Juvenile idiopathic arthritis in adulthood: fulfilment of classification criteria for adult rheumatic diseases, long-term outcomes and predictors of inactive disease, functional status and damage

Filipa Oliveira-Ramos,1,2 Mónica Eusébio,3 Fernando M Martins,3 Ana Filipa Mourão,2,4 Carolina Furtado,5 Raquel Campanilho-Marques,1,2 Inês Cordeiro,6 Joana Ferreira,7 Marcos Cerqueira,8 Ricardo Figueira,9 Iva Brito,10 Helena Canhão,1,2 Maria José Santos,2,6 José A Melo-Gomes,11 João Eurico Fonseca1,2

ABSTRACT

Objectives: To determine how adult juvenile idiopathic arthritis (JIA) patients fulfil classification criteria for adult rheumatic diseases, evaluate their outcomes and determine clinical predictors of inactive disease, functional status and damage.

Methods: Patients with JIA registered on the Rheumatic Diseases Portuguese Register (Reuma.pt) older than 18 years and with more than 5 years of disease duration were included. Data regarding sociodemographic features, fulfilment of adult classification criteria, Health Assessment Questionnaire, Juvenile Arthritis Damage Index—articular (JADI-A) and Juvenile Arthritis Damage Index—extra-articular (JADI-E) damage index and disease activity were analysed.

Results: 426 patients were included. Most of patients with systemic JIA fulfilled criteria for Adult Still’s disease. 95.6% of the patients with rheumatoid factor (RF)-positive polyarthritis and 57.1% of the patients with RF-negative polyarthritis matched criteria for rheumatoid arthritis (RA). 34.8% of the patients with extended oligoarthritis were classified as RA while 34.8% of the patients with persistence oligoarthritis were classified as spondyloarthritis. Patients with enthesitis-related arthritis fulfilled criteria for spondyloarthritis in 94.7%. Patients with psoriatic arthritis maintained this classification. Patients with inactive disease had lower disease duration, lower diagnosis delay and corticosteroids exposure. Longer disease duration was associated with higher HAQ, JADI-A and JADI-E. Higher JADI-A was also associated with biological treatment and retirement due to JIA disability and higher JADI-E with corticosteroids exposure. Younger age at disease onset was predictive of higher HAQ, JADI-A and JADI-E and decreased the chance of inactive disease.

Key messages

What is already known about this subject?

▸ Many patients with juvenile idiopathic arthritis (JIA) are followed into adulthood and frequently have their diagnosis freely reclassified using adult rheumatic diseases terminology.
▸ There is no published data on how adult patients with JIA fulfil classification criteria of adult rheumatic diseases, and very scarce information is available, especially in the postbiological treatments era, on functional status, damage and social outcomes, such as education and professional activity.

What does this study add?

▸ Our study is one of the longest and largest studies evaluating JIA in adulthood and was the first to evaluate how adult patients with JIA fulfil classification criteria of adult rheumatic diseases and to apply to these patients, activity scores validated for adult diseases.

How might this impact on clinical practice?

▸ We believe that understanding the way these juvenile diseases progress could add useful information for the ongoing discussion of a new classification capable of better unifying the language between paediatric and adult care and to contribute to a better understanding of the long-term outcomes and consequences of the current treatment regimes used in JIA.
▸ In our view, these results will be of interest to paediatric and adult rheumatologists who are involved in the clinical care of patients with JIA.
Conclusions: Most of the included patients fulfilled classification criteria for adult rheumatic diseases, maintain active disease and have functional impairment. Younger age at disease onset was predictive of higher disability and decreased the chance of inactive disease.

INTRODUCTION
The global burden of juvenile idiopathic arthritis (JIA) is difficult to be accurately established. Inconsistencies on classification and on evaluation of disease activity and loss of follow-up due to remission or change of medical care from paediatric into adult rheumatology have contributed to incomplete understanding of the adult impact of JIA.

Many patients with JIA are followed into adulthood. Indeed, in the Rheumatic Diseases Portuguese Register (Reuma.pt), 56% of the patients with JIA on follow-up have reached adulthood. Frequently, these patients have their diagnosis freely reclassified using adult rheumatic diseases terminology. However, there is no published data on how adult patients with JIA fulfill classification criteria of adult rheumatic diseases. In addition, very scarce information is available, especially in the postbiological treatments era, on functional status, damage and social outcomes, such as education and professional activity, of adults who are affected by these childhood-onset diseases.

Portugal offers an opportunity niche due to the existence of several institutions with an integrated follow-up, first of patients with juvenile rheumatic disease and then, later on, of adults with juvenile onset rheumatic conditions. Moreover, the Reuma.pt has the unique feature of having a complete integration of juvenile patients, assessed by validated tools, in the overall database, thus greatly facilitating the tracking of the transition into adulthood.

