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Original Article

Pulmonary involvement in children with Langerhans cell histiocytosis

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ABSTRACT

Background. Pulmonary Langerhans cell histiocytosis (pLCH) is a rare disease, mostly a component of multisystemic LCH. We aimed to investigate the clinical features and treatment results in children with pLCH.

Methods. We retrospectively reviewed the clinical, radiological, and treatment data of 37 patients with pLCH, diagnosed from 1974 to 2022.

Results. 10% (n=37) of 367 patients with LCH had lung involvement. The median age was 1.8 years (range: 0.4 & 17.7) with a male-to-female ratio of 2.3. At admission 29.7% (n=11) presented with respiratory symptoms. Imaging showed a spectrum from nodular opacities to multiple cysts. All but one patient had multisystem disease. Twenty-nine received vinblastine-containing therapy. Ten-year event-free (EFS) and overall survival (OS) rates were 47.8% and 63.3%, respectively. In children younger and older than two years of age, the 10-year EFS was 53.3% vs. 40.2% and the 10-year OS was 58.7% vs. 68.8%, respectively. In children with and without risk organ involvement, 10-year EFS was 51.9% vs. 46.3% and 10-year OS was 51.9% vs. 73.7%.

Conclusions. Lung and multisystem involvement are significant concerns in LCH, highlighting the need for careful management to reduce morbidity and mortality.

Key words: Langerhans cell histiocytosis, children, pulmonary involvement.

Pulmonary Langerhans cell histiocytosis (pLCH) is a distinct form of interstitial lung disease driven by the proliferation of Langerhans cells.[1] Accounting for 7-16% of Langerhans cell histiocytosis (LCH) cases[2], its pathogenesis remains elusive but has been increasingly described as 'inflammatory myeloid neoplasia'.[1,2] Clinical manifestations of LCH are diverse, and the clinical course of the multisystem LCH (MS-LCH) can range from spontaneous remission to fatality. Conversely, cases confined to a single organ or system generally predict a favorable outcome.[2,3] Although most pLCH instances occur within the context of multisystem disease[2], recent insights suggest that pulmonary involvement does not independently predict the prognosis in MS-LCH. Patients with concomitant liver, spleen, or bone marrow afflictions are identified as having 'high-risk disease', correlating with increased mortality.[2,3] In this study, we aimed to investigate the clinical features and treatment results in children with pLCH.

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Patients and Methods

This retrospective study examined the clinical records of 37 patients diagnosed and treated with pLCH at Hacettepe University İhsan Doğramacı Children's Hospital, Department of Pediatric Oncology from 1974 to 2022. Approved by the Cumhuriyet University Ethical Committee (21.09.2023, no: 2023-09/21) we collated demographic, clinical and survival data for these children. LCH was classified as single-system LCH when only one organ was involved, and as multisystem when two or more organs/systems were affected. Risk organ involvement included the hematopoietic system, liver, and spleen.[3]

Pulmonary involvement was initially identified via chest radiograph including interstitial infiltrates, reticulonodular change, cystic or honeycomb appearance in all patients, and/or evidence of disease by lung biopsy, and supplemented by computed tomography (CT) in 14 cases due to the non-availability of CT in the early years.[2,4–6] Patients for whom chest tomography could not be obtained were diagnosed based on clinical findings and chest X-ray findings. We retrieved reports of chest radiographs and CT scans from the patients' medical records to pinpoint diagnostic characteristics.

According to the Histiocyte Association criteria, the diagnosis of LCH was defined as definite (demonstration of Birbeck granules on electron microscopy or CD1a expression on lesion cells by immunohistochemistry) or probable (morphology compatible with LCH and staining of S-100 protein by immunohistochemistry).[2]

Patients with LCH who are younger than 2 years of age at diagnosis have a higher risk of organ involvement and a poor prognosis.[7–10] Therefore, patients were grouped as younger than 2 years old and aged 2 years and older. Event-free survival (EFS) and overall survival (OS) rates were compared between the two groups. Patients were evaluated from diagnosis to the latest uneventful follow-up, disease progression, relapse or death due to any cause for EFS, and from diagnosis to death for OS. EFS and OS rates were calculated for 5 years and 10 years. Continuous variables, median values, and ranges are presented. Median follow-up time was calculated for surviving patients. The Kaplan-Meier method for cumulative survival and the log-rank test were used for statistical analysis. A value of $p<0.05$ was considered statistically significant. The statistical analysis was performed with IBM SPSS Statistics for Windows (v21; Armonk, NY).

