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Lymphadenopathies Associated with Cat-Scratch Disease in Turkiye

Türkiye'de Kedi Tırmığı Hastalığı ile İlişkili Lenfadenopatiler

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Abstract

Aim: *Bartonella henselae* is the etiologic agent of cat-scratch disease. The disease affects children and young adults. The objective of this study is to analyze the epidemiology, clinical features, and course of this disease in Turkiye.

Material and Method: Children without immunodeficiency, with relevant clinical signs and symptoms, and positive serology were included in the study. Clinical, demographic and laboratory data of patients diagnosed with cat-scratch disease between October 2018 and February 2021 were evaluated retrospectively.

Results: A total of 46 patients were included. The mean age was 132 months (IQR 90- 153 months), and 69.6% (n=32) were male. There was a history of cat contact in 73.9% of the patients and 43.5% of these were with household cats. Most of the lymphadenopathies were axillary (73.9%), and generalized lymphadenopathy was not observed. The median duration of symptoms before admission was 4 weeks. The median ultrasonographic lymphadenopathy size was 4 cm. The median clinical improvement time was 6.5 weeks. Azithromycin was given in 18 patients and intravenous and/or oral beta-lactamase inhibitor combination therapy in 18 patients while no treatment was necessary in 10 patients.

Conclusion: The typical presentation is a solitary, enlarged lymph node, mostly in the axillary region. *Bartonella henselae* IgG level should be studied prior to invasive procedures. It should be known that cat- scratch disease can develop without a history of cat contact. Meanwhile, it should be known that contact with a house cat may cause disease more often than contact with street cats.

Keywords: *Bartonella henselae*, cat-scratch disease, children, lymphadenopathy

Öz

Amaç: *Bartonella henselae*, kedi tırmığı hastalığı etkenidir. Hastalık çocukları ve genç yetişkinleri etkiler. Bu çalışmanın amacı, Türkiye'de bu hastalığın epidemiyolojisini, klinik özelliklerini ve seyrini analiz etmektir.

Gereç ve Yöntem: İmmün yetmezliği olmayan, hastalık bulgu ve semptomlarına sahip ve pozitif serolojisi olan çocuklar çalışmaya dahil edildi. Ekim 2018 ile Şubat 2021 arasında kedi tırmığı hastalığı tanısı alan hastaların klinik, demografik ve laboratuvar verileri retrospektif olarak değerlendirildi.

Bulgular: Toplam 46 hasta çalışmaya dahil edildi. Ortalama yaş 132 ay (IQR 90-153 ay) ve %69,6'sı (n=32) erkekti. Hastaların %73,9'unda kedi teması öyküsü mevcuttu ve bunların %43,5'i evcil kediydi. Lenfadenopatilerin çoğu aksiller (%73,9) idi ve jeneralize lenfadenopati izlenmedi. Başvurudan önceki medyan semptom süresi 4 haftaydı. Medyan lenfadenopati boyutu 4 cm idi. Medyan klinik iyileşme süresi 6.5 haftaydı. 18 hastaya azitromisin, 18 hastaya intravenöz ve/veya oral beta-laktamaz inhibitör kombinasyon tedavisi verilirken, 10 hastaya tedavi gerekmedi.

Sonuç: Tipik prezentasyon, çoğunlukla aksiller bölgede soliter, büyümüş bir lenf nodudur. *Bartonella henselae* IgG düzeyi, invaziv prosedürlerden önce çalışılmalıdır. Kedi tırmığı hastalığının kedi teması öyküsü olmadan da gelişebileceği bilinmelidir. Aynı zamanda ev kedisi ile temasın sokak kedileriyle temastan daha sık hastalığa neden olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: *Bartonella henselae*, kedi tırmığı hastalığı, çocuklar, lenfadenopati

