A prediction rule for polyarticular extension in oligoarticular-onset juvenile idiopathic arthritis

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Abstract

Objective

To search for predictors of polyarticular extension in children with oligoarticular-onset juvenile idiopathic arthritis (JIA) and to develop a prediction model for an extended course.

Methods

The clinical charts of consecutive patients with oligoarticular-onset JIA and ≥2 years of disease duration were reviewed. Predictor variables included demographic data, number and type of affected joints, presence of iridocyclitis, laboratory tests including antinuclear antibodies, and therapeutic interventions in the first 6 months. Joint examinations were evaluated to establish whether after the first 6 months of disease patients had persistent or extended course (i.e. involvement of 4 or less, or 5 or more joints). Statistics included univariable and multivariable analyses. Regression coefficients (β) of variables that entered the best-fitting logistic regression model were converted and summed to obtain a "prediction score" for an extended course.

Results

A total of 480 patients with a median disease duration of 7.4 years were included. 61.2% had persistent oligoarthritis, whereas 38.8% experienced polyarticular extension. On multivariable analysis, independent correlations with extended course were identified for the presence of ≥2 involved joints and a CRP >0.8 mg/dl in the first 6 months. The prediction score ranged from 0 to 6 and its cut-off that discriminated best between patients who had or did not have polyarticular extension was >1. Sensitivity and specificity were 59.6 and 79.8, respectively.

Conclusion

The number of affected joints and the CRP level in the first 6 months were the strongest predictors of polyarticular extension in our children with oligoarticular-onset JIA.

Key words

juvenile idiopathic arthritis, oligoarthritis, extended oligoarthritis, polyarthritis, paediatric rheumatology, prediction rule

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Introduction

Oligoarthritis accounts for the majority (40–60%) of children with juvenile idiopathic arthritis (JIA) seen in Western countries (1). It is defined as arthritis that affects 4 or fewer joints during the first 6 months of illness (2). Although oligoarthritis is often described as the most benign subtype of JIA, 21-39.5% of patients have a progressive increase in the number of affected joints over time (so-called extended oligoarthritis) (3-5), so that by 1–2 years after onset, they have polyarthritis (affecting 5 or more joints). In this subgroup, structural joint damage is frequent and the probability of remission is low (3, 4). Hence, these patients usually require a more aggressive therapy with synthetic or biologic disease-modifying anti-rheumatic drugs (DMARDs). Conversely, persistent oligoarthritis may be relatively easy to control with non-steroidal anti-inflammatory drugs or intraarticular glucocorticoids (6), although some patients may develop spondyloarthritis during puberty.

Early prediction of the course of joint disease and, in particular, of the risk of arthritis extension is important to help setting up a tailored or "personalised" therapeutic approach aimed to achieve disease remission at an earlier disease stage, which would minimise the burden of disease, limit medication side effects, and improve the quality of life (7). In addition, it would enable to provide prognostic information and to present appropriate treatment options to patients and their families.

A number of predictors of disease extension in oligoarthritis have been proposed, including early presence of ankle and/or wrist disease, involvement of more than one joint, arthritis in at least 1 upper limb, symmetric joint disease, and an elevated erythrocyte sedimentation rate (ESR) (3, 5, 8). In addition, children with persistent or extended course were found to have significantly different immunologic characteristics in the synovial infiltrate, with a markedly greater enrichment of interleukin-17-producing T cells in the joints of those with the extended phenotype (9). The proportion of synovial lymphocytes, levels of CCL5, and differential gene expression were shown to be potential biomarkers with which to predict the likelihood of extension (10). However, currently there are no established algorithms that can be applied in daily clinical practice to select those children who have a high probability of an extended course and would need more careful monitoring and, perhaps, an early intervention with DMARDs. This information may be important to define the optimal time of start of transitional care in adolescents and young adults (11). Importantly, the results of all studies should be interpreted in the light of the heterogeneity of JIA and of the problems in its classification (12, 13).

To address this issue, we undertook the present study, whose primary aim was two-fold. First, we sought for predictors of arthritis extension in our population of children with oligoarticular-onset JIA. Second, we aimed to develop a prediction model that could help to identify in the first 6 months of disease the patients with a greater likelihood to experience a polyarticular course of their disease.

