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Original Article

Rehospitalization indications of children hospitalized for COVID-19 infections after discharge: Should we suspect long COVID?

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ABSTRACT

Background. Complications that may develop in children after coronavirus disease 2019 (COVID-19) infections are unknown. The "Long COVID" syndrome is a new process that can also be identified in children. Therefore, in this study, the conditions that may develop in children after COVID-19 infection were discussed, and the indications for rehospitalizations were reviewed.

Methods. This retrospective cohort study was conducted in a tertiary children's hospital in İzmir, Türkiye. All children who were rehospitalized in the study center after discharge, and the indications for readmissions were screened.

Results. Since the beginning of the pandemic, 777 children with COVID-19 infection were hospitalized, including 98 (12.6%) cases rehospitalized for any indication. Fifty-five (56.1%) patients were male, and 43 (43.9%) were female. The mean age of the study population was 79.3±63.5 months (1 month to 17 years). Among these 98 patients, 76 (77.6%) were rehospitalized because of the presence of their primary underlying disease, nonspecific infectious diseases unrelated to COVID-19, and the need to perform certain surgical procedures. The remaining 22 (22.4%) patients presented with symptoms such as fatigue, fever, abdominal pain, and myalgia after the COVID-19 infection. No other underlying cause was detected in approximately one-third of the patients, whose manifestations were found to be consistent with long COVID syndrome.

Conclusions. The findings of acute COVID-19 infection are well characterized, but there is still limited data on its long-term outcomes. The majority of the study population that had no underlying disease were thought to have complications from the COVID-19 infection. Therefore, although the incidence rate of long COVID syndrome in childhood has not been revealed so far, it should be kept in mind among relevant differential diagnoses.

Key words: Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), long COVID, rehospitalization.

After the resolution of the acute infection of coronavirus disease 2019 (COVID-19) in children, some conditions with synchronous involvement of the cardiac, neurologic, or gastrointestinal systems such as Kawasaki-like syndrome, post-COVID syndrome, or multisystem inflammatory syndrome (MIS-C), may be diagnosed in children.[1] However, there is no precise information about the clinical characteristics of the patients or the indications for hospital readmissions of children with COVID-19.[2]

Data on the rates of and indications for rehospitalizations after COVID-19 infection are mainly retrieved from adult reports, and

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it was emphasized that the leading causes for readmissions were thrombotic processes, reactivation, or reinfection of the COVID-19 disease.[3,4] There are currently limited studies concerning the rehospitalization rates of children excluding those with MIS-C or Kawasaki-like syndrome.[5] In addition, the "long COVID syndrome," which is thought to mainly affect adults, may also be identified in children more frequently than suspected.[6,7] However, to the best of our knowledge, there has been no study focusing on the rehospitalization rates of children who were hospitalized because of COVID-19 infection or the role of long COVID syndrome on readmissions.

Therefore, the objective of this study was to evaluate the rates of and reasons for rehospitalizations of children hospitalized with COVID-19, mainly focusing on patients with symptoms associated with long-term sequelae of the COVID-19 infection without any underlying disease.

Material and Methods

This retrospective cohort study was conducted in a tertiary children's hospital in İzmir, Türkiye, during the two-year pandemic period from March 11, 2020, to April 1, 2022.

All children previously hospitalized with the diagnosis of acute COVID-19 infection but rehospitalized after their discharge from the hospital were included in the study. In the first week after discharge, the patients had on-call visits, and complaints (if present) were reviewed. The indications for admission of patients requiring rehospitalization after discharge were screened for COVID-19 infection-related complications. Rehospitalizations of the patients due to their underlying primary diseases other than COVID-19-associated conditions were not discussed in the text. Additionally, patients hospitalized for the first time because of MIS-C were excluded from the study. Diagnoses of SARS-CoV-2 were confirmed in all patients by real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis of nasopharyngeal swabs and/or SARS-CoV-2 antibody testing. The decision to discharge the patient was made in each case according to the patient's clinical improvement and current guidelines.[8]

COVID-19 reinfection is defined in the literature as an infection in the same individual within a different period with evidence of genotypic variance, i.e.,post-discharge infection in an individual with two different viral strains within >45 days in highly suspicious cases of COVID-19 or >90 days in asymptomatic cases or cases with low suspicion.[9]

"Long COVID" is a general term used for people who have recovered from COVID-19 but continue to experience complaints such as headaches, fatigue, sleep disturbance, abdominal pain, myalgia or arthralgia, chest tightness, or pain, anosmia or rash for much longer than expected.[10] Regarding its description, various opinions have been expressed about the timeframe of the symptoms, and the Royal College of General Practitioners has defined long COVID as being characterized by "signs and symptoms developed during or following a disease consistent with COVID-19 that have persisted for more than four weeks and whose presence cannot be explained by other alternative diagnoses.[11] During the diagnostic process, additional ultrasonographic, echocardiographic, and, if necessary cranial imaging and laboratory examinations were performed to rule out other possible causes such as infectious causes, MIS-C, malignancy, neurological disorders, and rheumatological diseases.