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INTRODUCTION

Bartonella henselae is an uncommon, intracellular, slow-growing, Gram-negative bacillus and is the most common agent of cat-scratch disease (CSD).[1] Kittens, stray cats, and cats infested with fleas represent the main vectors for human infection. Transmission to humans can result from the scratch or bite of a cat infected with *B. henselae*, as well as from exposure to cat fleas infected with the microorganism. Transmission can also occur following the contact of cat saliva with broken skin or mucosal surfaces (e.g., the mouth and eyes).[2,3] A low percentage of healthy dogs have been found to be asymptomatic carriers of *Bartonella henselae* but their role in CSD remains unclear. However, the absence of a cat in the environment or the lack of a history of being scratched does not exclude the diagnosis of CSD. [4] No evidence of person-to-person transmission exists. The disease is especially prevalent in children and young adults.[2] CSD begins with a primary inoculation lesion, which typically persists for one to three weeks. Enlarged lymph nodes appear next to the inoculation site two weeks later. The adenopathy evolves to a suppurative phase in about 10-15% of the cases .[5,6] It's typical presentation is a self-limiting lymphadenitis of the regional lymph nodes that can be accompanied by constitutional symptoms (e.g., fever, malaise, headache, nausea, abdominal pain).[7-10] CSD sometimes presents atypical signs (such as fever of unknown origin, osteomyelitis, optic neuritis, encephalitis, and endocarditis) and can rarely become a disseminated disease.[2] The manifestations of CSD can include visceral organ (especially hepatosplenic), neurological, and ocular involvement (e.g., Parinaud's oculoglandular syndrome).[7] We conducted a retrospective study of lymphadenopathy caused by *B. henselae*, using the data from a region with unknown prevalence. The objective of this study was to analyze the epidemiology, clinical features, and course of this disease in a tertiary children's care hospital in Turkey.

MATERIAL AND METHOD

Study Design and Population

This retrospective study was conducted in the 2018-2021 period at the Samsun Training and Research Hospital, a tertiary pediatric care hospital in Samsun, Turkey. A total of 46 patients diagnosed with lymphadenopathy associated with CSD and referred to the Pediatric Infectious Diseases Clinic of the Samsun Training and Research Hospital from Samsun and neighboring provinces were analyzed retrospectively. The *Bartonella henselae* indirect immunofluorescence assay (IFA) for IgG was sent to the national reference laboratory (Republic of Turkey Public Health General Directorate, Microbiology Reference Laboratories and Biological Products Department, High Risk Pathogens Reference Central Laboratory) at least once in all patients with a pre-diagnosis of CSD. The demographic-clinical characteristics, contact history, laboratory and radiological findings, *Bartonella henselae* IFA IgG values, and response to treatment were statistically evaluated. Biochemical tests, acute phase reactants, and lymphadenopathy imaging were performed in all patients. In addition, the toxoplasma, cytomegalovirus, rubella, Epstein-Barr virus, and Francisella tularensis serology was evaluated together with the Brucella Coombs test regarding the etiology of the lymphadenopathy. The Mantoux test, abdominal ultrasound, and chest X-ray examinations were performed when necessary.

The diagnosis of CSD is based on a characteristic clinical presentation, history, and supportive serological and/or nonserological tests. A positive serological test titer is defined as ≥1:256 in CSD-associated lymphadenopathies. Titers of 1:64 or 1:128 represent possible Bartonella infection, and repeat testing should be performed in 14-21 days (Ig G seroconversion). Nonserological tests include tests such as histopathology, polymerase chain reaction (PCR), and blood or tissue cultures (2,3,5). In our study, the diagnosis was made by clinical and serological tests (*Bartonella henselae* IFA IgG).

Patients with systemic involvement and/or immunodeficiencies were excluded, and patients with isolated lymphadenopathy or lymphadenitis were included. Clinical improvement was defined as greater than 80% reduction in lymph node size, normalization of C reactive protein (CRP), and normalization of leukocytosis (in patients with this finding). Enlargement of the lymph nodes together with pain, skin changes, edema, fever, and/or purulent exudate was accepted as lymphadenitis.

Patients who were clinically and/or ultrasonographically compatible with lymphadenitis were given beta-lactamase inhibitor therapy until their serological tests were concluded. Oral azithromycin treatment was given to patients whose serology results, clinical history and examination findings were compatible with CSD. Patients diagnosed with CSD by serology tests were followed without treatment if they achieved clinical improvement in this period.[2,5]

Patients with and without treatment, patients with and without a history of contact, and patients with head-neck and axillary lymphadenopathy were compared with each other in terms of clinical and laboratory findings and treatment response. In addition, those with a history of cat contact were divided into those in contact with a household cat and those in contact with a stray cat, and clinical and laboratory findings and treatment responses were compared. Patient data were also compared in patients with and without signs of lymphadenitis, based on laboratory data and clinical responses.