Methods

Study design and patient selection

All consecutive patients who met the International League for Association of Rheumatology (ILAR) criteria for oligoarticular JIA (*i.e.* had 4 or less affected joints in the first 6 months of disease) (2), were followed at the IRCCS Fondazione Policlinico San Matteo of Pavia, Italy between 1990 and 2001 and at the IRCCS Istituto Giannina Gaslini of Genoa, Italy between 2002 and 2016, and had at least 2 years of disease duration between disease presentation (defined as the time when the first clinical manifestations consistent with JIA were noted) and last follow-up visit were included in the study. We set a 2-year timing for this study because polyarticular extension in oligoarthritis has been found to occur most frequently in the first 2 years after disease presentation (8). Because the study was retrospective, the number of visits between disease presentation and last follow-up visit was variable across patients and depended on the duration of follow-up and on the clinical needs related to the course of the disease.

The analysis was conducted through retrospective review of patient clinical charts and data stored in clinical databases. Patient information was collected by means of standardised case report form by 12 investigators (SR, FM, SP, SV, SL, VM, SDav, SDal, GCV, MB, CS, GB) and was, then, entered in a specialised database. The study protocol was approved by the ethics committee of the Istituto Giannina Gaslini, Genova, Italy.

Selection and assessment of predictive factors

The following variables were collected in each patient: sex, age at disease presentation, age at first observation at study center, and antinuclear antibody (ANA) status. Patients were defined as being ANA positive if they had at least 2 positive results on indirect immunofluorescence at a titre of ≥1:160, as reported (14). In addition, the following predictive factors were recorded in the first 6 months after disease presentation: number and type of affected joints, presence of iridocyclitis, white blood cell count, haemoglobin, platelet count, ESR, C-reactive protein (CRP), and therapeutic interventions. For each laboratory test, the result of the first available determination made after disease presentation was retained, whereas for the other variables the occurrence throughout the first 6 months after disease presentation was examined.

Assessment of articular course

The reports of joint examination were evaluated from disease presentation to last follow-up visit to establish whether after the first 6 months of disease the patient had a persistent oligoarticular course (*i.e.* involvement of 4 or less affected joints until last follow-up visit) or a polyarticular (extended) course (i.e. extension of arthritis to 5 or more joints). Patients in the latter group who had 10 or more affected joints were defined as having a worse extended course.

Statistics

Descriptive statistics were reported as medians and interquartile ranges (IQR) for continuous variables and as absolute frequencies and percentages for categorical variables. Comparisons of variables between patients with persistent or extended course were performed by the non-parametric Mann-Whitney U-test in case of quantitative data (as the variables were not normally distributed) and by chi-square or Fisher's exact test, as appropriate, for categorical data. The normality of the distributions was evaluated by means of the Shapiro-Wilk test.

Multiple logistic regression analysis was, then, performed, entering explanatory variables that showed significant results in univariable tests ($p<0.05$) or were considered a priori to be of foremost importance for the study outcome, with polyarticular extension as the outcome variable. Cases with missing variables were excluded from the analysis. Explanatory variables were all those listed in Table I. Before the application of logistic regression procedures, some continuous variables were dichotomised to binary variables. Cut-points were obtained through receiver operating characteristic (ROC) curve analysis. For age at disease presentation, the cut-points chosen were <2 years and ≥2 years, whereas for ESR and CRP the cut-points were ≤31 and >31 mm/h and ≤0.8 and >0.8 mg/dl, respectively. The step-down strategy of analysis was chosen; this consists of examining the effect of removing variables from the saturated model. The effect was expressed in terms of odds ratios, and 95% confidence intervals were calculated; statistical significance was tested by likelihood ratio test. The area under the ROC curve of the best-fitting model was used as an indicator of the predictive ability of the model.

To obtain a "prediction model" (15, 16) of polyarticular extension, the regression coefficients (β) of predictive variables that entered the best-fitting logistic regression model were converted into scores rounded to the nearest 0.5 and then summed to obtain a "prediction score". Subsequently, the cut-off in the score that discriminated best between patients who had or did not have a polyarticular extension was calculated by means of the ROC curve method. The predictive ability of the model was assessed by calculating sensitivity, specificity, positive and negative predictive value, Youden index (17) and area under the ROC curve (AUC).

