The Turkish Journal of Pediatrics 2022; 64: 1031-1040
https://doi.org/10.24953/turkjped.2022.545

Original Article

Clinical and radiologic manifestations of *Mycoplasma pneumoniae* infection in children

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ABSTRACT

Background. *Mycoplasma pneumoniae* (MP) is one of the most important etiological agents of community-acquired pneumonia in children.

Methods. The medical records of children with an MP infection between 2008 and 2015 were reviewed for their clinical, laboratory radiological features.

Results. This study included 244 patients (male 57.4%) with a median age of 80.5 months (IQR, 46.5-120 months). A total of 78 (32%) patients were < 5 years old, and 166 (68%) were ≥ 5 years old. The most common complaints before admission to the hospital were cough (84.8%), fever (57.4%), and weakness (18.9%). In the <5 years old age group, oxygen saturation was lower, and tachypnea was more common than in the ≥ 5 years old age group (p=0.02 and p=0.05, respectively). Similarly, the physical findings such as the prolonged expiration, presence of retractions, and rhonchi were more frequent in the < 5 years old age group (p=0.001, p=0.000, p=0.02, respectively). Extrapulmonary manifestations were present in 45 (18.4%) patients, and skin involvement was the most common one (7.7%). Two hundred-thirty-eight (97.5%) patients had chest radiographs, and 45 (18.4%) had normal radiography. The most common radiological involvement was peribronchial infiltration (n=70, 28.7%). Of the patients, 147 (60.2%) were hospitalized, and 97 (39.7%) were followed up as outpatients. It was determined that 156 (63.9%) patients had commenced macrolide empirically, and 61 (25%) patients were treated with positive serology results.

Conclusions. The prolonged fever, cough and expiration time, wheezing and rhonchi in younger children, and segmental-lober consolidation in chest radiography could be clues for MP infection. Further studies in different age groups can facilitate an understanding of MP infection's epidemic characteristics and clinical features that will provide early diagnosis and appropriate treatment.

Key words: children, infection, *Mycoplasma pneumoniae*, radiograph.

Mycoplasma pneumoniae (MP) is one of the most important etiological agents of community-acquired pneumonia in children. MP is responsible for 10-30% of community-acquired pneumonia cases in all age groups with insidious onset characteristics, mild pulmonary signs, and imaging specificity. MP infections are known to be also associated with extrapulmonary manifestations. In some cases, these manifestations can be independent of respiratory disease but are more often concomitant. These manifestations may originate from direct MP effects or autoimmune reactions.[1] Nervous system disease involvement such as encephalitis, acute disseminated encephalomyelitis, cerebellar ataxia, transverse myelitis, myocarditis, pericarditis, arthritis, Mycoplasma-induced rash and mucositis [MIRM] syndrome, hemolytic anemia, thrombocytopenic purpura are extrapulmonary and unusual manifestations.[2]

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Received 1st June 2022, revised 14th September 2022, accepted 20th September 2022.

Practical and sensitive laboratory diagnostic methods are the primary basis for diagnosing MP infection. There are many clinical methods for detecting MP, such as serology, and molecular-based methods. All have their advantages and disadvantages in clinical practice.[3] The serological assay is the most common method of diagnosing mycoplasma infection. The complement-fixation test, immunofluorescence, and enzyme immunoassays can be used as serologic tests. A fourfold rise in IgG antibody titer is a definite diagnosis. However, this test is not helpful in the acute phase of MP infection. IgM was regarded as an indicator of MP infection because it appears during the first week of the illness.[4]

This study aimed to describe the age-dependent clinical, laboratory, and radiologic features in children diagnosed with an MP infection.

Material and Methods

Selection of Patients and Data Collection

We conducted a retrospective study of children younger than 18 years of age tested for MP between 2008 and 2015 at Dr. Sami Ulus Maternity and Children's Research and Education Hospital. The patients who had positive *M. pneumoniae* IgM or 2 or 4-fold increase in *M. pneumoniae* IgG titers after 2 weeks of follow-up were enrolled. The patients with no increased IgG titers (2- or 4-fold) in 2 weeks of follow-up, and the patients who had a primary immune deficiency and hematological or oncological malignancies were excluded from the study.