Indications for readmissions were screened in all patients throughout the two-year study period after the first diagnosis of the COVID-19 infection.

Patients' data were collected from medical records, including demographic and clinical characteristics (age, gender, symptoms, and medical history), underlying diseases, the interval

between discharge and rehospitalization, the reasons for rehospitalizations, and COVID-19 positivity at the time of their rehospitalizations.

Statistical analysis

Statistical analyzes were performed using SPSS Statistical Software (version 22; SPSS, Chicago, IL, U.S.A.). Data with a normal distribution were expressed as mean±standard deviation (mean±SD). In addition, the chi-square test was used to investigate the correlations among variables (if any). The level of statistical significance was set at $p<0.05$.

Ethics approval for this study was obtained from the Institutional Review Board of Dr. Behcet Uz Children's Training and Research Hospital (decision no: 2021/15-08).

Results

From the beginning of the pandemic until April 2022, 777 children with COVID-19 were hospitalized in the pandemic clinic. Of these, 98 (12.6%) were rehospitalized for any reason. Fifty-five patients were male (56.1%), and 43 were female (43.9%). The mean age of the study population was 79.3±63.5 months (1 month to 17 years).

Among these 98 patients, 76 (77.6%) were rehospitalized because of their primary underlying diseases or a nonspecific infectious disease unrelated to COVID-19 or the need for a certain surgical procedure. Fig. 1 demonstrates the flow chart of the patients included in the study. The most common indication for rehospitalization was the presence of an underlying disease, and the majority of this group consisted of hematology-oncology and bone marrow transplant patients (n:22; 22.4%). Twenty-two (10.2%) patients required palliative treatment, and 7 (7.2%) had a neurological disease. The reasons for hospitalizations and the units they were hospitalized are given in Table I.

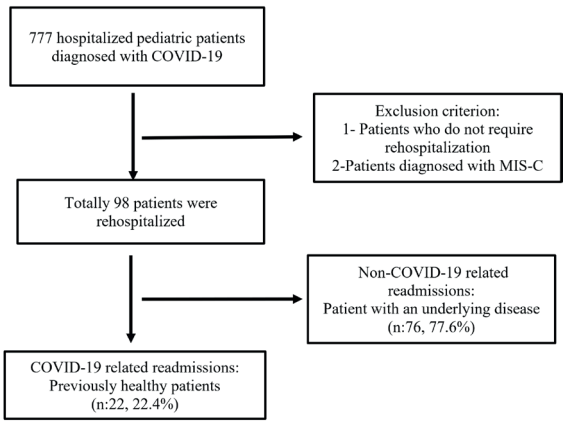

Fig. 1. Distribution of the patients included in the study.

Table I. Reasons for readmission after discharge of patients diagnosed with COVID-19 infection (n=98).

Distribution of rehospitalized patients according to the service	n (%)
Infectious disease unit	22 (22.4%)
Hematology-oncology unit	22 (22.4%)
Surgical unit	13 (13.3%)
Palliative unit	10 (10.2%)
Neurology unit	7 (7.2%)
Other units	24 (24.5%)
Number of patients according to hospitalization reasons	**n (%)**
Underlying diseases	59 (60.2%)
COVID-19 related conditions	22 (22.4%)
Surgical reasons	9 (9.2%)
Non-specific infectious diseases	8 (8.2%)
Total	98 (100%)

Only 22 (22.4%) patients, including 16 (72.7%) male and 6 (27.3%) female cases, were rehospitalized because of probable post-COVID-19-associated conditions. The mean age of these patients was 98.9±68.4 months (range from 2 months to 17 years). The median time interval between the readmission to the hospital after discharge was 32.5 days (range: 3- 521 days). The most common symptoms of presentation were fatigue, myalgia, and fever. In addition, the following symptoms observed were chest pain, severe abdominal pain, diarrhea, vomiting, headache, cough, and syncope (Table II).

