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Clinical science

How early is early for JIA? Insights from the infantile-onset juvenile idiopathic arthritis patients of the PERA research group cohort

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Abstract

Objective: Juvenile idiopathic arthritis (JIA) is the most common chronic childhood arthritis, with distinct categories based on pathophysiology and clinical manifestations. The age of onset varies by category but is reported to be approximately six years. This study aimed to evaluate the clinical, laboratory and outcome characteristics of patients with infantile-onset JIA.

Methods: This multicentre retrospective study included patients with JIA whose symptoms were onset before the age of two.

Results: This study included 199 patients with a median age at symptom onset of 17 months and a median age at diagnosis of 20 months. The most common JIA categories were persistent oligoarticular (59.8%), systemic (13.6%) and rheumatoid factor (RF)-negative polyarticular (11.6%). Patients with symptom onset ≤12 months had a significantly higher prevalence of RF-negative polyarticular and systemic JIA, whereas those with onset >12 months had a higher prevalence of persistent oligoarticular JIA. Antinuclear antibody positivity was significantly higher in patients with disease onset >12 months, whereas uveitis development was more common in those with onset ≤12 months. The wrist, hand proximal interphalangeal (PIP) and foot PIP joints were significantly more frequently affected in patients with early-onset disease. At the last visit, 59.8% of the patients were in remission with medication and 18.1% were in remission without medication.

Conclusion: This study suggests that patients with infantile-onset JIA exhibit distinct characteristics regarding JIA category, joint involvement and uveitis development, highlighting the need for further research and potential reconsideration of current age thresholds in the JIA classification.

Keywords: juvenile idiopathic arthritis, infantile-onset diseases, uveitis, antinuclear antibodies, treatment outcome.

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Rheumatology key messages

- Infantile-onset JIA has distinct characteristics, suggesting a need to reconsider current classification age thresholds.
- RF-negative polyarticular and systemic JIA are more common in patients with symptom onset before 12 months.
- Early diagnosis and treatment improve outcomes, leading to high remission rates despite severe joint involvement.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthritis in children and encompassing a heterogeneous group of conditions characterized by chronic inflammation of the joints with onset before the age of 16 [1]. It has been reported that the most common age of onset of JIA is 2 years and older, although it varies between subgroups and geographical regions [2–4]. A recent comprehensive study also showed that the median age at disease onset is lower in Southern Europe (3.5 years) than in other regions [3]. Current knowledge about JIA is primarily based on data from patients older than 2 years, highlighting a significant gap in understanding disease presentation in younger children.

According to the International League of Associations for Rheumatology (ILAR), JIA encompasses several categories, including oligoarticular JIA, polyarticular JIA, systemic JIA, psoriatic arthritis, enthesitis-related arthritis (ERA) and undifferentiated arthritis, each with distinct pathophysiological mechanisms and clinical manifestations [1]. While these categories highlight that the disease tends to peak at specific ages, they do not offer a clear definition of when it begins.

In the new classification proposed by the Pediatric Rheumatology International Trials Organization (PRINTO), early-onset antinuclear antibody (ANA)-positive JIA is characterized by onset before the age of 6 years, female predominance, high incidence of chronic iridocyclitis and ANA positivity [5]. The age cut-off was based on a study examining gene expression in oligoarticular and polyarticular JIA, which found that patients with early onset arthritis (≤6 years) were characterized by a certain B-cell signature independent of the number of joints involved [6]. It has been shown that ANA positivity typically emerges after the first year of life and becomes more reliably detectable with increasing age [7, 8]. The immune system undergoes rapid development after birth and exhibits significant maturation, particularly within the initial two years of life. It has been established that the production capacity of tumor necrosis factor (TNF)-α and other cytokines increase substantially from birth to 1 year of age; however, it does not attain adult levels [9]. Consequently, it is reasonable to postulate that patients with JIA aged ≤2 years may exhibit a distinct disease course.

Literature provides limited data on the presentation and prognosis of JIA with onset before the age of 2 years. The difficulties in diagnosing infants with systemic JIA have been discussed in case reports, and it may be confused with Kawasaki disease [10, 11]. Russo *et al.* reported that patients with systemic JIA onset before 18 months of age exhibited more severe disease manifestations, associated with more pronounced chronic disability [12]. In a case series of 12 patients with early-onset JIA, disease severity was not significantly different compared with older children with JIA; however, diagnosis was delayed, and more than half presented with contractures at the initial visit [13].

