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Original Article

Evaluation of childhood malignancies presenting with musculoskeletal manifestations from two different divisions: a multicenter study

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ABSTRACT

Background. The aim of the study was to evaluate the approaches of pediatric rheumatologists and pediatric hematologists to patients with similar musculoskeletal (MSK) complaints and to highlight the differences that general pediatricians should consider when referring patients to these specialties.

Methods. This is a cross-sectional study involving the patients who applied to pediatric rheumatology centers with MSK complaints and were diagnosed with malignancy, as well as patients who were followed up in pediatric hematology centers with a malignancy diagnosis, and had MSK complaints at the time of admission.

Results. A total of 142 patients were enrolled in the study. Of these patients, 83 (58.4%) applied to pediatric rheumatology centers, and 59 (41.6%) applied to pediatric hematology centers. Acute lymphoblastic leukemia (ALL) was the most common diagnosis among the patients who applied to both centers, with 80 cases (56.3%). The median age of diagnosis was 87 (interquartile range, IQR: 48-140) months. The most common preliminary diagnosis in pediatric rheumatology centers was juvenile idiopathic arthritis (JIA), with 37 cases (44.5%). MSK involvement was mainly seen as arthralgia, and bone pain. While arthralgia (92.7%) was the most common complaint in rheumatology centers, bone pain (88.1%) was more common in hematology centers. The most frequently involved joints were the knee (62.9%), ankle (25.9%), hip (25%), and wrist (14%). The most common laboratory abnormalities were high lactate dehydrogenase (LDH), high C-reactive protein (CRP), anemia, and high erythrocyte sedimentation rate (ESR). Thrombocytopenia, neutropenia, and high LDH were statistically significantly more frequent in patients admitted to hematology centers than in patients admitted to rheumatology centers ($p<0.001$, $p=0.014$, $p=0.028$, respectively). Patients who applied to rheumatology clinics were found to have statistically significantly higher CRP levels ($p=0.032$).

Conclusions. Malignancies may present with only MSK system complaints in childhood. Therefore, malignancies should be included in the differential diagnosis of patients presenting with MSK complaints.

Key words: musculoskeletal complaints, malignancy, pediatric rheumatology, pediatric hematology.

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Musculoskeletal (MSK) system complaints are one of the most common symptoms in childhood. It is observed in approximately half of the school-age children.[1] In the majority of patients, the underlying cause is of a traumatic or benign origin. Nevertheless, cancer patients can also present with MSK system complaints. Some patients presenting with only MSK complaints may have cancer as the underlying cause. While most of the patients present with systemic findings such as fever, weight loss, night sweats, pallor, palpable mass, bleeding, bruising, vomiting and headache, in some cases, MSK complaints are the first and only symptom.[2,3] As a result, patients are referred to other medical specialties, such as rheumatology. Moreover, because systemic symptoms such as fever, weakness, weight loss, and skin rash can be confused with the symptoms of systemic rheumatic diseases in cancer patients, rheumatologists may experience diagnostic delays when investigating the diagnosis of rheumatic disease. Used in treating rheumatic diseases, immunosuppressive agents and corticosteroids, may also cause delays in diagnosis. Whereas, the most critical condition that determines the 5-year survival of patients is the early diagnosis and treatment of cancer.[4]

The most common MSK complaints are bone pain, arthritis, and arthralgia. Primary tumors of bone, cartilage, muscle, or fibrous tissue, leukemic infiltration of bone, or paraneoplastic conditions are the causes of these complaints.[5] The character of the pain is very important for the differential diagnosis. Severe bone pain, especially at night, suggests malignancy, while pain with morning stiffness suggests juvenile idiopathic arthritis, but it is not always easy to make this distinction.

Since the time to diagnosis has a direct impact on the prognosis of these patients, the approaches and referrals of general pediatricians who see them for the first time are directly related to their prognosis. First of all, after a wide differential diagnosis including malignancies, traumatic, infectious, and rheumatic causes, the patients should be referred to the appropriate field based on the diagnosis considered.

Our aim in this study is to evaluate the approaches of pediatric rheumatologists and pediatric hematologists to patients with similar MSK complaints and to highlight the differences that general pediatricians should consider when referring patients to these specialties.

