RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Distinction and prognosis of early arthritis phenotypes: an analysis in three European cohorts

Alexandre Sepriano ,[1,2] Bastiaan van Dijk,[2] Sofia Ramiro ,[2,3] Annette van der Helm-van Mil ,[2] Bernard Combe ,[4] Dirkjan van Schaardenburg ,[5] Maarten de Wit ,[6] Alison Kent,[6] Elsa Mateus,[6] Robert Landewé [7,8]

To cite: Sepriano A, van Dijk B, Ramiro S, *et al*. Distinction and prognosis of early arthritis phenotypes: an analysis in three European cohorts. *RMD Open* 2023;**9**:e003611. doi:10.1136/rmdopen-2023-003611

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2023-003611).

Received 14 August 2023
Accepted 2 October 2023

For numbered affiliations see end of article.

Correspondence to
Dr Alexandre Sepriano; alexsepriano@gmail.com

ABSTRACT

Objectives The objective of this study is to evaluate whether there are differences in the long-term prognosis across various phenotypes of early arthritis (EA).

Methods Three EA cohorts (Reade, Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) and Early Arthritis Clinic (EAC)) were analysed. Clinical data were collected up to 24 years. Hands and feet radiographs were scored according to the Sharp van der Heijde (SvdH) method. Latent class analysis was applied to determine the EA phenotypes at baseline. Each class received a label reflecting its most prominent features. Prognostic outcomes included Health Assessment Questionnaire (HAQ), Short Form 36 (SF36) and SvdH score. The association between class membership and outcomes over time was tested in multivariable models.

Results In total, 390 (Reade), 798 (ESPOIR) and 3991 (EAC) patients were analysed separately. Two classes with symmetrical polyarthritis emerged; one of these labelled as autoimmune inflammatory polyarthritis (AIPA), had high likelihood of acute phase reactants (APR) elevation and autoantibody positivity, while the other (mild-inflammatory polyarthritis; MIPA) had not. A third class had oligoarthritis of upper limbs (OAUL) and could be subdivided into autoimmune OAUL and mild-inflammatory OAUL. A fifth class had oligoarthritis of lower limbs. The SvdH scores were worse in patients with APR/autoantibodies (AIPA) than in those without (MIPA). No clinically meaningful differences across classes in HAQ or SF36 over time were found.

Conclusion Radiographic progression over time primarily occurs in EA patients with APR/autoantibodies. The absence of these markers, however, does not necessarily translate into better long-term function and quality of life. Clinicians should not only aim at preventing joint damage, but look beyond structural progression in order to further improve the lives of people with EA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prognostic markers for patients with early arthritis (EA) have been identified previously. However, whether there are different EA phenotypes with distinct prognostic significance is yet unclear.

WHAT THIS STUDY ADDS

⇒ Five EA phenotypes, distinguished on the basis of their pattern of joint involvement, autoantibody positivity and elevation of acute phase reactants (APR), could be identified across different cohorts.

⇒ Radiographic progression primarily occurs in EA patients with autoantibodies and APR elevation (autoimmune inflammatory polyarthritis). Phenotypes that deviate from this classical 'RA construct' and have less structural progression still show similar levels of disability and impairment of quality of life.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinicians and researchers should aim at developing treatment strategies beyond those targeting the prevention of irreversible joint damage, in order to further improve the lives of people with EA.

INTRODUCTION

The field of rheumatoid arthritis (RA) has advanced significantly over the past decades. A better understanding of the mechanisms underlying the disease has translated into an exponential growth of therapeutic options. In this ever-evolving field, the rheumatology community has moved from testing new drugs in clinical trials of patients with 'advanced' RA to trials in patients with earlier forms of the disease.[1 2] This paradigm shift was driven by the evidence that the earlier the start of a disease-modifying antirheumatic drug (DMARD) the better the outcomes were (eg, higher chances of remission and lower probability of irreversible joint damage) and the term 'window of opportunity' was coined.[3–5]

The concept of 'window of opportunity' motivated rheumatologists to pursue ways of earlier identification of RA. Examples of such efforts include the development of referral

criteria,[3] the implementation of early arthritis (EA) clinics[6] and the validation of imaging methods for an earlier detection of synovitis (eg, by ultrasonography or MRI).[7–11] A key contribution was the development of the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology RA classification criteria,[12] which are more sensitive to capturing the rheumatologist's concept (Gestalt) of early RA than the more specific 1987 ACR classification criteria.[13–15]

One challenge of the early recognition of RA is that the earlier the disease is detected, the more heterogeneous and less 'typical' the disease manifestations will be. In fact, at disease presentation, it can be difficult to discern the patients with EA who will evolve into RA, or into another well-defined inflammatory rheumatic disease, from those who will spontaneously go into remission, remain undifferentiated forever or will continue as a 'low-inflammatory disease' (eg, inflammatory osteoarthritis; OA). Prognostic information can help clinicians in managing EA in clinical practice. Individual markers of persistent/erosive disease, such as a high number of swollen joints at presentation, positivity for rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA) have already been identified previously.[3] However, it is yet unclear whether combinations thereof with other EA features translate into clinically meaningful patterns (or phenotypes) with prognostic significance.

Experienced clinicians will intuitively recognise different forms of disease presentation, but 'intuitive phenotyping' will often be influenced by preconceived ideas about which characteristics are more important to the Gestalt of RA. For instance, seropositive (ie, RF/ACPA positive) and seronegative (RF and ACPA negative) RA are frequently studied RA phenotypes.[16] However, this split is based on the (prognostic) value attributed by rheumatologists to these autoantibodies. In addition, it is yet uncertain whether different phenotypes based on combinations of these, and other markers of joint damage will also translate into differences in clinical outcomes.

In this study, we propose to evaluate whether there are different phenotypes of EA, using an analytical approach that is less influenced by the rheumatologist's opinion. In particular, with this study we aim to: (1) evaluate the phenotypes of EA identified by a data-driven approach; (2) determine if EA patients change from one phenotype to another over time; (3) assess how many patients within each EA-phenotype fulfil RA classification criteria and (4) evaluate the clinical and imaging outcomes of the different phenotypes over time.

METHODS

Patients and study design

Patients from the Early Arthritis Cohort at Reade (Reade), from the Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort and from the Leiden Early Arthritis Clinic (EAC) were included. The three cohorts have been previously described in detail.[17–20] Briefly, Reade is a prospective cohort in which patients with ≥2 swollen joints (<2 years), or ≥1 swollen joint if positive for RF and/or ACPA, and who were naïve to DMARDs were included (patients with a diagnosis other than RA excluded). ESPOIR is a prospective cohort of patients with ≥2 swollen joints (≥6 weeks and ≤6 months), who are naïve to DMARDs and for whom the treating rheumatologists considered to have definite RA, probable RA or with the potential to become RA. Finally, the EAC is a prospective cohort of patients with arthritis (<2 years) confirmed by a rheumatologist (patients with a diagnosis of post-traumatic arthritis, crystal arthropathies or inflammatory OA excluded) recruited between 1993 and 2017. Databases were locked, for the current analysis, in June 2016 (Reade), October 2017 (ESPOIR) and February 2018 (EAC).

