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Clinical insights into heterogeneity of rheumatoid factor negative polyarticular juvenile idiopathic arthritis across the world

Roberta Naddei[1*], Marco Burrone[2,3], Francesca Ridella[2,3], Yosef Uziel[4], Maria Trachana[5], Pavla Dolezalova[6], Ingrida Rumba-Rozenfelde[7], Nicolino Ruperto[3], Angelo Ravelli[2,8] and Alessandro Consolaro[2,3]

Abstract

Background To our knowledge, limited information is available about the differences in the characteristics of rheumatoid factor (RF)-negative polyarticular juvenile idiopathic arthritis (JIA) throughout the world. This study was aimed to compare the demographic and clinical features of patients with RF-negative polyarthritis across the world.

Methods Patients were part of a multinational sample included in a study aimed to investigate the prevalence of disease categories, treatment regimens, and disease status in patients from different geographical areas (EPOCA Study). All patients underwent a retrospective assessment, based on the review of clinical chart, and a cross-sectional evaluation, which included assessment of physician- and parent-reported outcomes and collection of ongoing medications.

Results Among the 9081 patients enrolled in the EPOCA study, 2141 patients (23.6%) with RF-negative polyarthritis were included in the present analysis. The prevalence of RF-negative polyarthritis was highest in North America and lowest in Southeast Asia (12.7%). The age at disease onset was lower in Northern and Southern Europe, where the highest prevalence of uveitis was found. Uveitis was rare in Southeast Asia, Africa & Middle East and Latin America. Patients from Eastern Europe, Latin America and Africa and Middle East presented with the highest prevalence of active joints at the visit. The combination of early onset, ANA positivity, and uveitis was observed mainly in Southern Europe (39%).

Conclusions Our results confirm the wide heterogeneity of the clinical presentation and outcome of children with RF-negative polyarticular JIA throughout the world. In particular, relevant differences in the onset age were observed across geographic areas. The group of children with early onset polyarthritis, ANA positivity, and risk of uveitis is remarkably frequent in Southern Europe.

Keywords Juvenile idiopathic arthritis, Rheumatoid factor negative polyarticular juvenile idiopathic arthritis, Uveitis, Antinuclear antibody positivity, Children, Geographic differences, Rheumatic diseases

*Correspondence:
Roberta Naddei
roberta.naddei@unina.it

Full list of author information is available at the end of the article

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Introduction

Juvenile idiopathic arthritis (JIA) is not a single disease but rather an heterogeneous group of disorders, characterized by chronic inflammatory arthritis but presenting distinct clinical phenotypes, disease courses, outcomes, and presumably, genetic background and pathogenesis [1]. These arthritides are the most common chronic rheumatic diseases of childhood and represent a leading cause of short- and long-term disability. According to the International League of Associations for Rheumatology (ILAR) classification, seven different subtypes of JIA can be distinguished on the basis of the clinical and laboratory features present in the first 6 months of disease [2]. Over the last decades, several small epidemiological studies have unveiled a considerable variability in the distribution and the characteristics of the JIA subtypes among different geographic areas or ethnic groups [3], as afterwards documented by a multinational, cross-sectional, observational cohort study, the Epidemiology, treatment and Outcome of Childhood Arthritis (EPOCA) study, including more than 9000 patients with JIA from 49 countries [4].

Rheumatoid factor (RF)-negative polyarthritis is defined as an arthritis that affects five or more joints during the first 6 months of disease in the absence of IgM RF [2] and accounts for 12–30% of all JIA cases, with the highest prevalence observed in North America and the lowest in Southeast Asia [4]. However, the current classification scheme for JIA, particularly regarding the use of the number of affected joints or the presence of psoriasis as criteria to define homogeneous groups has raised several criticisms [4, 5]. Observations indicate that patients with early-onset (diagnosis before 6 years of age), antinuclear antibody (ANA)-positive, RF-negative JIA constitute a homogeneous disease entity, irrespective of the ILAR classification, irrespective of the number of affected joints [6, 7]. Those findings support the emerging concept that most patients included in the ILAR category of RF-negative polyarthritis share clinical features with patients affected with oligoarthritis [5].

The heterogeneity of RF negative polyarthritis in children, and its possible implication in the pathophysiology of the disease, is also demonstrated by recent genetic studies, showing that human leukocyte antigen (HLA) associations and peripheral blood transcriptomic signatures differ between children who present with arthritis at the age of 6 years and below and those who present at an older age [8, 9]. However, it is not at all clear if the different phenotypes of this JIA category are significantly different in the different geographic areas.

Against this background, aim of the present study was to better characterize the demographic and clinical features of patients with RF-negative polyarthritis enrolled in the EPOCA study, in order to gain further insights into the variability of this JIA subtype in the diverse parts of the world. Furthermore, we described the frequency and the disease characteristics of the subgroup of children with early disease onset, ANA positivity and uveitis within the RF-negative category of JIA.

Patients and methods

Study design and subjects

Data were extracted from a cross-sectional dataset of 9081 subjects with JIA from 49 countries enrolled in the EPOCA study [4]. Each center participating to the EPOCA project was asked to enroll all the patients (up to 100) with JIA that were seen consecutively within 6 months. For each visit, retrospective and cross-sectional data were collected, including demographic and clinical data, physician-centered and patient/parent reported outcome measures. All participating centers to EPOCA study obtained approval from their respective ethics committee and consent/assent from parents/patients based on existing national regulations. The involved countries were grouped into eight geographical areas, based on geographical proximity: Northern Europe, Western Europe, Southern Europe, Eastern Europe, North America, Latin America, Africa and Middle East, and southeast Asia. The list of countries and their grouping method are provided in the Table S1.

Clinical assessment and outcome measures

All patients underwent a retrospective data collection, based on the review of clinical charts, and a cross-sectional assessment, carried out at the study visit. Retrospective evaluation included demographic data, ILAR JIA category, history of uveitis, ANA determination and medications administered from disease onset to the date of the visit. Cross-sectional assessment included a standardized joint examination, a physician's global assessment of disease activity (PhGA) and the measurement of articular and extra-articular damage by the Juvenile Arthritis Damage Index (JADI) [10]. Before the cross-sectional visit, the parent (or the patient when judged able to understand) completed a multidimensional questionnaire, translated and cross-culturally validated into 54 languages of 52 countries [11], including the assessments of the child's physical function, overall wellbeing, pain intensity, health-related quality of life (HRQoL), and morning stiffness [12]. The Juvenile Arthritis Disease Activity Score-10 (JADAS-10) and its clinical version (c-JADAS10) at the cross-sectional visit were also computed and collected [13–15]. The frequency of the clinical inactive disease was evaluated using the Wallace criteria and the American College of Rheumatology 2021 cJADAS-10 criteria [16].