Results

From 1974 to 2022, among 367 children with LCH under 18 years who were treated at our hospital, 37 (10%) exhibited lung involvement, with a male-to-female ratio of 26:11 (2.3). Lung biopsies were performed on five patients,three by thoracotomy and two by thoracoscopy. In the remaining cases, the diagnosis of LCH was confirmed by skin biopsy (n=10), bone biopsy (n=7), lymph node biopsy (n=6), liver (2), palatal biopsy (n=2), bone marrow biopsy (n=1) and gingival biopsy (n=1). Both skin and bone biopsy, bone and bone marrow biopsy, bone marrow and lymph node biopsy were also performed on three patients.

Ages at diagnosis ranged from 0.4 to 17.7 years (median 1.8 and mean 4.3 years). Twenty patients (54%) were under two years of age. Multisystem involvement was present in all but one patient, who at 11.7 years old, was confirmed to have isolated lung involvement via biopsy. Additional organ involvement was as follows: bone, skin, liver, bone marrow, spleen, palate, and thyroid involvement were identified in 21, 20, 13, 6, 5, 2 and 1 patients, respectively. Risk organ involvement was noted in 18 patients, (liver 13, bone marrow 6, spleen 5 patients) (Table I).

At the time of diagnosing pulmonary involvement, clinical respiratory findings were reported in 30% (11 out of 37) of the patients characterized by dyspnea in 5 patients, cough

Table I. The characteristics of 37 patients with pulmonary LCH.

Characteristics	n	%
Multisystem disease with risk organ involvement	18	49
Organ involvement*		
Lung	37	100
Bone	21	57
Skin	20	54
Liver	13	35
Hematologic	6	16
Spleen	5	14
Thyroid	1	3

* Individual patients might have one or more involved sites.
LCH: Langerhans cell histiocytosis.

in 4, wheezing in 1, and chest pain in 1. Physical examination findings in patients with pulmonary involvement included rales, decreased breath sounds, tachypnea, rhonchi, nasal flaring, hypoxia, prolonged expiration, retraction, and bronchial sound in 15, 9, 5, 3, 3, 3, 2, 2 and 1 patient, respectively. Venous blood gas analysis was performed in ten patients, and only three of them had respiratory acidosis. Laboratory findings of these patients with respiratory failure were as follows (mean ± SD): venous pH, 7.32±0.01; venous HCO_3^-, 21.3±6.48 mmol/L; serum CO_2, 48.7±2.54 mmol/L. Transcutaneous oxygen saturation values of these three patients at room air were 78%, 85%, and 88%. Due to the retrospective nature of the study, the data for the other cases were not available. There were 7 patients with acute respiratory failure, 6 of whom were accompanied by sepsis. Three patients were admitted to the intensive care unit and required mechanical ventilation. One of these 3 patients required extracorporeal membrane oxygenation (ECMO). Three of the remaining 4 patients developed acute respiratory failure during their follow-up in the pediatric oncology unit and one patient died during the operation due to acute respiratory failure.

From the chest X-ray of all patients, the following were observed: interstitial infiltration (65%, n=24), cystic lesions (14%, n=5), pneumothorax (14%, n=5) (Fig. 1), nodular opacities (11%, n=4), and honeycomb appearance, ground-glass appearance, and left lower lobe atelectasis in one patient each (3%). Pulmonary involvement was defined by chest CT in 14 patients, revealing air cysts (Fig. 2), nodular opacity, and pneumothorax in 10 (27%), 6 (16%), and 5 (14%) patients, respectively. Additional chest CT findings included a honeycomb appearance, ground glass opacities, emphysematous appearance, pleural effusion, and left lower lobe atelectasis in one patient each.