This multicentre retrospective study aimed to evaluate the clinical, laboratory and outcome characteristics of patients with JIA symptom onset at or before 24 months in a large cohort. By examining variations in subtype, joint involvement, ANA status and uveitis occurrence according to the time of disease onset, we aimed to provide valuable information to inform clinical decision making and enhance patient management strategies for this rare condition.

Methods

Our multicentre retrospective cohort study included both inpatients and outpatients with JIA who had symptom onset before or at the age of 2 years and were followed for at least 6 months. Patients were identified via retrospective review of institutional databases and electronic medical records using diagnostic codes corresponding to JIA based on ILAR criteria, as recorded by pediatric rheumatologists [1]. Demographic, clinical, laboratory and treatment data were retrospectively obtained from the medical records of 14 participating pediatric rheumatology centres included in The Pediatric Rheumatology Academy-Research Group and recorded on case report forms [14]. The laboratory findings at admission including ANA, human leucocyte antigen-27, RF, erythrocyte sedimentation rate, C-reactive protein, white blood cell and platelet counts were also recorded. ANA testing was performed twice >3 months apart using the indirect immunofluorescence method on HEp-2 cells, and titres ≥1:160 were considered positive. Juvenile Arthritis Disease Activity Score (JADAS) and remission status according to the 2011 American College of Rheumatology/Wallace criteria were noted from the files [15, 16]. The patients were divided into two groups according to symptom onset time. Patients with an age of onset ≤12 months were identified as the early-onset group. Consanguinity was defined as parental relationship up to third-degree relatives (e.g. first or second cousins).

This study was conducted in compliance with the Helsinki Declaration as well as local laws and regulations. Written informed consent was received from the legal guardians of the children at the time of hospital visit. The study was approved by the Ministry of Health, İstanbul Medeniyet University Goztepe Education and Research Hospital, Clinical Research Ethics Committee (13/04/2022–2022/0236). The data were collected between June 2022 and December 2022.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 24.0; SPSS Inc., Chicago, IL, USA). Continuous variables were presented as either the mean ± standard deviation or the median (minimum-maximum), depending on their distribution, which was established using the Kolmogorov–Smirnov test. Categorical variables were assessed using the χ^2 test or Fisher's exact test, when applicable. The associations between continuous variables were assessed using the Mann–Whitney *U* test when abnormally distributed and Student's *t*

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tests when normally distributed. Statistical analyses were performed using univariate methods to compare clinical characteristics between the early-onset (≤12 months) and the other (>12 months) groups within both the whole and the non-systemic JIA cohort. Multivariate analyses were not conducted due to the limited sample size of the early-onset subgroup, in order to avoid overfitting and ensure the reliability of findings. As this was a retrospective study, no formal sample size or power calculation was performed prior to data collection. The significance level employed to determine statistical significance was set at $P < 0.05$, and Prism software (version 8, GraphPad Software, San Diego, CA, USA) was utilized to analyse and graph the data.

Results

Demographics, clinical, laboratory and treatment data of the whole cohort

A retrospective review of medical records was conducted for 201 patients with JIA who experienced symptom onset at ≤24 months of age. Two patients were excluded because of a short follow-up period. The study included 199 patients who were followed up for a minimum of 6 months after diagnosis. Of the patients, 151 (75.9%) were female. A history of consanguinity was observed in 10.6% of patients, while 17.1% reported a family history of rheumatic disease. The mean age of symptom onset was 16.9 ± 4.5 months, and the median age of diagnosis was 20 (6–41) months. The median time between symptom onset and diagnosis was 2 (1–24) months. The most frequently involved joints were the knee (87.4%), ankle (42.2%), wrist (21.1%) and hand proximal interphalangeal (PIP) (20.6%). The most common subgroups of JIA were persistent oligoarticular (59.8%), systemic (13.6%) and RF-negative polyarticular (11.6%) types. ANA positivity was observed in 69.8% of patients, while none of the patients exhibited RF positivity. Uveitis developed in 12.1% of the patients during the follow-up period.