Statistical analysis

For the purpose of this study, only data from patients with a diagnosis of RF negative polyarthritis were extracted and compared across the eight geographical areas. Descriptive statistics were reported as median and interquartile range (IQR) for continuous variables and as frequencies (%) for categorical ones. Quantitative measures were compared by Kruskal-Wallis test with Dunn's post hoc test. Percentages were compared by chi-square test, with Bonferroni correction used for post hoc analysis. For sake of simplicity, results of post-hoc analysis were reported only in the text.

All statistical tests were 2-sided; a p-value < 0.05 was considered statistically significant. Rstudio Team (2020, version: 1.3.1093) was used to conduct the statistical analysis.

Results

Among the 9081 patients enrolled in the EPOCA study, 2141 patients (23.6%) with RF negative polyarthritis were identified and included in the present analysis. According to their country of residence, these subjects were grouped into eight geographical areas, as reported in Table S1: Northern Europe (223 children), Western Europe (198), Southern Europe (480), Eastern Europe (539), North America (165), Latin America (217), Africa and Middle East (271), and southeast Asia (48). As already reported (4), the prevalence of RF negative polyarthritis was highest in North America, where it accounted for the 31.5% of all JIA patients enrolled, and lowest in southeast Asia (12.7%). The other areas showed similar frequency of RF-negative polyarthritis (Northern Europe and Eastern Europe: 26.4%; Western Europe: 23.8%; Southern Europe: 20%; Latin America: 25.6% and Africa and Middle East: 22.4%).

Clinical features

Demographic and clinical characteristics of subjects with RF negative polyarthritis across the eight geographical areas are presented in Table 1.

There was a predominance of female patients throughout all areas. The median age at disease onset ranged

Table 1 Demographic and clinical features of the patient sample*

	Northern Europe *N* = 223	Western Europe *N* = 198	Southern Europe *N* = 480	Eastern Europe *N* = 539	North America *N* = 165	Latin America *N* = 217	Africa & Middle East *N* = 271	South-east Asia *N* = 48
Demographic and clinical features								
Female (NS)	170 (76.2)	150 (75.8)	377 (78.5)	393 (72.9)	138 (83.6)	152 (70.0)	194 (71.6)	33 (68.8)
Age at onset, years (median [IQR])	3.5 [2.0, 7.9]	7.5 [3.0, 10.6]	3.5 [1.7, 7.0]	6.8 [3.0, 10.5]	7.3 [3.0, 10.6]	7.0 [4.0, 10.3]	6.8 [3.7, 9.8]	6.3 [2.6, 10.8]
Age at onset								
≤6 years of age	140 (62.8)	89 (44.9)	327 (68.1)	245 (45.5)	67 (40.6)	90 (41.5)	118 (43.5)	23 (47.9)
6–12 years of age	18 (8.1)	36 (18.2)	29 (6.0)	101 (18.7)	28 (17.0)	28 (12.9)	25 (9.2)	7 (14.6)
>12 years of age	65 (29.1)	73 (36.9)	124 (25.8)	193 (35.8)	70 (42.4)	99 (45.6)	128 (47.2)	18 (37.5)
Age at visit, years (median [IQR])	11.7 [8.2, 14.6]	12.5 [8.9, 15.6]	9.6 [5.8, 13.5]	12.8 [8.9, 15.7]	13.3 [10.7, 16.1]	13.3 [10.6, 15.2]	11.3 [8.0, 13.8]	11.3 [8.2, 14.1]
Disease duration, years (median [IQR])	5.4 [2.9, 8.5]	3.8 [1.6, 6.3]	4.2 [2.0, 7.2]	4.1 [1.9, 7.3]	4.4 [2.0, 8.8]	4.8 [2.4, 7.5]	3.2 [1.6, 6.0]	5.4 [2.9, 8.5]
Interval onset-referral, years (median [IQR])	0.2 [0.1, 0.7]	0.4 [0.2, 0.9]	0.3 [0.1, 0.8]	0.4 [0.1, 1.3]	0.3 [0.1, 0.8]	0.4 [0.2, 1.3]	0.5 [0.2, 1.6]	0.8 [0.4, 2.0]
Uveitis ever	47 (21.1)	19 (9.6)	68 (14.2)	43 (8.0)	15 (9.1)	4 (1.8)	12 (4.4)	2 (4.2)
Uveitis in patients with a disease duration > 4 years	36/146 (24.7)	14/92 (15.2)	45/254 (17.7)	25/278 (9.0)	13/89 (14.6)	3/123 (2.4)	5/107 (4.7)	2/27 (7.4)
Active uveitis at visit (NS)	12 (5.4)	6 (3.0)	17 (3.7)	19 (3.5)	3 (1.8)	0 (0.0)	5 (1.8)	1 (2.1)
ESR (median [IQR])	6.0 [3.0, 9.0]	8.0 [5.0, 14.0]	10.0 [5.0, 19.0]	12.0 [6.0, 21.0]	7.0 [4.0, 14.0]	16.0 [8.0, 27.0]	16.5 [8.8, 28.0]	21.0 [10.0, 31.2]
Antinuclear antibodies								
Positive	88 (39.5)	101 (51.0)	301 (62.7)	184 (34.1)	59 (35.8)	82 (37.8)	66 (24.4)	16 (33.3)
Negative	135 (60.5)	81 (40.9)	170 (35.4)	339 (62.9)	79 (47.9)	121 (55.8)	184 (67.9)	26 (54.2)
Not available	0 (0.0)	16 (8.1)	9 (1.9)	16 (3.0)	27 (16.4)	14 (6.5)	21 (7.7)	6 (12.5)
cDMARD ever	201 (90.1)	157 (79.3)	428 (89.2)	462 (85.7)	125 (75.8)	199 (91.7)	244 (90.0)	45 (93.8)
bDMARD ever	118 (52.9)	74 (37.4)	206 (42.9)	198 (36.7)	88 (53.3)	76 (35.0)	90 (33.2)	4 (8.3)

NS not significant, *IQR* interquartile range, *ESR* erythrocyte sedimentation rate, *cDMARDs* conventional disease modifying antirheumatic drugs, *bDMARDs* biological disease modifying antirheumatic drugs

*Values are numbers (%) unless indicated otherwise. All the differences are statistically significant ($p < 0.001$), apart from gender difference ($p = 0.19$) and frequency of active uveitis ($p = 0.39$). See main text for post-hoc analysis

from 6 to 7 years in all areas, except from Northern and Southern Europe where, in the post-hoc analysis, we observed a significantly lower median age at onset (3.5 years) than in the other geographical areas (Table 1; Fig. 1a). In all geographic areas, the frequency of children with JIA onset between the age of 6 and 12 was lower than 20%. In North and Latin America, the frequency of patients with disease onset after the age of 12 was greater than 45%.