The clinical, laboratory, and radiological features were evaluated from the medical records. Patients were grouped by age: < 5 years of age and ≥ 5 years for data analysis because *M. pneumoniae* epidemics are typically present in school-aged children and *M. pneumoniae* infection frequency is increasing in children aged 1-5 years so the clinical features may be different in these age groups. This study was conducted in compliance with the ethical principles according to the Declaration of Helsinki, and it was approved by the Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital Institutional Review Board (Number: 73799008-799).

Physical examination findings

Tympanic measurements of higher than 38°C were accepted as fever. The mean oxygen saturation percentages of the patients in room air were measured by transcutaneous pulse-oximetry. If the oxygen saturation was ≤92%, it was considered as low. Tachypnea and tachycardia were determined by evaluating the respiratory and heart rate per minute according to the age of the patient.[5]

Laboratory findings

Mycoplasma pneumoniae IgM and IgG antibodies were studied with the Enzyme-Linked Immuno-Sorbent Assay (ELISA) method on a Triturus grifols model device with the Vircell® commercial kit. The laboratory results included; blood count and differential, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver and kidney function tests, and microbiologic workup such as blood culture, throat culture, and respiratory multiplex polymerase chain reaction (PCR) results were recorded. Fast Track Diagnostics/ Respiratory Pathogens 21 (Luxemburg) (influenza virus A/ H1N1pdm, influenza virus B, rhinovirus, respiratory syncytial virus (RSV) A/B, human parainfluenzaviruses 1/2/3/4, coronaviruses OC43/229E/ NL63/ HKU1, parechovirus, enterovirus, adenovirus, human bocavirus, human metapneumovirus) commercial kit was used for the presence of respiratory tract viruses in the ABI 7500 Real-Time PCR (Applied Biosystems, USA) device.

Diagnosis

The patients' diagnoses were grouped into respiratory system diseases caused by MP and extrapulmonary system diseases. Pneumonia

was defined as fever, acute respiratory symptoms (cough, tachypnea, difficultly breathing), or both, plus the presence of a new infiltrate on chest radiography or consolidation not attributable to some other etiology.[6] Chronic cough, which is among the respiratory system symptoms, was defined as a cough that lasted for three weeks or more without improvement.[7] Prolonged fever was defined as fever lasting longer than expected for clinical diagnosis of a disease.[8] The diagnosis of encephalitis was made according to the specified criteria.[9]

Chest X-ray Findings

Chest radiographs were evaluated by the same radiologist. Findings were classified as hilar lymphadenopathy (LAP), peribronchial infiltration, peribronchial thickening, segmental-lobar consolidation, reticulonodular infiltration, atelectasis, and pleural effusion.

Statistical analysis

Clinical data of the separate groups were described by mean values and standard deviations or median and inter-quarter range, according to the type of variable. Students t-test and Mann-Whitney U-test were used to compare continuous variables between the group and the chi-square test and Fisher's exact test were used for categorical variables. A p-value of <0.05 was considered statistically significant.

Results

Two hundred forty-four patients were enrolled in this study, 140 (57.4%) were male, and the median age was 80.5 months [interquartile range (IQR), 46.5-120 months]. A total of 78 (32%) patients were < 5 years old, and 166 (68%) were ≥ 5 years old. The most common complaints before admission to the hospital were cough (84.8%), fever (57.4%), weakness (18.9%), and runny nose (16%). Patient characteristics and symptoms according to the age groups are presented in Table I. The seasons with the highest admissions were spring (33.2%) and summer (31.9%). Before admission, the fever duration (median (min-max), was 4.5 days (range, 1 day-30 days), and 8 (3.3%) patients had prolonged fever. The median cough duration was 10 days (range, 1day-300 days). A total of

Table I. Characteristics and symptoms of patients.