Methotrexate was the initial treatment administered to 192 (96.5%) patients because of high disease activity or poor prognostic features. Furthermore, systemic corticosteroids were administered to 68.8% of the patients as a bridging therapy or to treat systemic symptoms or severe arthritis. Following the initial treatment, 65.8% of the patients achieved inactive disease status. Among the patients who achieved inactive disease after initial treatment, 53.8% required biological disease-modifying anti-rheumatic drugs (bDMARDs) during follow-up. The most frequently used bDMARDs were etanercept (31.7%), adalimumab (22.1%) and tocilizumab (13.1%). Biological DMARDs were changed in 35 patients (17.6%). At the last visit, 22.1% of patients still had active disease, 59.8% were in remission with medication and 18.1% were in remission without medication, with a median follow-up of 44 (6–234) months. The demographics, clinical, laboratory and treatment data of the patients are detailed in Table 1.

Comparison of the whole cohort according to the age of symptom onset

When the patients were divided into two groups according to the time of symptom onset, 40 (20.1%) patients had early onset. Within this group, the most prevalent category of JIA was persistent oligoarticular (37.5%), followed by systemic

Table 1. Demographics, clinical, laboratory, treatment data of the patients with infantile-onset juvenile idiopathic arthritis ($n = 199$)

Sex (Female/Male) n/n	**151/48**
Age at disease onset, months, mean ± SD	16.9 ± 4.5
Age at diagnosis, months, median (min-max)	20 (6-41)
Duration of follow-up, months, median (min-max)	44 (6-234)
Categories of JIA[a] *n* (%)	
Oligoarticular JIA	141 (70,9)
Persistent	119 (59.8)
Extended	22 (11.1)
Systemic JIA	27 (13.6)
RF (–) polyarticular JIA	23 (11.6)
Psoriatic arthritis	8 (4)
Involved joint at disease onset, median (min–max)	2 (0–14)
Distribution of the affected joints, *n* (%)	
Hip	8 (4)
Knee	174 (87.4)
Ankle	84 (42.2)
Metatarsophalangeal	12 (6)
Foot proximal interphalangeal	7 (3.5)
foot distal interphalangeal	1 (0.5)
Elbow	22 (11.1)
Wrist	42 (21.1)
Metacarpophalangeal	22 (11.1)
Hand proximal interphalangeal	41 (20.6)
Hand distal interphalangeal	4 (2)
Temporomandibular	1 (0.5)
Uveitis, *n* (%)	24 (12.1)
Laboratory findings at admission	
White blood cell (mm^3), median (min-max)	11675 (4100–41230)
Platelets (mm^3), mean ± SD	469361 ± 148493
Erythrocyte sedimentation rate (mm/h), mean ± SD	44 ± 27
C-reactive protein (mg/dL), median (min-max)	3 (0.5–295)
Antinuclear antibody positivity, *n* (%)	139 (69.8)
Rheumatoid factor positivity, *n* (%)	0
Human leucocyte antigen-27	7 (3.5)
Cumulative treatment, *n* (%)	
Corticosteroid	137 (68.8)
Methotrexate	192 (96.5)
Etanercept	63 (31.7)
Adalimumab	44 (22.1)
Tocilizumab	26 (13.1)
Anakinra	9 (4.5)
Canakinumab	7 (3.5)
İnfliximab	6 (3)
Tofacitinib	1 (0.5)
Abatacept	1 (0.5)
Clinical and laboratory findings at last visit	
Joint with active arthritis, median (min-max)	0 (0-12)
Presence of systemic symptoms, *n* (%)	1 (0.5)
Active uveitis, n (%)	19 (9.5)
Physician's global assessment, median (min-max)	1 (0–8)
Morning stiffness ≥15 min, *n* (%)	27 (13.6)
Erythrocyte sedimentation rate (mm/h), mean ± SD	14.2 ± 13.5
C-reactive protein (mg/dL), median (min-max)	0.64 (0.5–183)
Disease activity status at the last visit, *n* (%)	
Active disease	44 (22.1)
Remission with medication	119 (59.8)
Remission without medication	36 (18.1)

[a] There were no patients in the RF positive polyarticular, enthesitis-related arthritis and undifferentiated arthritis subtypes.
JIA: juvenile idiopathic arthritis, RF: rheumatoid factor, SD: standard deviation, Min-max: minimum-maximum.

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(25%) and RF-negative polyarticular (25%). The knee and ankle joints were the most frequently affected, with 90% and 50% involvement, respectively. ANA positivity was observed in 55% of the patients and 22% developed uveitis. Among patients whose disease onset >12 months, persistent oligoarticular JIA was identified in 65.4%, followed by extended oligoarticular in 11.9% and systemic in 10.7%. In this group, the knee was the joint most frequently involved (86.8%), followed by the ankle (40.3%). ANA positivity was present in 73.6% of these patients and 10.1% developed uveitis during the follow-up period.

