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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

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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). 38.9% of the patients with extended oligoarthritis were classified as RA while 34.8% of the patients with persistent 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 for 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.[1 2] 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 fulfil 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.[1]

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,[3] 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.[2]

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 ≥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 (JADI), 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—polyarticular 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)[4], AS (1984 modified New York criteria)[5] and PsA (CASPAR criteria)[6] is specifically asked for in Reuma.pt.

Juvenile Arthritis Disease Activity Score (JADAS)[7] 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;[8–10] DAS 44<1.6;[11 12] ASDAS <1.3.[13] 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.[14]

Functional status was measured by HAQ,[15] 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.[16]

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.[17–19] 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).[20]

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 univariated linear regression for continuous response variables and univariated logistic regression for binary response variables. After assessing the differences, multivariate 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 multivariate logistic or linear regression analysis adjusted for ILAR category and disease duration.

In order to obtain the predictor models, we used three multivariable linear regression models for the continuous outcomes (HAQ, JADI-A, JADI-E) and one multivariate 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

Table 1 Characteristics of the 426 study patients

Variables	No. (%)/ Mean±SD
Female	288 (67.6%)
Male	138 (32.3%)
JIA ILAR category	
Persistent oligoarthritis	79 (18.5%)
Extended oligoarthritis	61 (14.3%)
RF-positive polyarthritis	71 (16.7%)
RF-negative polyarthritis	75 (17.6%)
Systemic	41 (9.6%)
Enthesitis-related arthritis	80 (18.8%)
Psoriatic arthritis	13 (3.1%)
Undifferentiated arthritis	6 (1.4%)
Age at disease onset (years) (n=423)	9.9±4.8
Age at diagnosis (years) (n=399)	14.4±9.9
Age at the time of last registered visit (years)	34.1±12.8
Disease duration (years) (n=423)	22.5±12.4
ANA+ (n=244)	75 (30.7%)
RF + (n=320)	88 (27.5%)
ACPA + (n=121)	37 (30.8%)
HLA B27 + (n=189)	75 (30.7%)
Years of education (n=234)	11.6±3.7
Current professional situation (n=234)	
Employed	168 (71.8%)
Unemployed	24 (10.3%)
Retired	11 (4.7%)
Retired due to JIA disability	31 (13.2%)
Disease activity (n=300)	
Active disease	201 (67%)
Inactive disease	99 (33%)
HAQ Score (n=426)	0.5±0.7
JADI-A Score (n=140)	7.7±14.5
JADI-E Score (n=111)	0.8±1.6
Past treatment	
Patients who had received corticosteroids (n=399)	80 (20%)
Patients who had received synthetic DMARDs (n=399)	84 (21%)
Patients who had received biological DMARDs (n=399)	31 (7.8%)
Current treatment	
Patients who were on corticosteroids (n=399)	103 (25.8%)
Patients who were on synthetic DMARDs (n=399)	245 (61.4%)
Patients who were on biological DMARDs (n=399)	140 (35.1%)
Cumulative corticosteroid exposure (years) (n=175)	8.3±8.9
Cumulative synthetic DMARDs exposure (years) (n=326)	10.6±9.5
Cumulative biological DMARDs exposure (years) (n=173)	6.1±3.7

ACPA, anticitrullinated protein antibodies; ANAs, antinuclear antibodies; DMARDs, disease-modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; ILAR, International League of Associations for Rheumatology; JADI-A, Juvenile Arthritis Damage Index—articular; JADI-E, Juvenile Arthritis Damage Index—extra-articular; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor.

B27 and 21.7% were ANA-positive. Furthermore, 59.1% of the patients who had persistent oligoarthritis remain unclassified, as well as 35.2% of the patients with extended oligoarthritis. Most of the patients with extended oligoarthritis were classified as RA (38.9%) or SpA (26%). Patients with ERA fulfilled criteria for any form of SpA in 94.7%. All patients with PsA maintained this classification. For 21% of the patients, it was impossible to classify them in any adult rheumatic disease. This adult unclassified population come mainly from RF-negative polyarticular and oligoarticular (mostly persistent oligoarticular) categories.

Disease activity, functional status and damage

Disease activity, HAQ, JADI and retirement due to JIA disability according to ILAR categories are shown in table 3.