Due to the young age of the patients and the retrospective nature of the study, pulmonary function tests (PFTs) were conducted in only four children. Three children had restrictive ventilation dysfunction, while the PFT results for the fourth child were normal. The FEV1/FVC ratios of these patients were 80%, 83.1%, and 114%, consistent with the restrictive pattern. Besides, predicted vital capacity

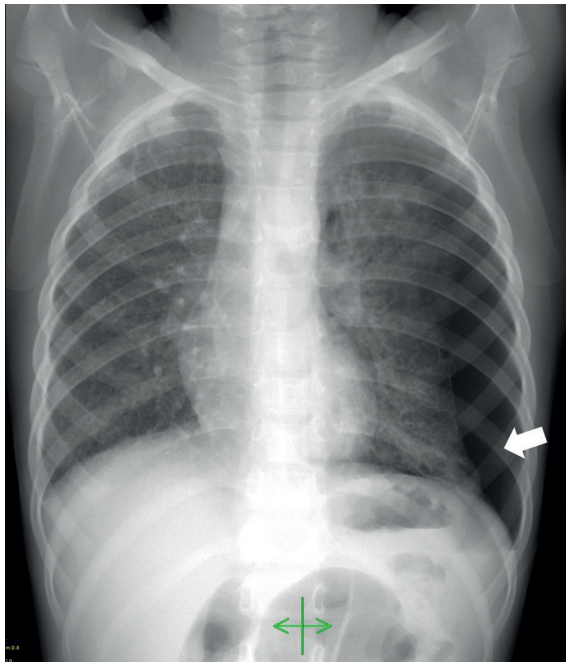

Fig. 1. 4-year-old boy with Langerhans cell histiocytosis. Posteroanterior chest radiograph shows left sided pneumothorax (arrow). There are widespread cystic changes and diffuse reticulonodular opacities in both lungs.

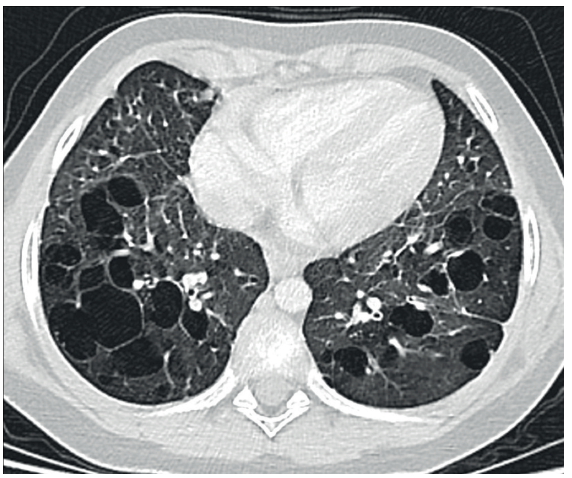

Fig. 2. 6-year-old boy with Langerhans cell histiocytosis. Axial computed tomography of the chest through lower lobes demonstrates numerous thin-walled lung cysts.

percentage values were low at 21%, 68%, and 74%. These tests were performed 1.5 and 12 months after the diagnosis in two patients and one year before the diagnosis of LCH in another patient. Due to the retrospective nature of the study, PFT findings during the follow-up were not available in the records of these patients. Additionally, bronchoalveolar lavage (BAL) was not utilized for diagnostic purposes in any of the cases.

Lung biopsy was performed on five patients. Wedge biopsies by thoracotomy in three patients and biopsies by video-assisted thoracoscopic surgery in two patients revealed prominent eosinophils and lymphoplasmacytic cell infiltration consisting of grooved or infolded nuclei histiocytic giant cells in the lung parenchyma. Histiocytic cells were positive for S-100 and CD1a by immunohistochemical staining. In addition, lung biopsies of two patients showed an appearance consistent with fibrosis in some areas.

Treatment primarily consisted of chemotherapy and targeted management for respiratory complications. Since 1974, the institution has utilized a variety of chemotherapy protocols. Vinblastine was the mainstay treatment for 26 patients, used either as a monotherapy or in combination with other drugs. Single-agent vinblastine was used in 8 patients (22%), while a vinblastine and prednisone combination was given to 18 patients. Treatment could not be given to one patient due to pneumonia. The remaining 10 patients were treated with vinblastine / prednisone / etoposide (n=2), vinblastine/prednisone/6-mercaptopurine (n=1), vinblastine / cyclophosphamide (n=1), prednisolone/etoposide (n=1), prednisolone only (n=1), 6-mercaptopurine / methotrexate (n=1) and cyclophosphamide / prednisone / vincristine (n=3) regimens.