Ethics Committee Approval

The study was carried out with the permission Samsun University Clinical Researches Ethics Committee (Date: 23.11.2022, Decision No: 2022/12/6). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analyses

All statistical analyses were conducted using SPSS software (version 25; IBM, Chicago, IL). The data of the patients were collected retrospectively from the hospital records. Normality of distribution of the continuous variables was measured with the one-sample Kolmogorov-Smirnov test. The continuous variables with a normal distribution were expressed as mean±SD and compared using Student's T-test, while the variables with a non-normal distribution were expressed as median (min-max) and compared using the Mann-Whitney U test. Categorical variables were compared using the 2 test or Fisher's exact test. A p value < 0.05 was considered to indicate statistical significance for all analyses.

RESULTS

A total of 46 patients were included. The median age was 132 months (IQR 90- 153 months), and 69.6 % (n=32) were male. The median duration of symptoms before admission was 4 weeks (3.75-6.5 weeks). Most lymphadenopathies (95.6%) were in a single region of the body, mainly the axillary (73.9%), while generalized lymphadenopathy was not observed. The demographics, clinical and laboratory findings, treatment, outcome, and exposure findings of the children with lymphadenopathies associated with CSD are shown in **Table 1**.

Table 1. Demographics, Clinical and Laboratory Findings, Treatment, Outcome, and Exposure among Children with Lymphadenopathies Associated with CSD

Characteristics	n=46	%
Age, months (median, IQR1)	132 (90-153)	
Age Groups		
0–6 years	8	17.4
6–12 years	12	26
13–18 years	26	56.5
Sex		
Female	14	30.4
Male	32	69.6
Cat Exposure		
Household cats	20	43.47
Stray cats	14	30.4
None	12	26
Location of solitary lymphadenopathies		
Axillary	34	73.9
Cervical	10	21.7
Submandibular	2	4.3
Presence of lymphadenitis signs		
Yes	18	39.1
No	28	60.9
Reason for prescribing antibiotic treatment		
Protracted lymphadenopathy	38	82.6
Lymphadenopathies associated with fever	8	17.4
Presence of leukocytosis		
Yes	18	39.1
No	28	60.9
Antibiotic prescribed		
Azithromycin	18	39.1
Azithromycin plus beta-lactamase inhibitor	18	39.1
None	10	21.7

1IQR: Interquatile range

Eight of the patients with lymphadenopathies were admitted and received treatment while being evaluated for the etiology as an inpatient. In the whole patient group (inpatient and outpatient), pathological, non-infectious ultrasound findings were detected in eight (17.3%) patients along with the lymphadenopathy while abscess findings were not detected in any of the patients on ultrasonography.

A lymph node biopsy was performed in four patients when the lymphadenopathy and/or lymphadenitis demonstrating pathological dimensions and ultrasonography findings did not improve with nonspecific treatment. These patients were referred to the Pediatric Infection Department when the pathology result was consistent with granulomatous inflammation. PCR hybridization tests were not evaluated for Bartonella in lymph node biopsies. One of these patients had a history of contact with a house cat. The granulomatous infectious causes were investigated in this patient and *Bartonella henselae* IgG titers were found to be high (1/512). The other three children did not have a history of cat contact but had high *Bartonella henselae* IgG values.

Eighteen (39.1%) of the patients had lymphadenitis findings. The lymphadenopathy was found to be larger (p:0.043) and the CRP value to be significantly higher (p:0.000) in this group when compared to the other patients. All patients with lymphadenitis had leukocytosis (p<0.001). The median CRP level was 10 mg/L (5-80). There was a positive correlation between the increase in lymphadenopathy size and the CRP level (p:0.003, r:0.424).

The median lymphadenopathy size (ultrasonographic measurement) was 4 cm (3-4 cm). The median clinical improvement time was 6.5 weeks (3-12 weeks). Increased lymphadenopathy size indicated a longer time until clinical improvement (p:0.023, r:0.335).