By exploring this unique research opportunity, our aim was to determine how adult patients with JIA fulfilled classification criteria of adult rheumatic diseases, evaluate their disease activity, damage, functional and social outcomes and determine clinical predictors of inactive disease, poor functional status and damage.

MATERIALS AND METHODS
Study design and patient selection
This is a cross-sectional analysis nested in a cohort study with the following inclusion criteria: patients with JIA according to the 2001 revised International League of Associations for Rheumatology (ILAR) criteria, registered in Reuma.pt, that at the time of data analysis (October 2015) were older than 18 years, had a disease duration of >5 years and available data in adulthood.

The Reuma.pt was developed by the Portuguese Society of Rheumatology, became active in June 2008 and includes patients with adult rheumatoid arthritis (RA), spondyloarthritis (SpA), JIA, systemic lupus erythematosus (SLE) and several other rheumatic diseases. It covers mainland Portugal, Madeira and Azores islands, involving over 70 centres and having included up to now more than 15,000 patients, with more than 112,000 medical appointments registered. Specifically, 1563 patients who had JIA with 11,828 medical visits have been registered so far.

At the time of this analysis, a total of 889 adult patients with JIA were registered in Reuma.pt. For 150 of these adult patients, there were no data registered in adulthood and they were excluded. Of the 739 patients eligible for this study, only 426 had complete data registered, by their attending rheumatologist, regarding ILAR category at onset and were included. From these 426 patients, 71 patients were registered in childhood and 355 patients were introduced in Reuma.pt already in adulthood and classified retrospectively according to the ILAR classification. Disease onset was defined by the date on which a physician first documented arthritis. Data before 2008 was registered retrospectively and from that date prospectively.

Registry of patient data in Reuma.pt was performed after signed informed consent was obtained. This study was approved by the scientific committee of Reuma.pt and by the ethics committee of Lisbon Academic Medical Centre. Reuma.pt was approved by the National Committee for Data Protection and by local ethics committees of the participating centres. The study was conducted according to the Declaration of Helsinki.

Clinical assessment
The following information registered in Reuma.pt at the time of patient’s last visit was obtained: gender, ethnicity, age at last visit, years of education, employment status (employed, unemployed, retired and retired due to JIA induced disability), ILAR category at onset, age at disease onset, disease duration (years), presence of rheumatoid factor (RF), anticitrullinated protein antibodies (ACPA), antinuclear antibodies (ANAs; considered positive if titres $\geq 1/160$) and human leucocyte antigen (HLA) B27, number of swollen/tender joints, patient and physician’s global assessment of disease activity (0–10), back pain (0–10), morning stiffness intensity (0–10), erythrocyte sedimentation rate (ESR, mm/first hour) and C reactive protein level (CRP, mg/dL), extra-articular manifestations, Health Assessment Questionnaire (HAQ), Juvenile Arthritis Damage Index (JAD), current and previous therapy with corticosteroids, disease-modifying antirheumatic drugs (DMARDs) and biological therapy. In the Reuma.pt JIA protocol, there is a field asking the physician to check if the adult patient fulfils classification criteria for any of the following adult rheumatic diseases: RA; ankylosing spondylitis (AS); psoriatic arthritis (PsA); undifferentiated spondyloarthritis (USpA); arthropathy of inflammatory bowel disease; adult Still disease (ASD)—persistent systemic, ASD—polycharticular course after systemic onset; non-classifiable. Data registered in this Reuma.pt field were
also exported. The information needed to verify classification criteria for RA (2010 ACR/EULAR), AS (1984 modified New York criteria) and PsA (CASPAR criteria) is specifically asked for in Reuma.pt.

Juvenile Arthritis Disease Activity Score (JADAS) shows limitations for the assessment of adults with JIA, particularly those with predominant axial disease. For that reason, we opted to apply disease activity scores specific for adult diseases. In this way, disease activity at the time of Reuma.pt last visit was assessed through disease-specific activity indexes according to the adult rheumatic disease: Disease Activity Score (DAS) 28 for patients classified as RA, DAS 44 for PsA and peripheral SpA and AS Disease Activity Score (ASDAS) for AS. Patients were classified as having inactive disease based on cut-offs defined for each index: DAS 28 < 2.6; DAS 44 < 1.6; ASDAS < 1.3. Patients classified as ASD or with non-classifiable adult rheumatic disease were considered to have inactive disease if they had no active arthritis; no fever, rash, serositis, splenomegaly or generalised lymphadenopathy attributable to JIA; no active uveitis; normal ESR and/or CRP; a physician’s global assessment of disease activity rated at the best score possible.

