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Predictors of persistent polyarticular involvement in patients with systemic juvenile idiopathic arthritis

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ABSTRACT

Objective: The aim of this study was to determine the predictors at the time of diagnosis that could predict the course of persistent polyarticular disease in systemic juvenile idiopathic arthritis (sJIA) patients at follow-up.

Material and Methods: This retrospective observational study was conducted in patients diagnosed with sJIA in Ankara Bilkent City Hospitalbetween January 2002 and August 2024. The relationship between demographic, clinical, laboratory findings and complications in sJIA patients with and without persistent polyarticular involvement was analyzed.

Results: Of the 56 patients diagnosed with sJIA, 27 (48.21%) patients had monocyclic, 8 (14.28%) polycyclic, and 21 (37.50%) persistent disease course. Persistent arthritis was observed in 16 (28.57%) patients, with polyarticular pattern in 11 (19.64%). Polyarticular involvement at the time of diagnosis and involvement of the knee, hip, wrist and small joints of the hand were associated with persistent polyarticular arthritis ($p<0.001$, $p<0.001$, $p=0.001$, $p<0.001$, $p=0.003$). In addition, the use of steroids, conventional disease-modifying antirheumatic drugs (cDMARD) and biological disease-modifying antirheumatic drugs (bDMARD) combination and methotrexate, etanercept and tocilizumab were more common in persistent polyarticular arthritis ($p=0.018$, $p=0.027$, $p=0.006$, $p=0.018$).

Conclusion: Approximately 40% of sJIA patients develop a persistent disease course. Patients with early polyarticular involvement should be followed closely and carefully for persistent polyarticular course.

Keywords: Arthritis, Disease progression, Juvenile, Polyarthritis, Risk factors, Systemic juvenile idiopathic arthritis

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) is a unique type of juvenile idiopathic arthritis (JIA) characterized by systemic features including fever, arthritis, rash, diffuse lymphadenopathy, hepatomegaly, splenomegaly and/or serositis (1). Unlike other JIA subtypes, arthritis may not be present at the time of diagnosis and may develop over weeks, months or even years (2).

Patients with sJIA have findings indicating systemic inflammation at the time of diagnosis and flare-ups resembling autoinflammatory diseases may develop in the follow-up. Approximately 40% of patients have a monocyclic course while 10% develop a polycyclic course. On the other hand, a persistent course is observed in about 50% of patients. Monocyclic disease typically presents with a short period of active symptoms and usually results in favorable outcomes. Prior to biologic therapies, patients with a chronic disease course often experienced severe, erosive polyarticular arthritis. This often required long-term glucocorticoid use for symptom management and led to side effects associated with long-term glucocorticoid exposure. It is still unclear which patients will develop a polycyclic or persistent pattern (3,4). Nigrovic et al. (5) reported that early use of biologic therapies after diagnosis may provide a window of opportunity and prevent the development of polyarticular involvement.

It is very tempting to identify sJIA patients who are likely to develop polyarticular involvement in follow-up at the time of diagnosis so that biologic agents can be started early in the required patients. Because, a persistent disease with synovitis in patients with polyarticular involvement poses a significant clinical challenge and increases morbidity. The aim of this study was to determine the predictors at the time of diagnosis that could predict the course of persistent polyarticular disease in sJIA patients at follow-up.

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MATERIALS and METHODS

This retrospective observational study included patients who met the International League of Rheumatology Societies (ILAR) classification criteria for sJIA and were followed up in the pediatric rheumatology clinic of Ankara Bilkent City Hospital for at least 6 months between January 2002 and August 2024 (1). Diseases that could mimic sJIA such as infections, malignancies and autoinflammatory diseases were excluded. Patients with sJIA who had missing data and a follow-up period less than 6 months were also excluded from the study (Figure 1).

Patients' data were collected from Ankara Bilkent City Hospital electronic health records. Age at diagnosis, gender, clinical findings, duration of symptoms, time from presentation to diagnosis, presence and distribution of joint involvement, laboratory findings including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, white blood cell count (WBC), neutrophil counts, biochemistry parameters, fibrinogen, triglyceride were recorded. Treatments [nonsteroidal anti-inflammatory drugs, steroids, conventional disease-modifying antirheumatic drugs (cDMARDs) and biological disease-modifying antirheumatic drugs (bDMARDs), intravenous immunoglobulin (IVIG), plasmapheresis], duration of treatments, and complications [macrophage activation syndrome (MAS), interstitial lung disease (ILD), uveitis and persistent arthritis] were also noted. Disease activity score was calculated with systemic Juvenile Arthritis Disease Activity Score (sJADAS71) (6).