There was no significant association in univariate analysis between current disease activity and baseline variables such as ILAR category at onset, ANA and RF. In multivariate analysis adjusted for ILAR category, inactive disease was associated with shorter disease duration (OR=0.95; 95% CI 0.9 to 1.0; p value<0.001), less diagnosis delay (OR=0.9; 95% CI 0.9 to 1.0; p value=0.017), lower HAQ (OR=0.1; 95% CI 0.1 to 0.2; p value<0.001) and less corticosteroid exposure (OR=1.0; 95% CI 0.99 to 1.00; p value=0.019), as shown in table 4.

In univariate analysis, there was a positive association with higher HAQ in patients with extended oligoarticular (β=0.3; 95% CI 0.1 to 0.5; p value=0.006), polyarticular RF-positive (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<0.001) 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-A 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).

Table 2 Classification according to adult rheumatic diseases

	Adult rheumatic disease classification at the last visit						
Onset ILAR category	**RA**	**AS**	**USpA**	**EA**	**PsA**	**ASD**	**Non-classifiable**
Systemic, n=39	2 (5.1%)	0	0	0	0	36 (92.3%)	1 (2.6%)
RF− poly, n=63	36 (57.1%)	2 (3.8%)	2 (3.8%)	0	8 (12.7%)	0	15 (23.8%)
RF+ poly, n=68	65 (95.6%)	1 (1.5%)	0	0	1 (1.5%)	0	1 (1.5%)
P. oligo, n=66	4 (6.1%)	5 (7.6%)	9 (13.6%)	4 (6.1%)	5 (7.6%)	0	39 (59.1%)
E. oligo, n=54	21 (38.9%)	2 (3.7%)	10 (18.5%)	1 (1.9%)	1 (1.9%)	0	19 (35.2%)
ERA, n=76	0	41 (53.9%)	21 (27.6%)	4 (5.3%)	6 (7.9%)	0	4 (5.3%)
PsA, n=13	0	0	0	0	12 (92.3%)	0	1 (7.7%)
Undif, n=6	3 (50%)	1 (16.7%)	0	1 (16.7%)	0	0	1 (16.7%)
Total	131 (34%)	52 (13.5%)	42 (10.9%)	10 (2.6%)	33 (8.6%)	36 (9.4%)	81 (21%)

AS, ankylosing spondylitis; ASD, adult Still disease; E. Oligo, extended oligoarthritis; EA, enteropathic arthritis; ERA, enthesitis-related arthritis; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; P. Oligo, persistent oligoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF− Poly, rheumatoid factor negative polyarthritis; RF+ poly, rheumatoid factor positive polyarthritis; Undif, undifferentiated arthritis; USpA, undifferentiated spondyloarthritis.

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 6.78 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

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

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

*Values are mean±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 negative polyarthritis; RF+ polyarthritis, rheumatoid factor positive polyarthritis; SoJIA, systemic onset juvenile idiopathic arthritis; Undif. arthritis, undifferentiated arthritis.

Table 4 Associations between variables collected at patient's last visit and current disease activity

Variables	Active disease		Inactive disease	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age of disease onset*	1.0 (0.9 to 1.0)	0.186	1.0 (1.0 to 1.1)	0.186
Disease duration*	1.1 (1.0 to 1.1)	<0.001†	1.0 (0.9 to 1.0)	<0.001†
Delay in diagnosis*	1.1 (1.0 to 1.1)	0.017†	0.9 (0.9 to 0.9)	0.017†
ANA*	0.9 (0.4 to 1.8)	0.682	1.2 (0.5 to 2.5)	0.682
RF*	1.5 (0.5 to 4.2)	0.472	0.7 (0.2 to 2.0)	0.475
B27*	1.5 (0.5 to 5.1)	0.481	0.6 (0.2 to 2.2)	0.481
ACPA*	2.5 (0.5 to 11.8)	0.239	0.4 (0.1 to 1.8)	0.239
Years of education*	1.0 (0.9 to 1.1)	0.686	1.0 (0.9 to 1.1)	0.686
Professional activity*‡				
Unemployed	0.6 (0.2 to 1.9)	0.352	1.8 (0.5 to 5.8)	0.352
Retired	NA	NA	NA	NA
Retired due to JIA disability	3.0 (0.8 to 1.9)	0.118	0.3 (0.1 to 1.3)	0.118
HAQ score*	9.1 (4.1 to 20.2)	<0.001†	0.1 (0.1 to 0.2)	<0.001†
Duration of corticosteroid therapy*	1.0 (1.0 to 1.0)	0.019†	1.0 (1.0 to 1.0)	0.019†
Exposure to corticosteroids*	1.6 (0.9 to 2.9)	0.077	0.6 (0.3 to 1.1)	0.077
Exposure to biological DMARDs*	1.3 (0.7 to 2.2)	0.375	0.8 (0.4 to 1.4)	0.375
Exposure to synthetic DMARDs*	0.8 (0.4 to 1.6)	0.552	1.2 (0.6 to 2.4)	0.552

†p Value<0.05.
*Adjusted for ILAR Category.
‡Compared to employed.
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 negative polyarthritis; RF+ polyarthritis, rheumatoid factor positive polyarthritis; SoJIA, systemic-onset juvenile idiopathic arthritis; Undif. arthritis, undifferentiated arthritis; USpA, undifferentiated spondyloarthritis.