EA features

Clinical features

In Reade, clinical data were collected at baseline, every 3 months for 1 year, at 18 and 24 months, and yearly thereafter up to 13 years. In ESPOIR, clinical data were collected at baseline, every 6 months for 2 years, and yearly thereafter up to 12 years. In EAC, clinical data were collected at baseline, 2 weeks, 3 or 4 months, 1 year and then yearly up to 24 years.

The following clinical features were collected at each visit: (1) arthritis of small joints (≥1 swollen small joint vs swollen large joints only), (2) (sub)acute onset of arthritis (subacute or acute vs insidious onset), (3) symmetric arthritis (≥1 joint with symmetric arthritis vs asymmetric arthritis only), (4) duration of morning stiffness (≥60 min vs <60 min), (5) arthritis in upper limbs (≥1 swollen joint in the upper limbs vs swollen joints in the lower limbs only), (6) polyarthritis (≥5 swollen joints vs <5 swollen joints), (7) elevated acute phase reactants (APR) (positive C reactive protein (CRP) or erythrocyte sedimentation rate (ESR) vs CRP and ESR negative), (8) presence of autoantibodies (positive RF or ACPA vs RF and ACPA negative), (9) family history of RA (present vs absent), (10) comorbidities (≥1 comorbidity vs none), (11) smoking status (current smoker vs past or never-smoker) and (12) overweight (body mass index (BMI)≥25 kg/m^2 vs BMI<25 kg/m^2).

Imaging features

Radiographs of the hands and feet were assessed in ESPOIR by three central readers at baseline, 2, 5, 7 and 10 years. In Reade, radiographs were assessed by one central reader at baseline and yearly up to 13 years. In EAC, baseline radiographs were scored by one of two readers; follow-up radiographs were scored by a single reader. In all cohorts, the readers scored the radiographs according to the Sharp van der Heijde (SvdH) method with known chronological order and blinded to clinical data. The SvdH score measures erosions and joint space narrowing in 44 different joints.[21 22] In each joint, the erosion score ranges from 0 to 5 in the hands and 0 to

Table 1 Observed baseline clinical features in each cohort

	Reade (n=390)	ESPOIR (n=798)	EAC (n=3991)
Symptom duration (months)	4.7 (6.0)*	3.4 (1.7)†	6.5 (14.2)‡
Age ≥50 years	205 (53)	406 (51)	2393 (60)
Female	284 (73)	614 (77)	2368 (59)
Arthritis of small joints	389 (100)	776 (97)	3142 (85)
(Sub)acute onset	NA	465 (58)†	2004 (54)‡
Symmetric arthritis	353 (91)	632 (79)	2227 (57)
Morning stiffness ≥60 min	230 (59)	418 (52)	1608 (42)
Arthritis in upper limbs	382 (98)	783 (98)	3094 (79)
Polyarthritis (≥5 swollen joints)	331 (85)	483 (61)	1640 (45)
ESR or CRP elevated¶	259 (68)	583 (74)	2377 (62)
Positive RF and/or ACPA	235 (70)*	411 (52)†	1331 (34)†
Family history of RA	141 (42)*	112 (89)§	787 (21)‡
≥1 comorbidity	2 (1)¶**	335 (42)†	1378 (37)‡
Current smoker	109 (32)‡	376 (47)†	923 (25)‡
Overweight (BMI≥25 kg/m^2)	214 (58)‡	343 (43)†	1510 (55)††
Current alcohol use	255 (75)*	138 (17)	2340 (63)‡

Values are mean (SD) for symptom duration and n (%) for all other variables.
*<15% of missing data.
†<2% of missing data.
‡<10% of missing data.
§n=126.
¶<5% of missing data.
**Includes only stroke, heart failure and lower limb claudication.
††n=2760.
ACPA, anticitrullinated protein antibodies; BMI, body mass index; CRP, C reactive protein; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; ESR, erythrocyte sedimentation rate; NA, not available; RA, rheumatoid arthritis; RF, rheumatoid factor.

10 in the feet. An erosion score of 1 is given if a clearly visible erosion is identified. The total score ranges from 0 to 448. Radiographic damage was defined as an erosion score ≥1 in ≥3 joints according to the agreement of ≥2 out of 3 readers in ESPOIR or according to one reader in Reade and EAC.

MRIs of the hands were available at the baseline of the EAC cohort only. Images were scored according to the Rheumatoid Arthritis MRI Score by two central readers, who were blinded to the clinical information. Bone marrow oedema (BME) and tenosynovitis on hand MRI was considered present if both readers agreed on its presence in ≥1 bone or tendon, respectively. In addition, lesions were only counted as positive if present at the same location in <5% of age-matched symptom-free controls.[23]

Radiographs and MRIs from different patients are available in the EAC. Radiographs were available for patients included between 1993 and 2007 ('radiograph phase') who fulfilled the 1987 RA classification criteria (baseline and follow-up radiographs) or had a diagnosis of undifferentiated arthritis (UA; baseline radiographs only). MRIs were available for those included between 2010 and 2017 (MRI phase). Scored imaging data were not available for EAC patients included between 2007 and 2010 and also for EAC-patients included between 1993 and 2007 without RA according to the 1987 RA criteria or UA.

Definition of a positive feature

At baseline, the 12 clinical features and the 3 imaging features (radiographic damage, BME and tenosynovitis) were considered positive if present at the time of the study visit. During follow-up, change in time-varying features (all except antibodies in ESPOIR and EAC and BME and tenosynovitis in EAC) was defined as 'once-a-feature-always-a-feature': patients positive at baseline remained positive in all follow-up visits, even if becoming negative or missing in between; patients negative at baseline, remained negative at follow-up if no switch to positive or if missing in between. A feature changed to positive if appearing anytime during follow-up.