A diagnosis of sJIA was established in children under 16 years old who met the ILAR criteria: fever for more than 2 weeks (including at least 3 consecutive days), arthritis, and two or more of the following: rash, hepatomegaly, splenomegaly, lymphadenopathy, or serositis. (1). The diagnosis of MAS was made according to the 2016 MAS criteria. (7).

Using the Wallace criteria, clinical remission was defined as a 3-month period of inactive disease without the use of medications (8). The clinical course of the disease is categorized into three different groups: monocyclic, polycyclic, and persistent. In the monocyclic course, sJIA presents with a single episode of systemic symptoms and arthritis that resolves within 24 months. The polycyclic course is characterized by multiple flare-ups of active disease, interspersed with periods of remission. Persistent sJIA is defined as a lack of response to IL-1 and IL-6 inhibitors or the need for ongoing treatment with long-term glucocorticoids (longer than 6 months) with persistence of systemic and/or arthritic features (4,9,10). Persistent sJIA arthritis is defined as arthritis that persists despite treatment with IL-1 or IL-6 inhibitors, requiring maintenance glucocorticoid therapy and without significant systemic symptoms (11).

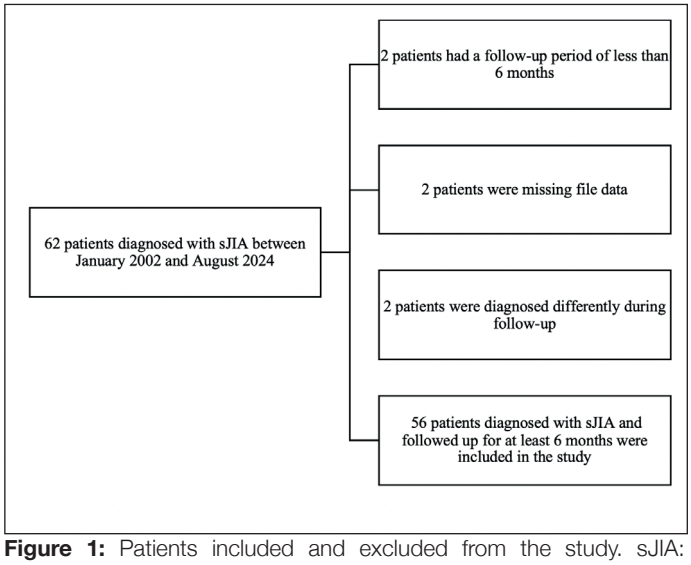

Figure 1: Patients included and excluded from the study. sJIA: systemic juvenile idiopathic arthritis

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Descriptive statistics were reported as, medians and interquartile ranges (IQR,Q1-Q3) for non-normally distributed and ordinal variables, and frequencies and percentagesfor categorical variables. For statistical comparisons, Mann–Whitney U test for non-normally distributed and ordinal variables, and chi-square or Fisher's exact tests for categorical variables. A p-value of less than 0.050 was considered statistically significant.

RESULTS

A total of 56 patients with sJIA were included in the study.

Demographic Characteristics, Clinical and Laboratory Findings of sJIA Patients

Of the 56 patients, 26 (46.42%) were female. The median (IQR) age at diagnosis was 89.50 (32.25-124) months. The median (IQR) duration of follow-up was 47 (17.50-63.75) months.

All patients had fever at diagnosis. The median (IQR) time from onset of fever to diagnosis was 20 (15-45) days. At the first flare-up, 45 (80.35%) patients had arthritis, of which 27 (48.21%) had oligoarticular involvement and 18 (32.14%) had polyarticular involvement.

Demographic characteristics, clinical features and laboratory findings at the onset of the disease are shown in Table I.

Course of sJIA Patients

Eleven patients (19.64%) developed MAS, 1 (1.78%) patient developed ILD, and 2 (3.57%) patients experienced uveitis as complications of the disease.