Table II. Demographic characteristics and the most common symptoms of patients rehospitalized related to COVID-19 (n=22).

Gender, n (%)	
Male	16 (72.7%)
Female	6 (27.3%)
Age, months (mean±SD)	98.9±68.4
The interval between discharge and rehospitalization, days (median; range)	32.5 days (range 3 to 521 days)
Patients with underlying disease, n (%)	4 (18.2%)
Duration of the first hospitalization, days (mean±SD)	6.9±6.1
Duration of rehospitalization, days (mean±SD)	7±4.6
Number of patients reinfected with COVID-19	3 (13.6%)
Most prevalent readmission signs and symptoms, n (%)	
Fatigue	18 (81.8%)
Myalgia, joint pain	10 (45.4%)
Fever	8 (36.4%)
Chest pain	4 (18.2%)
Severe abdominal pain	4 (18.2%)
Diarrhea, vomiting	4 (18.2%)
Headache	2 (9%)
Cough	1 (4.5%)
Syncope	1 (4.5%)

n: number, SD: standard deviation

Three of the 22 patients who presented with fever or fatigue with RT-PCR test positivity for the delta variant for the second time were followed up in consideration of COVID-19 reinfection. In addition, an RT-PCR positive male patient diagnosed with acute myeloid leukemia (AML) was rehospitalized 21 days after discharge.

Two patients presented with complaints of headache, myalgia, and fatigue. One of them, a 17-year-old boy without concomitant obesity or underlying disease, presented with sudden unilateral vision loss, severe headache, and syncope three months after the onset of the COVID-19 infection. Dural venous sinus thrombosis was detected in his cranial magnetic resonance imaging (MRI), necessitating subcutaneous enoxaparin treatment. This patient was maintained regularly on warfarin treatment after discharge.

One of the four patients who reported chest pain had a history of syncope, and the examinations revealed vasovagal syncope. At admission, another patient diagnosed with myocarditis had elevated serum troponin-c (TnC) and creatinine kinase-myocardial band (CKMB) that returned to average values during follow-up without specific therapy. In addition, increased serum TnC and CKMB levels were detected in the youngest patient of the study, who had been admitted with a fever. Concurrent control electrocardiograms (ECG) were unremarkable, and patent foramen ovale and suspicious myocarditis were observed in the echocardiography (ECHO) of the patient. Therefore, the patient was monitored for myocarditis for three weeks.

Seven patients presenting with common symptoms such as fever, fatigue, and diarrhea did not meet MIS-C criteria based on their medical history, laboratory findings, and physical examination findings. No other underlying infectious, rheumatological causes, or other reasons were observed in their detailed analysis. In addition, six out of 22 (27.3%)

patients (excluding one case) were readmitted at least three weeks after hospital discharge. While fatigue and myalgia were the main findings in these patients, cough, diarrhea-vomiting, joint pain, and fever were other accompanying findings.

The last four patients presented with severe abdominal pain, accompanied by fatigue or fever, and were diagnosed with acute appendicitis. The diagnosis of appendicitis was confirmed with a histopathology examination. In addition, perforated phlegmonous appendicitis was detected in two of them. Therefore, these patients were referred to the general surgery department after detailed radiological examinations and biochemical tests. The clinical characteristics of hospitalized patients associated with COVID-19 are detailed in Table III.

Discussion

Variable symptoms have been identified in people after the COVID-19 infection at varying time intervals. However, the most common symptoms of this condition, which have received epidemiologically different definitions, are fatigue, shortness of breath, chest pain, myalgia, and cognitive dysfunction, which

Table III. Clinical characteristics and readmission reasons of patients requiring rehospitalization caused by COVID-19-related-conditions.