During the study period, five children experienced pneumothorax incidents, with one patient having four recurrences, two patients with three recurrences each, and two others with two recurrences each. Of the pneumothorax episodes, six were on the left side and eight on the right. Notably, all three episodes in a single patient occurred on the right side, whereas in the other patients, the episodes were bilateral. Each of the five initial pneumothorax episodes was managed with chest tube drainage, followed by pleurodesis due to the recurrent nature of the condition. Pleurodesis was conducted an average of 59 days post-initial pneumothorax, 25 days after the second, and 8 days subsequent to any further occurrences. This procedure was carried out nine times in total, using talc in four instances, bleomycin in three, and tetracycline in two.

One patient died without treatment on the first day of hospitalization due to pneumonia. Six patients received radiotherapy, only one was given pulmonary radiotherapy.

Eleven children died. The causes of death for four could not be determined as they missed their regular check-ups. The average time from the date of admission to the date of death of the 11 patients was 7.6 months. The median follow-up for surviving children was 202.4 months (95% confidence interval: 168.6-236.1 months). One 11.7-year-old patient with isolated pulmonary

involvement is alive and well 12 years post-treatment. 5-year event-free survival (EFS) and OS were 54.7% and 63.3%, while 10-year event-free survival and OS were 47.8% and 63.3% in 37 patients with pLCH (Fig. 3). According to the comparison of survival rates of children <2 years old and ≥2 years old, the 10-year EFS rate was 53.3% vs. 40.2% (p= 0.79) and the 10-year OS rate was 58.7% vs. 68.8%, respectively (p=0.65) (Table II, Fig. 4). We also compared 10-year EFS and OS between pLCH children with (RO^+) or without (RO^-) risk organ involvement.

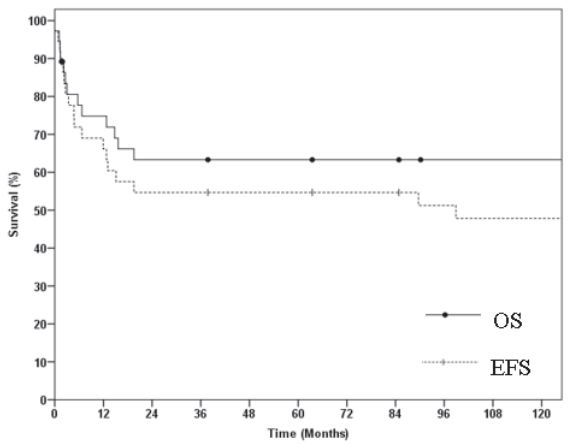

Fig. 3. Overall (OS) and event free survival (EFS) in 37 patients with pulmonary Langerhans cell histiocytosis.

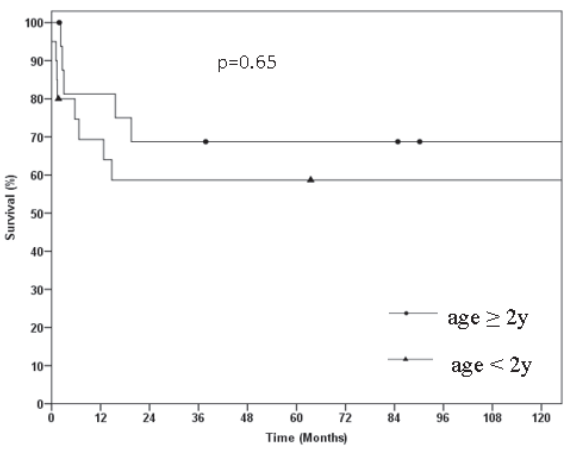

Fig. 4. Overall survival in 37 patients with pulmonary Langerhans cell histiocytosis according to age group.

In terms of the presence or absence of risk organ involvement, the 10-year EFS rates for patients were EFS (RO^+) 51.9% and EFS (RO^-) 46.3%, (p=0.83). The 10-year OS rates for patients with or without risk organ involvement were also OS (RO^+) 51.9% and OS (RO^-) 73.7% (p=0.17) (Table II, Fig. 5). The long-term pulmonary functions were not routinely monitored in the follow-up of the patients. The outcome of the patients are presented as overall and event-free survival based on the clinical follow-up.

Table II. The 5-year and 10-year EFS and OS rates of children with pLCH.