The disease course was monocyclic in 27 (48.21%) patients, polycyclic in 8 (14.28%) patients, and persistent in 21 (37.50%) patients. Persistent arthritis was observed in 16 (28.57%) patients, with oligoarticular pattern in 5 (8.92%) and polyarticular pattern in 11 (19.64%). During follow-up, persistent polyarticular

Table I: Demographic, clinical, and laboratory findings of systemic juvenile idiopathic arthritis patients

Variables	Values
Demographic Findings	
Gender*	56
Male	30 (53.57)
Female	26 (46.42)
Age, Months†	159 (88-201.75)
Time Between the Symptom Onset and Diagnosis, Days†	20 (15-45)
Age at Diagnosis, Months†	89.50 (32.25-124)
Follow-up Period, Months†	47 (17.50-63.75)
Baseline Clinical Findings*	
Fever	56
Arthritis	45 (80.35)
Oligoarthritis	27 (48.21)
Polyarthritis	18 (32.14)
Joint Involvement*	
Knee	28 (50)
Ankle	21 (37.50)
Hip	6 (10.71)
Small Joints of the Foot	1 (1.78)
Wrist	14 (25)
Elbow	3 (3.35)
Small Joints of the Hand	14 (25)
Rash*	43 (76.78)
Hepatomegaly*	24 (42.85)
Splenomegaly*	23 (41.07)
Lymphadenopathy*	27 (48.21)
Serositis*	10 (17.85)
Pleural	6 (10.71)
Pericardial	5 (8.92)
Peritoneal	2 (3.57)
Systemic JADAS71†	30.76 (26.17-34.52)
Baseline Laboratory Findings†	
WBCs, $\times 10^6$	14.725 (9575-19.437)
Neutrophil, $\times 10^6$	10.200 (5395-13.842)
Lymphocyte, $\times 10$	2400 (1500-3297)
Haemoglobin, g/dL	10.35 (9.10-11.52)
Platelet, $\times 10^6$	391.000 (294.750-604.500)
ESR, mm/h	70.50 (45-90.25)
CRP, mg/L	100.5 (27.60-142.25)
Ferritin, µg/L	463.5 (210.20-4133.50)
Ferritin/ESR	13.90 (2.85-57.68)
Aspartate aminotransferase, U/L	31.50 (22-56)
Alanine aminotransferase, U/L	17 (10.25-45.25)
Lactate dehydrogenase, U/L	408 (276.50-538.70)
Triglyceride, mg/dL	109 (80.25-197)
Fibrinogen, g/L	4.58 (3.22-6.61)

:** *n (%),* **†:** *median (IQR),* ***IQR: *interquartile range,* ***WBCs:*** *white blood cells,* ***JADAS71:*** *Juvenile Arthritis Disease Activity Score 71,* ***ESR:*** *erythrocyte sedimentation rate*

involvement developed in 11 (19.64%) patients. The knee joint was affected in all patients with persistent polyarticular arthritis. Eight (72.72%) patients had wrist involvement, 7 (63.63%) had ankle involvement, and 7 (63.63%) had involvement of the small joints of the hand, 5 (45.45%) had hip involvement and 4 (36.36%) had elbow involvement. Comparison of demographics, clinical and laboratory findings and complications of sJIA patients with and without persistent polyarticular arthritis are given in Table II.

Treatments of sJIA Patients

All patients received steroids at the time of diagnosis. Pulse methylprednisolone (PMP) therapy was administered to 24 (42.85%) patients. The dosing regimen was as follows: 2 doses in 4 (7.14%) patients, 3 doses in 15 (26.78%) patients, 5 doses in 3 (5.35%) patients, and 6 doses in 2 (3.57%) patients. The median (IQR) duration of steroid treatment was 215.88 (122.25-267.25) days. Fifteen (26.78%) of all patients received steroid treatment only. Details of cDMARD, bDMARD and other treatments given according to disease course are given in Table III.

Comparison of Patients with and without Persistent Polyarticular Arthritis in sJIA

Of the patients with persistent polyarticular arthritis, 10 (17.85%) had polyarticular involvement and 1 (1.78%) patient had oligoarticular involvement at diagnosis. Polyarticular onset was a significant predictor of persistent polyarticular arthritis ($p<0.001$). Persistent polyarticular arthritis was more frequently associated with involvement of the knee, hip, wrist, and small joints of the hand ($p<0.001$, $p=0.001$, $p<0.001$, $p=0.003$, respectively).

Rash at the time of diagnosis was statistically more common in patients without persistent polyarticular arthritis than in those with persistent polyarticular arthritis ($p=0.002$).

The median follow-up duration was longer in patients with persistent polyarticular arthritis, but this difference was not statistically significant ($p=0.063$).

Median white blood cell (WBC) and neutrophil counts at diagnosis were higher in patients without persistent polyarticular arthritis ($p=0.028$, $p=0.031$, respectively). Patients with higher ferritin levels at diagnosis had statistically less persistent polyarticular arthritis ($p=0.036$). Patients without persistent polyarticular arthritis had higher median lactate dehydrogenase levels at diagnosis ($p=0.016$). There was no significant statistical difference in other laboratory parameters between the two groups.