Case number	Sex	Age (months)	Underlying diseases	Time from positive to second hospitalization (days)	Presentation symptoms	COVID-19 reinfection
Case 1	M	96	Panic disorder	8	Chest pain, fatigue, myalgia	N
Case 2	M	36	N	236	Fever, fatigue, cough	N
Case 3	F	24	N	32	Fever, fatigue	N
Case 4	F	2	N	4	Fever	N
Case 5	M	144	N	16	Fatigue, severe abdominal pain, myalgia	N
Case 6	M	156	N	38	Chest pain, fatigue, myalgia	N
Case 7	F	144	N	6	Chest pain, fatigue, syncope, myalgia	N
Case 8	M	204	N	87	Headache, fatigue, syncope, myalgia	N
Case 9	M	156	Asthma	521	Fatigue, myalgia	Y
Case 10	M	168	Obesity	16	Headache, fatigue, vomiting-diarrhea, myalgia	N
Case 11	F	96	N	125	Fatigue, diarrhea, myalgia	N
Case 12	M	60	N	447	Fatigue	Y
Case 13	F	108	N	39	Fever, fatigue, severe abdominal pain	N
Case 14	M	2	N	3	Fatigue, vomiting	N
Case 15	F	120	N	10	Chest pain, fatigue, myalgia	N
Case 16	M	7	N	30	Fever, fatigue, diarrhea	N
Case 17	M	204	N	33	Fatigue, myalgia, joint pain	N
Case 18	M	8	N	18	Fever, diarrhea	N
Case 19	M	22	Tay-Sachs	64	Fever	Y
Case 20	M	108	AML	21	Fatigue	N
Case 21	M	132	N	44	Fatigue, severe abdominal pain	N
Case 22	M	180	N	175	Fever, severe abdominal pain	N

F: Female, M: Male, AML: Acute myeloid leukemia, N: None, Y:Yes

cannot be explained otherwise and impact daily life.[12] Although adult studies on this condition are frequently cited in the literature, pediatric studies are rarely mentioned.[2] Therefore, this study screened the indications for rehospitalizations after discharge of the patients due to the COVID-19 infection. In this study, 98 (12.6%) of the 777 patients diagnosed with COVID-19 infection were rehospitalized for different indications. Of these 98 patients, only 22 (22.4%) were hospitalized with a cause associated with COVID-19, and the remaining patients were rehospitalized due to their underlying diseases.

Similar to the literature[10,13], the most common presenting symptoms were fatigue, myalgia, and fever in our report, followed by chest pain, severe abdominal pain, diarrhea, vomiting, headache, cough, and syncope. These symptoms are also seen in other diseases, so it must not be forgotten that the diagnosis of post-COVID or long COVID should be considered a diagnosis of exclusion.

In the current study, COVID-19 reinfection was detected in three patients. While more adult studies[14] on COVID-19 reinfection have been published, studies on children have rarely been performed. While there is a case report[15] of COVID-19 reinfection in three children with underlying cancer in the literature, unlike our study, only one of these three patients had an underlying metabolic disease. In our study, a patient with acute myeloblastic leukemia (AML) was hospitalized again due to fatigue on the 21st day of his SARS-CoV-2 RT-PCR positivity. However, the patient whose SARS-CoV-2 RT-PCR positivity continued was not considered a COVID-19 reinfection. So in this report, the cause of these reinfections was associated with the emergence of new strains rather than underlying conditions.

One patient was hospitalized to investigate the causes of headache and loss of vision, he did not have any organic pathology such as hypertension, obesity, diabetes mellitus, etc., and a dural sinus venous thrombosis was detected in his cranial imaging. Hypercoagulation with vascular endothelial damage and the consequent risk of venous and arterial thrombotic complications are well-known and common findings that may accompany COVID-19 for a long time.[16] Pediatric hematologists have developed guidelines for thromboprophylaxis as cases of thrombosis concurrent with COVID-19 have increased. However, these guidelines were based on extrapolation of adult data and were not supported by data on the incidence of or risk factors for thrombosis in children or adolescents with acute or post-COVID-19.[17] A patient from the literature developed thrombosis 30 days after discharge, similar to our study. This study reported that age ≥12, cancer, central venous catheters, and MIS-C were significantly associated with thrombosis.[18] Similar to our case, he was an adolescent, but differently; he had an underlying cancer disease and a central venous catheter. As another cause of thrombosis, concomitant D-dimer elevation has been reported in patients diagnosed with COVID-19.[19] Unlike these reports, in our case, D-dimer and other coagulation parameters were within normal limits both during COVID-19 positivity and when the dural venous sinus thrombosis was detected. Therefore, no anticoagulant prophylaxis was initiated when the diagnosis of COVID-19 was made because the patient had no underlying risk factors. However, once thrombosis was detected, subcutaneous enoxaparin treatment was initiated, and the patient was maintained on regular warfarin treatment after discharge.

