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Evaluation of the Clinical and Laboratory Findings of Asthmatic Children with SARS-CoV-2 Infection

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Asthma · Child · Coronavirus disease 2019 · Coronavirus

Abstract
Introduction: There are a limited number of studies about the clinical findings of coronavirus infection in pediatric patients with asthma. We aimed to evaluate the clinical and laboratory characteristics of pediatric patients with asthma and healthy children without chronic disease who infected with SARS-CoV-2. ***Methods:*** This is a retrospective, case-control study comparing the asthma diagnosed and healthy children who were diagnosed as COVID-19 in our hospital between March 11 and November 10, 2020. ***Results:*** During the study period, 6,205 children were diagnosed with COVID-19 in our hospital. Only 54 (0.87%) patients had a diagnosis of asthma. The mean of the age was 10.5 years and 53.7% (*n*:29) of the patients with asthma were male. Cough, shortness of breath, emesis, and diarrhea were found to be significantly higher in asthma group than in the control group (respectively $p = 0.002$, 0.000, 0.002, 0.019, 0.015). Patients who were given SABA was significantly higher in asthma diagnosed patients ($p = 0.000$). Hospitalization was significantly higher in asthma group ($p = 0.025$), and the duration of hospitalization was significantly higher in control group ($p = 0.034$). There was no significant difference between the 2 groups in terms of requiring oxygen treatment and in laboratory findings between groups. ***Conclusion:*** This study revealed that pediatric patients diagnosed with asthma were in a mild clinic. According to these findings, asthma may not affect the course of the COVID-19 in children.

Introduction

SARS-CoV-2 is a new corona virus responsible for a pandemic called COVID-19. COVID-19 causes serious acute respiratory syndromes that can cause significant morbidity and mortality [1].

The spectrum of diseases caused by the coronavirus can range from the common cold to severe acute respiratory syndrome. In a systematic review, 1–5% of the patients diagnosed with COVID-19 were reported to be pediatric cases. Clinical manifestations in children are milder than in adults, and death due to coronavirus has been

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rarely seen in children [2, 3]. According to CDC (Center for Disease Control and Protection), 8.1% of the patients infected with COVID-19 were children, and the mortality rate in children was <0.1% [4].

Comorbidities such as hypertension, chronic obstructive pulmonary disease, diabetes mellitus, and obesity have been reported to affect the prognosis of COVID-19 [5]. According to Choi et al. [6], asthma was observed to lead poor outcomes and the mortality rate for COVID-19 patients with underlying asthma was significantly higher than other patients.

Asthma is the most common chronic disease seen in children, and its prevalence is increasing [7]. According to CDC, those with moderate and severe asthma are in the risk group for coronavirus infection. COVID-19 can affect the nose, throat, and lungs, causing asthma attack, pneumonia, and acute respiratory disease [8]. It is known that viral infections especially rhinovirus, RSV, and influenza can cause asthma attack [9]; however, it not yet clear whether asthma is a risk factor for COVID-19. In the previous coronavirus pandemics (SARS-CoV and MERS-CoV), asthma was not a risk factor for these infections [10]. There are limited studies on the prevalence, clinical symptoms, severity of COVID-19, and findings after improvement of infection in COVID-19 pediatric patients with asthma. In studies, the prevalence of asthma in adults and children diagnosed with COVID-19 was between 0.3–17.9 and 0–14%, respectively [2, 11–17]. We aimed to evaluate the clinical and laboratory characteristics of pediatric patients with SARS-CoV-2 infected asthma and healthy children compatible with the case group without chronic illness.

Methods

This is a retrospective, case-control study comparing the asthma diagnosed and healthy children who were diagnosed as COVID-19 in our hospital between March 11 and November 10, 2020. All of the patients diagnosed as asthma were included in the study. The age and gender similar control group without chronic disease was included in the ratio of 1:3. The COVID-19 diagnosis of the patients was made according to the reverse transcription-polymerase chain test of the nasopharyngeal and throat swabs. We collected data from medical records including medical history, demographic information such as age, gender, symptoms of COVID-19, time of onset of symptoms, the physical examination at admission, information on hospitalization, medications prescribed for COVID-19 treatment, laboratory examinations, and imaging tests which were performed for healthy control group and patients with asthma.