Upon comparison of the two groups, a statistically significant difference was observed with respect to the JIA category, joint involvement, ANA positivity and the presence of uveitis. RF-negative polyarticular (25% *vs* 8.2%, $P = 0.002$) and systemic JIA (25% *vs* 10.7%, $P = 0.002$) were significantly more common in patients with disease onset ≤12 months, whereas persistent oligoarticular JIA (65.4% *vs* 37.5%, $P = 0.002$) was more common in patients with disease onset >12 months. ANA positivity was also significantly higher in patients with disease onset >12 months (75.5% *vs* 55%, $P = 0.011$). However, patients with an age at disease onset ≤12 months were more likely to develop uveitis during follow-up (22.5% *vs* 10.1%, $P = 0.034$). Comparative data for the JIA category, ANA positivity and presence of uveitis are illustrated in Fig. 1. When the involved joints were evaluated according to the time of disease onset, it was found that wrist (40% *vs* 16.4%, $P = 0.001$), hand PIP (32.5% *vs* 17.6%, $P = 0.037$) and foot PIP (10% *vs* 1.9%, $P = 0.031$) were significantly more common in patients ≤12 months. Joint involvement according to disease onset time is shown in Fig. 2. At the end of the median follow-up duration of 54 months, remission was observed in 72.5% of the early-onset cohort. Comparatively, 79.2% of the other group achieved remission over a median follow-up duration of 38 months. There was no statistical difference between remission statuses ($P = 0.358$).

Comparisons of patients with infantile onset non-systemic juvenile idiopathic arthritis according to the age at symptom onset

Patients with non-systemic JIA ($n = 170$) were divided into two groups based on the age of symptom onset. Symptoms manifested at ≤12 months in 30 patients. The knee was the most frequently affected joint in both groups (96.7% *vs* 93.6%). Regarding joint involvement, it was observed that the PIP of the foot (10% *vs* 1.4%, $P = 0.039$) and wrist (43.3% *vs* 15%, $P < 0.001$) were significantly more affected in patients whose symptoms manifested at 12 months or earlier compared with the other group. When analysed within the non-systemic JIA subgroup, the difference in ANA positivity by age at disease onset disappeared, suggesting that the difference at baseline was confounded by the distribution of JIA category. While there was no discernible difference between the two groups regarding ANA positivity (70% *vs* 81.4%, $P = 0.160$), the incidence of uveitis during follow-up (26.7% *vs* 16%, $P = 0.042$) was significantly higher in the early onset group. Due to the limited number of patients with uveitis, particularly within the early-onset group, further subgroup analyses based on ANA status and age were not feasible. At the first visit, the early-onset cohort had a median JADAS-71 score of 18.5 (5.2–35), while the other group had a score of 18 (9–48.7), with no statistically significant difference ($P = 0.896$). The comparative analysis of demographic, clinical and laboratory findings of patients with non-systemic JIA according to age at symptom onset is presented in Table 2.

Discussion

In this most comprehensive study evaluating children with JIA symptoms onset before the age of two years, it was demonstrated that children with symptom onset at the age of one year or younger exhibited distinct characteristics regarding JIA category, joint involvement and uveitis development. This study also revealed that the early-onset ANA-positive JIA is not uniform and displays notably different traits when the onset age is further decreased.

It is well established that the distribution of JIA categories varies across geographical regions [3]. In Eastern Europe and in our country, the most frequently reported categories across all age groups are oligoarticular JIA, ERA, RF-negative polyarticular JIA and systemic JIA [3, 17]. In the present study, the most common categories were persistent oligoarticular, systemic and RF-negative polyarticular JIA. Given our focus on children with early disease onset, it is not unexpected that ERA was not observed. This contrasts with studies including broader age ranges, as ERA predominantly affects boys during late childhood and adolescence [18]. A remarkable finding of our study was the significant variation in JIA category frequencies based on age at onset. RF-negative polyarticular and systemic JIA were significantly more common in patients with disease onset ≤12 months, whereas persistent oligoarticular JIA predominated in those with onset after 12 months.