Functional status was measured by HAQ obtained in the last visit. For the purpose of this analysis, mild disability was considered for HAQ scores > 0 and ≤ 0.5, moderate disability > 0.5 and ≤ 1.5 and severe disability > 1.5.

Radiographs do not fully reflect the structural outcome of JIA, because they represent mainly cartilage and osseous changes, whereas part of the articular damage in JIA is in the soft tissues surrounding the bones. This extra-articular damage is not measured by the radiographic scores validated in JIA. The evaluation of JIA damage into adulthood lacks validation for radiographic assessment and for JADI application. In the absence of a validated score for adults with JIA, we opted to use JADI, as a more comprehensive way of assessing articular damage (JADI-A) and extra-articular damage (JADI-E).

Statistical analyses
Continuous covariates were expressed in terms of their mean and SD. Categorical covariates were described by frequency distribution.

Comparisons between groups of the covariates and the outcomes were evaluated using univaried linear regression for continuous response variables and univaried logistic regression for binary response variables. After assessing the differences, multivaried logistic or linear regression models were used to examine the association, adjusted for ILAR category, of a range of demographic and clinical variables with the following outcomes: HAQ, JADI-A and JADI-E as continuous variables and disease activity as a dichotomous variable. In order to compare the outcomes before and after biological era, we used multivaried logistic or linear regression analysis adjusted for ILAR category and disease duration.

In order to obtain the predictor models, we used three multivaried linear regression models for the continuous outcomes (HAQ, JADI-A, JADI-E) and one multivaried logistic regression model for the dichotomous outcome, by a stepwise selection method.

Missing data were interpreted as random missing data. In all analyses, significance level was set at 0.05.

All analyses were performed using Stata IC V.12 (StataCorp 2011. Stata Statistical Software: Release 12. College Station, Texas: StataCorp LP).

RESULTS
Patient characteristics
A total of 426 patients were included in the study, whose main demographic and clinical features are shown in table 1.

The mean age at the last registered visit was 34.1 ± 12.8 years, and the mean disease duration was 22.5 ± 12.4 years. Most of the patients (84.3%) had disease duration longer than 10 years, and 24.2% exceeded 30 years. Only 18.5% of the patients had persistent oligoarthritis, and JIA categories with polyarticular involvement and enthesitis-related arthritis (ERA) were the most prevalent ones, affecting 45.6% and 18.8% of the patients, respectively. Systemic-onset JIA (SoJIA) was found in 9.6% of the patients, PsA in 3.1% and undifferentiated arthritis in 1.4% of the patients. The prevalence of ANA, RF, ACPA and HLA B27 are shown in table 1 with random missed data that were not related to any specific clinical attitude.

This was a predominantly professionally active population (71.9% of the patients employed), with a mean 11.6 years of education. Almost 13% were retired due to JIA disability.

Most of the studied patients (67%) still had active disease, and 71.9% were on a synthetic or biological DMARD. Furthermore, 36.4% of the patients with inactive disease were off medication. Most of the patients (65.5%) had no or mild HAQ disability, and 11% had severe disability.

Fulfilment of classification criteria for adult rheumatic diseases
Data regarding fulfilment of classification criteria for adult rheumatic diseases (table 2) revealed that 92.3% of the patients with SoJIA could be classified as ASD, 58.3% with persistent systemic features and 41.6% with polyarticular predominant involvement. Furthermore, 95.6% of the patients with RF-positive polyarthritis and 57.1% of the patients with RF-negative polyarthritis fulfilled criteria for RA. The remaining patients with RF-negative polyarthritis could not be classified in 23.8% of the cases, and 12.7% of the patients were classified as PsA. The patients with persistent oligoarthritis were classified into several adult rheumatic diseases, with 34.8% classified as SpA, which included enteropathic arthritis in 6% of the cases. Only 13% of these patients had HLA


In univariate analysis, there was a positive association with higher HAQ in patients with extended oligoarticular (β=0.2; 95% CI 0.1 to 0.3; p value=0.006), polyarticular RF-negative (β=0.5; 95% CI 0.3 to 0.8; p value=0.001) and polyarticular RF-negative (β=0.4; 95% CI 0.1 to 0.6; p value=0.001), when comparing with persistent oligoarticular category. After adjustment to ILAR category, higher HAQ was associated with longer disease duration (β=0.03; 95% CI 0.02 to 0.03; p value=0.014) and exposure to biological treatments (β=0.2; 95% CI 0.04 to 0.3; p value=0.014). The persistence of systemic features was associated with lower HAQ (β=−0.6; 95% CI −1.0 to −0.2; p value=0.003), while RA classification was associated with higher HAQ (β=0.5; 95% CI 0.3 to 0.7; p value=0.001), when comparing to adult non-classifiable forms (table 5).