For patients diagnosed with asthma, we also collected data on the age of asthma diagnosis, atopy status, presence of asthma attack in the last year and the use of asthma medication in the last 3 months, the use of asthma medications in COVID-19 and the GINA asthma control in the last 3 months [18]. All the asthma diagnosed patients were called for evaluations of symptoms (cough, shortness of breath, and any other symptom) after recovery from COVID-19.

The criteria of hospitalization and treatments were applied in accordance with the Ministry of Health guidelines. During the first months of the pandemic, all COVID-19 patients were hospitalized without any treatment. The criteria were updated periodically in the following months. Later, patients with risk factors such as pneumonia and chronic diseases (cardiac diseases, chronic respiratory diseases, renal diseases, diabetes, and metabolic diseases) and immunodeficiencies were treated [19]. The study protocol was approved by the Institutional Ethics Committee of City Hospital (E2-20-72).

Statistical Analysis

SPSS 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Results were expressed as percentile (absolute numbers), as mean and standard deviation, or as median and interquartile range as required. χ^2 test was performed to compare the categorical variables, Mann-Whitney test was used to compare the non-normally distributed continuous variables, and the independent *t* test was used for normally distributed continuous data. p value <0.05 was considered statistically significant.

Results

There were 6,205 pediatric COVID-19 patients monitored in our hospital until 10 November. Fifty-four patients (0.87%) of them were diagnosed with asthma. As there were 54 patients in the case group, 162 patients were included in the control group.

In 54 patients with asthma, only 18 (33.3%) of the patients with asthma were atopic. Seventeen (31.5%) patients had concomitant allergic disease. Before the diagnosis of COVID-19, 23 (42.7%) of the patients with asthma were using asthma medication and 16 of these patients were using it irregularly. While taking the medication, 15 (27.8%) of the patients were using a metered dosed inhaler and 3 (5.6%) of the patient were using a dry-powder inhaler. In the last year, 2 (3.7%) of the patients developed an asthma attack. None of the patients were hospitalized for asthma in the last year. According to GINA guideline in the last 3 months prior to the diagnosis of COVID-19, asthma control data for only 46 patients were available. Thirty-six (66.7%) of the patients were defined as well controlled (Table 1).

There was no significant difference between the groups that were using asthma medication and were not using, and between the asthma controlled and not controlled group (both partly and uncontrolled) in the terms of hav-

Table 1. Demographic and clinical characteristics of patients diagnosed with asthma (n = 54)

	Patients with asthma
Age	
Age, yr, median (IQR)	10.5 (7–15)
Age at diagnosis of asthma, yr, median (IQR)	4 (1–9)
Gender (female/male)	0.86
Male, *n* (%)	29 (53.7)
Concomitant allergic diseases, *n* (%)	17 (31.5)
Allergic rhinitis	13 (24.1)
Food allergy	3 (5.6)
Atopic dermatitis	1 (1.9)
Chronic urticaria	1 (1.9)
Family member having allergic disease, *n* (%)	14 (25.9)
Atopy status, *n* (%)	
Aeroallergen sensitization	18 (33.3)
Pollen	12 (22.2)
House dust mite	7 (13)
Mold	2 (3.7)
Cat and dog dander	3 (5.6)
Cockroach	1 (1.9)
Used asthma maintenance therapy before COVID-19, *n* (%)	
Patients used asthma medications	23 (42.7)
Only using ICS	11 (20.4)
Only using antileukotrienes	5 (9.3)
Both using ICS and antileukotrienes	6 (11.1)
Both using ICS and LABA	1 (1.9)
Admission to clinic control during pandemic, *n* (%)	
Patients admitted to control for asthma	14 (25.9)
Asthma control, *n* (%)	
GINA assessment of asthma in the last 3 mo (*n*:46)	
Well controlled	36 (66.7)
Partly controlled	5 (9.3)
Uncontrolled	5 (9.3)
Patients having asthma attack in the last 1 yr	2 (3.7)

IQR, interquartile range; ICS, inhaled corticosteroids.

ing symptoms of COVID-19, being hospitalized for COVID-19, prescribing treatment for COVID-19, requiring oxygen and steroid treatment, having pathologic imaging findings, and having symptoms after improving of COVID-19 ($p > 0.05$).