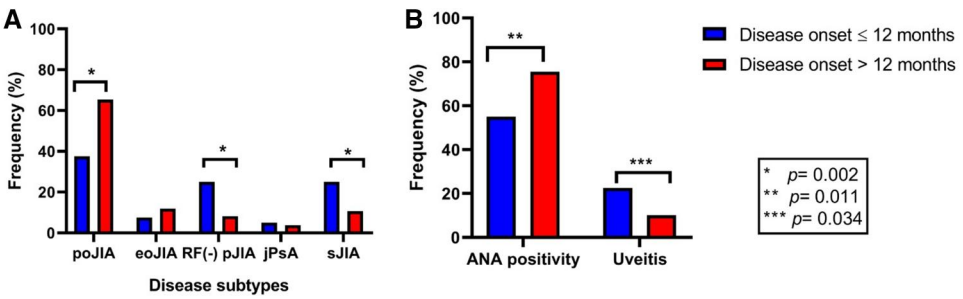


Figure 1. Comparative data for the juvenile idiopathic arthritis category, antinuclear antibody positivity and presence of uveitis. (**A**) Distribution of juvenile idiopathic arthritis categories according to time of disease onset. (**B**) Comparison of antinuclear antibody positivity and uveitis frequency according to time of disease onset. ANA: antinuclear antibody; eoJIA: extended oligoarticular juvenile idiopathic arthritis; jPsA: juvenile psoriatic arthritis; pJIA: polyarticular juvenile idiopathic arthritis; poJIA: persistent oligoarticular juvenile idiopathic arthritis; sJIA: systemic juvenile idiopathic arthritis

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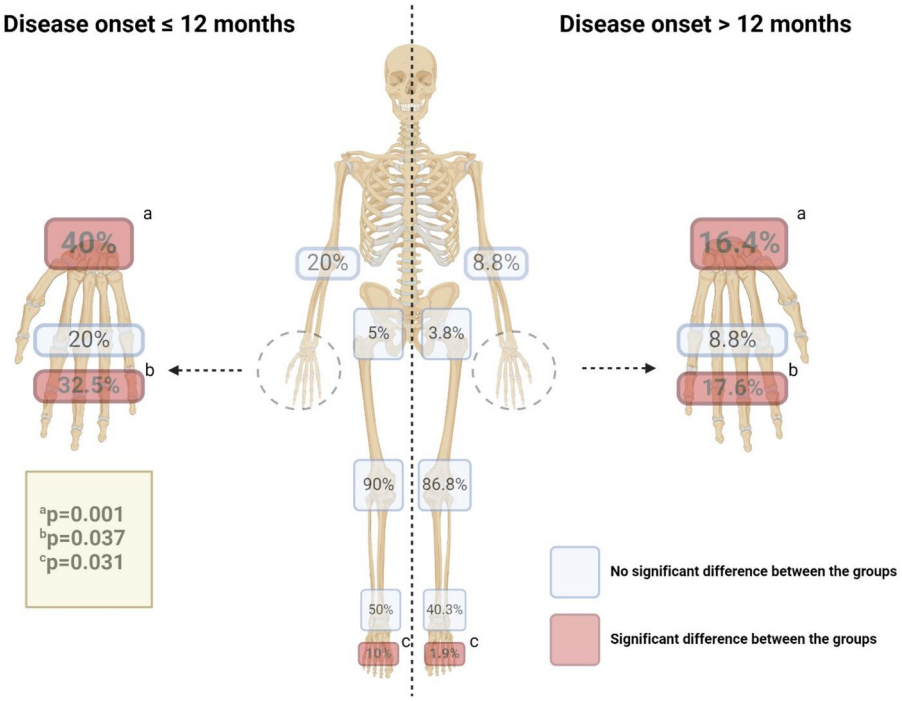


Figure 2. Joint involvement according to disease onset time

Table 2. Comparison of the demographics, clinical and laboratory findings of the patients with infantile onset nonsystemic juvenile idiopathic arthritis according to age at symptom onset ($n = 170$)