When comparing patients with and without persistent polyarticular arthritis, there was no significant difference in the frequency of MAS, ILD, or uveitis.

Concomitant use of steroid, cDMARD and bDMARD therapies was more common in patients with persistent polyarticular arthritis ($p=0.018$). Methotrexate, etanercept and tocilizumab treatments were more frequently used in patients with persistent polyarticular arthritis ($p=0.027$, $p=0.006$, $p=0.018$, respectively). There was no significant difference in the use of steroid, anakinra, canakinumab, tofacitinib, cyclosporine, etoposide, IVIG, plasmapheresis treatments between patients with and without persistent polyarticular arthritis ($p=1.000$, $p=0.708$, $p=0.196$, $p=1.000$, $p=1.000$, $p=0.180$, $p=1.000$, respectively). Similarly, sJADAS71 scores did not differ significantly between the two groups ($p=0.091$).

Table II: Comparison of demographics, clinical and laboratory findings and complications of systemic juvenile idiopathic arthritis patients with and without persistent polyarticular arthritis

	Persistent Polyarticular Arthritis (n=11,19.64%)	Other Patients (n=45, 80.35%)	p
Demographic Findings			
Age, Months*	179 (137-225)	143 (83.50-201.50)	0.173‡
Gender†			
Male	5 (8.92)	25 (44.64)	0.547§
Female	6 (10.71)	20 (35.71)	
Time Between the Symptom Onset and Diagnosis, Days*	45 (16-60)	20 (15-30)	0.143‡
Age at Diagnosis, Months*	100 (21-121)	75 (32.50-133.50)	0.951‡
Follow-Up Period, Months*	54 (39-96)	42 (13-58)	0.063‡
Baseline Clinical Findings†			
Fever	11 (19.64)	45 (80.35)	-
Arthritis			
Oligoarthritis	1 (1.78)	26 (46.42)	0.004§
Polyarthritis	10 (17.85)	8 (14.28)	<0.001§
Joint Involvement			
Knee	11 (19.64)	17 (30.35)	<0.001§
Ankle	7 (12.50)	14 (25)	0.080§
Hip	5 (8.92)	1 (1.78)	0.001§
Small Joints of the Foot	-	1 (1.78)	1.000§
Wrist	8 (14.28)	6 (10.71)	<0.001§
Elbow	4 (7.14)	9 (16.07)	0.259§
Small Joints of the Hand	7 (12.50)	7 (12.50)	0.003§
Rash	4 (7.14)	39 (69.64)	0.002§
Hepatomegaly	4 (7.14)	20 (35.71)	0.741§
Splenomegaly	3 (5.35)	20 (35.71)	0.496§
Lymphadenopathy	4 (7.14)	23 (41.07)	0.380§
Serositis	-	10 (17.85)	0.183§
Pleural	-	6 (10.71)	0.334§
Pericardial	-	5 (8.92)	0.571§
Peritoneal	-	2 (3.57)	1.000§
Systemic JADAS71*	34 (28.20-45)	30.60 (25.35-34.10)	0.091‡
Baseline Laboratory Findings*			
WBCs, $\times 10^6$	9800 (7200-14.690)	14.800 (10.330-21050)	0.028‡
Neutrophil, $\times 10^6$	6310 (3140-10.100)	10.700 (5955-17.465)	0.031‡
Lymphocyte, $\times 10$	2500 (1500-2940)	2300 (1500-3370)	0.992‡
Haemoglobin, g/dL	10.50 (9.40-11.60)	10.20 (9.05-11.50)	0.489‡
Platelet, $\times 10^6$	461.000 (365000-540.000)	389.000 (281.500-627.500)	0.571‡
ESR, mm/h	82 (22-91)	68 (48-89.50)	0.951‡
CRP, mg/L	108 (27.60-146)	93.40 (27.30-141)	0.765‡
Ferritin, µg/L	230 (219-444)	948 (234-4562.50)	0.036‡
Ferritin/ESR	4.53 (2.18-43.47)	19.56 (3.41-66.47)	0.130‡
Aspartate aminotransferase, U/L	24 (14-45)	32 (22.50-59.50)	0.327‡
Alanine aminotransferase, U/L	14 (10-60)	17 (11-44.50)	0.476‡
Lactate dehydrogenase, U/L	252 (219-495)	421 (320.50-564.50)	0.016‡
Triglyceride, mg/dL	109 (80.20-197)	113 (81.50-221.50)	0.261‡
Fibrinogen, g/L	3.90 (3.20-6.78)	4.70 (3.24-6.61)	0.726‡
Complications†			
Macrophage Activation Syndrome	2 (3.57)	9 (16.07)	1.000§
Interstitial Lung disease	-	1 (1.78)	1.000§
Uveitis	1 (1.78)	1 (1.78)	0.357§