	Survival		p
	5 years (%)	10 years (%)	
Age <2 years OS	58.7	58.7	0.651
Age ≥2 years OS	68.8	68.8	
Age <2 years EFS	53.3	53.3	0.786
Age ≥2 years EFS	56.3	40.2	
RO+ OS	51.9	51.9	0.171
RO- OS	73.7	73.7	
RO+ EFS	51.9	51.9	0.838
RO- EFS	57.9	46.3	
All OS	63.3	63.3	
All EFS	54.7	47.8	

EFS: Event-free survival, OS: Overall survival, pLCH: pulmonary Langerhans cell histiocytosis, RO-: Without "risk organ" involvement, RO+: With "risk organ" involvement.

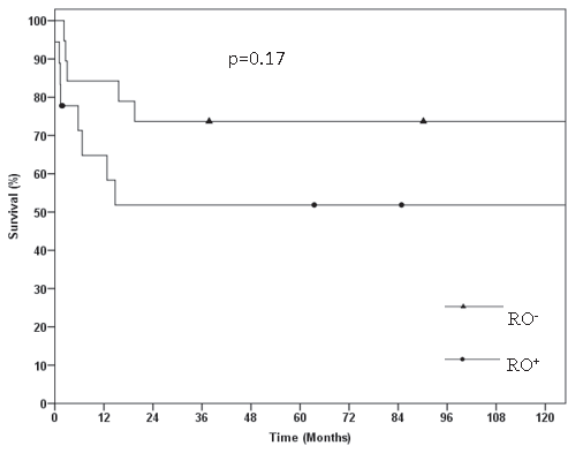

Fig. 5. Overall survival in 37 patients with pulmonary Langerhans cell histiocytosis, with or without risk organ (RO) involvement.

Discussion

Our work indicated a pLCH prevalence rate of 10%, which is consistent with the findings of Le Louet et al.[11] (7.4%) in a similar cohort. In children, pLCH usually part of broader multisystem LCH, with 10-30% displaying lung lesions. Isolated pLCH in children is rare, with unclear etiology. Our study includes a noteworthy case of an 11.7-year-old with isolated pulmonary involvement who, 12 years post-treatment is alive and well. pLCH presents with a range of symptoms, from chronic cough and dyspnea to no symptoms. The symptoms may begin insidiously.[8,12] Despite extensive lung involvement on imaging, only 30% of our patients exhibited respiratory symptoms. This underscores the need for routine lung radiological exams in all new LCH diagnoses, including chest X-ray and CT.[5,13]

Common radiological findings for pLCH include bilateral interstitial infiltrates, cysts, nodular opacities, and pneumothorax.[14] These findings could be isolated or mixed.[5] Chest radiography often reveals bilateral interstitial changes. Nodular changes, cystic changes, pneumothorax may also be seen.[2,6,15] However, its diagnostic utility is limited. Chest CT is more sensitive, showing detailed lung lesions, making it the preferred method for diagnosing pLCH. Chest CT frequently identifies a reticulonodular pattern early in the disease, with cystic changes becoming more prominent as the disease advances.[2,5,6,15] Chest CT is routinely used for the differential diagnosis of pLCH.[13] In our study, chest X-rays indicated bilateral interstitial changes in most patients as seen in literature, but chest CT was more likely to reveal cystic and nodular changes.

PFTs in pLCH can be normal or show restrictive or obstructive patterns. Initially, about 20% of patients may have normal PFT results, but as the disease progresses, a restrictive pattern due to limited ventilation can develop, potentially leading to obstructive dysfunction later.[1,15–18] In our study, PFTs indicated that three patients had a restrictive pattern, while one had normal pulmonary function. Young age population and retrospective nature of our work limits our further analysis of PFTs in this group.

If isolated pLCH is suspected, a lung biopsy is important in confirming the diagnosis and guiding treatment.[2] CD1a, S-100 positivity in immunohistochemical staining and detection of cytoplasmic Birbeck granules by electron microscopy are characteristics of LCH.[2,19] However, if clinical and radiological findings suggest pulmonary involvement and a biopsy from extra-pulmonary sites confirms LCH, the need for lung biopsy may be eliminated to avoid morbidity.[2] The diagnosis was confirmed with a biopsy in all cases. The lung biopsy was performed in 5 cases, the rest had biopsy from other involved sites.