Other variables

The following variables were collected at baseline: age, gender, fulfilment of the 1987 RA classification criteria (ESPOIR and EAC) and of the 2010 RA classification criteria. RA classification criteria were

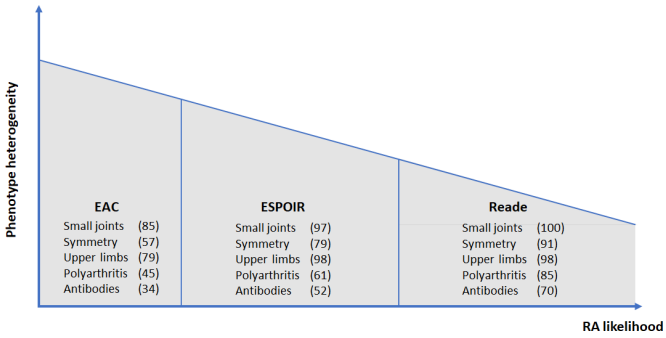

Figure 1 Most distinguishing characteristics of each cohort showing a spectrum between high heterogeneity in EAC and funnelling towards the classical RA phenotype in Reade. Values between brackets are percentages of each feature. EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; RA, rheumatoid arthritis.

assessed in all patients in Reade and ESPOIR and in patients with a diagnosis of RA in EAC. The 28-joint Disease Activity Score with ESR (DAS28-ESR) was collected in each visit of each cohort. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs), oral glucocorticoids, conventional synthetic DMARDs (csDMARDs) and biological DMARDs (bDMARDs) was collected in each visit of ESPOIR.

Outcomes

The following outcomes were assessed in each visit: functional disability, quantified by the Health Assessment Questionnaire (HAQ; range: 0–3),[24] quality of life (QoL) quantified by the Short Form 36 Physical (SF36 PCS) and Mental (SF36 MCS) Component Scores (range: 0–100),[25] presenteeism (percentage of productivity loss experienced by the patient during the past week; range: 0%–100%),[26] absenteeism (percentage of work hours lost to absence during the past 3 months; range: 0%–100%),[26] and the total SvdH score. SF36 was not available in Reade. In addition, SF36 and work outcomes were only available in the EAC for patients included from 2010 onwards.

Data analysis

Latent class analysis (LCA) was used to estimate the latent (ie, unobserved) Gestalt of EA with baseline data of each cohort separately. LCA splits patients into mutually exclusive classes (here called: phenotypes) based on the covariance of observed EA features.[26] All patients from Reade and ESPOIR were included in the analysis. To allow cross-cohort comparisons, the main LCA model in the EAC included only patients from the radiograph phase (recruited 1993–2007). Thirteen EA features (12 clinical plus radiographic damage) available in all cohorts (only subacute onset missing in Reade) were used in the main LCA. These features were selected based on content knowledge without predefined weights. Missing data on each feature was considered to be negative.

Starting with a one-class LCA model, the number of classes was increased, one-by-one, until the best model was found. The best model was defined by statistical criteria previously described in detail[27]; and by clinically recognisable patterns within each class. The classes of the final model were interpreted according to the probability of each feature and labelled by us as a clinically recognisable entity. Features were defined as: across-class dominant (highest probability across classes); within-class dominant (probability >50% within each class) and not dominant across or within classes. Individual patients were classified based on their posterior probability of class membership (as belonging to the class with the highest probability), which allowed us to further describe the classes and to evaluate the percentage of patients within each class fulfilling the 1987 (only in ESPOIR) and the 2010 RA classification criteria at baseline.

Follow-up data (at 1, 3, 5 and 10 years) of each cohort were used to perform a latent transition analysis (LTA) that serves to estimate the consistency and likelihood of change across classes over time.[28] LTA includes the same patients and variables as in each corresponding LCA model. The number of classes best fitting the baseline and follow-up LCA formed the basis of each LTA model. Classes at baseline and follow-up can be assumed as: having the same meaning (full invariance) or a different meaning (full non-invariance). The final LTA model had the number of classes at baseline and follow-up and class-(in)variance that best fitted the data, provided it was clinically meaningful.

To assess the prognosis of the latent classes, we tested the association between class membership at baseline and each outcome (HAQ, SF36 PC, SF36 MC, presenteeism, absenteeism and SvdH score) over time using generalised estimating equations models, adjusted for potential confounders that were chosen on clinical grounds: Age, gender, DAS28-ESR (all cohorts) and treatment with NSAIDs, glucocorticoids, csDMARDs and bDMARDs (only in ESPOIR).

Sensitivity analyses

Predefined sensitivity analyses were conducted to assess the robustness of the latent classes identified in the main analysis: (1) the same LCA model but assuming missing data to be at random (MAR) instead of assuming it to be negative by using full information maximum likelihood approach to estimate the model parameters including data from cases with missing values (all cohorts)[29 30]; (2) LCA with the two additional MRI features (BME and tenosynovitis) and with erosions defined on MRI (only in the EAC). Finally, to evaluate the possible impact of selecting patients in the EAC based on imaging availability, one additional analysis was performed and (3) LCA with no imaging features, which allowed to include all patients of the EAC. The analysis of prognosis was also performed in this population to allow the evaluation of work outcomes not available to patients included in the

Table 2 LAC models in Reade, ESPOIR and EAC

	Reade (N=390)				ESPOIR (N=798)				EAC (N=1878)				
											OAUL (p=0.29)		
	AIPA (p=0.71)*	MIPA (p=0.15)*	OAUL (p=0.13)*	OALL (p=0.00)	AIPA (p=0.50)*	MIPA (p=0.15)*	OAUL (p=0.33)*	OALL (p=0.02)*	AIPA (p=0.26)*	MIPA (p=0.23)*	AIOAUL (p=0.08)*	MIOAUL (p=0.21)*	OALL (p=0.22)*
Arthritis of small joints	1.00	1.00	0.98		1.00	1.00	0.99	0.00	1.00	0.98	0.73	1.00	0.00
(Sub)acute onset	NA	NA	NA		0.60	0.56	0.57	0.54	0.57	0.59	0.37	0.66	0.71
Symmetric arthritis	0.98	1.00	0.41		0.99	0.99	0.42	0.50	0.96	1.00	0.45	0.05	0.29
Morning stiffness ≥60 min	0.56	0.89	0.39		0.62	0.48	0.39	0.46	0.66	0.48	0.45	0.21	0.20
Arthritis in upper limbs	1.00	0.98	0.87		1.00	1.00	1.00	0.22	0.99	0.91	0.88	0.82	0.09
Polyarthritis	0.98	1.00	0.00		0.89	1.00	0.02	0.00	0.96	0.78	0.00	0.13	0.00
ESR and/or CRP elevated	0.75	0.48	0.41		1.00	0.00	0.65	0.81	0.86	0.63	0.65	0.55	0.65
Positive RF and/or ACPA	0.74	0.00	0.59		0.61	0.35	0.48	0.08	0.63	0.17	0.71	0.17	0.12
Family history of RA	0.39	0.19	0.42		0.13	0.21	0.13	0.15	0.28	0.19	0.25	0.19	0.14
≥3 joints erosion score ≥1†	0.08	0.00	0.03		0.02	0.00	0.02	0.00	0.55	0.00	0.58	0.02	0.03
≥1 comorbidity	0.01	0.00	0.00		0.44	0.49	0.38	0.25	0.41	0.28	0.42	0.34	0.31
Current smoker	0.28	0.28	0.29		0.46	0.47	0.48	0.49	0.25	0.24	0.23	0.27	0.25
Overweight	0.56	0.65	0.40		0.47	0.37	0.41	0.28	0.39	0.29	0.33	0.33	0.24

