141.7±29	132.9±19.9	0.317				
Abbreviations: SD = standard deviation								

At presentation, children hospitalized in the PICU (Group 2) had significantly higher rates of shortness of breath, diarrhea, nausea/vomiting, fever, weight loss, fatigue, and muscle/joint pain compared to children who were not hospitalized (Group 1) (p=0.001, p=0.031, p=0.001, p=0.001, p=0.024, p=0.001, p=0.001). On the other hand, cough was more common in Group 1 at the onset of the disease (p=0.007). We also found that hospitalized and non-hospitalized COVID-19 patients experienced throat pain equally at presentation. In the postacute period, fatigue was significantly higher in Group 2 (p=0.001). A comparison of the groups in terms of respiratory, gastrointestinal, musculoskeletal, and systemic symptoms is presented in Table 2. In the post-acute period, the most frequently reported symptoms among all participants were anxiety (11.1%; 95% CI: 4.8-20%), fatigue (21.1%; 95% CI: 13.3-31.1%), sleep disorders (13.3%; 95% CI: 6.7-21%), and headache (11.1%; 95% CI: 5.6-18.9%).

Table 2. Frequency and Distribution of Long COVID Symptoms by Group						
Symptoms	Period	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value	Post Hoc
Throat pain, n (%)	Acute	10 (47.6)	10 (47.6)	1 (4.8)	0.007	1<2 1<3
	Post-acute	2 (33.3)	4 (66.7)	0 (0)	0.117	
Shortness of breath, n (%)	Acute	4 (19)	14 (66.7)	3 (14.3)	0.001	2>1 2>3
	Post-acute	2 (20)	5 (50)	3 (30)	0.455	
Cough, n (%)	Acute	14 (51.9)	10 (37)	3 (11.1)	0.007	1>3
	Post-acute	3 (50)	3 (50)	0 (0)	0.201	
Diarrhea, n (%)	Acute	5 (26.3)	11 (57.9)	3 (15.8)	0.031	2>1 2>3
	Post-acute	1 (20)	4 (80)	0 (0)	0.064	
Nausea/ vomiting, n (%)	Acute	8 (27.6)	17 (58.6)	4 (13.8)	0.001	2>1 2>3
	Post-acute	3 (42.9)	4 (57.1)	0 (0)	0.133	
Fever, n (%)	Acute	22 (44.9)	27 (55.1)	0 (0)	0.001	3<1 3<2
	Post-acute	0 (0)	1 (100)	0 (0)	0.364	
Weight loss, n (%)	Acute	3 (25)	8 (66.7)	1 (8.3)	0.024	2>1 2>3
	Post-acute	1 (20)	4 (20)	0 (0)	0.064	
Fatigue, n (%)	Acute	20 (43.5)	22 (47.8)	4 (8.7)	0.001	3<1 3<2
	Post-acute	8 (42.1)	11 (57.9)	0 (0)	0.001	3<1 3<2
Muscle/ joint pain, n (%)	Acute	17 (39.5)	24 (55.8)	2 (4.7)	0.001	3<1 3<2
	Post-acute	6 (35.3)	9 (52.9)	2 (11.8)	0.068	

Comparison of groups in terms of neuropsychiatric symptoms is demonstrated in **Table 3**. Group 2 (hospitalized children) experienced higher rates of anxiety both during the acute and post-acute periods compared to Group 1 (p=0.001, p=0.016). Sleep disorders were also significantly more common in Group 2 during both periods (p=0.001, p=0.02). Additionally, headache was more common in Group 2 as a persistent symptom and continued in the post-acute period (p=0.037, p=0.043). Loss of taste was the only symptom reported exclusively by infected children.

Table 3. Comparison of groups in terms of neuropsychiatric symptoms							
Symptoms	Period	Group 1 (n=30)	Group 2 (n=30)	Group 3 (n=30)	p value	Post Hoc	
Loss of taste, n (%)	Acute	3 (60)	2 (40)	0 (0)	0.227		
	Post-acute	2 (100)	0 (0)	0 (0)	0.129		
Loss of smell, n (%)	Acute	4 (36.4)	6 (54.5)	1 (9.1)	0.141		
	Post-acute	2 (33.3)	3 (50)	1 (16.7)	0.585		
Anxiety, n (%)	Acute	11 (33.3)	20 (60.6)	2 (6.1)	0.001	2>1 2>3	
	Post-acute	3 (30)	7 (70)	0 (0)	0.016	2>1 2>3	
Sleep disorders, n (%)	Acute	8 (26.7)	20 (66.7)	2 (6.7)	0.001	2>1 2>3	
	Post-acute	3 (25)	9 (75)	0 (0)	0.002	2>1 2>3	
Headache, n (%)	Acute	9 (34.6)	13 (50)	4 (15.4)	0.037	2>1 2>3	
	Post-acute	4 (40)	6 (60)	0 (0)	0.043	2>1 2>3	

Distribution of statistically significant long COVID symptoms across three groups are summarized in **Figure 1**.