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 become 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 evaluated regarding disease activity with tools validated in adult population, according to their current rheumatic condition. For example, it is not suitable to evaluate the disease activity of a patient with JIA who evolved, in adulthood, to a predominantly axial SpA, with JADAS,[7] as this index does not reflect axial activity and is not validated in adults. In fact, even in children with ERA, JADAS should be better evaluated, as validation in this JIA subtype has involved very few patients.[24]

In our study, we found that most of the patients were still on non-biological or biological DMARD and 67% have disease activity, which contrast with a lower activity profile depicted in other long-term studies. Selvaag *et al*[21] reported that 41% of the patients with JIA maintained disease activity after 30 years and other studies reported active disease in 37–43% of the patients.[22] However, these studies were based on different disease activity parameters. Studies with shorter follow-up period[25 26] reported rates of disease activity similar to ours (50–67%), but again different parameters were used to measure disease activity. The tools to measure disease activity that we applied were chosen according to current adult rheumatic disease classification, and they might be more sensitive to detect disease activity in an adult population. This could be particularly relevant in patients with predominant axial involvement, as the ones classified as AS, who represent 13.5% of this population. Another possible reason for this high percentage of patients with active disease is because JIA categories with better outcomes, as persistent oligoarthritis, are under-represented in this study, as many go into remission and do not require any treatment neither adult rheumatology care. On the other hand, patients treated with biologics might be overrepresented in these type of registries and this might be reflected, for instance by a higher percentage of patients with RF-positive polyarthritis.

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

Table 5 Associations between variables collected at patient's last visit, HAQ and JADI