JADI-A and JADI-E were available in only 140 (32.8%) and 111 (26%) patients, respectively. We only included in JADI analysis patients with these data available. In univariate analysis, patients with RF-positive polyarthritis (β=17.5; 95% CI 8.1 to 26.8; p value<0.001), RF-negative polyarthritis (β=8.8; 95% CI 1.6 to 16.0; p value=0.018) and SoJIA (β=12.2; 95% CI 2.8 to 21.5; p value=0.011) had higher association with JADI-E when comparing to patients with persistent oligoarthritis. After adjustment for ILAR category, retired patients due to JIA disability had higher JADI-A scores than employed patients (β=29.1; 95% CI 19.9 to 38.3; p value<0.001). Longer disease duration (β=0.3; 95% CI 0.1 to 0.5; p value=0.001) and past or current biological treatment (β=6.9; 95% CI 1.3 to 12.5; p value=0.016) were also associated with higher JADI-A scores, after adjustment for ILAR category (table 5).
Worse JADI-E was associated with longer disease duration (β=0.04; 95% CI 0.02 to 0.06; p value=0.001) and corticosteroids exposure (β=1.2; 95% CI 0.5 to 1.9; p value=0.001), after adjustment for ILAR category. The severity of extra-articular damage was similar across the different JIA categories and had no association to the different adult rheumatic diseases each patient fulfilled criteria for (table 5).

In order to assess the differences between outcomes of patients with disease onset before and after the biological era, we compared the outcomes of patients with disease onset before and after 2001. After adjustment for ILAR category and for disease duration, we found no differences between inactive disease, HAQ and JADI in both groups (see online supplementary table S1).

Predictors of inactive disease, poor functional status and damage

For inactive disease, a multivariate logistic stepwise regression model was used. Clinical variables were selected regarding their statistical and clinical relevance (table 6). Older age at disease onset increased the chance of inactivity of disease at the last registered visit (OR=1.4; 95% CI 1.1 to 1.8; p=0.008). ACPA positivity decreased the likelihood of disease inactivity by 93.1% (OR=0.07; 95% CI 0.01 to 0.7; p=0.028).

Predictors of poor functional status were analysed by a multivariate linear stepwise regression model, and we found that younger age at disease onset was the only variable that could predict higher HAQ scores in adulthood (β=−0.02; 95% CI −0.04 to −0.00; p=0.021). Younger age at disease onset was also associated with higher JADI-A (β=−0.9; 95% CI −1.4 to −0.3; p=0.003) and JADI-E (β=−0.1; 95% CI −0.2 to −0.03; p=0.008). RF-positive polyarthritis (β=16.20; 95% CI 7.68 to 25.63; p=0.001) and SoJIA (β=10.2; 95% CI 1.0 to 19.3; p=0.029) were predictive of worse JADI-A, using persistent oligoarthritis as reference. Corticosteroid exposure was also predictive of worse JADI-E (β=1.1; 95% CI 0.4 to 1.9; p=0.002).

DISCUSSION

This is a long-term follow-up study of patients with JIA (mean disease duration of 22.5±12.4 years), with 24.2% of the patients having more than 30 years of disease duration. The majority of patients (34%) were in the Systemic category, followed by RF+ polyarthritis (23%), P. oligoarthritis (22%), SoJIA (21%), and ERA (19%). The HAQ score was highest in ERA, followed by SoJIA and PsA.

### Table 2: Classification according to adult rheumatic diseases

<table>
<thead>
<tr>
<th>Onset ILAR category</th>
<th>RA</th>
<th>AS</th>
<th>USpA</th>
<th>EA</th>
<th>PsA</th>
<th>ASD</th>
<th>Non-classifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic, n=39</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>36 (92.3%)</td>
</tr>
<tr>
<td>RF− poly, n=63</td>
<td>36</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>RF+ poly, n=68</td>
<td>65</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.5%)</td>
</tr>
<tr>
<td>P. oligo, n=66</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>39 (59.1%)</td>
</tr>
<tr>
<td>E. oligo, n=54</td>
<td>21</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>19 (35.2%)</td>
</tr>
<tr>
<td>ERA, n=76</td>
<td>0</td>
<td>41</td>
<td>21</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>4 (5.3%)</td>
</tr>
<tr>
<td>PsA, n=13</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>1 (7.7%)</td>
</tr>
<tr>
<td>Undif, n=6</td>
<td>3</td>
<td>1</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>52</td>
<td>42</td>
<td>10</td>
<td>9</td>
<td>33</td>
<td>81 (21%)</td>
</tr>
</tbody>
</table>