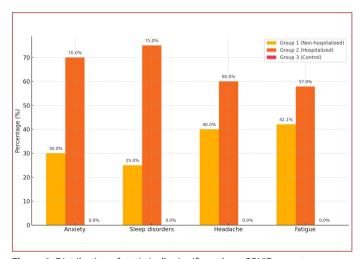


Figure 1. Distribution of statistically significant long COVID symptoms across three groups. This bar chart illustrates the percentage of participants in each group who reported various symptoms commonly associated long COVID. Group 1 (non-hospitalized patients) is shown in orange, Group 2 (hospitalized patients) in dark orange, and Group 3 (control group) in red. The hospitalized group (Group 2) showed the highest rates across all symptoms: anxiety (70.0%), sleep disorders (75.0%), headache (60.0%), and fatigue (57.9%). The non-hospitalized group (Group 1) also reported notable rates, especially for fatigue (42.1%) and headache (40.0%). In contrast, the control group (Group 3) did not report any of these symptoms.

DISCUSSION

This prospective follow-up study analyzed the symptoms of 30 hospitalized and 30 non-hospitalized PCR-confirmed COVID-19 patients, as well as 30 children previously uninfected by COVID-19. Our findings showed that children hospitalized in the PICU for COVID-19 experienced fatigue more frequently. We also found that neuropsychiatric symptoms, including anxiety, sleep disorders, and headache were more common in this group.

In February 2023, the WHO defined long COVID or Post-COVID-19 condition as symptoms lasting at least two months and occurring within three months of the acute onset of COVID-19 in children with a history of probable or confirmed SARS-CoV-2 infection.[11] The prevalence of long COVID has been reported as 25.24% by Lopez-Leon et al.[8], 20% by Bloise et al.[12], and 16.5% by Calcaterra et al.[13] While the exact pathogenic mechanism remains unclear, long COVID may result from persistent virus or viral components, tissue damage from the viral infection, autonomic and endothelial dysfunction, autoimmunity, and coagulopathy. [14-16] Vaccination against COVID-19 has been shown to reduce the risk of developing long COVID.[17,18] Previous studies have indicated that in children pre-existing diseases, female gender, and older age are associated with an increased risk of long COVID.[14,19,20] Seery et al.[2] reported cough, headache and fatigue as the most common persistent physical symptoms. On the other hand, a systematic review and meta-analyses demonstrated that compared to controls, children infected with SARS-CoV-2 experienced persistent fever, dyspnea and anosmia/ageusia.[8] A meta-analyses focusing on persistent symptoms following SARS-CoV-2 infection declared that, comparing control studies (5 studies) headache, cognitive difficulties, loss of smell, sore throat and eyes were common however, fever, cough, dyspnea, myalgia, abdominal pain, fatique, diarrhea and dizziness were not.[19] According to a WHO report, common long COVID symptoms in children include anosmia, fatigue, loss of appetite, headache, anxiety, shortness of breath, chronic gastrointestinal symptoms, rash, food intolerances and allergies, cognitive dysfunction, sensory abnormalities, dizziness, nausea, changes in eating habits, behavioral changes, and regression of developmental delay, with fatigue, anxiety, and altered smell/anosmia being the most common.[11] In this study, we found that fatigue, anxiety, sleep disorders, and headache were more common in children who were hospitalized in the PICU and later diagnosed with long COVID.