There was a history of cat contact in 73.9% of the patients, and 43.5% of these were with household cats. None of the patients had a history of dog bite or contact. Only one of the patients had a history of a papule at the bite or/and scratch site. The mean clinical improvement time following a scratch by a household cat was shorter than that of stray cat contact (p:0.004). Axillary lymphadenopathy was more common in those with a history of cat contact, while cervical and submandibular lymphadenopathy was more common in those without a contact history (p:0.001). There was no significant correlation in lymphadenopathy size, clinical improvement time, duration of symptoms before admission, *Bartonella henselae* (IFA) IgG titer, CRP levels, location of lymphadenopathy, and history of azithromycin therapy between the patients with and without a contact history (**Table 2**).

Table 2. The clinical and laboratory characteristics of the patients according to cat contact history

	Patients with cat contact history	Patients without cat contact history	p
Lymphadenopathy size (cm)	4 (3-4)	4 (4-4)	0.423
Time to clinical improvement (weeks)	6 (6-8)	5 (4-8)	0.304
Duration of symptoms before admission (weeks)	4 (3-8)	4 (4-4)	0.539
Location of lymphadenopathy Axillary Cervical and submandibular	 30 4	 4 8	0.001
CRP1 (mg/L)	8 (4.75-74)	44 (6-80)	0.269
Azithromycin treatment Yes No	 28 6	 8 4	0.416

1CRP: C reactive protein

Hepatomegaly was noticed on the physical exam in 5 of the 46 (10.8%) patients and on ultrasonography in 7 (15.2%) patients. Splenomegaly was not detected in any patient. None of the patients had microabscesses in the liver and/or spleen on ultrasonography.

Time of symptom onset was most commonly the autumn (43.5%), followed by the winter (26%), summer (21.7%), and spring (8.7%). Most of the diagnoses were made during October (n=8, 17.4%) (**Figure 1**).

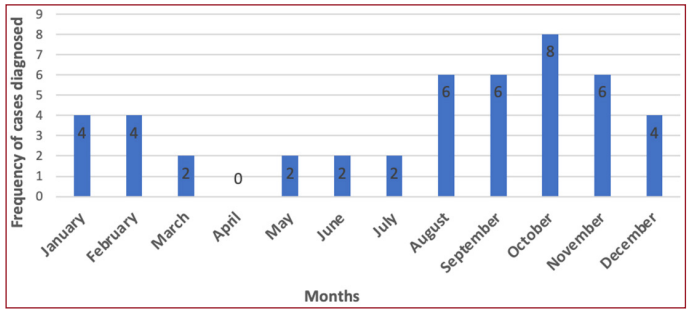

FIGURE 1- Number of lymphadenopathies associated with CSD in each month, n=46

The *Bartonella henselae* (IFA) IgG titer was 1/1024 in 6/46 patients (13%), 1/512 in 22/46 (47.8%), 1/256 in 16/46 (34.8%), and 1/128 in 2/46 (4.3%). Both of the patients with a titer of 1/128 had a history of contact and straching, and the lymphadenopathy regressed after treatment. For socioeconomic reasons, the patients did not apply for the control *Bartonella henselae* IgG test for IgG seroconversion. Clinical improvement was achieved in these two patients after treatment. There was a negative correlation between the *Bartonella henselae* (IFA) IgG titer and the duration of symptoms before admission (p:0.001, r: -0.474).

The patients received oral azithromycin 10 mg/kg on day 1 followed by 5 mg/kg for 4 days, and intolerance was not observed. Azithromycin was given to 18/46 (39.1%) patients while intravenous and/or oral combination beta-lactamase inhibitor and azithromycin therapy was given in 18/46 (39.1%) patients. Ten (21.7%) of the patients did not receive any treatment. All patients who received dual therapy had findings of lymphadenitis. No side effects related to azithromycin were observed. The dimensions of the lymphadenopathy in the follow-up of patients who did not receive antibiotics regressed until the time that results of tests such as serology and radiological imaging were obtained, and no signs of disseminated disease developed in the follow-up. Azithromycin treatment was given more frequently to patients with axillary lymphadenopathy (p:0.012). Those who received azithromycin treatment had higher CRP values than those who did not (p:0.001). There was no statistically significant difference in time from onset of symptoms to diagnosis, the lymphadenopathy size, time to clinical improvement and *Bartonella henselae* (IFA) IgG titer between the groups that received and did not receive treatment (**Table 3**).