:** *median (IQR),* **†:** *n(%),* **‡:Mann-Whitney U Test,* **§:** *Fisher's Exact Test*

DISCUSSION

Systemic juvenile idiopathic arthritis is a chronic disease that causes significant morbidity in children and in some cases can remain active for years. Although three different disease courses have been described, the predictors that determine the disease course are still unclear. This study aimed to investigate the determinants of persistent polyarticular arthritis in a cohort of sJIA patients with a persistent disease course. In the present study, patients with polyarticular involvement at the time of

Table III: Treatments used in systemic juvenile idiopathic arthritis patients with and without persistent polyarticular arthritis

Treatment	All patients (n=56)	Persistent Polyarticular Arthritis (n=11, 19.64%)	Other Patients (n=45, 80.35%)	p
Only Steroid	15 (26.78)	1 (1.78)	14 (25)	0.255‡
Steroid+bDMARDs	17 (30.35)	3 (5.35)	14 (25)	1.000‡
Steroid+cDMARDs	14 (25)	2 (3.57)	12 (21.42)	0.711‡
Steroid+bDMARDs+cDMARDs	10 (17.85)	5 (8.92)	5 (8.92)	0.018‡
bDMARD Switch	10 (17.85)	3 (5.35)	7 (12.50)	0.393‡
Pulse Methylprednisolone*	24 (42.85)	2 (3.57)	22 (39.28)	0.093‡
Methylprednisolone 2 mg/kg/d*	56 (100)	11 (100)	45 (100)	-
Total Steroid Duration, Day†	215.88 (122.25-267.25)	220.64 (90-304)	214.71 (123-200)	0.813§
Anakinra*	12 (21.42)	2 (3.57)	10 (17.85)	1.000‡
Canakinumab*	15 (26.78)	2 (3.57)	13 (23.21)	0.708‡
Tocilizumab*	10 (17.85)	5 (8.92)	5 (8.92)	0.018‡
Etanercept*	3 (5.35)	3 (5.35)	-	0.006‡
Tofacitinib*	1 (1.78)	1 (1.78)	-	0.196‡
Methotrexate*	18 (32.14)	7 (12.50)	11 (19.64)	0.027‡
Cyclosporine*	6 (10.71)	1 (1.78)	5 (8.92)	1.000‡
Etoposide*	1 (1.78)	-	1 (1.78)	1.000‡
IVIG*	9 (16.07)	-	9 (16.07)	0.180‡
Plasmapheresis*	3 (5.35)	-	3 (5.35)	1.000‡

:** *n (%),* **†:** *median (IQR),* **‡ :** *Fisher's Exact Test,* **§:Mann-Whitney U Test,* ***bDMARDs:** Biological Disease-Modifying Antirheumatic Drugs,* ***cDMARDs:** Conventional Disease-Modifying Antirheumatic Drugs,* ***IVIG:** Intravenous Immunoglobulin*

diagnosis may also have a persistent polyarticular course in follow-up. On the other hand, rash, elevated WBC and ferritin at baseline were observed more frequently in patients without polyarticular involvement at follow-up.

Long-term follow-up of our sJIA cohort showed three different disease courses: 48.21% of patients had a monocyclic course, 37.50% a persistent course, and 14.28% a polycyclic course. Half of those with a persistent course had persistent polyarticular arthritis. In contrast to Singh-Grewal et al. (3), who reported a higher prevalence of persistent disease, our study found a higher proportion of patients with a monocyclic disease course. Increased awareness of sJIA, rapid initiation of appropriate treatment, and the advantage of being in the biological era to provide intensive treatment in necessary patients may play a role in the change in the distribution of the disease course.

Half of our sJIA patients with persistent course had persistent polyarticular arthritis. Of the patients with persistent polyarticular arthritis, 91% had polyarticular involvement at diagnosis. Polyarticular onset was a significant predictor of persistent polyarticular arthritis. Walliman and colleagues found that nearly all patients with a persistent disease course had arthritis at the time of diagnosis, with half presenting with polyarticular involvement (12). Persistent polyarticular arthritis was associated with a higher involvement of the knee, hip, wrist, and small joints of the hand. Modesto et al. (13) showed that polyarticular involvement was associated with worse outcomes.