Despite the unclear characteristics of long COVID, worldwide reports show that long COVID particularly affects the motor system so that fatigue is the most common persistent symptom at any age. Ashkenazi-Hoffnung et al.^[21] conducted a prospective study with 90 children diagnosed with long COVID and showed that 71.1% of the children had fatigue as the most frequent persistent symptom. Camporesi et al.^[22] prospectively followed up children previously diagnosed

with SARS-CoV-2 infection at the 3rd, 6th, 12th, 18th, and 24th months following the onset of infection. They found that fatigue was the main persistent symptom, with rates of 13.1% at 3 months, 6.5% at 6 months, 3.8% at 12 months, 2.6% at 18 months, and 3.6% at 24 months post-infection onset. Similarly, a study conducted with 643 Icelandic children diagnosed with SARS-CoV-2 demonstrated that fatigue and loss of concentration were the most reported symptoms, at 22% and 23%, respectively.[23] A systematic review and meta-analysis by Lopez-Leon et al.[24], which included 47.910 patients (aged 17-87 years), reported that the three most common symptoms were fatigue (58%), headache (44%), and attention disorder (27%). Stephenson et al.[25] conducted a longitudinal cohort study in England and found that at three months after testing the top three main symptoms among test positive group were tiredness (39%), shortness of breath (23.4% and headache (23.2%). Consistent with the literature, we found that fatique was the most common persistent symptom in both non-hospitalized and hospitalized children (42.1% and 57.9%, respectively).

Previous studies have shown that SARS-CoV-2 infection can cause neurologic manifestations and increase neurologic complications by more than 30%.[26] Moreover, Ellul et al.[27] demonstrated the presence of SARS-CoV-2 in cerebrospinal fluid in some patients, and Paniz-Mondolfi et al.[28] showed SARS-CoV-2 in frontal lobe tissue obtained during postmortem examination. According to a systematic review, the most common persistent symptoms in children and adolescents were fatigue (2-87%) and headache (3.5-80%). [29] According to a meta-analysis and systematic review from China revealed that the prevalence of neurologic symptoms were 13.51% and headache (15.88%) was third the most common symptom.[30] Similar to the literature, headache was reported as a symptom in 44% of cases by Lopez-Leon et al.[24] In our study, our findings were compatible with the literature, and one of the most frequent neuropsychiatric symptoms was headache particularly in hospitalized patients.

Sleep disturbances, including insomnia or excessive sleepiness, anxiety, depression, mood swings, and irritability are the most frequently reported psychological symptoms associated with long COVID.[8,31] According to a report, mood symptoms were found in 16.5%, and sleep disorders were present in 8.42%, as the most prevalent clinical manifestations associated with long COVID.[8] A study conducted in Italy revealed that pediatric patients with long COVID had sleeping problems (13%) and behavioral-cognitive problems (14%), including anxiety.[32] Miraglia Del Giudice et al.[33] conducted a study with 107 children to assess the impact of COVID-19 infection on behavior and sleep using two standardized questionnaires. They reported that COVID-19 significantly caused mental health issues, including behavior and sleep disorders, among children and adolescents. Furthermore, they found that adolescents were the most affected population including anxiety and depression. It is worth noting that, quarantine regimes, lock down and social distancing may cause negative impact on children's mental health which may confuse the clinician. Consistent with the literature, in the present study, we found that anxiety and sleep disorders were the most frequently reported symptoms in children hospitalized for COVID-19 infection.

Given the high frequency of fatigue, anxiety, sleep disturbances, and headache particularly in children hospitalized for COVID-19, our findings suggest that pediatric patients diagnosed with long COVID may require structured multidisciplinary follow-up care, including pediatric, psychiatric, and neurological assessments. Additionally, school reintegration programs should consider the neurocognitive and emotional challenges these children may face. Educational support, individualized learning plans, and school-based mental health services could be crucial in promoting a successful return to school and preventing long-term academic and psychosocial consequences.

This study has some limitations. Firstly, the follow-up duration was relatively short. Secondly, the study was hospital-based rather than population-based. Finally, we did not differentiate the etiology of neuropsychiatric symptoms, whether they were sequelae of COVID-19 infection or associated with pandemic-related restrictions.

CONCLUSION

This study highlights the long-term effects of COVID-19 on pediatric patients, particularly those hospitalized in the PICU. Our findings suggest that fatigue, anxiety, sleep disorders, and headache were the most prevalent persistent symptoms among hospitalized children, which were more significant compared to non-hospitalized children. These symptoms align with the broader literature on long COVID, underlining the significant impact of the disease on children's physical and mental well-being. These findings support the implementation of structured post-COVID follow-up and the incorporation of psychosocial support services for pediatric patients experiencing persistent symptoms.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 15.06.2022, Decision No: E-460596653-020).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed. Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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