The table displays the main results of the LCA separately in each cohort.
*Probability of the latent class. Values in cells are the conditional probability for each feature within each latent class (range: 0–1). Heatmap legend: red: highlights dominant features across latent classes; yellow: highlights dominant features (probability >50%) within each class but not across classes; blank: not dominant neither across nor within classes.
†Sharp van der Heijde erosion score ≥1 in ≥3 joints according to ≥2 out of 3 central readers in ESPOIR and according to one central reader in Reade and EAC.
ACPA, anticitrullinated protein antibodies; AIOAUL, autoimmune inflammatory OAUL; AIPA, autoimmune inflammatory polyarthritis; CRP, C reactive protein; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; ESR, erythrocyte sedimentation rate; LAC, latent class analysis; MIOAUL, mild inflammatory OAUL; MIPA, mild inflammatory polyarthritis; NA, not available; OALL, oligoarthritis of lower limbs; OAUL, oligoarthritis of upper limbs; RA, rheumatoid arthritis; RF, rheumatoid factor.

Box 1 Phenotypes of early arthritis

⇒ Autoimmune inflammatory polyarthritis (AIPA).
⇒ Mild inflammatory polyarthritis (MIPA).
⇒ Autoimmune inflammatory oligoarthritis of upper limbs (AIOAUL).
⇒ Mild inflammatory oligoarthritis of upper limbs (MIOAUL).
⇒ Oligoarthritis of lower limbs (OALL).

main analysis. LCA and LTA were performed in MPlus V.7. Stata V.15.1 was used for all other analyses.

RESULTS

Baseline characteristics

In total, 390 (Reade), 798 (ESPOIR) and 3991 (EAC) patients were analysed. Of the total 3991 patients in EAC, 1878 were from the radiograph phase (1009 with scored baseline radiographs available), 1422 from the MRI phase (1039 with scored baseline MRIs available) and 691 from the no-imaging phase. Patients in Reade (73%) and ESPOIR (77%) were more often female than patients in EAC (59%). Symmetric polyarthritis and involvement of the small joints of the upper limbs was more frequent in ESPOIR than in the EAC and most frequent in Reade (table 1). A similar gradient was observed for the presence of autoantibodies (figure 1). Radiographic damage was less frequent in Reade (23/387; 6%) and in ESPOIR (12/445; 3%) than in the EAC (410/1009; 40%). BME (449/1038; 43%) and tenosynovitis (604/1030; 59%) were frequent in the EAC.

Latent phenotypes of EA at baseline

In Reade, three latent classes could be distinguished (table 2 and box 1). Two classes had a high likelihood of symmetric polyarthritis of the small joints of the upper limbs. One of these, which we labelled as autoimmune inflammatory polyarthritis (AIPA), had a high likelihood of ESR/CRP elevation and autoantibodies positivity, while the other (labelled as mild inflammatory polyarthritis; MIPA) had not. The third class resembled AIPA, but with fewer joints involved (oligoarthritis of upper limbs, OAUL). The same classes were identified in ESPOIR and an additional fourth class of patients with oligoarthritis of the lower limbs (OALL) emerged. The LCA in EAC including patients from the radiograph phase (N=1878) was similar to that in ESPOIR, but here the OAUL-class allowed a further subdivision into autoimmune OAUL (AIOAUL) and mild inflammatory OAUL (MIOAUL). Details on model selection criteria in each cohort are provided in online supplemental tables S1–S3.

Sensitivity analysis 1 (assuming MAR), yielded results consistent with the main analysis of each cohort (data not shown). Sensitivity analysis 2 in the EAC (adding MRI variables), yielded the same latent classes as in the main analysis (online supplemental table S4), but the distinction between AIPA and MIPA (and between AIOAUL and MIOAUL) was primarily driven by a higher likelihood of BME/tenosynovitis in the former than in the latter. The LCA model in EAC without imaging features (sensitivity analysis 3) also yielded the same classes as the main analysis, with the exception of the two oligoarticular classes of the upper limbs being split based on the symmetry of joint involvement (online supplemental table S5).

Observed characteristics and fulfilment of RA classification criteria across phenotypes at baseline

Even though the percentage of patients with elevated ESR/CRP was consistently higher for the AIPA (range: 100%–77%) than the MIPA (0%–66%) class, patients from both classes had a similarly high number of swollen joints at baseline in all cohorts (range 9–15) (table 3). In ESPOIR, the percentage of patients who received a b/csDMARD in ≥1 visit was higher in the AIPA class (89%) than in the MIPA (80%), OAUL (76%) or OALL (50%) classes. OALL patients were younger than in other classes (table 3) and had mono (ESPOIR: 45%; EAC: 64%) or oligoarthritis (ESPOIR: 55%; EAC: 36%) mostly in the lower limbs (ESPOIR 75%; EAC: 85%).

Patients in the AIPA-class more often fulfilled the 2010 RA classification criteria than those in the MIPA-class, in each cohort (Reade: 92% vs 61%; ESPOIR: 94% vs 87%; EAC: 86% vs 36%) (table 4). Fulfilment of the 2010 RA classification criteria was not uncommon for patients with OAUL (Reade: 48%; ESPOIR: 68%); but more likely (in EAC) if autoantibodies and elevation of ESR/CRP were present (AIOAUL: 66% vs MIOAUL: 17%). Patients with OALL were unlikely to fulfil the 2010 classification criteria for RA (ESPOIR: 16%; EAC: 5%). The results were similar for the 1987 ACR RA classification criteria, except that the OAUL class less often fulfilled the 1987 than the 2010 criteria (43% vs 68%).

Transition probabilities over time

In total, 163 (Reade), 504 (ESPOIR) and 322 (EAC) patients attended the 10-year visit. The limited number of patients in Reade did not allow for LTA to be performed in this cohort. In ESPOIR, LTA models were possible to fit in all prespecified visits (1, 3, 5 and 10 years) and in the EAC, LTA was possible only at the 1-year visit (N=1261), due to the limited number of patients thereafter. Details on model selection criteria are provided in online supplemental table S6. The transition probabilities for the 1-year, 3-year and 5-year models in ESPOIR are shown in online supplemental table S7. In ESPOIR, patients from the OAUL-class were most likely to not transition (69%) at all, but some transitioned to AIPA (21%) or MIPA (10%) after 10 years (table 5). Similarly, in the EAC, there were transitions from each oligoarticular class to into their respective polyarticular classes already after 1 year (AIOAUL to AIPA: 14% and MIOAUL to MIPA: 3%). Patients from the AIPA and MIPA classes did not transition to other classes in both cohorts. The OALL class was not identified anymore at follow-up in ESPOIR and mostly did not transition to other classes after 1 year in EAC (92%).