Post-hoc analysis also showed that Southern and Northern Europe presented with a significantly higher prevalence of uveitis (21.1% and 14.2%, respectively), as compared to Western and Eastern Europe (9.6% and 8%) and North America (9.1%), and to Southeast Asia (4.2%), Africa & Middle East (4.1%) and Latin America (1.8%), which exhibited the lowest frequencies of uveitis (Fig. 1b). Although with an overall higher uveitis prevalence, similar differences resulted when considering solely patients with a disease duration longer than 4 years (Table 1). The frequency of active uveitis at the cross-sectional examination was slightly higher in European areas compared to the others, although not significantly (Table 1).

Western and Southern Europe showed the higher prevalence of ANA positivity (51% and 62.7%, respectively, $p < 0.001$ in all post-hoc comparisons with other geographic areas) (Table 1; Fig. 1c). Of note, ANA were not available in 12.5% of patients from Southeast Asia and 16.4% of patients from North America (Table 1). Interval between disease onset and referral to a pediatric rheumatology center ranged from 0.2 years in Northern Europe to 0.8 years in Africa and Middle East.

Treatment

The proportion of patients treated with conventional disease-modifying antirheumatic drugs (DMARDs) ranged from 75.8% (North America) to 93.8% (Southeast Asia), whereas biological DMARDs were used mostly in Northern Europe and North America and less frequently in southeast Asia (Table 1). Oral corticosteroids were prescribed less frequently in Western Europe (24%) and North America (20%); in the other geographic areas they were prescribed in ≥ 50% of patients. More than 75% of patients in Northern Europe received intra-articular steroid injections, whereas no more than 15% of children received this treatment in North and Latin America and in South-East Asia. The proportions of the most

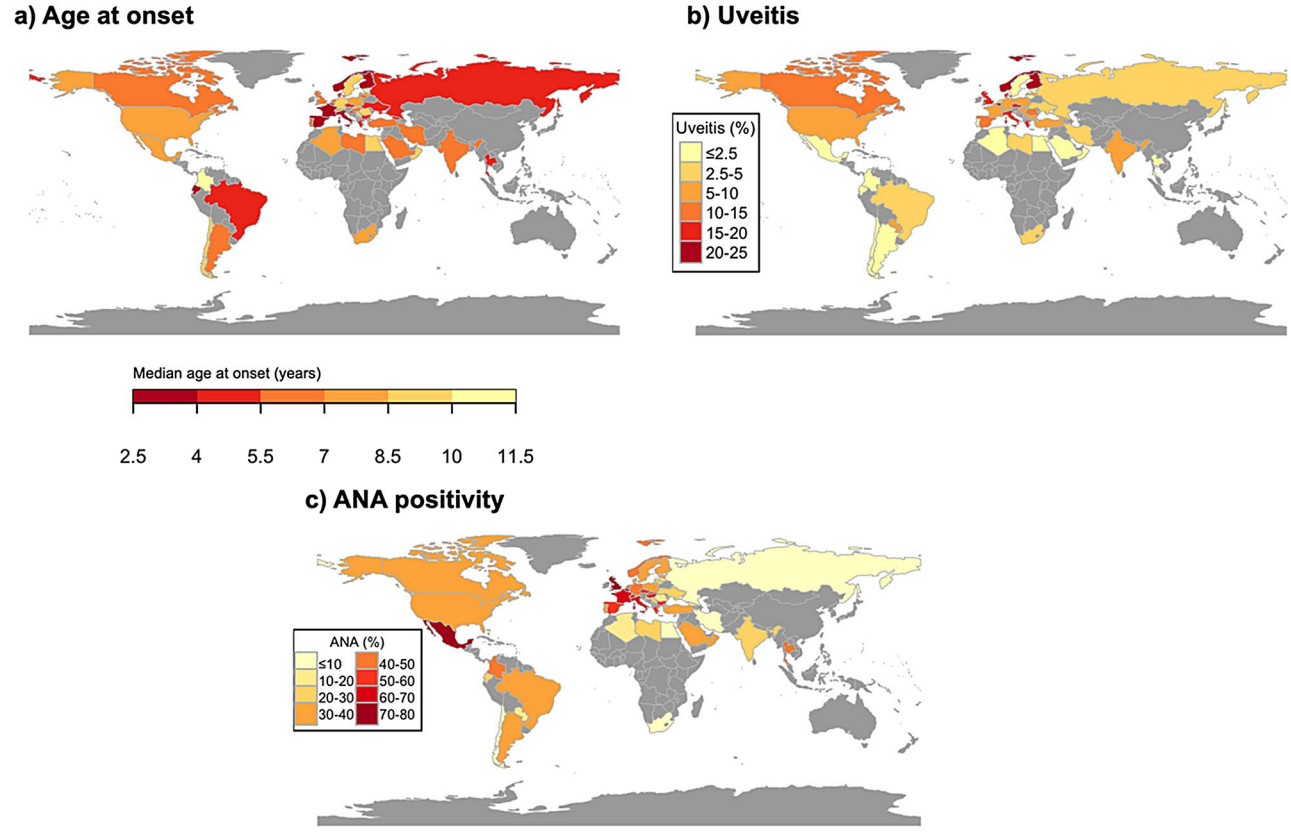

Fig. 1 Median age at disease onset (**a**), prevalence of uveitis (**b**) and ANA positivity (**c**) in patients with RF negative polyarthritis included in the EPOCA study across the world

prescribed medications across the eight geographical areas are shown in supplementary Table S2.