Fourteen (25.9%) of the patients with asthma were hospitalized due to COVID-19 and 12 (22.2%) were treated. Four of the patients required oxygen treatment. None of the patients required intensive unit care. Systemic steroid treatment was given to 3 of the patients. Two of the patients were given due to an asthma attack and 1 patient for angioedema and urticaria. These 2 patients were in the uncontrolled group according to GINA guidelines.

Ten of the patients, who did not receive treatment, were started asthma medication after COVID-19. In 1 patient's drug was adjusted as an increasing the step.

Forty-six patients with asthma were reached after improvement of COVID-19. Ten (18.5%) of the patients had symptoms after recovery from COVID-19. Cough (*n*:3), fatique (*n*:2), headache (*n*:1), and chest tightness (*n*:1) were observed (Table 2).

Comparison of Patients with Asthma and Control Group

The findings of the asthma diagnosed and control group are given in Table 2. Fifty-one (94.4%) of the patients with asthma and 139 (85.8%) of the patients in the control group had COVID-19 symptoms at the admission. Cough, shortness of breath, emesis, diarrhea, and loss of appetite were found to be statistically significantly higher in the group with asthma (respectively, $p = 0.002$, 0.000, 0.002, 0.019, and 0.015). The duration of symptoms before admission to the hospital was statistically significantly higher in the group diagnosed with asthma ($p = 0.016$) (Table 2).

Physical examination findings of the asthma diagnosed and control group are given in Table 2. Eleven (20.4%) of the patients with asthma and 48 (29.6%) of the patients in control group had a pathological physical examination. There was no significant difference between 2 groups in the terms of having hypoxia, tachypnea, rales, and ronchus ($p > 0.05$).

There was no significant difference between 2 groups in the terms of receiving treatment. Patients given SABA were found to be statistically significantly higher in the asthma diagnosed group ($p = 0.000$) (Table 2). Hospitalization was significantly higher in asthma group ($p = 0.025$), and the duration of hospitalization was significantly higher in control group ($p = 0.034$). There was no significant difference between the 2 groups in terms of requiring oxygen treatment and in laboratory findings between groups (Table 2).

Laboratory tests were performed significantly more in the asthma group ($p = 0.007$). In laboratory tests, there was no significant difference in complete blood counts, acute phase reactants (C-reactive protein level, procalcitonin level, and ferritin level) between the 2 groups (Table 3).

One of the patients diagnosed with asthma was admitted to our hospital with COVID-19 symptoms again 4 months after her first coronavirus infection. On her first admission, she had fever, cough, shortness of breath, vomiting, and diarrhea. On the second admission, she

Table 2. During COVID-19, clinical, laboratory, and treatment features of the patients with and without asthma

	Patients diagnosed with asthma (n = 54)	Patients not diagnosed with asthma (n = 162)	p value
Age			
Age, yr, median IQR	10.5 (7–15)	11.5 (7–15)	0.863•
Gender, *n* (%)			
Male	29 (53.7)	85 (52.5)	0.875
Contact history, *n* (%)			
Family cluster	24 (44.4)	90 (55.6)	0.157
Unidentified source of infection	30 (55.6)	72 (44.4)	
Symptoms at admission			
Having symptoms, *n* (%)	51 (94.4)	139 (85.8)	0.091
Duration of symptoms before admission to hospital, days, mean ± SD	2.97±2.18	2.11±1.43	**0.016**•
Symptoms♦, *n* (%)			
Fever	13 (27.5)	84 (51.9)	0.814
Throat pain	10 (18.5)	43 (26.5)	0.235
Cough	32 (59.3)	57 (35.2)	**0.002**
Short of breath	12 (22.2)	7 (4.3)	**0.000**
Chest tightness	1 (1.9)	6 (3.7)	0.683*
Rhinorrhoea	6 (11.1)	11 (6.8)	0.307
Nonrespiratory system symptoms	32 (59.3)	79 (48.8)	0.181
Emesis	10 (18.5)	8 (4.9)	**0.002**
Vomiting	8 (14.8)	10 (6.2)	0.47
Abdominal pain	2 (3.7)	11 (6.8)	0.525*
Diarrhea	13 (24.1)	18 (11.1)	**0.019**
Joint pain	6 (11.1)	16 (9.9)	0.795
Myalgia	2 (3.7)	7 (4.3)	1*
Headache	5 (9.3)	30 (18.5)	0.110
Fatique	9 (16.7)	26 (16)	0.915
Loss of smell or taste	2 (3.7)	8 (4.9)	1*
Loss of appetite	3 (5.6)	0 (0)	**0.015***
Physical examination, *n* (%)			
Having pathologic physical finding	11 (20.4)	48 (29.6)	0.186
Having hypoxia	3 (5.6)	2 (1.2)	0.101*
Having tachypnea	1 (1.9)	4 (2.5)	1*
Having rales	0	2 (1.2)	1*
Having ronchus	2 (3.7)	1 (0.6)	0.155*
Treatment, *n* (%)			
Patients being given drugs during COVID-19	12 (22.2)	25 (15.4)	0.251
Favipiravir	1 (1.9)	2 (1.2)	
Hydroxychloroquine	2 (3.7)	1 (0.6)	
Oseltamivir	2 (3.7)	0	
Antibiotic	7 (13)	22 (13.6)	0.908
Short-acting beta-agonists	11 (20.4)	2 (1.2)	**0.000***
Systemic steroid	3 (5.6)	2 (1.2)	0.097*
Hospitalization			
Hospitalized, *n* (%)	14 (25.9)	21 (13)	**0.025**
Duration of hospitalization, days, mean	3.6	5.5	**0.034**°
Hospitalized in intensive care unit, *n* (%)	0	1 (0.6)	
Requiring oxygen, *n* (%)	4 (7.4)	5 (3.1)	0.232*
Requiring oxygen via high flow nasal oxygen, *n* (%)	0	2 (1.2)	