Table 3 Observed baseline characteristics across classes in each cohort

	Reade (N=390)*				ESPOIR (N=798)†				EAC (N=1878)‡				
	AIPA (N=266)	MIPA (N=68)	OAUL (N=56)	OALL (N=0)	AIPA (N=383)	MIPA (N=122)	OAUL (N=273)	OALL (N=20)	AIPA (N=490)	MIPA (N=433)	AIOAUL (N=154)	MIOAUL (N=392)	OALL (N=409)
Age (years), mean (SD)	55 (13)	55 (11)	53 (11)		48 (13)	50 (10)	48 (13)	39 (12)	59 (16)	50 (18)	58 (15)	50 (17)	45 (16)
Female, n (%)	192 (72)	50 (74)	42 (75)		278 (73)	110 (90)	209 (77)	17 (85)	317 (65)	279 (64)	102 (66)	214 (55)	198 (48)
Sympt. duration (months), mean (SD)	4 (6)	5 (5)	5 (7)		3 (2)	4 (1)	3 (2)	3 (2)	7 (8)	6 (9)	8 (13)	5 (7)	4 (10)
DAS28 ESR, mean (SD)	5 (1)	5 (1)	4 (1)		6 (1)	5 (1)	4 (1)	4 (1)	6 (1)	5 (1)	4 (1)	4 (1)	3 (1)
N swollen joints, mean (SD)§	13 (6)	15 (7)	3 (1)		10 (5)	9 (4)	3 (1)	2 (1)	13 (7)	10 (7)	3 (1)	3 (2)	1 (1)
N tender joints, mean (SD)§	11 (8)	13 (8)	6 (6)		11 (7)	10 (7)	5 (5)	3 (5)	20 (12)	15 (13)	10 (11)	9 (10)	4 (5)
Elevated ESR/CRP, n (%)	203 (77)	32 (49)	24 (45)		383 (100)	0 (0)	184 (68)	16 (80)	428 (88)	270 (66)	100 (69)	221 (62)	264 (68)
Positive RF/ACPA, n (%)	202 (82)	0 (0)	33 (79)		241 (63)	42 (35)	127 (47)	1 (5)	357 (73)	31 (7)	124 (81)	77 (20)	48 (12)
Total SvdH score (0–448), mean (SD)	3 (8)	1 (1)	2 (6)		3 (6)	1 (3)	3 (5)	1 (2)	11 (12)	3 (3)	11 (9)	2 (4)	6 (7)
HAQ (0–3), mean (SD)	1.2 (0.8)	1.4 (0.5)	0.8 (0.6)		1.2 (0.7)	0.9 (0.6)	0.7 (0.6)	0.8 (0.6)	1.1 (0.7)	0.9 (0.7)	0.9 (0.8)	0.6 (0.6)	0.6 (0.5)
SF36 PC (0–100), mean (SD)	NA	NA	NA		35 (8)	39 (9)	40 (9)	37 (10)	NA	NA	NA	NA	NA
SF36 MC (0–100), mean (SD)	NA	NA	NA		39 (11)	41 (10)	40 (11)	34 (12)	NA	NA	NA	NA	NA
Current NSAID, n (%)	NA	NA	NA		296 (78)	80 (66)	178 (66)	9 (45)	NA	NA	NA	NA	NA
Current GC, n (%)	NA	NA	NA		5 (1)	2 (2)	2 (1)	0 (0)	NA	NA	NA	NA	NA
Current csDMARD, n (%)	NA	NA	NA		32 (8)	3 (3)	15 (6)	0 (0)	NA	NA	NA	NA	NA
Current bDMARD, n (%)	NA	NA	NA		0 (0)	0 (0)	0 (0)	0 (0)	NA	NA	NA	NA	NA

*Missing data <2% for all characteristics in Reade except for symptom duration (n=332), antibodies (n=335) and HAQ (n=378).
†Missing data <2% for all characteristics in ESPOIR except for the SvdH score (n=445).
‡Missing data in EAC: symptom duration (n=144), DAS28 ESR (n=1222), SJC-66 (n=174), TJC-68 (n=1148), ESR/CRP (n=93), RF/ACPA (n=12), Total SvdH score (n=1195), HAQ (n=400).
§ESPOIR (28 joints); Reade (38 joints); EAC (68 joints).
ACPA, anticitrullinated protein antibodies; AIOAUL, autoimmune inflammatory OAUL; AIPA, autoimmune inflammatory polyarthritis; bDMARDs, biological disease-modifying antirheumatic drugs; CRP, C reactive protein; csDMARDs, conventional synthetic DMARDs; DAS28, Disease Activity Score of 28 joints; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; HAQ, Health Assessment Questionnaire; MC, mental component; MIOAUL, mild inflammatory OAUL.; MIPA, mild inflammatory polyarthritis; N, number; NA, not available; NSAID, non-steroidal anti-inflammatory drugs; OALL, oligoarthritis of lower limbs; OAUL, oligoarthritis of upper limbs; PC, physical component; RF, rheumatoid factor; SJC, swollen joint count; SvdH, Sharp van der Heijde; Sympt, symptom; TJC, tender joint count.

Table 4 Fulfilment of RA classification criteria across latent classes of EA in each cohort

Latent class / 1987 criteria	RA	No RA		% Classification
ESPOIR				
AIPA	358	25	383	93
MIPA	101	21	122	83
OAUL	117	155	272	43
OALL	1	19	20	5
Total	577	220	797*	72
Latent class / 2010 criteria	**RA**	**No RA**		**% Classification**
Reade				
AIPA	243	22	265	92
MIPA	39	25	64	61
OAUL	27	29	56	48
Total	309	76	385*	80
ESPOIR				
AIPA	358	23	381	94
MIPA	103	16	119	87
OAUL	177	82	259	68
OALL	3	16	19	16
Total	641	137	778*	82
EAC				
AIPA	422	68	490	86
MIPA	158	275	433	36
AIOAUL	101	53	154	66
MIOAUL	67	325	392	17
OALL	7	402	409	2
Total	755	1123	1878	40

*Missing data for the classification according to the 1987 ACR classification criteria: ESPOIR: 1 patient; missing data for the 2010 EULAR/ACR classification criteria: Reade: 5 patients, ESPOIR: 20 patients and EAC: 0 patients.
ACR, American College of Rheumatology; AIOAUL, autoimmune inflammatory OAUL; AIPA, autoimmune inflammatory polyarthritis; EA, early arthritis; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; EULAR, European Alliance of Associations for Rheumatology; MIOAUL, mild inflammatory OAUL; MIPA, mild inflammatory polyarthritis; OALL, oligoarthritis of lower limbs; OAUL, oligoarthritis of upper limbs; RA, rheumatoid arthritis.