Physician- and parent-reported outcomes

At the cross-sectional visit, the prevalence of patients with active joints at clinical examination was significantly lower in Northern and Southern Europe, and higher in Eastern Europe in the post-hoc analysis (Table 2). Patients from Eastern Europe and Africa and Middle East showed higher disease activity in terms of PhGA. Overall, patients from Southeast Asia showed the lowest disease activity according to the physician-reported measures, even though not significantly at the post-hoc analysis (Table 2).

The prevalence of limited joints in subjects with inactive disease according to the physician (PhGA = 0) was

Table 2 Physician and parent/patient reported outcome measures, composite disease activity score and prevalence inactive disease at the cross-sectional visit*

	Northern Europe *N* = 223	Western Europe *N* = 198	Southern Europe *N* = 480	Eastern Europe *N* = 539	North America *N* = 165	Latin America *N* = 217	Africa & Middle East *N* = 271	South-east Asia *N* = 48
Physician-centered measures								
Swollen joint count > 0	73 (32.7)	83 (41.9)	169 (35.2)	271 (50.3)	60 (36.4)	110 (50.7)	122 (45.0)	11 (22.9)
Tender joint count > 0	87 (39.0)	82 (41.4)	129 (26.9)	282 (52.3)	51 (30.9)	83 (38.2)	138 (50.9)	11 (22.9)
Limited joint count > 0	94 (42.2)	110 (55.6)	197 (41.0)	309 (57.3)	80 (48.5)	130 (59.9)	152 (56.1)	22 (45.8)
Active joint count > 0	84 (37.7)	93 (47.0)	184 (38.3)	315 (58.4)	69 (41.8)	117 (53.9)	146 (53.9)	13 (27.1)
Active joint count (median [IQR])	0.0 [0.0, 1.0]	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	1.0 [0.0, 6.0]	0.0 [0.0, 2.0]	1.0 [0.0, 4.0]	1.0 [0.0, 4.0]	0.0 [0.0, 1.0]
Less than 5 active joints	203 (91.0)	169 (85.4)	430 (89.6)	384 (71.2)	141 (85.5)	164 (75.6)	222 (81.9)	44 (91.7)
5 to 9 active joints	14 (6.3)	16 (8.1)	32 (6.7)	75 (13.9)	16 (9.7)	27 (12.4)	29 (10.7)	1 (2.1)
10 active joints or more	6 (2.7)	13 (6.6)	18 (3.8)	80 (14.8)	8 (4.8)	26 (12.0)	20 (7.4)	3 (6.2)
PhGA > 0§	135 (60.5)	128 (64.6)	237 (49.5)	432 (80.1)	98 (59.4)	131 (60.4)	206 (76.0)	24 (50.0)
PhGA (median [IQR])	1.0 [0.0, 2.0]	1.0 [0.0, 2.9]	0.0 [0.0, 2.0]	2.0 [0.5, 4.0]	1.0 [0.0, 2.5]	1.0 [0.0, 3.0]	2.5 [0.5, 4.2]	0.2 [0.0, 1.5]
JADI score > 0#	37 (31.1)	20 (28.2)	48 (25.4)	114 (52.8)	18 (24.7)	45 (42.9)	47 (53.4)	9 (56.2)
JADI-articular score > 0#	31 (26.1)	15 (21.1)	36 (19.0)	99 (45.8)	15 (20.5)	44 (41.9)	42 (47.7)	8 (50.0)
JADI-extra-articular score > 0#	15 (12.6)	8 (11.3)	23 (12.2)	59 (27.3)	6 (8.2)	12 (11.4)	27 (30.3)	5 (31.2)
Parent/patient reported measures								
PaGA > 0§	169 (76.1)	164 (82.8)	250 (52.5)	393 (73.5)	101 (62.7)	119 (54.8)	183 (68.5)	27 (56.2)
PaGA (median [IQR])	1.5 [0.5, 3.5]	2.0 [1.0, 5.0]	0.5 [0.0, 3.0]	1.5 [0.0, 4.0]	0.5 [0.0, 2.5]	0.5 [0.0, 2.5]	2.0 [0.0, 5.0]	0.5 [0.0, 2.0]
Pain intensity > 0§	165 (74.3)	151 (76.3)	226 (47.5)	383 (71.6)	112 (69.6)	120 (55.3)	162 (60.7)	23 (47.9)
Pain intensity (median [IQR])	1.8 [0.0, 4.5]	2.0 [0.5, 5.0]	0.0 [0.0, 2.5]	1.5 [0.0, 4.0]	1.0 [0.0, 3.0]	0.5 [0.0, 2.0]	1.5 [0.0, 5.0]	0.0 [0.0, 2.5]
Morning stiffness > 15 min	76 (34.7)	62 (31.6)	62 (13.1)	122 (22.8)	36 (22.4)	42 (19.4)	52 (19.8)	7 (14.6)
Physical function score > 0†	143 (64.4)	130 (66.0)	230 (48.1)	344 (64.3)	88 (54.7)	124 (57.1)	193 (71.5)	26 (54.2)
HRQoL score > SD 1 in healthy children‡	147 (67.4)	130 (67.4)	219 (48.5)	359 (68.8)	84 (53.8)	114 (53.3)	189 (71.1)	19 (41.3)
Composite disease activity scores								
cJADAS10 (median [IQR])	3.0 [0.5, 7.0]	5.0 [1.5, 9.5]	2.0 [0.0, 7.0]	6.5 [1.5, 13.0]	3.0 [0.5, 7.5]	3.5 [0.0, 11.0]	7.0 [1.5, 12.0]	2.0 [0.0, 5.0]
JADAS10 (median [IQR])	3.0 [1.0, 7.4]	4.9 [2.0, 8.5]	2.2 [0.0, 7.3]	7.0 [2.0, 14.1]	3.0 [0.5, 7.5]	3.6 [0.3, 12.0]	6.7 [1.5, 13.5]	2.5 [0.3, 6.1]
Inactive disease								
By ACR clinically inactive disease [17]	67 (30.0)	51 (25.8)	203 (42.3)	86 (16.0)	59 (35.8)	68 (31.3)	52 (19.2)	16 (33.3)
By ACR 2021 cJADAS10 criteria [16]	104 (46.8)	75 (37.9)	268 (56.3)	174 (32.5)	80 (49.7)	103 (47.5)	84 (31.5)	30 (62.5)