Survival analysis, with polyarticular extension as the event of interest, was conducted by Kaplan-Meier method. Survival curves were compared by log-rank test. To account for the role of time to the event, factors significantly associated with polyarticular extension were tested in a Cox proportional hazards regression model. A "backward" strategy was used for model fitting. The effect was expressed in terms of Hazard Ratios with 95% confidence intervals. Statistical significance was tested by likelihood-ratio test. A $p<0.05$ was considered as statistically significant.

Power was calculated *a posteriori* for the Cox Regression model (using 2 covariates) according to Latouche *et al*. (18) and using R software ("PowerSurvEpi" Package). Given a sample of n=355, estimating theta as the lowest observed (HR) = 1.7, $p=0.468$, $q=0.104$, $p_0=0.459$, $p_1=0.541$, psi (proportion of events) =0.375, rho=0.0499 and alpha error =0.05, the power obtained was equal to 0.873.

The statistical packages used were Statistica (v. 9.0, StatSoft Corp., Tulsa, OK) for univariable analyses and "Stata release 7" (Stata Corporation, TX, USA) for multivariable analysis, and RStudio (release 1.2.1335) for power calculation.

Results

Patient characteristics

A total of 712 patients with a diagnosis of oligoarticular JIA seen in the study period were identified. 180 of them were excluded due to a follow-up shorter than 2 years, and 47 were excluded because they were found to have more than 4 joints affected in the first 6 months or a different illness, such as reactive arthritis or systemic connective tissue disease. The remaining 480 patients, whose main demographic features and clinical and therapeutic characteristics in the first 6 months of disease are shown in Table I, were included in the study.

Overall, the characteristics of the patients reflect the high prevalence in Italy of the JIA subset characterised by early onset, female predilection, oligoarticular presentation, presence of circulating

Table I. Demographic, clinical, laboratory and therapeutic characteristics of study patients, considered as a whole and divided by articular course, in the first 6 months of disease*

	All patients (n=480)	Persistent course (n=294)	Extended course (n=186)	*p-value*°
Female	394 (82.1)	239 (81.3)	155 (83.3)	0.57
Median (IQR) age at disease presentation, years	2.9 (1.8–4.8)	3 (2–5.1)	2.7 (1.7–4.5)	0.07
Median (IQR) age at first observation, years	3.9 (2.3–6.8)	3.8 (2.4–6.7)	3.9 (2.3–6.9)	0.81
Patients with iridocyclitis[@]	51 (10.6)	34 (11.6)	17 (9.1)	0.40
Patients with positive ANA	412 (85.8)	250 (85)	162 (87.1)	0.53
No. of involved joints				<0.0001
One	203 (42.3)	156 (53.1)	47 (25.3)	
Two	138 (28.7)	89 (30.3)	49 (26.3)	
Three	94 (19.6)	41 (13.9)	53 (28.5)	
Four	45 (9.4)	8 (2.7)	37 (19.9)	
Type of involved joints				
Temporomandibular	2 (0.4)	1 (0.3)	1 (0.5)	1
Shoulder	2 (0.4)	1 (0.3)	1 (0.5)	1
Elbow	19 (4)	9 (3.1)	10 (5.4)	0.21
Wrist	23 (4.8)	5 (1.7)	18 (9.7)	<0.0001
Metacarpophalangeal	17 (3.5)	2 (0.7)	15 (8.1)	<0.0001
Proximal interphalangeal	37 (7.7)	15 (5.1)	22 (11.8)	0.007
Distal interphalangeal	6 (1.3)	2 (0.7)	4 (2.1)	0.16
Hip	12 (2.5)	7 (2.4)	5 (2.7)	0.83
Knee	406 (84.6)	254 (86.4)	152 (81.7)	0.17
Ankle	171 (35.6)	95 (32.3)	76 (40.9)	0.056
Subtalar joints	31 (6.5)	15 (5.1)	16 (8.6)	0.13
Intertarsal joints	9 (1.9)	5 (1.7)	4 (2.1)	0.72
Metatarsophalangeal	9 (1.9)	3 (1)	5 (2.7)	0.27
Toe	20 (4.2)	8 (2.7)	12 (6.5)	0.046
Cervical spine	5 (1)	1 (0.3)	4 (2.1)	0.08
Median (IQR) value of laboratory tests				
White blood cell count, $x10^9$/litre[£]	10 (8.1–12.3)	9.8 (7.7–11.9)	10.1 (8.4–13)	0.08
Haemoglobin, gm/dl[§]	11.9 (11.1–12.5)	12 (11.3–12.7)	11.7 (10.9–12.3)	0.002
Platelet count, $x10^9$/litre[&]	403 (336–495)	397 (332–489)	420 (338–505)	0.24
Erythrocyte sedimentation rate, mm/hour[§]	33 (19–50)	31 (19–50)	35 (20–55)	0.11
C-reactive protein, mg/dl[#]	0.7 (0.5–2.2)	0.5 (0.5–1.5)	1.4 (0.5–3.1)	<0.0001
Drug therapies				
Non-steroidal anti-inflammatory drugs	378 (78.8)	226 (76.9)	152 (81.7)	0.21
Intraarticular glucocorticoids	289 (60.2)	185 (62.9)	104 (55.9)	0.13
Systemic glucocorticoids	55 (11.5)	28 (9.5)	27 (14.5)	0.09
Methotrexate	27 (5.6)	15 (5.1)	12 (6.6)	0.5
Etanercept	1 (0.2)	0	1 (0.5)	0.38
Cyclosporine	3 (0.6)	3 (1)	0	0.29