	Disease onset ≤12 months ($n = 30$)	Disease onset >12 months ($n = 140$)	*P*
Sex (female/male), *n*/*n*	21/9	114/26	0.160
Duration of follow-up, months, median (minimum-maximum)	57 (6–184)	43.5 (3–191)	0.159
Distribution of affected joint, *n* (%)			
Hip	1 (3.3)	4 (2.9)	1
Knee	29 (96.7)	131 (93.6)	0.513
Ankle	14 (46.7)	52 (37.1)	0.331
Metatarsophalangeal	1 (3.3)	9 (6.4)	1
Foot proximal interphalangeal	3 (10)	2 (1.4)	**0.039**
Foot distal interphalangeal	1 (3.3)	0	0.176
Elbow	5 (16.7)	14 (10)	0.336
Wrist	13 (43.3)	21 (15)	**<0.001**
Metacarpophalangeal	7 (23.3)	14 (10)	0.063
Hand proximal interphalangeal	10 (33.3)	26 (18.6)	0.073
Hand distal interphalangeal	2 (6.7)	1 (0.7)	0.081
Temporomandibular	0	1 (0.7)	1
Antinuclear antibody positivity, *n* (%)	21 (70)	114 (81.4)	0.160
Uveitis n (%)	8 (26.7)	16 (11.4)	**0.042**
JADAS-71 at the first visit, median (minimum-maximum)	18.5 (5.2–35)	18 (9–48.7)	0.896
JADAS-71 at the last visit, median (minimum-maximum)	5 (0–28.2)	2 (0–24.1)	0.173
Use of biological therapies, *n* (%)	16 (53.3)	74 (52.9)	0.962

JADAS: juvenile arthritis disease activity score. Bold text indicates statistically significant *P*-values.

Notably, despite the relative homogeneity of this cohort characterized by symptom onset before the age of 2 years, substantial variation in disease categories persists.

In our cohort, the knee, ankle, wrist and hand PIP joints were the most frequently affected, consistent with previously reported patterns of joint involvement across all JIA subgroups [19]. However, when patients were categorized according to age at disease onset, it was observed that wrist, hand and foot PIP joints were more frequently affected in patients with early-onset disease. The observed variation could be attributed to the differing frequencies of the JIA categories among the two groups. This assertion is supported by

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established knowledge that the wrist and small joints of the hand are predominantly affected in children with the RF-negative polyarticular category [19].

ANA positivity was observed in approximately three-quarters of the patients in our study cohort. Although this rate varied in studies conducted across all age groups in our country, it was found to be lower than that in the present study [17, 20, 21]. Our findings revealed a higher prevalence of ANA positivity in our study group, which included only patients under two years of age, compared with research encompassing all age groups. This finding suggests that ANA positivity in children with JIA may follow a different age-related pattern compared with healthy children.

It is evident that the prevalence of uveitis, similar to JIA categories, varies across geographical regions [3]. In our study, even when the entire cohort was considered, the frequency of uveitis exceeded 10%, and this rate is considerably higher compared with studies with large groups of patients conducted in our country [17, 20, 21]. It has been speculated that the low incidence of uveitis in our country may be attributable to the low ANA positivity [22]. In contrast with this explanation, in this study, especially in the early-onset group, uveitis was significantly more common during follow-up without any difference in ANA positivity, suggesting that age is an important factor in uveitis. Disease onset before the age of 7 years is a known risk factor for uveitis [23]. In this cohort, in which all patients developed arthritis before the age of two, uveitis was notably more frequent among those with disease onset before the age of one. This finding is consistent with previous studies that have identified younger age at onset as a risk factor for uveitis [24, 25].

Approximately half of our patients required bDMARDs during treatment. Current research indicates that bDMARDs are requisite for 30–50% of patients diagnosed with JIA [26]. This rate has been reported as 26–47% in our country, and the uveitis frequency in the study with a high rate of bDMARD use is comparable to ours [20, 21]. Furthermore, considering that our study cohort comprised a higher proportion of joints associated with poor prognosis, such as the wrist and small joints, the increased requirement for biological therapy was not unexpected.

In the literature, remission rates of patients demonstrate considerable variation contingent upon both geographical regions and disease categories [3, 27, 28]. Two studies conducted in our country encompassing all JIA subgroups reported remission rates of 69% and 91%, respectively [20, 21]. It is noteworthy that ∼80% of our patients achieved clinical remission after a follow-up period of about 4 years, despite the presence of unfavorable prognostic factors such as wrist and small joint involvement, as well as uveitis. This favorable outcome may be partly attributed to the relatively short diagnostic delay observed in our cohort (median 2 months), which is shorter than delays typically reported in the literature [20, 21, 27]. In a previously reported case series of infantile JIA, disease severity was comparable to that observed in older children; however, there was a delay in diagnosis and a higher rate of joint contractures at the initial visit [13]. The health policy in our country provides for more frequent medical check-ups in the first two years of life due to both developmental assessments and vaccinations. Therefore, it can be inferred that our patients were diagnosed early and did not miss the 'window of opportunity' for treatment, ultimately affording them the potential to achieve remission.