	Total	<5 years old	≥5 years old	p-Value
Number of children, n (%)	244	78 (32)	166 (68)	-
Male, n (%)	140	42 (53.8)	98 (59)	0.44
Respiratory symptoms, n (%)				
Cough	207 (84.8)	69 (88.4)	138 (83.1)	0.37
Rhinorrhea	39 (16)	17 (21.7)	22 (13.3)	0.13
Wheezing	26 (10.7)	16 (20.5)	10 (6)	0.01
Shortness of breath	21 (8.6)	7 (8.9)	14 (8.4)	1
Extrapulmonary symptoms, n (%)				
Fever	140 (57.4)	48 (61.5)	92 (55.4)	0.36
Vomiting	33 (13.5)	13 (16.7)	20 (12)	0.43
Rash	19 (7.8)	4 (5.1)	15 (9)	0.65
Headache	11 (4.5)	1 (1.3)	10 (6)	0.96
Abdominal pain	9 (3.7)	3 (3.8)	6 (3.6)	0.9
Diarrhea	7 (2.9)	3 (3.8)	4 (2.4)	0.45
Chest pain	6 (2.5)	-	6 (3.6)	-
Seizures	4 (1.6)	2 (2.6)	2 (1.2)	0.54
Speech impairment	2 (0.8)	-	2 (1.2)	-

155 (63.5%) patients had community-acquired pneumonia, 44 (18%) patients had a chronic cough, and 45 (18.4%) patients had only extrapulmonary involvement. A preexisting disease was present in 31 (12.7%) children, and 6/31 (19.3%) had been diagnosed with asthma.

On admission, physical examination of patients with pneumonia revealed that 103 (42.2%) had tachypnea, 59 (24.2%) had low oxygen saturation, 27 (11%) had a fever, and 14 (5.7%) had tachycardia. The body temperature (mean±SD) was 38.3±0.46°C, and the oxygen saturation (mean±SD) was 89.3±6.3%. In the <5 years old age group oxygen saturation was lower, and tachypnea presence was higher compared to the ≥ 5 years old age group (p=0.02 and p=0.05, respectively). Similarly, when we consider the patients' respiratory system findings, the frequency of the prolonged expiration, presence of retractions, and rhonchi was higher in the < 5 years old age group than in the group with ≥ 5 years old age. (p = 0.001, p<0.001, p=0.02 respectively).

Extrapulmonary manifestations were present in 45 (18.4%) patients. Skin involvement was the most common extrapulmonary finding (19/244, 7.7%). Central nervous system manifestations were seen in 16 (6.5%), hematologic involvement in 5 (2%), and musculoskeletal involvement in 5 (2%) patients. The summary of extrapulmonary manifestations are shown in Table II.

The comparison of patients with laboratory examinations by age group is shown in Table III. The leukocyte count and lymphocyte percentage in patients < 5 years old age group were statistically significantly higher than in the ≥ 5 years old age group. There was no statistically significant difference in ESR and CRP values between different age groups.

Table II. Extrapulmonary manifestations of *Mycoplasma pneumonia* infection.

	N (%)
Dermatological involvement	19 (7.8)
Maculopapular rash	7 (2.9)
Petechiae	4 (1.6)
Urticarial Plaque	2 (0.8)
Erythema Nodosum	2 (0.8)
Erythema Multiforme	2 (0.8)
Vesicle	1 (0.4)
Bulla	1 (0.4)
Neurological involvement	16 (6.6)
Suspected encephalitis	12 (4.9)
Guillain-Barré syndrome	4 (1.6)
Hematologic involvement	5 (2)
Immune thrombocytopenic purpura	4 (1.6)
Hemolytic anemia	1 (0.4)
Musculoskeletal involvement	5 (2)
Arthralgia/artritis	5 (2)

Lumbar puncture was performed in 14 (87.5%) of 16 patients with neurological findings at admission. The cerebrospinal fluid (CSF) cell count ranged from 0 to 150 cells/mm^3, with a median of 12 cells/mm^3. Analysis of CSF biochemical findings revealed the mean CSF protein was 51.2±34.1 mg/dl, and CSF glucose

Table III. The comparison of laboratory examinations by age group.

	< 5 years	≥ 5 years	P
Leukocyte count (mm^3)*	12.060±5450	10.400±4830	0.019
Neutrophil percentage (%)	55±18	59±15	0.1
Lymphocyte percentage (%)	44±17	39±15	0.02
Hemoglobin (g/dl)*	11.8±1.6	12.7±1.4	0.00
Platelet count (mm^3)*	373000±143400	357150±134200	0.4
ESH (mm/hr)*	45±34.7	48.8±33.9	0.5
CRP (mg/l), median (min-max)	14.5 (1-483)	16 (1-388)	0.6

*Mean±standart deviation; CRP: C-reactive protein; ESH: erythrocyte sedimentation rate.

was 77.2±21.9 mg/dl. All the CSF cultures were negative.