IQR interquartile range, *PhGA* physician global assessment of disease activity, *JADI* Juvenile Arthritis Damage Index, *PaGA* parent global assessment of disease activity, *HRQoL* health-related quality of life scale, *SD* standard deviation, *cJADAS10* clinical Juvenile Arthritis Disease Activity Score 10, *JADAS10* Juvenile Arthritis Disease Activity Score 10, *ACR* American College of Rheumatology

*Values are numbers (%) unless indicated otherwise. All the differences are statistically significant ($p < 0.001$). See main text for the post-hoc analysis

§Measured with a visual analogue scale on a 21-numbered circle visual analogue scale, ranging from 0 (best) to 10 (worst)

#The JADI score is computed only in patients with a disease duration longer than 5 years

†Score ranges from 0 (no disability) to 45 (maximum disability). ‡Score ranges from 0 to 30, with higher scores indicating worse HRQoL. The SD in healthy children was calculated for each geographical area on questionnaires completed by the parents of these children

higher in Eastern Europe and Latin America, although not significantly ($p = 0.23$, Table S3). In those two areas, along with Southeast Asia, a greater frequency of damage by JADI measurement was found (Table 2).

With regard to patient/parent reported outcomes (Table 2), the post-hoc analysis showed that subjects from Southern Europe presented less frequently with pain, morning stiffness and impairment of overall well-being, quality of life and function ability. On the other hand, pain was more common in patients from Northern, Western and Eastern Europe, who also showed more frequently impairment of overall well-being, together with subjects from Africa and Middle East. The frequency of morning stiffness was higher in Northern and Western Europe. Subjects from Eastern Europe reported more frequently impaired health-related quality of life.

The frequency of inactive disease was significantly higher in patients from Southern Europe, and, to a lower extent from Southeast Asia and North America. On the other end, subjects from Africa and Middle East and Eastern Europe showed the highest scores of composite disease activity measures, also at the post-hoc analysis (Table 2). The distribution of the JADAS10 components across the 8 geographic areas is displayed in Fig. 2. Of note North, West and South European and North American children had lower erythrocyte sedimentation rate (ESR) levels (Table 1; Fig. 2).

Early onset polyarthritis

To examine if the cluster of JIA patients with early-onset, ANA positivity and uveitis was differently distributed throughout the world among patients with RF negative polyarthritis, we compared the proportion of patients presenting the association of at least two of those three clinical features across the eight geographic areas (Fig. 3). As shown in the post-hoc analysis, those associations were significantly more frequent in patients from Southern Europe (39%).

In comparison to other RF negative polyarthritis patients, children with at least two among early onset polyarthritis, ANA positivity, and uveitis had similar number of joints with active arthritis, higher count of joints with pain, lower physician global assessment, better parent/patient reported outcomes, and lower frequency of articular damage (Table 3).

Discussion

We provide herein a thorough overview of the features of more than 2000 children with RF-negative polyarticular JIA coming from 8 different geographic areas. Our results provide further insights into the wide variability of RF-negative polyarthritis throughout the world. Firstly, as already reported, the prevalence of this JIA subtype was highest in North America, where it was comparable to oligoarthritis, and lowest in Southeast Asia, where patients with JIA were more likely to have systemic JIA or enthesitis-related arthritis [4].

As expected, most patients were female in all geographic areas. Studies have shown a biphasic distribution in age at onset in RF-negative polyarticular JIA, including a peak in young children (2–4 years) and a later peak at 6–12 years [1, 5].

Patients from Northern Europe and Southern Europe showed similar demographic features. They had a lower