Prognosis

In all cohorts, the total SvdH score was consistently lower in the MIPA- than in the AIPA class over time (table 6). Patients in the MIPA-class had on average 7, 4 and 19 SvdH-units less over time than patients in the AIPA-class in Reade, ESPOIR and EAC, respectively (table 6). In ESPOIR, there was an improvement over time for all classes on the mean SF36 PCS (range at baseline 35–40; range at 12 years: 43–51), SF-36 MCS (baseline: 34–41; 12 years: 40–48) and HAQ (baseline: 0.7–1.2; 12 years: 0.3–0.6). Similar improvements in the HAQ score were observed in the other cohorts (data not shown). Contrary to the SvdH score, there were no meaningful differences across classes with regard to the mean HAQ scores and SF36 scores over time, also after adjustment for DMARD-therapy in ESPOIR (table 6). The analysis in EAC including all patients (sensitivity analysis 3) has shown no difference across classes also in terms of presenteeism and absenteeism over time (online supplemental table S8).

DISCUSSION

In this study, we have analysed three independent EA cohorts and found that the Gestalt of EA comprises five recognisable clinical entities, distinguished by their pattern of joint involvement, autoantibody positivity and elevation of APR. Unlike previous studies, which mostly grouped patients according to individual features (eg, RF/ACPA positive vs negative), these phenotypes were here identified using a technique (LCA) that takes several EA features into account without predefined weights, therefore, avoiding circular reasoning. Expectedly, patients with phenotypes, at presentation, that are most consistent with the classical 'RA-construct' (ie, AIPA) fulfil the RA classification criteria most often and develop more radiographic damage over time than other EA phenotypes. However, patients with phenotypes that do not fit this construct (eg, MIPA), who have lower levels of systemic inflammation and joint damage over time, also often classify as RA. The absence of these markers, however, does not necessarily translate into better function and QoL on the long term. These data shed new light on the earliest clinical disease stages of RA and provide new prognostic information to further help clinicians to manage EA patients in clinical practice.

Synovitis, typically identified as a swollen joint at physical examination, is the defining feature of EA and is therefore the common inclusion criterion of the three cohorts in this study. Apart from this communal feature, patients with EA may present with a variety of clinical patterns. The more restrictive the inclusion criteria for a cohort are, the narrower is the range of possible patterns. In Reade, for instance, patients with features that in the opinion of the clinician were consistent with a diagnosis other than RA were excluded upfront. This restriction was not in place in the EAC cohort. Differences in study design can, therefore, explain the narrower phenotypical diversity in Reade at one end of the spectrum, as compared with the EAC at the other end, and with ESPOIR somewhat in between. The phenotype labelled by us as AIPA closely resembles what many clinicians will describe as a textbook example of RA. The finding that this phenotype was far more likely in Reade (71%) than in the EAC (26%), is therefore consistent with the background population of each cohort and adds credibility to our analysis.

Table 5 Latent transition analysis in ESPOIR (10 years) and EAC (1 year)

Baseline / Follow-up	AIPA	MIPA	OAUL	AIOAUL	MIOAUL	OALL
ESPOIR (N=504)						
AIPA	100	0	0	NA	NA	NE
MIPA	0	100	0	NA	NA	NE
OAUL	21.0	10.2	68.7	NA	NA	NE
OALL	NE	NE	NE	NA	NA	NE
EAC (N=1261)						
AIPA	100	0	NA	0	0	0
MIPA	0	100	NA	0	0	0
AIOAUL	14.2	0	NA	85.8	0	0
MIOAUL	0	2.9	NA	0	97.1	0
OALL	0.3	1.0	NA	0.3	6.6	91.7

Values come from LTA models with full invariance and are transition probabilities across classes from the baseline to the follow-up visit (10 years in ESPOIR and 1 year in EAC).
AIOAUL, autoimmune inflammatory OAUL; AIPA, autoimmune inflammatory polyarthritis; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; LTA, latent transition analysis; MIOAUL, mild inflammatory OAUL; MIPA, mild inflammatory polyarthritis; NA, not applicable (class not identified); NE, not possible to estimate; OALL, oligoarthritis of lower limbs; OAUL, oligoarthritis of upper limbs.

Classification criteria for RA include features that are deemed important by experts for 'capturing' the Gestalt of RA. As mentioned, patients from the AIPA-class have several of these features (eg, symmetric polyarthritis, elevation of APR, autoantibodies) and therefore almost all (85%–94%) classify as RA, at presentation. Patients from the AIPA class had already more radiographic damage at inclusion and were more likely to experience radiographic progression over time than the other classes. This finding is in agreement with the literature, confirming that features that are common in these patients (eg, elevation of

Table 6 Prognosis of EA phenotypes: impact of the different classes on outcomes over time

	HAQ (0–3) β (95% CI)*	SF36 PCS (0–100) β (95% CI)*	SF36 MCS (0–100) β (95% CI)*	SvdH (0–448) β (95% CI)*
Reade				
MIPA vs AIPA	**0.22 (0.10; 0.33)**	NA	NA	**7.00 (–9.42; –4.52)**
OAUL vs AIPA	0.04 (–0.17; 0.10)	NA	NA	2.73 (–5.94; 0.49)
ESPOIR				
MIPA vs AIPA	0.01 (–0.1; 0.08)	0.20 (–1.46; 1.06)	0.21 (–1.75; 1.34)	**4.33 (–6.47; –2.18)**
OAUL vs AIPA	**0.07 (–0.13; –0.01)**	0.45 (–0.50; 1.40)	0.74 (–1.95; 0.47)	0.79 (–3.05; 1.47)
OALL vs AIPA	0.04 (–0.19; 0.10)	0.97 (–3.36; 1.42)	1.73 (–5.14; 1.69)	**4.48 (–6.80; –2.17)**
EAC				
MIPA vs AIPA	**0.09 (–0.18; 0.00)**	NA	NA	**18.5 (–25.2; –11.9)**
AIOAUL vs AIPA	0.01 (–0.11; 0.12)	NA	NA	0.7 (–5.3; 6.7)
MIOAUL vs AIPA	0.08 (–0.16; 0.01)	NA	NA	6.3 (–15.1; 2.6)
OALL vs AIPA	0.06 (–0.18; 0.05)	NA	NA	6.8 (–19.2; 5.5)

Data availability: ESPOIR: N=797 for HAQ, SF36 PC and SF36 MC (12 years) and N=453 for SvdH (10 years). Reade: N=387 for HAQ (3 years) and N=390 for SvdH (13 years). EAC: N=1478 for HAQ (up to 24 years), N=683 for SvdH (up to 14 years). Models in ESPOIR adjusted for age, gender, DAS28, NSAIDs, GCs, csDMARDs, bDMARDs. In Reade and EAC, models are adjusted for age, gender and DAS28.
*Estimated difference in the average outcome value over time between each class and the reference (AIPA).
AIOAUL, autoimmune inflammatory OAUL; AIPA, autoimmune inflammatory polyarthritis; bDMARDs, biological disease modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDs; DAS28, Disease Activity Score of 28 joints; EA, early arthritis; EAC, early arthritis clinic; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; GC, glucocorticoids; HAQ, Health Assessment Questionnaire; MIOAUL, mild inflammatory OAUL; MIPA, mild inflammatory polyarthritis; NA, not available; NSAID, non-steroidal anti-inflammatory drugs; OALL, oligoarthritis of lower limbs; OAUL, oligoarthritis of upper limbs; SF36 MCS, Short Form 36 Mental Component Score; SF36 PCS, SF36 Physical Component Score; SvdH score, Sharp van der Heijde score.