Disease activity is a term representing the signs and symptoms associated with inflammation (14,15). Prolonged synovial inflammation can lead to joint destruction and consequent growth abnormalities and functional disability. Therefore, assessment of ongoing inflammation or disease activity in sJIA is crucial to prevent long-term complications and manage the disease (16,17). The presence of elevated systemic inflammatory markers, including ESR, CRP, WBC and ferritin levels, helps to diagnose sJIA and their use as a prognostic factor has also been investigated (18). In our study, no significant relationship was found between sJADAS scores used to assess disease activity and persistent polyarticular involvement. On the other hand, there was no significant correlation between baseline ESR and CRP levels and the persistence of polyarticular arthritis in our cohort. However, we found a positive correlation between elevated WBC and neutrophil counts, and higher ferritin levels, and the absence of persistent polyarticular disease. While autoinflammatory mechanisms play a role in the pathogenesis of the disease in the early stages, autoimmune mechanisms come to the fore in the later stages when persistent arthritis develops. Elevated inflammatory markers in the early phase of our study seem to indicate autoinflammation, whereas low baseline WBC and neutrophil counts in patients with persistent arthritis seem to indicate an autoimmune component in the pathogenesis.

Nigrovic et al. (5) reported that early initiation of biologic agents may provide a therapeutic window of opportunity to prevent disease progression. Our study demonstrated that half of

patients exhibited a monocyclic disease course, which was not associated with the use of biologic agents. However, persistent disease activity was observed in 21.42% patients who initiated therapy with a biologic agent at disease onset. These results suggest that the course of the disease may not be related solely to the time of starting the biologic agent. Statistical analysis revealed no significant association between the use of steroids, anakinra, canakinumab, tofacitinib, cyclosporine, etoposide, IVIG, or plasmapheresis and the specific disease subgroup. In contrast, patients receiving methotrexate, etanercept, or tocilizumab demonstrated a more persistent course of polyarticular arthritis. The treatment approach for these children often reflects that of polyarticular JIA rather than sJIA. This difference may be explained by the clinician's choice of treatment based on polyarticular involvement, as the present study showed that the main determinant of persistent polyarticular course was initial polyarticular involvement. Janow et al. also reported that cDMARDs and IL-6 inhibitors such as tocilizumab were more commonly used in patients with persistent arthritis. Anti-TNF drugs are commonly used to treat sJIA patients with persistent arthritis (19). According to the BIKER registry, patients with sJIA who no longer have systemic symptoms can achieve favorable results with anti-TNF agents (20). The use of a combination of steroids, cDMARDs, and bDMARDs was more common among patients with persistent polyarticular arthritis. These pediatric patients typically exhibit a higher number of affected joints, a decreased quality of life, and increased functional abnormalities. As a result, healthcare providers may need to make complex therapeutic choices in the persistent polyarticular course (12).

The main limitations of our study are its retrospective nature, single-center design, and relatively small sample size. On the other hand, the determination of predictors of persistent polyarticular course of sJIA that may result in destructive joint damage is a strength of our study.

In conclusion, sJIA is a challenging disease with both its early systemic findings and its persistent polyarticular course during follow-up. Patients with polyarticular involvement at the time of diagnosis may have a persistent polyarticular course during follow-up. Therefore, patients with early polyarticular involvement should be followed closely and carefully for persistent polyarticular course. Multicenter studies are needed to reveal other predictors of persistent polyarticular course in this rare disease.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (Date: 04 September 2024; No: TABED 2-24-436).

Contribution of the authors

Conceptualization: ***Uğur Es Y, Çelikel Acar B***; Methodology: ***Uğur Es Y, Çelikel Acar B, Çelikel E, Ekici Tekin Z, Ertem Ş***; Formal analysis and investigation: ***Polat Mc, Işıklar Ekici M, Öztürk D, Yoğun Sn, Erdem Torun Ş***; Writing - original draft preparation: ***Uğur Es Y, Çelikel Acar, B Elif Çelikel, Ekici Tekin Z***; Writing - review and editing: ***Uğur Es Y, Çelikel Acar B***; The final manuscript was approved by all the authors. Funding acquisition: None ; Resources: None; Supervision: ***Çelikel Acar B***.

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Conflict of interest

The authors declare that there is no conflict of interest.

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