*Data are the number (percentage) unless otherwise indicated; °*p*-values refer to the comparison between the persistent and extended groups [@]Defined according to SUN criteria (Bloch-Michel E *et al*. *Am J Ophthalmol* 1987; 103: 234-5); [£]available for 314 patients (196 persistent and 118 extended); [§]available for 306 patients (189 persistent and 117 extended); [&]available for 294 patients (185 persistent and 109 extended); [§]available for 355 patients (222 persistent and 133 extended), normal values <20 mm/hour; [#]available for 359 patients (223 persistent and 136 extended), normal values <0.5 mg/dl.

ANAs, asymmetric arthritis, and high risk of chronic iridocyclitis (8, 19). In the first 6 months, 42.3% of patients had involvement of 1 joint, whereas 48.3% had arthritis in 2 or more joints; only 9.4% had 4 affected joints. The most frequently involved joint was the knee (84.6%), followed by the ankle (35.6%); all other joints were affected in less than 8% of patients. The most common therapeutic interventions were NSAIDs (78.8%) and intraarticular glucocorticoids (60.2%); 5.6% of patients were given methotrexate and only one received biologic therapy. Notably, NSAID therapy was generally used in the initial disease stages and for a maximum of 2–4 weeks.

The median disease duration from disease presentation to last follow-up visit was 7.4 years (IQR 4.9–10.7 years). The evaluation of the course of joint disease revealed that 294 patients (61.2%) had persistent oligoarthritis, whereas 186 (38.8%) developed polyarticular extension. Forty-two patients (8.8%) experienced a worse extended course (*i.e*. involvement of ≥10 joints). In patients with extended course, the median time to arthritis extension was 1.9 years (IQR 1–4.2 years). No patient enrolled in the study changed JIA category (*e.g*. developed psoriatic arthritis, enthesitis-related arthritis or RF-positive polyarthritis).

Comparison of predictive variables between patients with persistent and extended oligoarthritis

The comparison of the demographic features and clinical characteristics in the first 6 months of disease between patients with persistent oligoarticular course and those with polyarticular extension is presented in Table I. As compared to patients with persistent oligoarthritis, patients with extended course had a lower frequency of involvement of one single joint, a higher frequency of involvement of wrist, toe, and small hand joints, and a higher value of CRP. The demographic features, the frequency of ANA positivity and iridocyclitis

Table II. Best-fitted model obtained through logistic regression procedures and prediction score*

	β	OR (95% CI)	$p^{§}$	Prediction score
No. of joints involved in first 6 months (reference category: One joint)			<0.0001	
Two joints	0.53	1.7 (0.9–3.1)		0.5
Three joints	1.42	4.1 (2.2–7.8)		1.5
Four joints	3.01	20.2 (7.5–54.2)		3
CRP >0.8 mg/dl (reference category: ≤0.8 mg/dL)	1.12	3.1 (1.9–5.0)	<0.0001	1

*Polyarticular extension was the dependent variable. Complete data were available on 355 patients. The area under the receiver operating characteristic curve of the model was 0.77.
OR: odds ratio; 95% CI: 95% confidence interval, §by Likelihood Ratio test.