### Table 3: Disease activity, HAQ Score, JADI Score and retirement due to JIA disability, according to ILAR subgroups

<table>
<thead>
<tr>
<th>ILAR category</th>
<th>Disease activity, active/inactive</th>
<th>HAQ Score*</th>
<th>JADI-A Score*</th>
<th>JADI-E Score*</th>
<th>Patients retired due to JIA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. oligoarthritis</td>
<td>34/22 (n=56)</td>
<td>0.26±0.4 (n=79)</td>
<td>0.8±1.4 (n=26)</td>
<td>0.2±0.7 (n=19)</td>
<td>1 (2.9) (n=34)</td>
</tr>
<tr>
<td>E. oligoarthritis</td>
<td>39/10 (n=49)</td>
<td>0.58±0.8 (n=61)</td>
<td>7.6±15 (n=22)</td>
<td>0.7±1.3 (n=18)</td>
<td>8 (25.8) (n=31)</td>
</tr>
<tr>
<td>RF+ polyarthritis</td>
<td>36/14 (n=50)</td>
<td>0.80±0.7 (n=71)</td>
<td>18.3±17.6 (n=13)</td>
<td>0.7±1.4 (n=9)</td>
<td>11 (22) (n=50)</td>
</tr>
<tr>
<td>RF− polyarthritis</td>
<td>39/19 (n=58)</td>
<td>0.61±0.7 (n=75)</td>
<td>9.6±15.2 (n=33)</td>
<td>1.3±2.3 (n=28)</td>
<td>6 (13.6) (n=44)</td>
</tr>
<tr>
<td>SoJIA</td>
<td>20/12 (n=32)</td>
<td>0.43±0.6 (n=41)</td>
<td>13±21.8 (n=13)</td>
<td>1.2±1.9 (n=9)</td>
<td>0 (n=15)</td>
</tr>
<tr>
<td>ERA</td>
<td>28/18 (n=46)</td>
<td>0.45±0.7 (n=80)</td>
<td>5.5±12.2 (n=31)</td>
<td>0.7±1.2 (n=26)</td>
<td>3 (6.3) (n=48)</td>
</tr>
<tr>
<td>PsA</td>
<td>5/4 (n=9)</td>
<td>0.40±0.4 (n=13)</td>
<td>0±0 (n=2)</td>
<td>0±0 (n=2)</td>
<td>1 (16.6) (n=6)</td>
</tr>
<tr>
<td>Undif. arthritis</td>
<td>n=0</td>
<td>0.69±0.2 (n=6)</td>
<td>n=0</td>
<td>n=0</td>
<td>1 (16.6) (n=6)</td>
</tr>
</tbody>
</table>

*Values are means±SD.

E. oligoarthritis, extended oligoarthritis; ERA, enthesitis-related arthritis; HAQ, Health Assessment Questionnaire; ILAR, International League of Associations for Rheumatology; JADI, Juvenile Arthritis Damage Index; JIA, juvenile idiopathic arthritis; P. oligoarthritis, persistent oligoarthritis; PsA, psoriatic arthritis; RF+ polyarthritis, rheumatoid factor positive polyarthritis; RF− polyarthritis, rheumatoid factor negative polyarthritis; SoJIA, systemic onset juvenile idiopathic arthritis; Undif. arthritis, undifferentiated arthritis.
duration. There are only a limited number of published studies with such a long follow-up period \(^{21–23}\) but describing smaller JIA cohorts and most of them reported before biological therapy became available. In order to reflect the current long-term outcome of JIA, studies should include patients who had the opportunity to be treated with biological therapy if they had indication for receiving it. In our study, this occurred at least in 25% of the patients who had their disease onset after 2001. On the other hand, an adult population should be dated in adults. In fact, even in children with ERA, JADAS should be better evaluated, as validation in this condition. For example, it is not suitable to evaluate...