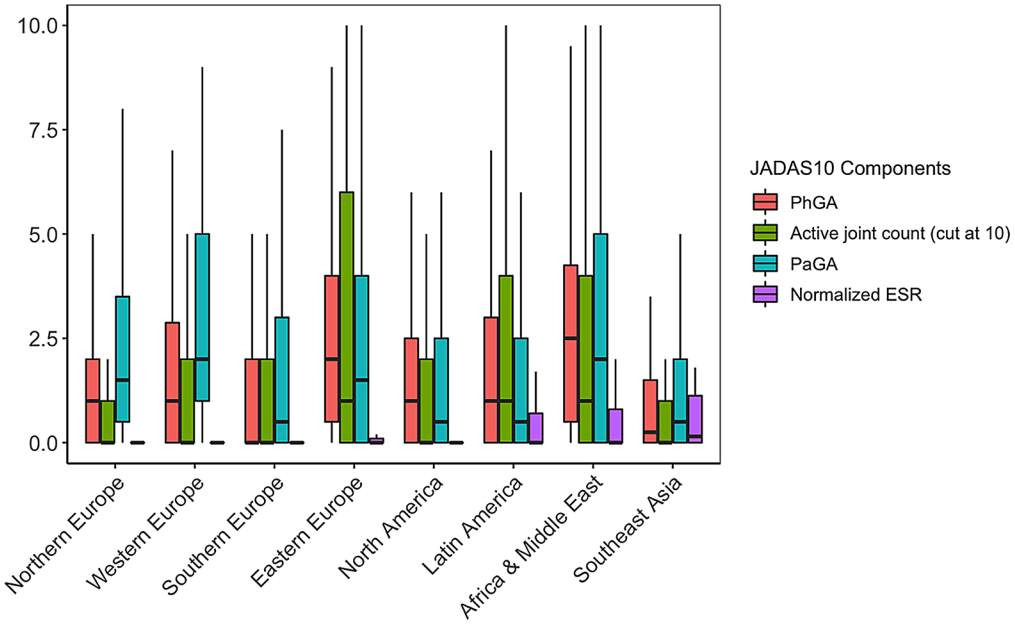

Fig. 2 Distribution of the JADAS10 components across the 8 geographic areas

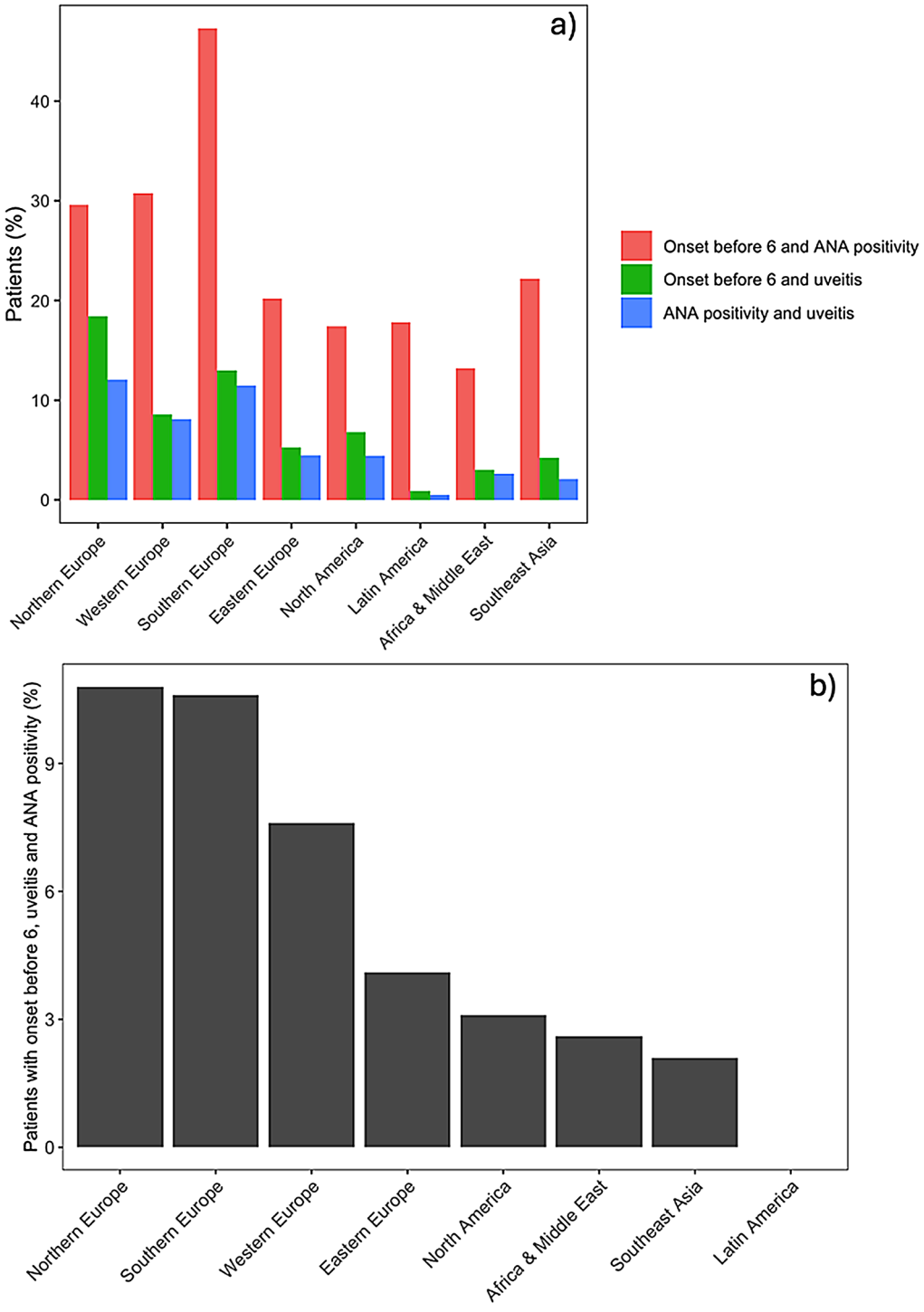

Fig. 3 Proportion of patients with RF negative polyarthritis included in the EPOCA study presenting the combination of two (**a**) or three (**b**) features among early disease onset, ANA positivity and uveitis

age at onset (3.5 years), with more than 60% of patients with JIA onset before the age of 6 years. In Southern and Northern Europe, the frequency of uveitis in RF-negative polyarthritis was significantly higher (14% and 21% respectively). The interval between disease onset and referral to pediatric rheumatology center was short. ANA positivity was higher in Southern Europe (63%). However, uveitis was also reported in a considerable proportion of subjects from North America and other European settings, whereas it was far less common in Southeast Asia, Africa and Middle East, and Latin America. Among European areas, uveitis was less prevalent in Eastern

Table 3 Comparison of geographic distribution, physician and parent/patient reported outcome measures, composite disease activity score and prevalence inactive disease at the cross-sectional visit between children with at least two features among early onset of polyarthritis, ANA positivity, and uveitis and other children with RF-negative polyarthritis*

	Early onset, ANA positive, uveitis associated polyarthritis *N* = 613	**Other RF-negative polyarthritis *N* = 1384**	***p***
Geographic area (%)			< 0.001
Northern Europe	86 (14.0)	136 (9.8)	
Western Europe	63 (10.3)	115 (8.3)	
Southern Europe	239 (39.0)	225 (16.3)	
Eastern Europe	112 (18.3)	402 (29.0)	
North America	31 (5.1)	104 (7.5)	
Latin America	39 (6.4)	161 (11.6)	
Africa & Middle East	32 (5.2)	210 (15.2)	
Southeast Asia	11 (1.8)	31 (2.2)	
Swollen joint count > 0	248 (40.5)	586 (42.3)	0.460
Tender joint count > 0	204 (33.3)	592 (42.8)	< 0.001
Limited joint count > 0	279 (45.5)	719 (52.0)	0.009
Active joint count > 0	274 (44.7)	665 (48.0)	0.182
Active joint (%)			0.002
Less than 5 active joints	531 (86.6)	1113 (80.4)	
5 to 9 active joints	49 (8.0)	142 (10.3)	
10 active joints or more	33 (5.4)	129 (9.3)	
PhGA (median [IQR])	1.0 [0.0, 2.5]	1.0 [0.0, 3.5]	< 0.001
PhGA > 0§	354 (57.7)	932 (67.4)	< 0.001
ESR (median [IQR])	10.0 [5.0, 20.0]	10.0 [5.0, 21.0]	0.445
PaGA (median [IQR])	1.0 [0.0, 3.0]	1.0 [0.0, 4.0]	0.001
PaGA > 0§	359 (59.3)	940 (68.4)	< 0.001
Physical function score > 0†	305 (50.3)	870 (63.1)	< 0.001
HRQoL score > SD 1 in healthy children ‡	3.0 [0.0, 6.0]	4.0 [1.0, 8.0]	< 0.001
Pain intensity (median [IQR])	0.5 [0.0, 3.0]	1.0 [0.0, 4.0]	< 0.001
Pain intensity > 0§	340 (56.1)	908 (66.1)	< 0.001
ACR clinically inactive disease [17]	201 (32.8)	369 (26.7)	0.006
cJADAS10 (median [IQR])	3.0 [0.0, 8.5]	4.5 [1.0, 10.5]	< 0.001
cJADAS10 state (%) [16]			0.010
ID	299 (49.4)	572 (41.6)	
MiDA	79 (13.1)	188 (13.7)	
MoDA	174 (28.8)	460 (33.5)	
HDA	53 (8.8)	155 (11.3)	
JADI score > 0#	160 (26.6)	452 (32.8)	0.007
JADI-articular score > 0#	121 (20.1)	400 (29.0)	< 0.001
JADI-extra-articular score > 0#	87 (14.5)	163 (11.8)	0.121