Table III. Sensitivity and specificity for each score cut-off

Prediction score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index (%)
≥0	100	0	37.9	-	0
>0	91.2	33.6	45.6	86.2	24.8
>0.5	81.6	52.0	50.9	82.3	33.6
> 1	67.6	70.4	58.2	78.1	38.1
>1.5	46.3	91.9	77.8	73.7	38.3
>2.5	24.3	97.3	84.6	67.8	21.6
>3	14.7	99.1	90.9	65.6	13.8
>4	0	100	-	62.1	0

Area under the ROC curve: 0.76; 95% confidence interval: 0.72–0.81.
PPV: positive predictive value; NPV: negative predictive value.

Table IV. Best-fitted model obtained through Cox regression procedure.*

	Hazard ratio (95% CI)	$p^{§}$
no. of joints involved in first 6 months (reference category: One joint)		<0.0001
Two joints	1.7 (1.0–2.8)	
Three joints	3.5 (2.2–5.7)	
Four joints	8.1 (4.9–3.5)	
CRP >0.8 mg/dl (reference category: ≤0.8 mg/dL)	2.2 (1.5–3.1)	<0.0001

*Polyarticular extension was the dependent variable; time was measured in years. Complete data were available on 355 patients. 95% CI = 95% confidence interval; §by Likelihood Ratio test.

as well as the therapeutic choices were comparable between the two groups.

Results of multivariable analysis

For the multivariable analysis, data were available for 355 patients. The best-fitting model obtained through logistic regression procedures, in which polyarticular extension was the dependent variable, is presented in Table II. Independent correlations with polyarticular extension were identified for the presence of ≥2 involved joints (*vs*. 1 affected joint) and a CRP value greater than 0.8 mg/dl. Among patients with ≥2 affected joints, the risk of extension increased progressively from the involvement of 2 joints to the involvement of 3 or 4 joints. The AUC of the model was 0.77.

Development of prediction model

The score assigned to each variable independently associated with polyarticular extension in multivariable analysis is shown in Table II. The prediction score obtained through the sum of the individual scores ranged from 0 to 6. Sensitivity and specificity were calculated for several cut-offs of the predictions score, as shown in Table III. The cut-off score that discriminated best between patients who had or did not have a polyarticular extension was >1. Its sensitivity and specificity were 67.6 and 70.4, respectively. The assessment of accuracy through the ROC curve analysis yielded an AUC of 0.76.

Survival analysis and Cox model

The survival analysis, with polyarticular extension as the event of interest, by number of affected joints or by CRP value in the first 6 months is shown in Figures 1 and 2, respectively. This analysis confirmed that patients with ≥2 affected joints or a CRP value greater than 0.8 mg/dl had a greater probability of experiencing polyarticular extension and that this probability increased progressively in parallel with the increase in the number of involved joints. The predictive role of these variables was confirmed by Cox regression analysis (Table IV).

Discussion

This study was performed to seek for predictors of polyarticular extension in children with oligoarticular-onset JIA and to create a prediction model that could help to identify in the first 6 months of disease the patients with a greater likelihood to experience a polyarticular course of their disease. The size of our sample, which included nearly 500 patients, is one of the largest ever studied. The general features of our patient group are similar to those described in previous studies that addressed the same issue (3-5), although our patients have a younger age at disease presentation and a higher rate of ANA positivity. The observed distribution of joint involvement, with the knee, ankle, and proximal interphalangeal joints being the articular sites most frequently affected in the first 6 months, is similar to that reported by other investigators (4, 5).