Table 3. The clinical and laboratory characteristics of the patients according to azithromycin treatment

	Patients with azithromycin treatment	Patients without azithromycin treatment	p
Lymphadenopathy size (cm)	4 (3-4)	4 (3-4)	0.427
Time to clinical improvement (weeks)	6 (4-8)	6 (5.25-6.5)	0.319
Duration of symptoms before admission (weeks)	4 (3.25-8)	4 (3.75-4)	0.256
Location of lymphadenopathy Axillary Cervical and submandibular	 30 6	 4 6	0.012
CRP1 (mg/L)	41 (7-80)	5 (4-6)	0.001

1CRP: C reactive protein

DISCUSSION

Infections due to *Bartonella henselae* have a worldwide distribution and affect both the adult and pediatric population. CSD can present with a broad range of clinical symptoms ranging from asymptomatic infection to disseminated disease (7-9). CSD has been found to cause solitary lymphadenopathy most commonly in pediatric patients.[7,11]

The differential diagnosis for lymphadenopathy in pediatrics is broad. Often, the history and physical examination allow the determination of the correct diagnosis and beginning the appropriate treatment quickly. However, it may be difficult to determine the cause of lymph node enlargement, especially in the case of persistent lymphadenopathy, and the exact etiology may not be determined despite extensive investigations and invasive procedures such as histopathological examination. While most studies have reported higher rates of head and neck lymphadenopathy (52-65%),[7,11] we found axillary lymphadenopathy, which generally requires further evaluation, to be more common (73.9%) with most of these patients having a history of cat contact. This provides the opportunity to follow up patients

with axillary lymphadenopathy without the need for a histopathological sample. In the present study, most of the lymphadenopathies were persistent lymphadenopathy, and the median duration of lymphadenopathy was four weeks. The *Bartonella henselae* IgG assay should be performed before invasive procedures such as pathology, as it is known that the serological response develops when symptoms begin.[5] However, four of our patients were referred to the Department of Pediatric Infectious Disease for diagnosis with the pathology results after a lymph node biopsy had been performed. In addition to the lymphadenopathy dimensions, 17.3% of the patients in our study had pathological, non-infectious USG findings. While all these reasons require the etiology to be found quickly, querying a cat contact history in the anamnesis should not be forgotten and CSD should also be considered.

There is no clear consensus regarding the necessity of treatment in lymphadenopathies due to *Bartonella henselae* in immunocompetent children. While some publications recommend follow-up without treatment,[8-13] some have demonstrated that antibiotic therapy reduces the duration of symptoms.[5,14-6] Practice guidelines for the treatment of CSD, the Italian guidelines, and the Infectious Diseases Society of America (IDSA) recommend oral therapy with azithromycin.[13,17] In some patients, the lymph nodes may be painful and there may be a protracted course with the formation of abscesses and fistulas. Some studies have highlighted the need for antibiotic therapy or even multiple drainage procedures in these patients.[5] If a suppurative process develops, evacuative aspiration is recommended but an incision and drain placement are not as a chronic fistula may develop.[6] A high percentage of patients received treatment, and azithromycin was used in all. Although lymphadenitis and/or suppuration findings were present in patients with lymphadenopathy due to CSD, beta-lactamase inhibitor combination therapy was also given to 18 of the patients due to the lymphadenitis findings. Serology tests were conducted at the national laboratory and the results were delayed, and some patients did not have a history of cat contact. Azithromycin treatment was not given to ten patients due to regression of lymphadenopathy dimensions before the serology and laboratory results were obtained. No progression to abscess formation or disseminated disease was observed in the follow-up of the patients.

The infection is transmitted by direct inoculation through the scratch or bite of the reservoir, especially cats, although exposure to dogs and flea bites have also been linked to this infection. Some publications report that the disease can be transmitted to humans through the bite of a flea (Ctenocephalides felis), the vector responsible for horizontal transmission of the disease among cats. It is also mentioned that tick bites could transmit the bacteria.[18] A contact history with an animal is reported with varying frequencies in different studies (68.7%-92.4%).[7,19] In our study, a cat contact history was present in 73.9% of the cases, and axillary lymphadenopathy was more common in such patients. However, the absence of this epidemiological history in children with a clinically and serologically diagnosed disease may be due to sporadic contact unrecognized by the family or to another type of infection that has not been determined yet.