	HAQ		JADI-A		JADI-E	
Variables	**β (95% CI)**	**p Value**	**β (95% CI)**	**p Value**	**β (95% CI)**	**p Value**
ILAR category*						
E. oligoarticular	0.3 (0.1 to 0.5)	0.006†	6.8 (−1.2 to 14.7)	0.094	0.5 (−0.5 to 1.6)	0.335
RF+ polyarticular	0.5 (0.3 to 0.8)	<0.001†	17.5 (8.1 to 16.8)	<0.001†	0.5 (−0.8 to 1.7)	0.484
RF-poly articular	0.4 (0.1 to 0.6)	0.001†	8.8 (1.6 to 16.0)	0.018†	1.1 (0.2 to 2.1)	0.022†
Systemic	0.2 (−0.1 to 0.4)	0.193	12.2 (2.8 to 21.5)	0.011†	1.0 (−0.3 to 2.3)	0.123
ERA	0.2 (−0.0 to 0.4)	0.077	4.7 (−2.6 to 12.0)	0.208	0.4 (−0.5 to 1.4)	0.363
PsA	0.1 (−0.2 to 0.5)	0.480	−0.8 (−21.0 to 19.3)	0.934	−0.2 (−2.6 to 2.2)	0.860
Undiff arthritis	0.4 (−0.1 to 1.0)	0.130	NA	NA	NA	NA
Adult rheumatic disease‡§						
PsA	0.2 (−0.1 to 0.5)	0.194	1.5 (−13.2 to 16.1)	0.844	0.1 (−1.7 to 1.9)	0.913
RA	0.5 (0.3 to 0.7)	<0.001†	4.4 (−3.6 to 12.4)	0.275	0.5 (−0.6 to 1.6)	0.358
ASD—systemic persistent	−0.6 (−1.0 to −0.2)	0.003†	NA	NA	−0.8 (−3.1 to 1.4)	0.448
ASD—polyarticular predominant	NA	NA	17.2 (2.1 to 32.3)	0.026†	NA	NA
USpA	0.0 (−0.3 to 0.3)	0.965	−1.8 (−12.2 to 8.5)	0.729	−0.2 (−1.6 to 1.2)	0.752
AS	0.3 (0.4 to 0.6)	0.024†	−0.2 (−10.2 to 9.8)	0.971	0.5 (−0.9 to 1.8)	0.466
EA	−0.0 (−0.5 to 0.4)	0.882	−3.6 (−19.8 to 12.6)	0.663	−0.4 (−2.9 to 2.1)	0.752
Age at disease onset‡	−0.0 (−0.0 to 0.0)	0.767	−0.7 (−1.3 to −0.2)	0.010†	−0.1 (−0.1 to 0.0)	0.095
Disease duration‡	0.0 (0.0 to 0.0)	<0.001†	0.3 (0.1 to 0.5)	0.001†	0.0 (0.0 to 0.1)	0.001†
Delay in diagnosis‡	0.0 (0.0 to 0.0)	<0.001†	−0.0 (−0.3 to 0.2)	0.787	−0.0 (−0.1 to 0.0)	0.157
ANA‡	0.0 (−0.1 to 0.2)	0.732	6.0 (−1.2 to 13.3)	0.102	1.1 (0.1 to 2.1)	0.033†
RF‡	0.1 (−0.2 to 0.4)	0.606	−1.5 (−11.9 to 8.8)	0.772	−0.2 (−1.8 to 1.3)	0.784
B27‡	0.0 (−0.2 to 0.3)	0.748	−6.6 (−15.2 to 2.0)	0.132	−0.5 (−1.5 to 0.5)	0.286
ACPA‡	0.2 (−0.3 to 0.7)	0.398	−3.5 (−31.9 to 24.9)	0.804	4.1×10^{-15} (−6.1 to 6.1)	≈1
Professional activity‡¶						
Unemployed	0.0 (−0.3 to 0.3)	0.904	1.1 (−7.8 to 10.0)	0.811	1.0 (−0.5 to 2.4)	0.178
Retired due to JIA disability	1.0 (0.7 to 1.3)	<0.001†	29.1 (19.9 to 38.3)	<0.001†	1.4 (0.2 to 2.6)	0.028†
Years of education‡	−0.0 (−0.1 to −0.0)	0.001†	−0.1 (−0.9 to 0.7)	0.795	−0.1 (−0.2 to 0.1)	0.367
HAQ Score‡			12.5 (10.2 to 14.9)	<0.001†	1.1 (0.7 to 1.4)	<0.001†
Duration of corticosteroid therapy‡	0.0 (0.0 to 0.0)	<0.001†	0.0 (0.0 to 0.0)	0.020†	0.0 (0.0 to 0.0)	<0.001†
Exposure to corticosteroids‡	0.3 (0.2 to 0.5)	<0.001†	4.5 (−1.1 to 10.2)	0.112	1.2 (0.5 to 1.9)	0.001†
Exposure to biological DMARDs‡	0.2 (0.0 to 0.3)	0.014†	6.9 (1.3 to 12.5)	0.016†	0.6 (−0.1 to 1.3)	0.080
Exposure to synthetic DMARDs‡	−0.1 (−0.3 to 0.1)	0.394	−1.2 (−7.4 to 5.0)	0.699	−0.1 (−0.9 to 0.8)	0.864

†p Value <0.05.
*Compared to persistent oligoarticular.
‡Adjusted for ILAR category.
§Compared to non-classifiable.
¶Compared to employed.
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; HAQ, Health Assessment Questionnaire; ILAR, International League of Associations for Rheumatology; JADI, Juvenile Arthritis Damage Index; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RF, rheumatoid factor; RF+ polyarthritis, rheumatoid factor negative polyarthritis; RF+ polyarthritis, rheumatoid factor positive polyarthritis; SoJIA, systemic-onset juvenile idiopathic arthritis; Undif arthritis, undifferentiated arthritis; USpA, undifferentiated spondyloarthritis.