IQR interquartile range, *PhGA* physician global assessment of disease activity, *PaGA* parent global assessment of disease activity, *ESR* erythrocyte sedimentation rate, *HRQoL* health-related quality of life scale, *SD* standard deviation, *ACR* American College of Rheumatology, *cJADAS10* clinical Juvenile Arthritis Disease Activity Score 10, *ID* inactive disease, *MiDA* minimal active disease, *MoDA* moderate active disease, *HDA* high disease activity, *JADI* Juvenile Arthritis Damage Index

*Values are numbers (%) unless indicated otherwise

§Measured with a visual analogue scale on a 21-numbered circle visual analogue scale, ranging from 0 (best) to 10 (worst)

†Score ranges from 0 (no disability) to 45 (maximum disability). ‡Score ranges from 0 to 30, with higher scores indicating worse HRQoL. The SD in healthy children was calculated for each geographical area on questionnaires completed by the parents of these children. #The JADI score is computed only in patients with a disease duration longer than 5 years

Europe. It is well-known that chronic anterior uveitis is associated with early age at onset, female sex, and ANA positivity [7]. As a matter of fact, the new preliminary criteria for JIA outlined by the Pediatric Rheumatology International Trials Organization proposed the new category of early-onset ANA-positive JIA, solely based on the presence of arthritis (irrespective of the number of joint involved), the age of onset (< 6 years of age) and the ANA positivity [17]. That, in our study, children with RF-negative polyarthritis from Northern and Southern Europe, in addition to a younger age at disease onset, had the highest prevalence of uveitis reinforces the concept that a sizeable proportion of patients included in this JIA subtype shares clinical aspect with those with oligoarthritis,

the only difference being in the number of joints involved, which may be simply a marker of disease severity. Children with early onset, ANA positive polyarthritis seem to show a somewhat joint milder disease, with less pain and better parent/patient reported outcomes.

Other studies have indeed shown that in some areas, such as Costa Rica, New Zealand and India, where early-onset, ANA positive, uveitis-associated oligoarticular arthritis is rare, also RF-negative polyarticular JIA is less commonly observed [5]. Consistent with that, evidence has been provided that European ancestry may be an important predisposing factor for ANA-positive JIA associated with iridocyclitis [3]. In the EPOCA cohort, RF negative polyarthritis patients with positive ANA, younger age at onset, and affected with uveitis were more frequent in the pediatric rheumatology units in Northern and Southern Europe (≥ 10%) than in other regions (< 5%). Remarkably, children in countries grouped in the Western Europe area had high frequency of ANA positivity, but older age at onset and low rate of uveitis.

Looking at the joint disease, North, West and South European and North American children showed similar outcomes in terms of prevalence of active joints and ESR levels, and median active joint count at the cross-sectional visit was lower as compared to patients from Eastern Europe, Africa and Middle East and Latin America, which exhibited the higher disease activity according to the physician-reported outcome measures. Taken together, all these findings may suggest that patients with RF-negative polyarthritis from most European countries and North America tend to develop a less aggressive joint involvement with a higher prevalence of uveitis, compared to subject from Africa, Middle East and Latin America. The joint disease was also associated to better outcomes in pain intensity, quality of life and functional status according to parents/patients in Southern Europe. On the other hand, patients from Southeast Asia exhibited the better outcomes in terms of not only physician-reported outcome measures, but also according to the parent/patient perspective and the composite disease activity tools, suggesting that RF-negative polyarticular JIA is not only a rare JIA subtype in this geographic area, but it also seems to be associated to a lower disease activity, even though the frequency of damage was higher in this area.

No substantial discrepancies were observed with regard to the DMARDs used in RF-negative polyarthritis worldwide, except from a lower use of conventional DMARDs in favor of biological DMARDs in North America and a very low use of biological DMARDs in Southeast Asia. Notably, adalimumab was more frequently administered in Northern Europe, where the highest prevalence of uveitis was found. Also of note is that the proportion of patients undergone to intra-articular joint injections was particularly high in Northern and Southern Europe, whereas the use of systemic corticosteroids was higher in Africa and Middle East and Southeast Asia. The lesser use of biological agents, in favor of the higher use of systemic glucocorticoid, in lower-income settings might be, at least partly, related to reduced accessibility to healthcare facilities or treatment availability. As above-mentioned, the presence of damage was higher in Southeast Asia, along with Eastern Europe and Africa and Middle East. A factor key associated to the disease damage lies in the higher use of systemic corticosteroids in those areas, as shown by the higher frequency of extra-articular damage. Moreover, Southeast Asia showed the longest interval between symptoms onset and the first observation to the referral center, which also has been associated to worst disease outcomes [18].

Our study should be interpreted in light of some limitations. Disparities in availability of ophthalmologic screening programs may explain in part the different rates of uveitis. So, it cannot be entirely excluded that less rigorous screening schedules could account for the lower frequencies of uveitis in some geographic context. The frequency of ANA testing and the test methodology was widely variable in the different geographic areas, with ANA being more tested where a higher frequency was observed; moreover, a less stringent definition of ANA positivity was used for this analysis in comparison to previous studies. In the EPOCA cohort, ANA were measured with indirect immunofluorescence in 74% of positive cases; when ANA were reported to be negative, ANA determination methodology was not collected. That, together with the differences in the frequency and methodology of ANA testing, might represent a potential confounding factor in the analysis of the ANA results across the eight geographic areas. Moreover, our findings could be biased by the geographic differences in the healthcare access and cultural factors across the world. Indeed, it is possible that only JIA patients with poor clinical status visit clinics in countries with lower gross domestic product, and patients with better status in rich countries seek medical care. Finally, difficulties in the accessibility to biological agents might, at least partly, account for higher disease activity in lower income settings.