<table>
<thead>
<tr>
<th>Variables</th>
<th>Active disease</th>
<th>Inactive disease</th>
<th>p Value</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of disease onset*</td>
<td>1.0 (0.9 to 1.0)</td>
<td>1.0 (1.0 to 1.1)</td>
<td>0.186</td>
<td>0.186</td>
</tr>
<tr>
<td>Disease duration*</td>
<td>1.1 (1.0 to 1.1)</td>
<td>1.0 (0.9 to 1.0)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Delay in diagnosis*</td>
<td>1.1 (1.0 to 1.1)</td>
<td>0.9 (0.9 to 0.9)</td>
<td>0.017†</td>
<td>0.017†</td>
</tr>
<tr>
<td>ANA*</td>
<td>0.9 (0.4 to 1.8)</td>
<td>1.2 (0.5 to 2.5)</td>
<td>0.682</td>
<td>0.682</td>
</tr>
<tr>
<td>RF*</td>
<td>1.5 (0.5 to 4.2)</td>
<td>0.7 (0.2 to 2.0)</td>
<td>0.472</td>
<td>0.475</td>
</tr>
<tr>
<td>B27*</td>
<td>1.5 (0.5 to 5.1)</td>
<td>0.6 (0.2 to 2.2)</td>
<td>0.481</td>
<td>0.481</td>
</tr>
<tr>
<td>ACPA*</td>
<td>2.5 (0.5 to 1.1)</td>
<td>0.4 (0.1 to 1.8)</td>
<td>0.239</td>
<td>0.239</td>
</tr>
<tr>
<td>Years of education*</td>
<td>1.0 (0.9 to 1.1)</td>
<td>1.0 (0.9 to 1.1)</td>
<td>0.686</td>
<td>0.686</td>
</tr>
<tr>
<td>Professional activity*‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>0.6 (0.2 to 1.9)</td>
<td>1.8 (0.5 to 5.8)</td>
<td>0.352</td>
<td>0.352</td>
</tr>
<tr>
<td>Retired due to JIA disability</td>
<td>3.0 (0.8 to 1.9)</td>
<td>0.3 (0.1 to 1.3)</td>
<td>0.118</td>
<td>0.118</td>
</tr>
<tr>
<td>HAQ score*</td>
<td>9.1 (4.1 to 20.2)</td>
<td>0.1 (0.1 to 0.2)</td>
<td>&lt;0.001†</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Duration of corticosteroid therapy*</td>
<td>1.0 (1.0 to 1.0)</td>
<td>1.0 (1.0 to 1.0)</td>
<td>0.019†</td>
<td>0.019†</td>
</tr>
<tr>
<td>Exposure to corticosteroids*</td>
<td>1.6 (0.9 to 2.9)</td>
<td>0.6 (0.3 to 1.1)</td>
<td>0.077</td>
<td>0.077</td>
</tr>
<tr>
<td>Exposure to biological DMARDs*</td>
<td>1.3 (0.7 to 2.2)</td>
<td>0.8 (0.4 to 1.4)</td>
<td>0.375</td>
<td>0.375</td>
</tr>
<tr>
<td>Exposure to synthetic DMARDs*</td>
<td>0.8 (0.4 to 1.6)</td>
<td>1.2 (0.6 to 2.4)</td>
<td>0.552</td>
<td>0.552</td>
</tr>
</tbody>
</table>

†p Value<0.05. ‡Adjusted for ILAR Category. 
ACPA, anticitrullinated protein antibodies; ANAs, antinuclear antibodies; AS, ankylosing spondylitis; ASD, adult Still disease; DMARDs, disease-modifying antirheumatic drugs; E. oligoarthritis, extended oligoarthritis; EA, enteropathic arthritis; ERA, enthesitis-related arthritis; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; RF+ polyarthritis, rheumatoid factor positive polyarthritis; SoJIA, systemic-onset juvenile idiopathic arthritis; Undif. arthritis, undifferentiated arthritis; USpA, undifferentiated spondyloarthritis.

To the best of our knowledge, this is the first long-term follow-up study to evaluate how adult patients with JIA fulfilled classification criteria for adult rheumatic diseases. Only 21% of the patients were unclassifiable in any adult rheumatic disease. This percentage could have been higher if the oligoarticular-onset categories would have been more represented in this study. We found that patients with RF-positive polyarthritis onset could be classified in 95.6% of the cases as RA and 94.7% of the patients with ERA as SpA. Regarding patients with SoJIA, it was also clear that in adulthood they could be classified as ASD and all juvenile-onset PsA maintained the diagnosis of PsA in adulthood. Thus, for these
conditions, it seems acceptable to group in common designations juvenile and adult onset patients. However, it is less clear-cut how the oligoarticular and polyarticular RF-negative forms evolve into adulthood. In addition, for undifferentiated JIA category, that had a low prevalence in this study probably due to the long-term follow-up that reduces diagnosis uncertainty, no possible conclusions can be drawn on its evolution in adulthood.