Transbronchial biopsies and BAL might be useful in patients undergoing bronchoscopy, with >5% CD1a and CD207 positive cells in BAL fluid being significant.[2,13,20–22] However, a positive result is seen in only up to 25% of cases, and less than 5% CD1a positive cells do not rule out pLCH.[15,22,23] Challenges in transbronchial biopsy include sampling errors and the risk of pneumothorax due to the irregular distribution of diseased tissue.[21] Additionally, the infrequent staining of BAL cells with CD1a in labs, cost, and quality control issues are noted.[21,24] Studies show a low diagnostic sensitivity for BAL.[15,17,24] In our series, no patients required bronchoscopy and BAL for diagnostic purposes.

LCH treatment follows the Histiocyte Society's LCH-IV protocol, which doesn't specify a lung involvement treatment arm. Standard initial therapy includes prednisone and vinblastine.[15,25] In our study, 29 patients received vinblastine-based treatments, while others received varying regimens. Clofarabine and targeted mitogen-activated protein kinase (MAPK) pathway therapies like BRAF and MEK inhibitors show promise for refractory LCH.[15,25]

The best approach to prevent recurrent pneumothorax in childhood LCH is not fully established.[11,26] Tube thoracotomy and

pleurodesis are common treatments, with pleurodesis recommended after the first recurrence.[15,27] Although chemotherapy protocols for LCH can slow disease progression, they don't prevent pneumothorax. In our study, all patients with pneumothorax underwent pleurodesis after being treated with chest tube drainage, using agents like talc, bleomycin, and tetracycline, in line with literature findings.[26,28,29] Patients with severe cases may require intensive care, and strategies to prevent air leak recurrences are crucial. ECMO can provide support during intensive care or bridge to lung transplantation.[2,12,15] Le Louet et al.[11] showed that 17 (15%) of 111 children diagnosed with pLCH required intensive care, and 10 of 17 children required mechanical ventilation.

In pediatric LCH, organ involvement significantly impacts prognosis. Single-system LCH boasts nearly 100% survival, but multisystem disease increases mortality risks, with a higher rate of recurrence and complications. Multisystemic LCH without risk organ involvement has a 5-year survival of 98%, dropping to 77% with such involvement.[30] Ronceray et al.[3] reported that 52% of pLCH patients had risk organ involvement, which didn't affect survival at diagnosis. Similarly, our study found 49% with risk organ involvement, with no impact on 10-year survival outcomes. Pulmonary LCH, often part of multisystemic LCH, contributes to morbidity but isn't a standalone prognostic factor. Studies report a 5-year OS of about 93.6% and event-free survival of about 55.7% for children with pulmonary LCH, with intensive care cases showing a 62.7% survival rate.[1,11] In our study, the 10-year OS rate was 63.3%. This rate is considered low and is likely due to most patients being diagnosed and treated before the 1990s, which implies that recent advancements in treatment and supportive care have improved outcomes. Even with severe lung involvement, early diagnosis and treatment lead to a good prognosis for pLCH. Early management can mitigate complications like pneumothorax and respiratory failure, reducing the risk of chronic conditions like fibrosis and restrictive lung disease.[12,19]

Our study on pLCH in children faces limitations due to its retrospective nature, limited patient data, and being a single-center study with a small sample size. Additionally, not all patients had lung biopsies, and early cases lacked a chest CT. Despite these constraints, our study contributes valuable insights into pLCH, an area lacking comprehensive data in Türkiye.

In summary, children with pLCH have high survival rates, yet pulmonary involvement, while not independently impacting survival, can cause serious long-term effects if untreated. Prompt and effective treatment is essential for managing pulmonary symptoms and preventing irreversible damage. As Türkiye lacks specific data on pLCH in children, aligning local findings with global research is critical to establishing national guidelines.

Ethical approval

Approval was obtained from the Non-Interventional Clinical Researches Ethics Board of Cumhuriyet University (dated 21.09.2023, no: 2023-09/21). The study was conducted according to the principles of the Declaration of Helsinki.

Author contribution

The authors confirm their contribution to the paper as follows: study conception and design: ÇC, TK; data collection: ÇC, TK; analysis and interpretation of results: ÇC, TK, BY, BO, DO, EY, EM, İYB, UÖ, BA, NK, AV, MH; draft manuscript preparation: ÇC, TK. 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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