The 38.8% frequency of polyarticular extension recorded in our sample is comparable to that reported by Al-Matar *et al*. (39.5%) (5) and Guillaume *et al*. (an estimated 30% at 2 years) (3), but higher than that seen by Oen *et al*. (21% within 2 years) (4). The rate of worse extended course (*i.e*. involvement of ≥10 joints) (8.8%) was equivalent to the estimated 8% after 2 years reported by Guillaume *et al*., but lower than the 17.6% observed by Al-Matar

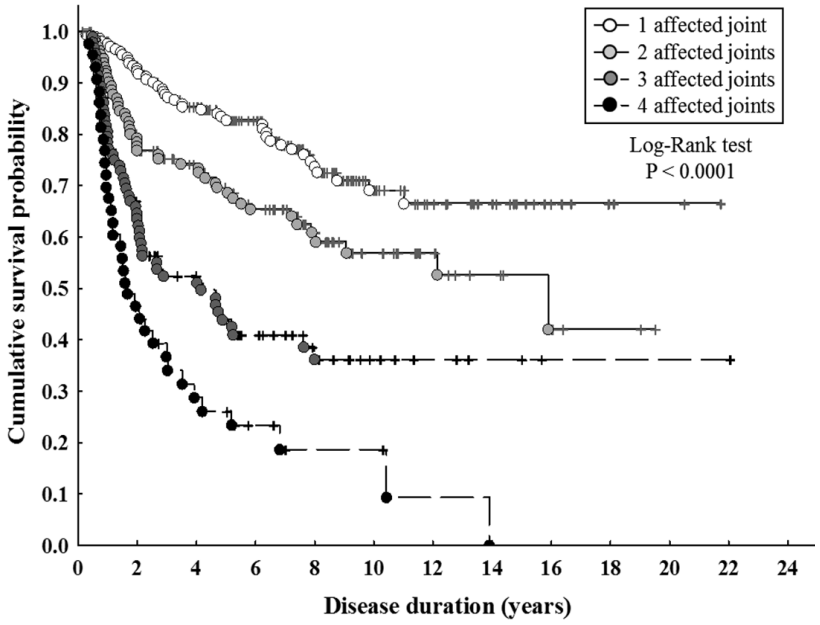

Fig. 1. The survival analysis, with polyarticular extension as the event of interest, by number of affected joints in the first 6 months.

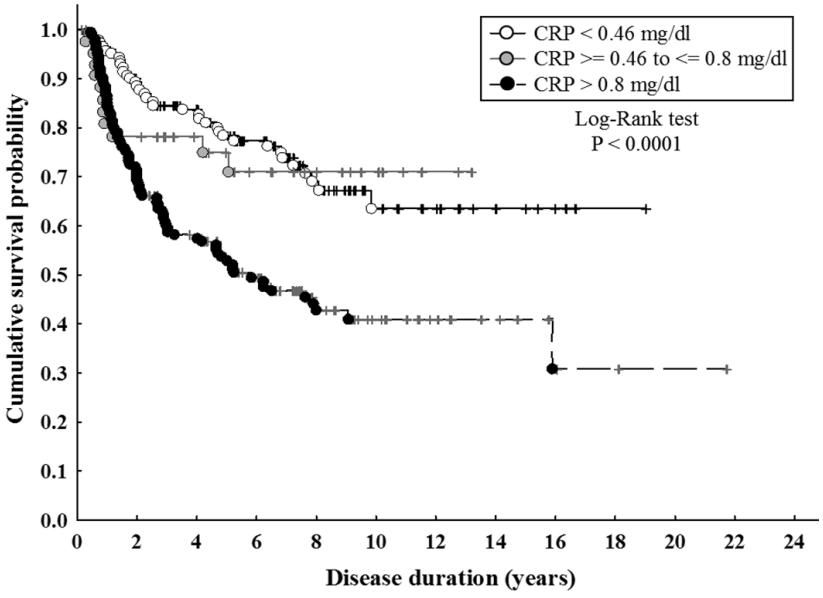

Fig. 2. The survival analysis, with polyarticular extension as the event of interest, by C-reactive protein (CRP) value in the first 6 months.

et al. (5). These disparities may depend, at least in part, on differences in patient characteristics, time of assessment of arthritis extension, and duration of follow-up.

In univariable analysis, we found that patients with extended course had a higher frequency of arthritis in ≥2 joints, a higher rate of involvement of wrist, toe, and small hand joints, and a higher value of CRP in the first 6 months of disease than patients with persistent oligoarthritis. These findings are similar to those of Guillaume *et al*. (3), who found that the presence of more than 1 affected joint, the involvement of at least 1 upper limb joint, or a high ESR at onset independently predicted a polyarticular disease course. The early presence of wrist involvement, and elevated ESR were significantly predictive of a polyarticular extension in the study by Al-Matar *et al*. (5). Early wrist disease was also found to be more common in oligoarticular-onset patients who progressed to polyarthritis in our previous smaller studies focused on ANA-positive patients (8).