The degree of disability in our patients mirrored the ones found in other recent studies of adult outcomes in JIA. The follow-up that reduces diagnosis uncertainty, no possible conclusions can be drawn on its evolution in adulthood.
Table 6 Predictors of functional status, damage and inactive disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>HAQ</th>
<th>JADI-A</th>
<th>JADI-E</th>
<th>Inactive disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>(95% CI)</td>
<td>p Value</td>
<td>β</td>
</tr>
<tr>
<td>Gender—female</td>
<td>-0.03</td>
<td>(-0.2 to 0.2)</td>
<td>0.771</td>
<td>2.0</td>
</tr>
<tr>
<td>Age at the time of last visit (years)</td>
<td>0.03</td>
<td>(0.0 to 0.04)</td>
<td>&lt;0.0001*</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
<td>-0.02</td>
<td>(-0.04 to -0.0)</td>
<td>0.021*</td>
<td>-0.9</td>
</tr>
<tr>
<td>Years of education</td>
<td>-0.02</td>
<td>(-0.1 to 0.0)</td>
<td>0.055</td>
<td>-</td>
</tr>
<tr>
<td>JIA ILAR category†</td>
<td>-</td>
<td>0.4129</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>E. oligo</td>
<td>0.04</td>
<td>(-0.3 to 0.4)</td>
<td>0.798</td>
<td>4.5</td>
</tr>
<tr>
<td>RF+ poly</td>
<td>0.34</td>
<td>(0.0 to 0.7)</td>
<td>0.036</td>
<td>16.2</td>
</tr>
<tr>
<td>RF– poly</td>
<td>0.10</td>
<td>(-0.2 to 0.4)</td>
<td>0.501</td>
<td>6.2</td>
</tr>
<tr>
<td>SoJIA</td>
<td>0.05</td>
<td>(-0.5 to 0.5)</td>
<td>0.085</td>
<td>10.2</td>
</tr>
<tr>
<td>ERA</td>
<td>0.12</td>
<td>(-0.1 to 0.5)</td>
<td>0.016</td>
<td>6.4</td>
</tr>
<tr>
<td>PsA</td>
<td>0.1</td>
<td>(-0.5 to 0.6)</td>
<td>0.044</td>
<td>0.2</td>
</tr>
<tr>
<td>Corticosteroids exposure (yes)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACPA positive</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RF positive</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Statistical significance.
†Persistent oligoarthritis used as comparator.
ACPA, anticitrullinated protein antibodies; E. oligo, extended oligoarthritis; ERA, enthesitis-related arthritis; HAQ, Health Assessment Questionnaire; ILAR, International League of Associations for Rheumatology; JADI, Juvenile Arthritis Damage Index; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RF– poly, rheumatoid factor negative polyarthritis; RF, rheumatoid factor; RF+ poly, rheumatoid factor positive polyarthritis; SoJIA, systemic arthritis.

Over the past three decades, some of the long-term outcome studies based on JIA cohorts attempted to identify early prognostic factors and predictors of a poor outcome. In our study, younger age at disease onset and disease duration were predictive of worse functional status (HAQ), damage (JADI-A) and JADI-E, while female gender was associated with higher HAQ, JADI-A and JADI-E. Additionally, higher educational level and higher ACPA positivity were associated with worse functional status (HAQ) and damage (JADI-A) and JADI-E. Conversely, higher ACPA positivity was associated with lower damage (JADI-E), and higher PsA was associated with lower disease activity (JADI-A).

Retirement due to disability was higher than the average for the Portuguese population, which was 3.8% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%). This aspect could have influenced our observation regarding the association between younger age of onset and worse prognosis over the past few years. A decade ago, JIA outcome studies described poorer functional outcomes, as in the study of 87 patients with JIA followed up for a median of 40 years (20.8–57) that depicted severe disability in 10% of patients who were employed. The unemployed proportion of patients was similar to the current Portuguese population, which was 3.4% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%). In our study, a decade ago, JIA outcome studies described poorer functional outcomes, as in the study of 87 patients with JIA followed up for a median of 40 years (20.8–57) that depicted severe disability in 10% of patients who were employed. The unemployed proportion of patients was similar to the current Portuguese population, which was 3.4% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%). In our study, younger age at disease onset and disease duration were associated with higher JADI and JADI-E. In a study of 83 patients with JIA followed up for a median of 40 years (20.8–57), the most pronounced deterioration in JADI was observed in patients not only with SoJIA but also with RF– poly and RF+ poly disease. In our study, patients with SoJIA and RF– poly disease had more articular damage than those with RF+ poly disease. Lower disease duration and past or current treatment with corticosteroids were associated with higher JADI and JADI-E. In a study of 103 patients with JIA, with median disease duration of 19 years, that educational attainment was in a cohort of 103 patients with JIA, with a median disease duration of 19 years, that educational attainment was higher than the average for the Portuguese population, which was 3.4% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%). Over the past three decades, some of the long-term outcome studies based on JIA cohorts attempted to identify early prognostic factors and predictors of a poor outcome. In our study, younger age at disease onset and disease duration were predictive of worse functional status (HAQ), damage (JADI-A) and JADI-E, while female gender was associated with higher HAQ, JADI-A and JADI-E. Additionally, higher educational level and higher ACPA positivity were associated with worse functional status (HAQ) and damage (JADI-A) and JADI-E. Conversely, higher ACPA positivity was associated with lower damage (JADI-E), and higher PsA was associated with lower disease activity (JADI-A).