Table 2 (continued)

	Patients diagnosed with asthma (n = 54)	Patients not diagnosed with asthma (n = 162)	p value
Imaging tests, n (%)			
Having chest graphy	42 (77.8)	96 (59.3)	**0.014**
Having pathologic radiographic findings	19 (35.2)	49 (30.2)	0.494
Infiltration	4 (7.4)	13 (8)	
Ground glass opacity	0	2 (2.1)	
Stripe shadowing	10 (18.5)	17 (10.5)	
Hilar enlargement	5 (9.3)	17 (10.5)	
Having thorax CT	3 (5.6)	3 (1.9)	0.167*
Infiltration	2 (3.7)	3 (1.9)	0.10*
Ground glass opacity	2 (3.7)	2 (1.2)	1*

IQR, interquartile range. χ^2 test. *Fisher test. •Mann-Whitney test. °Student t test/Independent T test. ♦Column percentage.

Table 3. Laboratory findings of patients with and without comorbid asthma

Laboratory findings	Patients diagnosed with asthma (n = 54)	Patients not diagnosed with asthma (n = 162)	p value
Laboratory test performed, n (%)	40 (74.1)	86 (53.1)	**0.007**
Total white blood cell count, median, IQR	5,205 (4,275–7,680)	5,960 (4,572–7,772)	0.708•
Serum haemoglobin level, mean, ±SD	14 (±1.48)	13.7 (±1.55)	0.341°
Serum neutrophil level (absolute number), median, IQR	2,920 (2,332–4,312)	2,900 (1,935–4,622)	0.379•
Serum lymphocyte level (absolute number), median, IQR	1,760 (1,197–2,382)	1,845 (1,477–2,565)	0.263•
Serum eosinophil level (absolute number), median, IQR	70 (40–140)	50 (30–100)	0.079•
Serum eosinophil level (percent), median, IQR	1.30 (0.70–2.60)	1.10 (0.4–1.72)	0.137•
Serum platelet level, mean, ±SD	273.000 (±83.000)	263.000 (±66.000)	0.480°
C-reactive protein level, median, IQR	0.003 (0.0006–0.007)	0.003 (0.0019–0.007)	0.377•
Procalcitonin level, median, IQR	0.02 (0.003–0.495)	0.035 (0.030–0.05)	0.269•
Ferritin level, median, IQR	36 (13–43)	33 (18–45)	0.902•
APTT level, mean, ±SD	26.5 (±2.17)	26.3 (±2.52)	0.677°
INR level, median, IQR	1.03 (0.99–1.11)	1.03 (1–1.10)	0.994•
D-dimer level, median, IQR	0.3 (0.20–0.63)	0.41 (0.22–0.65)	0.425•
AST level, mean, ±SD	24.2 (±10.6)	24.2 (±11.5)	0.990°
ALT level, median, IQR	17 (14–24)	18 (15–22)	0.636•
Serum urine level, median, IQR	24 (21.2–27.9)	24 (21–28)	0.717•
Serum creatinine level, mean, ±SD	0.57 (±0.20)	0.55 (±0.18)	0.549°

IQR, interquartile range. χ^2 test. •Mann-Whitney test. °Student t test/Independent T test.

had loss of smell and taste, joint pain, and shortness of breath, and PCR test was resulted positive in second time. We included the symptoms of the first admission to our study. She was not hospitalized on both admissions and also had no asthma attack. All patients diagnosed with COVID-19 in the asthma and control group recovered.