This study is limited by its retrospective design and the relatively small sample size of patients with disease onset before the age of 12 months. Its primary strength resides in its inclusion of the largest cohort of patients with infantile-onset JIA, which is likely to engender new discussions based on its findings.

In conclusion, this study demonstrated that patients with symptom onset during the infantile period may exhibit differences in terms of JIA category, affected joints and development of uveitis. Therefore, we suggest that the question of 'how early is early' should be asked when referring to the age of disease onset in JIA. As this study included only patients with disease onset ≤24 months of age, direct comparisons with children aged 2–6 years are not feasible. Future studies that incorporate older age groups will provide a more comprehensive understanding of early-onset JIA. Furthermore, it is incontrovertible that the classification of JIA poses considerable difficulties.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contribution statement

K.O. conceptualized and designed the study, conducted the data analyses, drafted the initial manuscript and had full access to all the data in the study. T.A., G.O.B., E.B., H.Ko., H. Ki., D.G.Y., F.G.D., G.O.Y., M.Ç., B.K.D., H.A.D., G.K., H. E.S. and S.T. were responsible for data collection. B.B., S.Y., N.A.A., S.B., M.K., S.S.K., S.O., B.S. and E.U. drafted the initial manuscript. All authors reviewed and revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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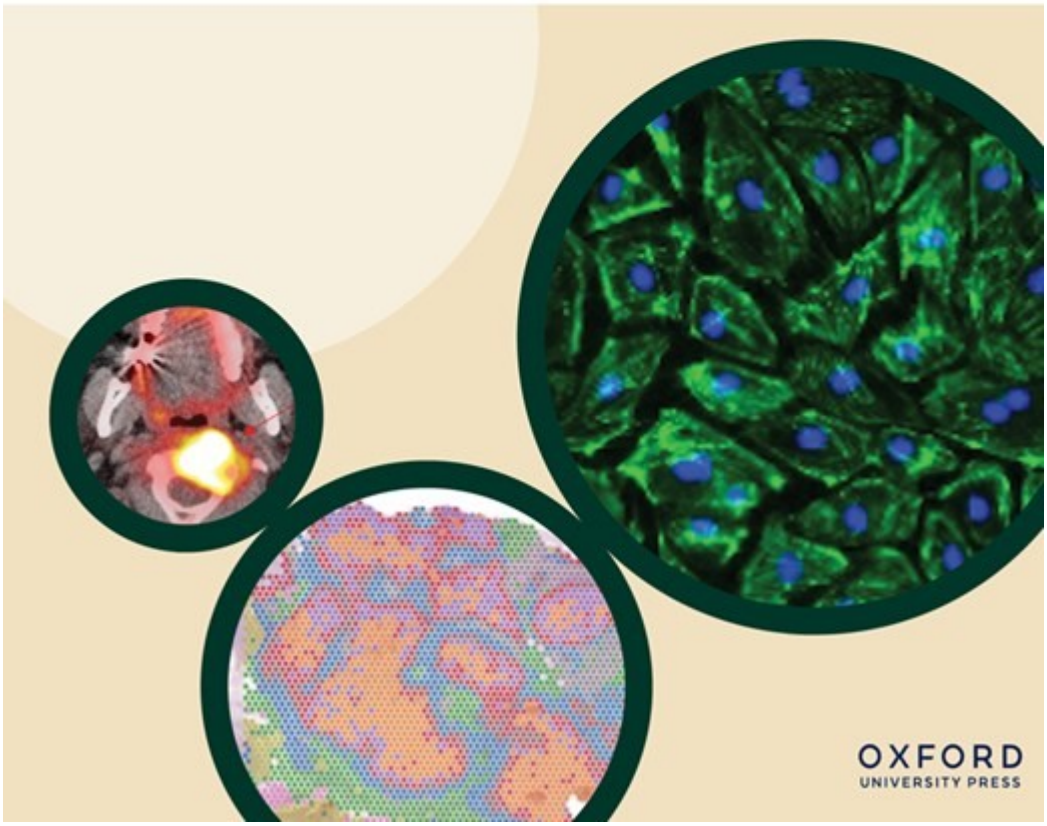
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