A total of 26 children were simultaneously tested with PCR for respiratory viruses. Viral coinfections were identified in 17 (65.4%) patients, mostly rhinovirus (5 cases, 19.2%) followed by influenza A and bocavirus (3 cases, 11.5% and 2 cases, 7.7% patients, respectively).

The chest radiographs of the patients were evaluated; 238 (97.5%) patients had radiographs. Chest radiographs of 45 (18.4%) patients were normal. The radiological characteristics of patients are summarized in Table IV. Peribronchial infiltration was more common in bilateral lower lobes (30%). Pleural effusion and segmental-lobar consolidation were found in the left lower lobe at 68% and 39.7%, respectively. The radiological findings according to age groups are shown in Figure 1.

Of the patients, 147 (60.2%) were hospitalized, and 97 (39.7%) were followed up as outpatients. A total of 60 (77%) patients < 5 years were hospitalized. It was determined that 156 (63.9%) patients had commenced macrolide empirically, and 61 (25%) patients were treated with positive serology results.

Table IV. Radiological characteristics of patients.

	N (%)
Peribronchial infiltration	70 (28.7)
Segmental-lobar consolidation	68 (27.9)
Reticulonodular infiltration	41 (16.8)
Pleural effusion	25 (10.3)
Atelectasis	14 (5.7)
Hilar lymphadenopathy	9 (3.7)

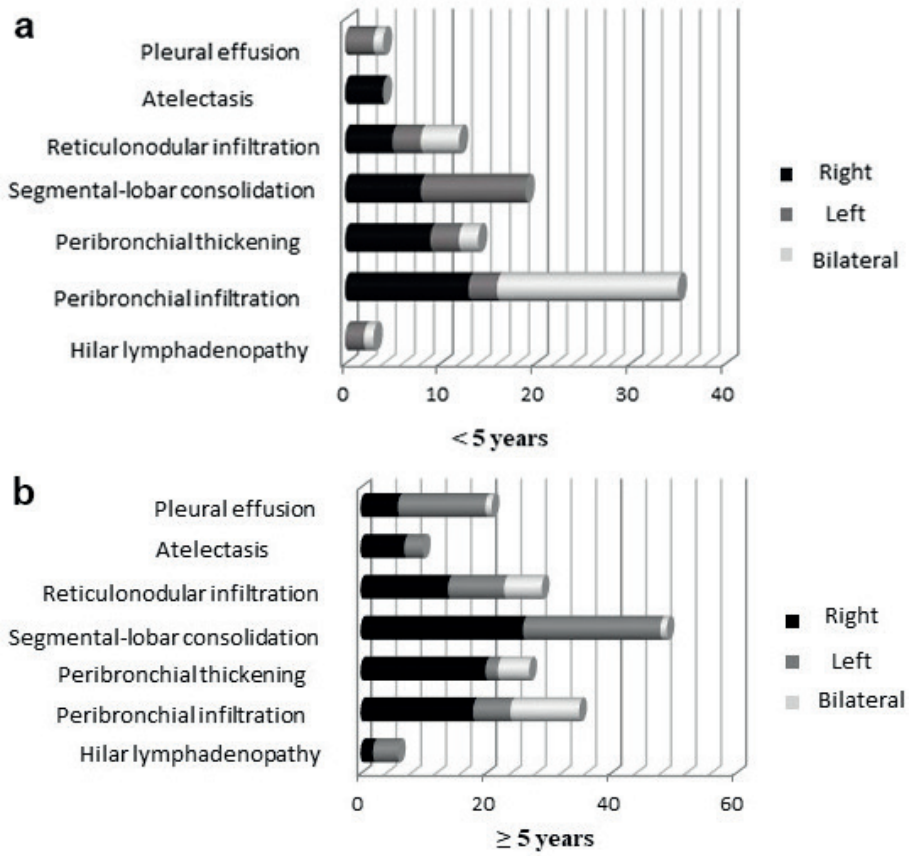

Fig. 1. The radiological findings according to age groups; a <5 years and b ≥5 years.