Discussion

In our study, among 6,205 patients, only 54 (0.87%) of COVID-19 patients were diagnosed with asthma. The clinical course was mild in both groups.

There are substantial global variations in the prevalence of asthma in children between countries [20]. In 2 studies from Turkey, the prevalence of asthma in children

was found to be 8.6–12.6% [21, 22]. Whether patients with asthma are at higher or lower risk of being infected with COVID-19 may depend on geography, age, other multi-morbidities, genetic predispositions, ethnicity, social behavior, and access to healthcare or other factors [23]. Studies on the prevalence of asthma in pediatric COVID-19 patients were limited. In studies, the prevalence of asthma in pediatric and adult COVID-19 patients was between 0 and 17.9% (12–15). According to Bialek et al., among 345 pediatric patients infected with coronavirus, the most common underlying condition was observed to be chronic lung disease (including asthma). Forty (11.5%) of the patients had chronic lung disease, and the authors did not quantify exact prevalence of asthma [24]. According to Hui et al. [2], among 182 pediatric patients with COVID-19, only 1 (0.54%) had asthma. In a study conducted in New York and UK, the prevalence of asthma among 5,700 and 16,749 pediatric and adult hospitalized patients for COVID-19 was 9 and 14%, respectively [11, 16]. A multicenter cohort study involving 82 participating centers in 25 European countries reported that among 582 COVID-19 pediatric patients, 2.7% (*n*:16) had asthma [17]. In our study, there were 54 (0.87%) patients diagnosed with asthma in COVID-19 patients among 6,205 pediatric patients. The lower prevalence of asthma in pediatric COVID-19 patients may be due to the milder course of children in COVID-19. Compared to adults, most infected children appear to have a milder clinical course and asymptomatic infections are common [13]. Asymptomatic patients may not be included in the studies as they will not be admitted to the hospital. Patients are better protected due to doing better hand cleaning and using of masks, hence they may have reduced the frequency of attacks [25]. The closure of schools in our country due to the pandemic may have led to the protection of our patients with asthma from COVID-19.

In several studies, it was observed that there was no significant difference between the patients with and without asthma in adult and pediatric COVID-19 patients in terms of duration of hospitalization [5, 26–28]. In our study, 14 (25.9%) of the patients were hospitalized in asthma group. In our study, hospitalization was significantly higher in asthma group but duration of hospitalization was significantly higher in control group.

There are studies reporting insufficient and delayed natural antiviral immune response as a result of deficiency and delay in the lung cell interferon (IFN)-α, IFN-beta, and IFN-λ responses in patients with asthma, and IFN deficiency responsible for the increase in asthma severity [9]. There is also a risk that viruses especially rhinovirus, RSV, and influenza may cause asthma exacerbations. Thus COVID-19 should trigger viral-induced asthma exacerbations [29]. It is also known that if asthma is not well controlled, the severity of exacerbation caused by virus worsens depending on the degree of lack of control [7]. In our study, the clinical course of all COVID-19 patients diagnosed with asthma was mild. Most of the patients in this group (36 [66.7%]) were well controlled, and this may have caused a mild clinical course in COVID-19. In 2 patients who had required systemic steroid for asthma attack during COVID-19, were in the uncontrolled group according to GINA guidelines. The low number of uncontrolled patients may have caused no difference in clinical and hospitalization in the COVID-19 case and control group in this study.

In a study, ACE2 gene expression was investigated in patients with asthma because SARS-CoV-2 binds to the ACE2 receptor and enters the cell. Allergic sensitization, type 2 biomarkers, and IL-13 expression in the nasal epithelium and ACE2 gene expression in the nasal epithelium were inversely related to COVID-19 [21]. In addition, with the use of inhaled corticosteroids, ACE2 level, and transmembrane protease serine 2 were found to be decreased in the sputum of patients with asthma [22]. Another study found no difference in ACE2 levels between healthy controls and patients with a diagnosis of asthma [30]. Due to the limited studies on this subject, the rate and prognosis of coronavirus infection in patients with asthma are still uncertain.

In ARIA-EAACI statement on asthma and COVID-19, it was recommended to remain on and continue maintenance of asthma medications such as inhaled corticosteroids or antileukotrienes, during COVID-19 if they are well controlled. Reducing or suspending use of controller asthma medications can worsen asthma control and increase the risk of severe exacerbations [23]. According to Hui et al., it was reported that hospitalization did not increase in patients diagnosed with asthma compared to those without asthma, and it also did not increase in patients with asthma using inhaler medications compared to those who did not [5]. In our study, 23 (42.7%) of the patients were using asthma medication and had a mild clinical course in COVID-19. However, patients who did not use asthma medication also followed a mild clinical course.

In the ARIA-EAACI statement, it is recommended to use systemic steroids in COVID-19 infected asthma patients for an asthma attack during the pandemic [23]. In our study, 2 of the patients required systemic steroid for asthma attack.

According to Hui et al. [2], there was no significant difference in symptoms of COVID-19 between the pediatric patients with and without allergic disease. In our study, cough, and shortness of breath and in non-respiratory symptoms, emesis, and diarrhea were found to be statistically significantly higher in the group with asthma.

According to Hui et al. [2], there was no significant difference between the pediatric patients with and without having allergic diseases in terms of treatments that were given during COVID-19. In our study, patients who were given SABA were found to be statistically significantly higher in asthma diagnosed patients.

According to Chibba et al. [5], white blood cell count and eosinophil count did not differ significantly between COVID-19 adult patients with and without asthma. Unlike these studies, according to Green et al. [28], COVID-19 patients with asthma had significantly higher eosinophil levels. In some studies, eosinopenia was observed in COVID-19 patients, which was more prominent in severe patients than in mild patients [31]. Ferastraoaru, in patients having asthma, eosinophilia (AEC >150 cells/μL) was observed to be protective from COVID-19-associated hospitalization and was associated with reduced mortality during hospitalization [32]. In our study, laboratory findings did not differ between groups. A mild clinical course was observed in our pediatric COVID-19 patients diagnosed with asthma, therefore eosinopenia was not observed. Further studies are needed to confirm the theoretical protective role of eosinophils in SARS-CoV-2 infection and the potential impact of allergy-induced eosinophilic inflammation on the course of COVID-19 disease.

According to Leung, there are adverse health outcomes in short- and long-term due to COVID-19. Major adverse outcomes were found to affect different body systems: immune system, respiratory, cardiovascular, and neurological system, cutaneous and gastrointestinal manifestations, impaired hepatic and renal function. In long-term of respiratory system, impairment of pulmonary functions and reduced exercise capacity were observed [33]. In our study, after improvement from COVID-19, in the group with asthma, symptoms were observed in only 10 patients. Cough (*n*:3) and dyspnea (*n*:4) were observed The limitation of the study is that the sample of pediatric patients diagnosed as asthma is relatively small.

There is limited research on the clinic and prognosis of pediatric patients diagnosed with asthma in COVID-19. In our study, we investigated that cough, shortness of breath, and the use of SABA were higher in children with asthma compared to the control group. There was no significant difference between the 2 groups in terms of requirement of oxygen.

This study demonstrated that pediatric patients with asthma had a mild clinic in COVID-19, and asthma was not a risk factor for developing and severity of COVID-19 and did not affect the disease course of COVID-19. COVID-19 infected pediatric asthma patients had mild clinic and good prognosis.

Statement of Ethics

The study protocol was approved by the Institutional Ethics Committee of City Hospital (E2-20-72). Obtained informed consent was taken from parents.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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Author Contributions

Azize Pınar Metbulut made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafted the article or reviewed it critically for important intellectual content; Özlem Mustafaoğlu, Gülşah Şen, and Saliha Kanık Yüksek made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, İlknur Külhaş Çelik and Halise Akça drafted the article or reviewed it critically for important intellectual content. Prof Dibek Mısırlıoğlu had given final approval of the version to be published and agreed to be accountable for all aspects of the work related to its accuracy or integrity.

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