Chest pain and heart failure were also important reasons for readmission within the first 14 days after discharge and in the long term.[20] Four patients presented with chest pain as the primary complaint in our study within the first two weeks of their COVID-19 positivity. In our study, the most common symptom was chest pain detected on cardiac evaluation after acute COVID-19 infection, similar to the relevant literature findings.[21] In addition, similar to our research, ECHO findings were completely normal in the cited study, but differently,

sinus bradycardia was detected on the ECG of a smaller number of patients, and it has been stated in the literature that there is no routine ECG and echo requirement in asymptomatic children.[21] However, another issue that should not be forgotten is that myocarditis results in sudden death among children.[22] Diagnosis and treatment of myocarditis are controversial in pediatric patients, and clinical findings, ECG, elevated troponin levels, cardiac enzymes, and echo are helpful diagnostic tools.[23] During the pandemic, elevations of cardiac enzymes such as TnC and CKMB caused anxiety in patients infected with COVID-19. In the pediatric age, the role of troponin in myocarditis has been much less defined than in adults. However, data on increased troponin I levels as a marker of myocardial injury in children is still accumulating.[24]

Although cardiological involvement in children with COVID-19 is rarely seen, it should be emphasized that all pediatric patients should be evaluated in terms of cardiologic abnormalities.[21] In the example given in our study, a 6-fold increase in cardiac enzymes was detected in an infant who presented with a history of fever, weakness, and vomiting, and he was followed up and treated in favor of myocarditis with additional cardiological evaluation.

Gastrointestinal (GI) symptoms, such as diarrhea and abdominal pain, are prevalent features of the SARS-CoV-2 infection. Moreover, case reports of appendicitis have been reported in the literature in SARS-CoV-2-positive patients.[25,26] Four patients in our report presented with severe abdominal pain and were diagnosed with appendicitis. In the literature, cases of perforated appendicitis accompanying COVID-19 were mainly emphasized, and their presence was attributed to delays in diagnosis.[27]

Similarly, two of the four cases of appendicitis detected in our study were perforated. In addition, a study by Malhotra et al.[28] compared the cases with SARS-CoV-2 infection having a longer duration of symptoms before admission with those SARS-CoV-2 negative patients. According to the study, the presence of intense inflammation raises the risk of rupture. Likewise, it is unknown whether a COVID-19 infection accompanied by an exaggerated inflammatory response is also a potential trigger for appendicitis. Although the triggering mechanism of appendicitis has not been clarified yet, clinicians should be informed that appendicitis may occur in children as an infectious manifestation of the SARS-CoV-2 infection.

Long COVID syndrome is another current issue with the COVID-19 pandemic, and data on pediatric patients has just begun to be presented. Although no universally accepted definition of this syndrome exists, persistent fatigue, shortness of breath, cough, joint pain, chest pain, myalgia, headache, and other symptoms following COVID-19 should be considered if they cannot be attributed to another cause.[7] Studies focusing on long COVID syndrome in children are rare, despite evidence showing that children and young people are also affected by long COVID syndrome.[2] Similar to the literature[29], fatigue, and myalgia were the most prevalent readmission symptoms of long COVID in this report. The median time interval between readmission to the hospital and hospital discharge was 32.5 days, while it was longer in other studies, which were associated with discrepancies in inclusion criteria. Unlike other studies, this report included all readmitted patients and long COVID cases to evaluate post-COVID complications.

Some considerations should be noted when interpreting the results. Firstly, this was a retrospective study with inherent limitations compared to randomized trials. Secondly, only hospitalized patients were evaluated, and outpatients were excluded from the study.

However, it must be emphasized that the current study is the first report characterizing pediatric patients with COVID-19 who were followed up for a long time and readmitted after discharge in case of need.

In our study, patients readmitted with one of the symptoms of COVID-19 after discharge were discussed, and other underlying indications for readmissions were screened. As previously stated, three patients had reinfections, and four had appendicitis. The medical histories of all the remaining COVID-19 patients revealed that their symptoms persisted after their discharge from the hospital. However, all of the cases included in the study, as well as patients with appendicitis, are thought to have complications associated with the COVID-19 infection. In addition, the duration of symptoms, like the definition of long COVID syndrome, is not delineated, and in our study, the course of symptoms was variable. In conclusion, further research on complications that may arise after COVID-19 infection, precise definitions, and durations of long COVID syndrome are required.

Ethical approval

Ethics approval was obtained from the Institutional Review Board of Dr. Behcet Uz Children's Training and Research Hospital (decision no: 2021/15-08).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: EC, İD, NB; data collection: EB, EK, MG, AAK, ŞŞ, MYÇ, GGÖ; analysis and interpretation of results: EC, İD; draft manuscript preparation: EC, İD, NB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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