Multivariable logistic regression procedures showed that only the presence of ≥2 involved joints and a CRP value greater than 0.8 mg/dl in the first 6 months were independently associated with an extended course. The risk of polyarticular extension augmented progressively with the increase in the number of affected joints (from 2 to 4), and was much more pronounced in patients with 4 affected joints. The strong effect of these factors was confirmed by survival analysis and by Cox regression procedures. These findings indicate that a greater extent of joint disease in the early disease stages and a higher level of systemic inflammation are the major determinants of subsequent arthritis progression in children with oligoarticular-onset JIA. Our observation corroborates the criticism raised to the ILAR classification that the number of joints involved may not be an appropriate classification tool, as it may simply reflect a more rapid extension of arthritis within the same disease (20). A recent proposal for a new classification of JIA has outlined a subgroup of children with early-onset (*i.e*. ≤6 years) ANA-positive JIA (13). In our patients aged 6 years or younger, the frequency of extension was 137/354 (38.7%) among ANA-positive and 34/52 (65.4%) among ANA-negative (p<0.0001). Notably, the involvement of specific joints did not affect the outcome as the type of affected joints did not enter the best fitting model of multivariable analysis.

Based on the results of multivariable analysis, we devised a prediction score for polyarticular extension, which ranged from 0 to 6. The score cut-off that discriminated best between patients with persistent and extended oligoarthritis was >1, which means that the presence of 3 or 4 affected joints, whose score was 1.5 and 3, respectively, was sufficient alone to identify patients who were more likely to experience a polyarticular course of their disease. Involvement of 2 joints and a CRP >0.8 mg/dl, whose score was 0.5 and 1, respectively, assumed a predic-

tive value only when present in association. That the ESR was not a predictor unlike previous studies (3) may depend on differences in patient population, study design, therapeutic interventions and statistical methods. Of the 114 patients who had a prediction score >1 and whose follow-up information was available, 89 (78.1%) had started a DMARD. Conversely, only 73 of 201 (36.3%) patients who had a prediction score ≤1 had started a DMARD ($p<$ 0.0001). This finding suggests that patients who have a score cut-off above 1 at first observation may deserve early introduction of DMARD therapy.

We acknowledge the limitations imposed by the retrospective design of our study. In some patients the topography of the affected joints at earlier time points was retrieved by reviewing patient histories recorded in clinical charts, leading to a potentially inaccurate estimation of the distribution of arthritis. Furthermore, joint assessment was made clinically and we cannot exclude that an ultrasound evaluation could have disclosed more joints affected subclinically. Although the cohort was represented by every consecutive patient seen at a large tertiary care center, the study was referral based, and thus we cannot exclude a selection of severe cases. Although patients with early remission were not excluded by the study design, those who entered remission within 2 years were more likely to have been lost to follow-up, and not including this patient population may have introduced a further bias. Many data in the early disease stages were collected retrospectively through the analysis of patient history. However, we are confident that our prediction rule would perform well in patients seen at first visit. Because our patients were almost exclusively of Italian ancestry, our results might not be generalisable to patient populations seen in different geographic areas, where the disease phenotype prevalent in our sample may be less common (1). During the time period in which these patients were recruited there were many therapeutic advances, including the introduction of methotrexate, the more widespread use of intraarticular glucocorticoid injections, and the marketing of a variety of biologic medications. It is not known how these medications influence the extension of arthritis. This potential confounding factor could not be addressed. Notably, a recent randomised controlled trial in oligoarthritis showed that oral methotrexate might not prevent arthritis extension (21).

Conclusion

We found that the number of affected joints and the CRP level in the first 6 months were the strongest predictors of polyarticular extension in our children with oligoarticular-onset JIA. These findings help to outline the characteristics of patients who may deserve a more careful monitoring and a more aggressive therapeutic intervention from the disease outset. Future studies should scrutinise the capability of therapeutic interventions to prevent arthritis extension in children with oligoarthritis.

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