ESR/CRP) increase the likelihood of irreversible joint damage over time.[31 32]

One key finding of this study is that approximately one fourth of all EA patients present with an AIPA-like phenotype in terms of high number of swollen joints at study entry, but with a lower likelihood of objective signs of inflammation (eg, elevation of APR) and autoimmunity (RF/ACPA). These patients, which we labelled as MIPA may have an inflammatory rheumatic disease other than RA (such as: PsA or systemic lupus erythematosus). In fact, diseases other than RA could in principle be included in each cohort, especially in EAC which had the least restrictive inclusion criteria, and the features we have preselected do not necessarily capture the Gestalt of these other diseases as well as they do for RA. One alternative explanation is that MIPA patients have a disease with joint effusion within a wider-than-expected spectrum of what clinicians call RA. Expectedly, patients with the MIPA-phenotype often fulfil the 2010 classification criteria for RA (36%–87%), which heavily weigh the number of swollen joints,[12] but to a lower extent than those with an AIPA phenotype, given the absence of other important classifying features (elevated APR and autoantibodies). A better understanding of the MIPA phenotype is warranted in future studies, perhaps created by researchers using molecular phenotyping of synovial tissue which may better differentiate clinically similar EA phenotypes and therefore provide better prognostic information.[33 34]

Of note, despite the clear difference in structural prognosis, patients from the AIPA classes and MIPA classes had similarly high levels of disability (HAQ: 0.3–0.6) and impaired QoL (SF36 PCS/MCS: 40–50) at the end of the follow-up, which were both worse than those reported for the general population (HAQ: 0.25; SF36: 64–93).[35 36] These data are important to clinicians who manage patients with EA in clinical practice; the data suggest that EA patients presenting without known prognostically unfavourable features (eg, elevated APR and autoantibodies) do not necessarily have better clinical outcomes on the long-term as compared with those who have these markers at presentation. Most patients from the AIPA classes and MIPA classes were treated with DMARDs. It is possible that AIPA patients treated with anti-inflammatory treatment show mean values of HAQ and SF36 similar to those that the MIPA-patients would have achieved even without treatment. However, this study cannot provide resolution as it was not designed for testing treatment effects.

We have also identified two classes of EA-patients who resemble either AIPA or MIPA but with fewer joints involved at presentation (oligoarthritis of the upper limbs). Only a fraction (about 30% in 10 years) of these patients evolve into the more typical symmetric polyarthritis phenotype over time. It should be noted, however, that the phenotype with fewer affected joints did not translate, into a phenotype with more favourable outcomes over time. The fact that these oligoarticular cases are better captured by the 2010 RA classification criteria than the 1987 criteria adds to the body of evidence that shows the former are more sensitive than the latter in early disease.[14]

The least common of the five phenotypes was characterised by a younger group of patients who had mostly monarthritis or OALL, frequent elevation of APR and a low probability of positivity for RF or ACPA. These patients, who rarely fulfilled RA classification criteria, have a phenotype that is possibly consistent with the construct of (peripheral) spondyloarthritis.[37] The fact that these patients are absent in Reade and are most common in the EAC is again concordant with the background population of the study cohorts.

Our study has some strengths and many limitations. While we aimed at ruling out the influence of expert opinion, this aim can only be partially achieved, as our analysis relies on the patients included in each cohort, based on their inclusion criteria, and on the opinion-based features used to derive the EA phenotypes. However, our unsupervised analytical approach is not dependent on the opinion of clinicians regarding a diagnosis. Moreover, the fact that similar phenotypes emerged from three cohorts with different source populations suggests a limited influence of clinician bias. Missing data could also have influenced our results, in particular for radiographic damage, which could only be assessed in a fraction of patients in the EAC. Also, it should be acknowledged that the maximum follow-up time was not the same across cohorts, being shortest in ESPOIR and longest in the EAC (up 12 and 24 years, respectively). Even though selection bias cannot be ruled out, extensive sensitivity analysis with different methods for handling missing data (completers vs assuming MAR) and including all patients from the EAC (without considering imaging features) revealed similar results, and therefore, support the robustness of the main analysis.

In summary, EA patients with elevated APR and autoantibodies (the phenotype most consistent with the 'classic RA-construct') develop more radiographic damage, but do not have worse function or QoL over time, than those without these markers. These data provide relevant prognostic information to clinicians managing patients with different EA phenotypes in clinical practice. In addition, this study suggests that future research should go beyond the prevention of irreversible joint damage towards optimising treatment strategies (pharmacological or non-pharmacological) with the ultimate goal of improving the lives of people living with arthritis.

Author affiliations
[1]NOVA Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
[2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands
[3]Rheumatology, Zuyderland Medical Centre Heerlen, Heerlen, Netherlands
[4]University of Montpellier, Montpellier, France
[5]Rheumatology, Reade and Amsterdam University Medical Center, Amsterdam, Netherlands
[6]EULAR Patient Research Partner Network, Zurich, Switzerland
[7]Amsterdam Rheumatology Center, AMC, Amsterdam, Netherlands

[8]Rheumatology, Zuyderland Medical Centre, Heerlen, Netherlands

Acknowledgements The authors sincerely thank all patients, the staff, and all recruiting rheumatologists of the Reade, ESPOIR and EAC cohorts.

Contributors All authors made contributions to conception and/or implementation of the study. AS and BTvD performed the analysis. All authors contributed to the interpretation of the results. AS wrote the first draft of the manuscript and all authors were involved in reviewing the manuscript and gave final approval to the version to be published.

Funding This study was supported by a grant of the Foundation for Research in Rheumatology (FOREUM), under the topic call on Innovative Medicine 2019 (project ID: 036). ESPOIR Funding: An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years of the cohort study. Two additional grants from INSERM supported part of the biological database. The French Society of Rheumatology, Abbvie, Pfizer, Lilly and more recently Fresenius and Galapagos supported the ESPOIR cohort study.