Discussion

Mycoplasma pneumoniae predominantly causes upper and lower respiratory tract infections in children and has various clinical manifestations.[10] Previous studies reported that MP community-acquired pneumonia is more prevalent in children 6-18 years old and less in preschool children. However, recent reports have shown that MP is also a significant respiratory pathogen in young and preschool children.[1] The epidemic outbreaks occur worldwide every 3-7 years and more frequently in winter and autumn.[11] In countries with temperate climates MP may be detected in summer and early autumn.[12] Our results showed that MP infection is more common in >5 years old children, and about two-thirds of the patients were admitted during the summer and spring seasons.

Despite some symptoms and signs supporting a possible diagnosis of MP infection, none of these are sufficient to confirm the diagnosis. A study comparing 302 pediatric patients diagnosed with MP positive and MP negative pneumonia found that fever and cough duration differed from patient to patient. The authors used age, cough, and fever duration as variables to predict the diagnosis and reported that the negative predictive value was 96%, and the sensitivity was 85%.[13] In our study, the mean fever duration was 4.5 days, and the mean cough duration was 10 days. A study evaluating 179 children with a persistent cough reported that the children with positive MP serology had a median of 39 days of cough.[14] The duration of the cough was thought to be a clue for possible MP infection if there is a suspicion of an infectious cause.

There may be age-related clinical differences at presentation in MP infection. A study from China that evaluated clinical features according to age groups reported fever for three days was more common in the 9 to <12 months age group.[15] A study describing the epidemiological and clinical features of infants and children during the MP epidemic in Denmark in 2010 and 2011 specified the clinical presentation as cough, asthma-like symptoms, and low-grade fever. They also suggest that small children with wheezing and rhinorrhoea should simultaneously be tested for MP and respiratory viral infections.[16] In both of these studies, the preschool age group had a higher hospitalization rate as well as more oxygen, and fluid requirement.[15,16] A study conducted during the MP epidemic in Norway reported a higher risk of severe pneumonia in preschool children.[17] Our results showed that MP infection was more common in children aged >5 years. However, preschoolers suffered a severe course of the disease, and approximately 70% of patients in this age group required hospitalization. The presence of wheezing, low oxygen saturation, tachypnea, retraction, rhonchi, and prolonged expiration under 5 years of age was found to be statistically significant compared to the older ones.

The respiratory system was primarily involved in MP infection; however, extrapulmonary manifestations may also cause various symptoms. Rash has been reported in 3% to 33% of children during infection.[18] In a study evaluating 353 pediatric patients positive for MP, extrapulmonary involvement was evident in 26% of all children. Skin involvement (18%) was the most common with nonspecific maculopapular rash or urticaria.[1] In this study, 18.4% of children had extrapulmonary manifestations, mostly dermatological (7.7%) and commonly observed as a maculopapular rash.

Approximately 1-10% of serologically confirmed MP infections may result in serious neurological complications requiring hospitalization.[19] The clinical manifestations of MP encephalitis are highly heterogeneous, and more than half of patients had seizures during the acute phase.[20] In a study evaluating 61 patients with neurological involvement with MP infection, encephalitis was diagnosed in 45 pediatric patients, and it was reported that patients presented with changes in consciousness (35%), seizures (45%), and meningeal irritation findings (78%).[21] In our study, 12 suspected

encephalitis associated with MP were observed. Patients were serologically MP positive with negative CSF results for other infectious pathogens. The most common complaints of these patients were headaches, vomiting, and seizures. GuillaineBarré syndrome (GBS) is an acute immune-mediated disorder characterized by acute, progressive weakness, hyporeflexia or areflexia, and elevated protein levels in the cerebrospinal fluid (CSF). Infection with MP has been reported in up to 5% of GBS patients.[22] We observed a 6.5% neurological involvement in our study population, and 1.6% were diagnosed with MP-related GBS.

The most common hematological complication of MP is hemolytic anemia secondary to cold agglutinin antibodies against I antigen on erythrocytes.[23] Thrombocytopenia associated with MP infection is rare. The pathogenesis of thrombocytopenia is autoimmune. In a study, 7 cases between 7 months and 44 years of age were discussed, and it was reported that five of these patients were under 8 years of age. The platelet counts were between 2000-66000/mm^3. It was stated that all patients were given effective antibiotics for mycoplasma in addition to IVIG, steroids, or both treatments.[24] In our study, four patients had thrombocytopenia, and these patients were given IVIG and clarithromycin treatment.