Retirement due to disability was higher than the average for the Portuguese population, which was 3.4% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%). In our study, a decade ago, JIA outcome studies described poorer functional outcomes, as in the study of 87 patients with JIA followed up for a median of 40 years (20.8–57) that depicted severe disability in 10% of patients who were employed. The unemployed proportion of patients was similar to the current Portuguese population, which was 3.4% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%). In our study, younger age at disease onset and disease duration were associated with higher JADI and JADI-E. In a study of 83 patients with JIA followed up for a median of 40 years (20.8–57), the most pronounced deterioration in JADI was observed in patients not only with SoJIA but also with RF– poly and RF+ poly disease. In our study, patients with SoJIA and RF– poly disease had more articular damage than those with RF+ poly disease. Lower disease duration and past or current treatment with corticosteroids were associated with higher JADI and JADI-E. In a study of 103 patients with JIA, with median disease duration of 19 years, that educational attainment was higher than the average for the Portuguese population, which was 3.4% in 2016. However, we found that higher HAQ was associated with lower employment rate (11.8%).
However, our findings were in line with other previous studies. For instance, NORDAL et al.\textsuperscript{36} observed that fewer young onset children achieved disease remission off medication as compared with children with late-onset disease, independent of ILAR categories. In a short-term follow-up study, ACPA positivity seems to provide predictive information on severity of disease course and radiological outcome.\textsuperscript{39}

Our study has some limitations. First, its cross-sectional design may not accurately estimate the overall disease activity, as it misses fluctuations over time. Second, selection bias of the registry may over-represent more severe cases and some categories of JIA, as many patients in remission could have been lost for follow-up.

This study has also several strengths, as the long follow-up and the use of validated disease activity adult tools applied according to adult disease classification. It is also the first long-term study to evaluate how patients fulfill classification criteria for adult rheumatic diseases. In fact, previous studies evaluated changing ILAR categories over time,\textsuperscript{36} but fulfillment of criteria for adult rheumatic diseases was never verified.

This study shows that JIA represents a group of very different diseases that evolve differently in adulthood. We found that most patients with JIA followed in adult rheumatology clinics fulfilled classification criteria for adult rheumatic diseases, maintain active disease and functional impairment at long-term follow-up. Younger age at disease onset showed to be predictive of higher HAQ, JADI-A and JADI-E and decreased the chance of inactivity of the disease in adulthood.

The results of this study are consistent with previous criticisms to the current JIA classification and nomenclature.\textsuperscript{40} Understanding the way these juvenile diseases progress could add useful information for the ongoing discussion of a new classification capable of better unifying the language between paediatric and adult care.

Author affiliations

1Rheumatology Department, Santa Maria Hospital-CHLN, Lisbon Academic Medical Center, Lisbon, Portugal
2Rheumatology Research Unit, Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal
3Portuguese Society of Rheumatology, Lisbon, Portugal
4Rheumatology Department, Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal
5Rheumatology Department, Hospital do Divino Espírito Santo, Ponta Delgada, Portugal
6Rheumatology Department, Hospital Garcia de Orta, Almada, Portugal
7Rheumatology Department, Centro Universitário Hospitalar de Coimbra, Coimbra, Portugal
8Rheumatology Department, ULSAM—Hospital Conde de Berlindos, Ponte de Lima, Portugal
9Rheumatology Department, Hospital Dr Nélio Mendonça, Funchal, Portugal
10Rheumatology Department, Hospital de São João and Faculdade de Medicina da Universidade do Porto, Porto, Portugal
11Instituto Português de Reumatologia, Lisbon, Portugal

Acknowledgements The authors thank all patients and their families, as well as all the rheumatologists and paediatricians who contributed to Reuma.pt registry.

Contributors The corresponding author confirms that all the individuals listed as authors fulfill the uniform authorship credit requirements for manuscripts submitted to medical journals as they all contributed to the manuscript based on substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests None declared.

Ethics approval The study was reviewed and approved by scientific committee of Reuma.pt and by Ethics committee of Lisbon Academic Medical Centre. Reuma.pt was approved by the National Committee for Data Protection and by local ethics committees of the participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES