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

Table 6 Predictors of functional status, damage and inactive disease

Variables	HAQ		JADI-A		JADI-E		Inactive disease	
	β (95% CI)	p Value	β (95% CI)	p Value	β (95% CI)	p Value	OR (95% CI)	p Value
Gender—female	−0.03 (−0.2 to 0.2)	0.771	2.0 (−3.1 to 7.1)	0.436	−0.03 (−0,7 to 0.7)	0.937	2.3 (0.2 to 31.3)	0.528
Age at the time of last visit (years)	0.03 (0.0 to 0.04)	<0.0001*	0.3 (0.1 to 0.5)	0.004*	0.02 (−0.0 to 0.1)	0.102	0.9 (0.9 to 1)	0.031*
Age at disease onset (years)	−0.02 (−0.04 to −0.0)	0.021*	−0.9 (−1.4 to −0.3)	0.003*	−0.1 (−0.8 to −0.0)	0.008*	1.4 (1.1 to 1.8)	0.008*
Years of education	−0.02 (−0.1 to 0.0)	0.055	–	–	–	–	–	–
JIA ILAR category†	–	0.4129	–	0.0349*	–	0.5406	–	0.5123
E. oligo	0.04 (−0.3 to 0.4)	0.798	4.5 (−3.2 to 12.2)	0.246	0.5 (−0.6 to 1.5)	0.372	–	–
RF+ poly	0.34 (0.0 to 0.7)	0.036	16.2 (6.8 to 25.6)	0.001*	−0.2 (−1.6 to 1.2)	0.744	8.6 (0.3 to 221.7)	0.194
RF− poly	0.10 (−0.2 to 0.4)	0.501	6.2 (−0.8 to 13.2)	0.081	0.8 (−0.2 to 1.7)	0.124	5.1 (0.2 to 116.9)	0.311
SoJIA	0.05 (−0.4 to 0.5)	0.805	10.2 (1.0 to 19.3)	0.029*	0.3 (−1.0 to 1.7)	0.635	4.2 (0.1 to 314.6)	0.513
ERA	0.2 (−0.1 to 0.5)	0.116	6.4 (−0.8 to 13.6)	0.082	0.7 (−0.3 to 1.7)	0.148	20.4 (0.5 to 853.8)	0.114
PsA	0.1 (−0.5 to 0.6)	0.844	0.2 (19.2 to 19.5)	0.987	0.3 (−1.9 to 2.6)	0.773	–	–
Corticosteroids exposure (yes)	–	–	–	–	1.1 (0.4 to 1.9)	0.002*	–	–
ACPA positive	–	–	–	–	–	–	0.1 (0.0 to 0.7)	0.028*
RF positive	–	–	–	–	–	–	12.9 (0.8 to 200.2)	0.068

*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.

JIA, which have shown a tendency towards an improvement in the functional outcome of these patients over the last few years. A decade ago JIA outcome studies described poorer functional outcomes, as in the Foster *et al*[27] study that found a median HAQ of 1.13 (0–3) or the Packham and Hall[22] report that depicted severe disability in 42% of the patients. In our study, the mean HAQ was 0.52±0.68 and 11% of the patients had severe disability. We found that higher HAQ was associated with longer disease duration and with polyarticular involvement at disease onset. Unlike other studies,[22 25] we did not notice a higher functional limitation in patients with SoJIA.

The educational level of these patients was higher than the average for the Portuguese population, which was 7.4 years in 2014.[28] However, the mean age of this study population (34.1 years) is lower than the mean age of the Portuguese population (43.1 years),[29] and schooling has increased over recent years. Malviya *et al*[30] found in a cohort of 103 patients with JIA, with a median disease duration of 19 years, that educational attainment was influenced by functional disability rather than by JIA category. However, we did not found any strong association between HAQ and educational level.

Retirement due to disability was higher than the general Portuguese population, which was 3.4% in 2013.[31] As expected, we found that retired patients due to JIA disability had more articular damage than the ones who were employed. The unemployed proportion of patients was similar to the current Portuguese unemployment rate (11.8%).[32]

Longer disease duration and exposure to biological treatment were associated with higher JADI-A. Longer disease duration and past or current treatment with corticosteroids was also associated with higher JADI-E. In a study of 87 patients with JIA followed up for a median of 4.0 years (2.0–5.2),[33] the most pronounced deterioration in JADI-A was observed in patients with SoJIA with prolonged active disease. In our study, not only SoJIA but also RF-positive and RF-negative polyarthritis onset were associated with higher JADI-A. This is the first long-term study to analyse damage, measured by JADI in all categories of JIA, and thus we have no comparable published data.

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.[34–38] In our study, younger age at disease onset was predictive of higher HAQ, JADI-A and JADI-E and decreased the chance of inactive disease in adulthood. ACPA positivity decreased the likelihood of disease inactivity by 93.1% and RF-positive polyarthritis and SoJIA were predictive of a worse JADI-A, using persistent oligoarthritis as reference. JIA persistent oligoarthritis, usually associated with a younger age at onset, was under-represented in this study. This aspect could have influenced our observation regarding the association between younger age of onset and worse prognosis.

However, our findings were in line with other previous studies. For instance, Nordal *et al*[26] 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.[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 fulfil classification criteria for adult rheumatic diseases. In fact, previous studies evaluated changing ILAR categories over time,[26 34] but fulfilment 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.[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.

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