Mycoplasma pneumoniae associated arthritis in children has been reported between 0.9-3.0%. A study reported 13 cases of arthritis out of 1259 patients diagnosed with MP infection, five of them were children between the ages of 1-7 years, and monoarthritis was found in four of them.[25] In a study of 348 MP IgM positive patients aged 1-15 years, 4 (1.1%) patients were reported to have monoarthritis.[26] We found monoarthritis in 2.5% of the patients.

Regarding laboratory tests, a study from Italy that included 102 hospitalized children with MP pneumonia reported preschool children had a higher lymphocyte and monocyte count.[12] Gordon et al.[1] reported a higher number of white blood cells (WBC) and platelets in preschool children with MP infection. However, all these results were in normal ranges for age. In a study from Spain, 162 children were diagnosed with MP pneumonia, and higher WBC and lymphocytes were detected in infants.[27] Similarly, in our study, leukocyte counts and lymphocyte percentages were significantly higher in patients < 5 years of age.

In various studies, co-infection with viral pathogens has been reported ranging from 35% to 78%, depending on the age of the patients, the season, and the method used to detect the agent. In a study investigating the causative respiratory agent by PCR in 407 patients < 5 years of age, it was reported that two or more pathogens were detected in 19.3% of children with MP infection.[28]Another study identified 145 patients with MP, and viral co-infection was found in 16 (11%) patients, mostly RSV.[29] In the present study, concomitant respiratory tract virus infection was detected in 17 (7%) patients. The low co-infection rates in our study can be explained by the retrospective nature of the study and the low number of multiplex PCR requests sent from the study group. Co-infecting viruses were found as rhinovirus, RSV, and influenza virus A-B, in order of frequency.

Usually, chest radiography is the first imaging technique obtained to evaluate acute respiratory symptoms. However, the patterns of presentation of MP pneumonia on chest radiographs are nonspecific, consisting of patchy areas, consolidation, reticular interstitial infiltrates, or both.[30] In a study including 68 children with MP pneumonia, the most common chest X-ray findings were reported as perihilar linear opacity, reticulonodular infiltration, and segmental-lobar consolidation.[31] In another study evaluating 81 chest graphs of 102 pediatric patients with MP infection, 76 (93.8%) were interpreted as abnormal, and consolidation was reported as the most common and pleural effusion as the least detected finding. It was observed that interstitial changes were more common in children < 5 years of age, and consolidation was more common in children aged > 5 years.[12] Similarly, in our study, the

most common chest X-ray findings were peribronchial infiltration and segmental-lobar consolidation. Peribronchial infiltration was the most common chest X-ray finding at <5 years of age, while segmental-lobar consolidation was more common at ≥ 5 years and older. The least common finding in both age groups was hilar LAP. In addition, although there is no definite pattern for lobar involvement, it was determined that the lower lobes were more involved than the upper lobes. Pleural effusion was detected in 10% of patients. In various studies, MP-associated pleural effusion has been reported between 5-20%, mainly on the left side.[32,33]

The role of macrolide therapy in changing the clinical course of pediatric MP infection is controversial. Further studies are required to investigate this aspect, as suggested by a recent Cochrane Review.[34] In our study, macrolides were started empirically in the vast majority of patients, and one-fourth of them were started after they were proven serologically. About 10% of patients recovered without taking macrolides.

In conclusion, this study suggests that MP infection occurs mainly in the spring and summer seasons, mostly ≥ 5 years. Wheezing, tachypnea, retraction, prolonged expiration, rhonchi, and desaturation, as well as leukocytosis and lymphocytosis, were found to be more common in MP pneumonia in children < 5 years of age than the older ones. The clinical picture in young children is more similar to viral lower respiratory tract infections. Extrapulmonary MP findings support the current literature. There is no distinctive chest X-ray finding in MP infection, but segmental-lobar consolidation is more common in children aged ≥ 5 years, and the left lower lobe is more commonly involved. Clinicians should be aware of different MP clinical presentations to provide early diagnosis and appropriate treatment.

Ethical approval

This study was approved by the Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital Institutional Review Board (Number: 73799008- 799).

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: MO, FNÖ, GT; data collection: MO; chest evaluated: HGÇ; analysis and interpretation of results: MO, FNÖ, GT; draft manuscript preparation: MO, FNÖ, GT. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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