While we cannot exclude this possibility, the study was designed to incorporate a consecutive cross-section of patients seen in various countries. There was a disproportion in the number of patients included in the various geographic areas and this limitation may affect the generalizability of our findings. We acknowledge that our modality of grouping of countries in geographic areas may be regarded as arbitrary.

Conclusions

In conclusion, our results confirm the wide heterogeneity of the clinical presentation and outcome of children with RF-negative polyarticular JIA throughout the world. While the discrepancies in the treatment modalities and in the outcome can be at least in part explained by the unbalanced availability of resources in the different geographic areas, the observation that children with features considered typical of oligoarthritis (i.e. lower age at onset, ANA positivity and higher frequency of uveitis) are significantly more prevalent in some European countries, remains unexplained. This finding could be the key to understand the genetic and environmental factors involved in the pathophysiology of this group of JIA patients that may represent the only disease category observed solely in children.

Abbreviations

JIA	Juvenile idiopathic arthritis
ILAR	International League of Associations for Rheumatology
EPOCA	Epidemiology, treatment and Outcome of Childhood Arthritis
RF	Rheumatoid factor
ANA	Antinuclear antibody
HLA	Human leukocyte antigen
PhGA	Physician's global assessment of disease activity
JADI	Juvenile Arthritis Damage Index
HRQoL	Health-related quality of life
JADAS-10	Juvenile Arthritis Disease Activity Score-10
c-JADAS10	Clinical Juvenile Arthritis Disease Activity Score-10
IQR	Interquartile range
DMARDs	Disease-modifying antirheumatic drugs
ESR	Erythrocyte sedimentation rate

Supplementary Information

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Supplementary Material 1

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Author contributions

Study conception: AR, AC. Study design: RN, AR, AC. Acquisition of data: YU, MT, PD, IRR and NR. Analysis and interpretation of data and drafting of the manuscript: RN, MB and FR. All authors reviewed the manuscript and approved the final version.

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Data availability

All data generated by the research are available upon request to the authors.

Declarations

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All participating centers to EPOCA study obtained approval from their respective ethics committee and consent/assent from parents/patients based on existing national regulations.

Consent for publication

Granted by all authors.

Competing interests

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Author details

[1]Dipartimento di Scienze Mediche Traslazionali, Università degli Studi di Napoli Federico II, Via Sergio Pansini n. 5, 80131 Naples, Italy
[2]Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno Infantili (DINOGMI), Università degli Studi di Genova, Genova, Italy
[3]UOC Reumatologia e Malattie Autoinfiammatorie, IRCCS Istituto Giannina Gaslini, Genoa, Italy
[4]Meir Medical Center, Kfar Saba and School of Medicine, Tel Aviv University, Tel Aviv, Israel
[5]Paediatric Immunology and Rheumatology Referral Centre, Hippokration General Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece
[6]Centre for Paediatric Rheumatology and Autoinflammatory Diseases, Charles University and General University Hospital in Prague, Prague, Czech Republic
[7]Faculty of Medicine, University of Latvia, Riga, Latvia
[8]Direzione Scientifica, IRCCS Istituto Giannina Gaslini, Genoa, Italy

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References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369(9563):767–78.
2. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
3. Consolaro A, Ravelli A. Unraveling the phenotypic variability of juvenile idiopathic arthritis across races or geographic areas - key to understanding etiology and genetic factors? J Rheumatol. 2016;43(4):683–5.
4. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. Lancet Child Adolesc Health. 2019;3:255–63.
5. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? J Rheumatol. 2003;30(9):1900–3.
6. Ravelli A, Felici E, Magni-Manzoni S, Pistorio A, Novarini C, Bozzola E, et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. Arthritis Rheum. 2005;52(3):826–32.
7. Ravelli A, Varnier GC, Oliveira S, Castell E, Arguedas O, Magnani A, et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. Arthritis Rheum. 2011;63(1):267–75.

8. Nigrovic PA, Colbert RA, Holers VM, Ozen S, Ruperto N, Thompson SD, et al. Biological classification of childhood arthritis: roadmap to a molecular nomenclature. Nat Rev Rheumatol. 2021;17(5):257–69.
9. Barnes MG, Grom AA, Thompson SD, Griffin TA, Luyrink LK, Colbert RA, et al. Biologic similarities based on age at onset in oligoarticular and polyarticular subtypes of juvenile idiopathic arthritis. Arthritis Rheum. 2010;62(11):3249–58.
10. Viola S, Felici E, Magni-Manzoni S, Pistorio A, Buoncompagni A, Ruperto N, et al. Development and validation of a clinical index for assessment of long-term damage in juvenile idiopathic arthritis. Arthritis Rheum. 2005;52:2092–102.
11. Bovis F, Consolaro A, Pistorio A, Garrone M, Scala S, Patrone E, et al. Cross-cultural adaptation and psychometric evaluation of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) in 54 languages across 52 countries: review of the general methodology. Rheumatol Int. 2018;38:5–17.
12. Filocamo G, Consolaro A, Schiappapietra B, Dalprà S, Lattanzi B, Magni-Manzoni S, et al. A new approach to clinical care of juvenile idiopathic arthritis: the Juvenile Arthritis Multidimensional Assessment Report. J Rheumatol. 2011;38(5):938–53.
13. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum. 2009;61(5):658–66.
14. McErlane F, Beresford MW, Baildam EM, Chieng SE, Davidson JE, Foster HE, et al. Validity of a three-variable Juvenile Arthritis Disease Activity score in children with new-onset juvenile idiopathic arthritis. Ann Rheum Dis. 2013;72(12):1983–8.
15. Consolaro A, Negro G, Gallo MC, Bracciolini G, Ferrari C, Schiappapietra B, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. Arthritis Care Res (Hoboken). 2014;66:1703–9.
16. Trincianti C, Van Dijkhuizen EHP, Alongi A, Mazzoni M, Swart JF, Nikishina I, et al. Definition and validation of the American College of Rheumatology 2021 Juvenile Arthritis Disease activity score cutoffs for disease activity states in juvenile idiopathic arthritis. Arthritis Rheumatol. 2021;73(11):1966–75.
17. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol. 2019;46(2):190–7.
18. McErlane F, Foster HE, Carrasco R, Baildam EM, Chieng SE, Davidson JE, et al. Trends in paediatric rheumatology referral times and disease activity indices over a ten-year period among children and young people with juvenile idiopathic arthritis: results from the childhood arthritis prospective study. Rheumatology (Oxford). 2016;55(7):1225–34.

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