Material and Methods

This was a cross-sectional study involving both pediatric rheumatology and pediatric hematology centers. Patients from nine pediatric rheumatology centers and three pediatric hematology centers in Türkiye were included in the study between June 2016 and October 2022. Patients who applied to pediatric rheumatology centers with MSK complaints and were diagnosed with malignancy, as well as patients who were followed up in pediatric hematology centers with a malignancy diagnosis, and had MSK complaints at the time of admission, were selected.

Clinical and laboratory features were recorded from the medical charts and electronic files of the patients retrospectively. In all cases, a definitive diagnosis was made by bone marrow examination or histological examination of surgical specimens.

C-reactive protein (CRP) > 5 mg/L and the first hour's erythrocyte sedimentation rate (ESR) > 20 mm were defined as elevated inflammatory markers. White blood cell (WBC) >10000 10^6/L was defined as leukocytosis, WBC <4000 10^6/L as leukopenia, absolute neutrophil count (ANC) <1500 10^6/L as neutropenia, absolute lymphocyte count (ALC) < 1500 10^6/L as lymphopenia, hemoglobin <12 g/dL as anemia, platelet count <150000 10^6/L as thrombocytopenia, lactate dehydrogenase (LDH) > 225 U/L as high LDH, and uric acid >5.5 mg/dL as hyperuricemia. Patients with pain intensities of 7 or higher on the visual analog scale were classified as having severe pain.

The study protocol was reviewed and approved by the Ethics Committee of the University of Health Sciences, Ümraniye Training and Research Hospital (Approval No: B.10.1.TKH.4.34.H.GP.0.01/336) with the ethical principles laid down in the Declaration of Helsinki.

Statistical analysis

The statistical analyses were made using SPSS version 25.0. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether or not they were normally distributed. In the descriptive analysis, normally distributed variables were presented as mean ± standard deviation (SD), and non-normally distributed variables were presented as median and interquartile range (Q1-Q3). Categorical variables were compared with the chi square test. The Mann–Whitney *U* test was used to compare the non-normally distributed variables between independent two groups. One-way ANOVA was used to compare the parameters between the groups. An overall *p* value of less than 0.05 was considered to show a statistically significant difference.

Results

A total of 142 patients were enrolled in the study. Of these patients, 83 (58.4%) applied to pediatric rheumatology centers, and 59 (41.6%) applied to pediatric hematology centers. Among them, 67 (47%) were female and 75 (53%) were male. The median age of diagnosis was 87 (interquartile range, IQR: 14-211) months. The demographic, clinic, and laboratory characteristics of the patients are described in Table I.

The time between applying to pediatric rheumatology or pediatric hematology centers and receiving a diagnosis ranged from one day to 20 months. Acute lymphoblastic leukemia (ALL), and acute myeloblastic leukemia (AML) patients had the shortest time to diagnosis, with a median of 4 (IQR: 1-10) days, and 5 (IQR: 4-7) days. The patient with the longest diagnosis time of 600 days had recurrent arthralgia complaints, was diagnosed with familial Mediterranean fever (FMF), and was later diagnosed with Ewing sarcoma due to increased pain intensity in follow-ups. Fatigue (63.3%), fever (47.8%), hepatomegaly (45%), lymphadenopathy (44.3%), and splenomegaly (41.5%) were the most common findings accompanying MSK involvement. The duration of the fever ranged from one to 180 days. Patients with Ewing sarcoma had the shortest duration of fever, with mean of 3.5±0.7 days, while patients with neuroblastoma had the longest duration, with median of 19.5 (IQR: 11-97.5) days. The most common laboratory abnormalities were high levels of LDL (83.8%), high levels of CRP (80.9%), anemia (78.1%), and high levels of ESR (75.3%). Thrombocytopenia, neutropenia, and high levels of LDH were statistically significantly more frequent in patients admitted to hematology centers than in patients admitted to rheumatology centers ($p<0.001$, $p=0.014$, $p=0.028$, respectively). Patients who applied to rheumatology centers were found to have statistically significantly higher CRP levels ($p=0.032$) (Table I).

MSK involvement was mainly seen as arthralgia, and bone pain. While arthralgia (92.7%) was the most common complaint among patients admitted to rheumatology centers, bone pain (88.1%) was more common among patients admitted to hematology centers. The most frequently involved joints were the knee (38.7%), hip (17.6%), ankle (14%), and wrist (9.8%). The most common sites of bone pain were the lower extremity (52%), generalized bone pain (36.6%) and the lumbar region (16.9%). The details of MSK involvement are shown in Supplementary Table S1.

ALL was the most common diagnosis among patients who applied to both pediatric rheumatologists and pediatric hematologists. Eight patients were diagnosed with AML, all of whom were diagnosed at pediatric hematology centers. While non-Hodgkin lymphoma (NHL) and neuroblastoma were frequently diagnosed in pediatric rheumatology centers, other

Table I. Demographic, clinic, and laboratory characteristics of the patients in pediatric rheumatology and pediatric hematology centers.

	Rheumatology (n=83)	Hematology (n=59)	Total (n=142)	P value
Diagnosis age (months), median (IQR)	85 (47-141)	92 (48-140)	87 (48-140)	0.524
Gender (F/M)	36/47	31/28	67/75	0.284
Time to diagnosis (day), Median (IQR)	14 (3-41.2)	4 (2-10)	7 (2-30)	**0.002**
Fever days , Median (IQR)	7.5 (4-22.5)	5 (4-8)	7 (4-10)	0.056
Musculoskeletal involvement, n (%)	83 (100)	59 (100)	142 (100)	
Arthritis	16 (19.2)	11 (18.6)	27 (19)	0.552
Arthralgia	77 (92.7)	28 (47.4)	105 (73.9)	**<0.000**
Bone pain	47 (56.6)	52 (88.1)	99 (69.7)	**<0.000**
Constitutional symptoms, n (%)	57 (68.6)	44 (74.5)	101 (71.1)	0.283
Fever	39 (68.4)	29 (65.9)	68 (67.3)	0.466
Fatigue	49 (85.9)	41 (93.1)	90 (89.1)	0.107
Weight loss	21 (36.8)	15 (34)	36 (35.6)	0.569
Night sweats	10 (12)	8 (13.5)	18 (12.6)	0.491
Skin rash, n (%)	14 (16.8)	2 (3.3)	16 (11.2)	**0.010**
Lymphadenopathy, n (%)	27 (32.5)	36 (61)	63 (44.3)	**0.001**
Hepatomegaly, n (%)	26 (31.3)	38 (64.4)	64 (45)	**<0.000**
Splenomegaly, n (%)	21 (25.3)	38 (64.4)	59 (41.5)	**<0.000**
Abdominal pain, n (%)	22 (26.5)	11 (18.6)	33 (23.2)	0.187
Chest pain, n (%)	4 (4.8)	2 (3.3)	6 (4.2)	0.512
Headache, n (%)	4 (4.8)	5 (8.4)	9 (6.3)	0.294
Leukopenia, n (%)	9 (10.8)	7 (11.8)	16 (11.2)	0.527
Leukocytosis, n (%)	34 (40.9)	28 (47.4)	62 (43.6)	0.275
Neutropenia, n (%)	18 (21.6)	24 (40.6)	42 (29.5)	**0.014**
Lymphopenia, n (%)	11 (47.8)	4 (6.7)	15 (10.5)	0.190
Thrombocytopenia, n (%)	14 (16.8)	36 (61)	50 (35.2)	**<0.000**
Anemia, n (%)	65 (78.3)	46 (77.9)	111 (78.1)	0.560
High CRP, n (%)	72 (86.7)	43 (72.8)	115 (80.9)	**0.032**
High ESR, n (%)	70 (84.3)	37 (62.7)	107 (75.3)	0.512
High LDH, n (%)	65 (78.3)	54 (91.5)	119 (83.8)	**0.028**
High uric acid, n (%)	14 (16.8)	14 (23.7)	28 (19.7)	0.223

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, LDH: lactate dehydrogenase

cancers such as Hodgkin lymphoma (HL), osteosarcoma, Langerhans cell histiocytosis (LCH), and Ewing sarcoma were diagnosed in both centers (Fig. 1).

The most common preliminary diagnosis of patients who were referred to the pediatric rheumatology centers was juvenile idiopathic arthritis (JIA), with 37 cases (44.5%). Reactive arthritis, systemic JIA (sJIA)/macrophage activation syndrome (MAS), autoinflammatory diseases (AID), connective tissue disease (CTD), and vasculitis were the other preliminary diagnoses. The majority of patients who were referred with a preliminary diagnosis of JIA, reactive arthritis, sJIA/MAS, or AID were eventually diagnosed with ALL. Two of the four patients referred with a preliminary diagnosis of CTD were diagnosed with HL and two with NHL. Two patients who were referred with a preliminary diagnosis of vasculitis were diagnosed with NHL (Table II).

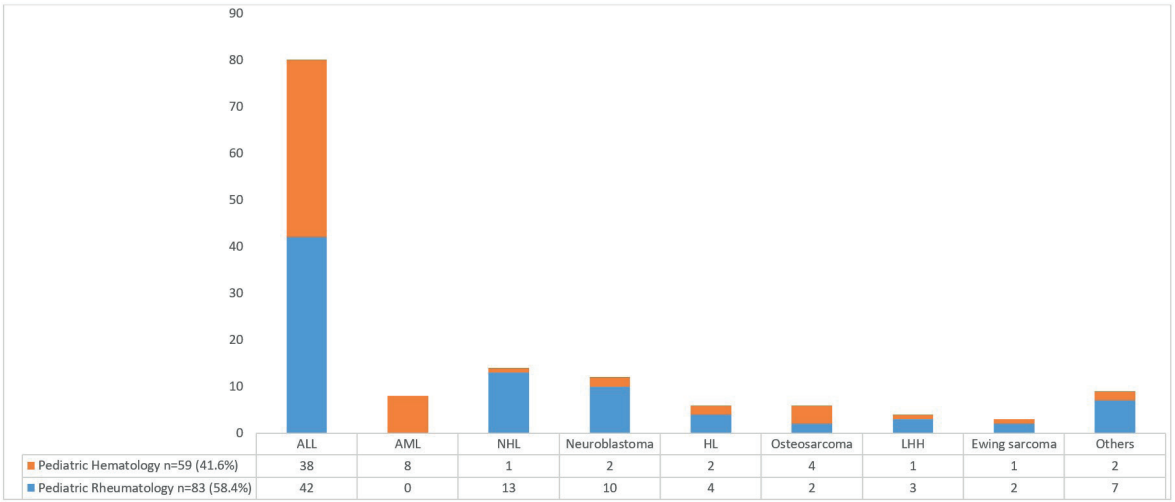

Fig. 1. The final diagnoses of the patients according to center type.

ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; NHL, Non-Hodgkin lymphoma; HL, Hodgkin lymphoma; LCH, Langerhans cell histiocytosis

Table II. The preliminary and final diagnoses of the patients referred to rheumatology centers.

		Preliminary Diagnoses						
		JIA n= 37	Reactive arthritis n= 17	sJIA/MAS n=13	AID n= 9	CTD n= 4	Vasculitis n= 2	Other n= 1
Final Diagnoses	ALL, n= 42	21	10	6	5	0	0	0
	Neuroblastoma, n= 10	2	3	4	1	0	0	0
	NHL, n= 13	4	1	3	1	2	2	0
	HL, n= 4	1	0	0	1	2	0	0
	Ewing sarcoma, n= 2	0	1	0	1	0	0	0
	LCH, n= 3	3	0	0	0	0	0	0
	Osteosarcoma, n= 2	2	0	0	0	0	0	0
	Other, n= 7	4	2	0	0	0	0	1

AID, autoinflammatory diseases; ALL, acute lymphoblastic leukemia; CTD, connective tissue disease; HL, Hodgkin lymphoma; JIA, juvenile idiopathic arthritis; LCH, Langerhans cell histiocytosis; NHL, Non-Hodgkin lymphoma; sJIA/MAS, systemic juvenile idiopathic arthritis/macrophage activation syndrome

In this study, 88 patients (61.9%) were diagnosed with hematological malignancy, whereas 54 patients (38.1%) were identified with solid malignancy. Among the subset of patients admitted to pediatric rheumatology, 50.6% were diagnosed with hematological malignancies. In contrast, a higher proportion (77.9%) of patients admitted to pediatric hematology clinics were diagnosed with a hematological malignancy. Patients with hematological malignancies had a younger age at diagnosis, shorter diagnosis time, fewer days with fever, and a higher proportion of males. Bone pain, constitutional findings, hepatomegaly, and splenomegaly were observed more frequently in hematological malignancies. In hematological malignancies, leukopenia, neutropenia, thrombocytopenia, anemia, high levels of ESR, and high levels of LDH were more common (Table III).

In hematological malignancies, the most common MSK involvement was bone pain, while arthralgia was the most common in solid malignancies. Hip pain was statistically more common in patients with solid malignancies (p=0.036). Lower limb pain was

Table III. Demographic, clinic, and laboratory characteristics of the patients in hematological and solid malignancies.

	Hematological malignancies (n=88)	Solid malignancies (n=54)	P value
Diagnosis age (months), median (IQR)	83 (45-114)	126 (59-176)	**<0.000**
Gender, (F/M)	35/53	32/22	**0.018**
Time to diagnosis (day), median (IQR)	4 (2-10)	30 (11-52)	**<0.000**
Fever days, median (IQR)	5 (3-10)	10 (4-30)	**0.019**
Musculoskeletal involvement, n (%)	88 (100)	54 (100)	
Arthritis	15 (17)	12 (22.2)	0.291
Arthralgia	61 (69.3)	44 (81.4)	0.078
Bone pain	70 (79.5)	29 (53.7)	**0.001**
Constitutional symptoms, n (%)	69 (78.4)	32 (59.2)	**0.013**
Fever	44 (63.7)	24 (75)	0.319
Fatigue	65 (94.2)	25 (78.1)	**0.001**
Weight loss	19 (27.5)	17 (53.1)	0.132
Night sweats	11 (12.5)	7 (12.9)	0.565
Skin rash n (%)	7 (7.9)	9 (16.6)	0.095
Lymphadenopathy, n (%)	41 (46.6)	22 (40.7)	0.286
Hepatomegaly, n (%)	47 (53.4)	17 (31.4)	**0.008**
Splenomegaly, n (%)	46 (52.7)	13 (24.1)	**0.001**
Abdominal pain, n (%)	19 (21.6)	14 (25.9)	0.346
Chest pain, n (%)	4 (4.5)	2 (3.7)	0.586
Headache, n (%)	7 (7.9)	2 (3.7)	0.263
Leukopenia, n (%)	15 (17)	1 (1.8)	**0.003**
Leukocytosis, n (%)	36 (40.9)	26 (48.1)	0.251
Neutropenia, n (%)	40 (45.4)	2 (3.7)	**<0.000**
Lymphopenia, n (%)	7 (7.9)	8 (14.8)	0.149
Thrombocytopenia, n (%)	48 (54.5)	2 (3.7)	**<0.000**
Anemia, n (%)	76 (86.3)	35 (64.8)	**0.003**
High CRP, n (%)	72 (81.8)	43 (79.6)	0.455
High ESR, n (%)	70 (79.5)	37 (68.5)	**0.032**
High LDH, n (%)	81 (92)	38 (70.3)	**0.001**
High uric acid, n (%)	21 (23.8)	7 (12.9)	0.108

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase

statistically more common in hematological malignancies (p=0.004). MSK involvement in hematological and solid malignancies is shown in Supplementary Table S2.

Discussion

To the best of our knowledge, this is the first study to compare patients with MSK complaints who applied to pediatric rheumatology and pediatric hematology centers and were diagnosed with a malignancy. In the literature, the studies of patients who initially present with MSK involvement and are subsequently diagnosed with malignancy are generally presented as case series.[6-10] Therefore, there is limited information available on this topic. We aimed with this study to determine which patients should be referred

to the pediatric hematology centers and which patients applying to the pediatric rheumatology centers should exercise greater attention.

In our study, ALL was the most common diagnosis among both pediatric rheumatologists and pediatric hematologists. In the literature, similar to our study, ALL is the most common childhood malignancy, and MSK complaints are frequently observed in these patients.[11,12] In the studies, the frequency of MSK complaints in ALL patients was found to be between 7.1% and 62.3%[2,13,14], while the frequency of malignancy in patients presenting with MSK complaints was between 0.25-2%.[5,6] That is why it should be kept in mind that patients who apply with MSK complaints could have a cancer, and physicians should be careful during the follow-up process.

Patients with ALL and AML had the shortest time to diagnosis in our study. In some subtypes of JIA such as systemic JIA, especially in patients with atypical involvement or complicated findings, the differential diagnosis of leukemia mostly needs to be made by bone marrow aspiration, and this may explain why the diagnosis time of ALL and AML patients is shorter than other malignancies.

In the present study, patients admitted to pediatric hematology had shorter intervals between diagnoses. Due to the fact that rheumatic diseases were considered in the differential diagnosis of patients admitted to pediatric rheumatology and anti-rheumatic drugs were administered to some of these patients, the time between diagnosis was lengthened. In the study of Kang et al.[15], they compared ALL cases with and without MSK complaints and found that those with MSK involvement had a longer time to be diagnosed. In the study of Brix et al.[3], it was reported that patients with arthritis had a long time to diagnosis compared to patients with arthralgia. Kittivisuit et al.[14] reported that patients with MSK involvement had fewer hematological abnormalities and peripheral blasts compared to those without. The results of these studies support the finding that the diagnosis time of patients who apply to pediatric rheumatology centers is prolonged.

In the present study, 16.8% of patients diagnosed with a malignancy in pediatric rheumatology centers complained of a rash. Because rashes are often the first symptom of most rheumatic diseases, especially sJIA, and vasculitis, these patients are frequently referred to pediatric rheumatology centers. As a result of this study, we concluded that in these patients, special attention should be paid to the presence of hepatomegaly, splenomegaly, and lymphadenopathy, and hematological parameters should be carefully evaluated.

In the present study, we observed that, among the patients referred with MSK involvement, arthralgia was most common in those referred to pediatric rheumatology centers, while bone pain was most common in those referred to pediatric hematology centers. Patients with arthritis were rarer in both groups. Similar to our study, the most common MSK finding in the literature was arthralgia, with the most commonly involved joints being the knee, hip, and ankle.[14,16,17] In the study of Civino et al.[18], hip involvement was found to be the most frequently involved joint in malignancies and was associated with malignancy. In the present study, hip involvement was observed more frequently, especially in solid malignancies. Therefore, in patients presenting with complaints of hip pain and low back pain, patients should be evaluated for malignancies such as osteosarcoma, Ewing sarcoma, neuroblastoma, and NHL before attributing the cause of pain to spondylitis, scoliosis, or mechanical low back pain. Bone pain, especially in the lower extremities, was observed more frequently in hematological malignancies in our study. Therefore, we believe that these patients should be approached with greater attention. Although pain with morning stiffness is an expected finding of JIA, it was seen in 5% of the patients in our study. For this reason, malignancy should always be kept in mind in the follow-up of patients who are considered to have JIA.

Joint diversity was found to be higher in patients who applied to pediatric rheumatology centers. We believe this is because the joint examination is part of the rheumatological assessment.

Thrombocytopenia was observed in 61% of patients who applied to pediatric hematology centers, while this rate was only 16% in pediatric rheumatology centers. In the study by Tamashiro et al.[19] in which they compared sJIA, and ALL patients, they found that thrombocytopenia was the most important factor that differentiated ALL from sJIA. Therefore, in the presence of thrombocytopenia accompanying MSK complaints, malignancy must be excluded.

The main limitation of our study was its cross-sectional design which was based on the clinical experience of pediatric rheumatologists and pediatric hematologists. Another limitation was that we did not compare the results with patients who applied to these centers and were diagnosed with non-malignant diseases. We believe that more prospective studies are needed on this topic.

In conclusion, malignancies may present with only MSK system complaints in childhood. Therefore, malignancies should be included in the differential diagnosis of patients presenting with MSK complaints. Especially in patients with bone pain, hip joint involvement, an atypical course, and thrombocytopenia, malignancy should be considered first and these patients should be referred to pediatric hematologists.

Supplementary materials

Supplementary materials for this article are available online at https://doi.org/10.24953/turkjped.2023.446

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the University of Health Sciences, Ü mraniye Training and Research Hospital (Approval No: B.10.1.TKH.4.34.H.GP.0.01/336) with the ethical principles laid down in the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BS and ŞÇ; data collection: ŞÇ, BŞK, ÖB, EB, BK, DGY, ACA, MÇ, GOY, KÖ, FÇ, HES, APK; analysis and interpretation of results: BS and ŞÇ draft manuscript preparation: BS and ŞÇ. All authors reviewed 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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