Although *Bartonella henselae* can be found in up to 71.4% of cats, the infected cats generally do not show any sign of disease.[20] The prevalence in cats varies depending on geographic location, the climate, the cat population, flea infestations, and age. *Bartonella henselae* can found in both household and stray cats. It is more common in cats under the age of one.[21-24] Contrary to publications showing that contact with stray cats more commonly leads to the disease,[23,25,26] contact with household cats was more frequent in our study, similar to the study of Derebegius et al.[11] The reason may be that household cats are mostly domestic cats that are allowed to go outdoors, and their interaction with the environment could have resulted in their becoming infected. The mean time to clinical improvement following a scratch by a household cat was shorter than that of stray cat contact. The reason could be fewer bacteria, or fewer fleas that carry these bacteria, in household cats. In other words, even if CSD is more common following contact with a household cat, recovery was achieved in a shorter time. A negative correlation was found between the *Bartonella henselae* (IFA) IgG titer and the duration of symptoms before admission in this study. This may be associated with the low serological response that occurs with low bacterial load in immunocompetent subjects, as evaluated in this study, and the prolonged time required for clinical signs to appear.

Bartonella infection has a clear affinity for the pediatric population and temperate regions with a greater incidence in the late summer, autumn, and winter seasons.[5,7,19,24,27] Some authors believe that seasonal changes in animal reproductive behavior or flea seasonality may be an explanation for this seasonal preference.[19,24,28,29] Cats usually become pregnant in the spring or early autumn, and the gestation lasts about nine weeks. Contact of kittens with children, which is a common cause of the disease, and possible transmission of CSD usually occur in the late summer and mid-winter.[19,29] The link between seasons and CSD incidence has been described in the USA, Japan, and France with increased incidence in the autumn and a decrease in the spring.[29] The patients who presented at our hospital lived in the Black Sea region, with a temperate and humid climate. As with other studies, we found that most cases were diagnosed in the autumn.[5,7,19,24,27]

The current study has the highest number of lymphadenopathy cases due to CSD in pediatric patients in Turkey, as far as we are aware, and confirms that CSD is not rare in Turkey. Most of the lymphadenopathies were persistent cases in the current study, and the median duration of lymphadenopathy was four weeks. Clinicians should have a high degree of suspicion for CSD as early diagnostic tests can

accelerate the diagnosis and facilitate patient care, especially in patients presenting from a temperate climate zone and in autumn. The *Bartonella henselae* IgG assay should be performed before invasive procedures. The treatment rate was high in the current study. None of the patients with persistent lymphadenopathy developed disseminated disease, an abscess, or fistula during follow-up, and no treatment-related side effects were observed. Querying cat exposure will facilitate the diagnosis. However, it should be known that CSD can develop without a history of cat contact, and contact with a household cat may also cause the disease (even more commonly). We should accept that this is not a rare condition, as CSD can vary from harmless to very serious forms and the diagnosis and treatment should be quickly and carefully performed. Studies showing disease prevalence rates in cats, and clinical and therapeutic studies of CSD are needed.

Infections due to *Bartonella henselae* have a worldwide distribution and affect especially children. CSD can present with a broad range of clinical symptoms ranging from asymptomatic infection to disseminated disease and solitary lymphadenopathy most commonly in pediatric patients. In the present study, lymphadenopathies were commonly axillary lymphadenopathy. CSD can mostly develop after animal contact, also it can occur without contact, while contact with household cat may also cause the disease, even more frequently than contact with stray cats. There is no clear consensus regarding the necessity of treatment in lymphadenopathies due to *Bartonella henselae* in immunocompetent children. A high percentage of our patients received treatment, and azithromycin was used in all. The diagnosis is based on a clinical suspicion for lymphadenopathies associated with CSD, as early diagnostic tests can accelerate the diagnosis and facilitate patient care, especially in patients presenting from a temperate climate zone and in autumn.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission Samsun University Clinical Researches Ethics Committee (Date: 23.11.2022, Decision No: 2022/12/6) .

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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