Competing interests AS: speaking and/or consulting fees from Abbvie, Novartis, UCB and Lilly. Bastiaan van Dijk: None. Sofia Ramiro: research grants and/or consultancy fees: AbbVie, Eli Lilly, Galapagos, MSD, Novartis, Pfizer, UCB, Sanofi. AvdH: None. BC: consulting fees from AbbVie, Celltrion, Chugaï, Eli-Lilly, Galapagos, Gilead, Janssen, Merck, Novartis, Pfizer. DvS: speaking fees from Janssen, Galapagos. MdW: Over the last three years Stichting Tools has received fees for lectures or consultancy provided by MdW from Celgene, Eli Lilly, Pfizer and UCB. Alison Kent: None. EF-M: Consulting fees from Boehringer Ingelheim Portugal. Over the last three years, the Portuguese League Against Rheumatic Diseases (LPCDR) received non-financial and financial support from AbbVie, A. Menarini Portugal—Farmacêutica, S.A., Amgen Biofarmacêutica, Grünenthal S.A., GSK, Lilly Portugal, Medac, MSD, Novartis, Pfizer, Roche. RL: Received consulting fees from AbbVie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Roche, UCB and is Director of Rheumatology Consultancy bv

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study was conducted according to Good Clinical Practice guidelines and approved by the appropriate local ethical committees. Written informed consent was obtained from participating patients before inclusion in each cohort.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

ORCID iDs
Alexandre Sepriano http://orcid.org/0000-0003-1954-0229
Sofia Ramiro http://orcid.org/0000-0002-8899-9087
Annette van der Helm-van Mil http://orcid.org/0000-0001-8572-1437
Bernard Combe http://orcid.org/0000-0003-4002-1861
Dirkjan van Schaardenburg http://orcid.org/0000-0003-4006-3762
Maarten de Wit http://orcid.org/0000-0002-8428-6354
Robert Landewé http://orcid.org/0000-0002-0577-6620

REFERENCES

1 van Schaardenburg D, Dijkmans BAC. Clinical approaches to early inflammatory arthritis. *Nat Rev Rheumatol* 2009;5:627–33.
2 van Steenbergen HW, da Silva JAP, Huizinga TWJ, *et al*. Preventing progression from arthralgia to arthritis: targeting the right patients. *Nat Rev Rheumatol* 2018;14:32–41.
3 Hua C, Daien CI, Combe B, *et al*. Diagnosis, prognosis and classification of early arthritis: results of a systematic review informing the 2016 update of the EULAR recommendations for the management of early arthritis. *RMD Open* 2017;3:e000406.
4 Combe B, Landewe R, Daien CI, *et al*. Update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis* 2017;76:948–59.
5 Emery P. Evidence supporting the benefit of early intervention in rheumatoid arthritis. *J Rheumatol Suppl* 2002;66:3–8.
6 Ivorra JAR, Martínez JA, Lázaro P, *et al*. Quality-of-care standards for early arthritis clinics. *Rheumatol Int* 2013;33:2459–72.
7 Kaeley GS, Bakewell C, Deodhar A. The importance of ultrasound in identifying and differentiating patients with early inflammatory arthritis: a narrative review. *Arthritis Res Ther* 2020;22:1.
8 Burgers LE, Nieuwenhuis WP, van Steenbergen HW, *et al*. Magnetic resonance imaging-detected inflammation is associated with functional disability in early arthritis-results of a cross-sectional study. *Rheumatology (Oxford)* 2016;55:2167–75.
9 Duer-Jensen A, Hørslev-Petersen K, Hetland ML, *et al*. Bone edema on magnetic resonance imaging is an independent Predictor of rheumatoid arthritis development in patients with early undifferentiated arthritis. *Arthritis Rheum* 2011;63:2192–202.
10 Nieuwenhuis WP, Krabben A, Stomp W, *et al*. Evaluation of magnetic resonance imaging-detected Tenosynovitis in the hand and wrist in early arthritis. *Arthritis Rheumatol* 2015;67:869–76.
11 Colebatch AN, Edwards CJ, Østergaard M, *et al*. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis* 2013;72:804–14.
12 Aletaha D, Neogi T, Silman AJ, *et al*. Rheumatoid arthritis classification criteria: an American college of rheumatology/European League against rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
13 Biliavska I, Stamm TA, Martinez-Avila J, *et al*. Application of the 2010 ACR/EULAR classification criteria in patients with very early inflammatory arthritis: analysis of sensitivity, specificity and predictive values in the SAVE study cohort. *Ann Rheum Dis* 2013;72:1335–41.
14 van der Linden MPM, Knevel R, Huizinga TWJ, *et al*. Classification of rheumatoid arthritis: comparison of the 1987 American college of rheumatology criteria and the 2010 American college of rheumatology/European League against rheumatism criteria. *Arthritis Rheum* 2011;63:37–42.
15 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
16 Heutz J, de Jong PHP. Possibilities for Personalised medicine in rheumatoid arthritis: Hype or hope. *RMD Open* 2021;7:e001653.
17 Combe B, Benessiano J, Berenbaum F, *et al*. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. *Joint Bone Spine* 2007;74:440–5.
18 Combe B, Rincheval N, Berenbaum F, *et al*. Current favourable 10-year outcome of patients with early rheumatoid arthritis: data from the ESPOIR cohort. *Rheumatology (Oxford)* 2021;60:5073–9.
19 de Rooy DPC, van der Linden MPM, Knevel R, *et al*. Predicting arthritis outcomes--what can be learned from the Leiden early arthritis clinic *Rheumatology (Oxford)* 2011;50:93–100.
20 Turk SA, van Schaardenburg D, Boers M, *et al*. An unfavorable body composition is common in early arthritis patients: A case control study. *PLoS One* 2018;13:e0193377.
21 van der Heijde D. How to read Radiographs according to the sharp/Van der Heijde method. *J Rheumatol* 2000;27:261–3.
22 van der Heijde DM, van Riel PL, Nuver-Zwart IH, *et al*. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036–8.
23 Boer AC, Burgers LE, Mangnus L, *et al*. Using a reference when defining an abnormal MRI reduces false-positive MRI results-a longitudinal study in two cohorts at risk for rheumatoid arthritis. *Rheumatology (Oxford)* 2017;56:1700–6.
24 Fries JF, Spitz P, Kraines RG, *et al*. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.
25 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. *Medical Care* 1992;30:473–83.
26 Schreiber JB. Latent class analysis: an example for reporting results. *Res Social Adm Pharm* 2017;13:1196–201.
27 Sepriano A, Ramiro S, van der Heijde D, *et al*. What is axial Spondyloarthritis? A latent class and transition analysis in the SPACE and DESIR cohorts. *Ann Rheum Dis* 2020;79:324–31.

28 Lanza ST, Patrick ME, Maggs JL. Latent transition analysis: benefits of a latent variable approach to modeling transitions in substance use. *J Drug Issues* 2010;40:93–120.
29 Cham H, Reshetnyak E, Rosenfeld B, *et al*. Full information maximum likelihood estimation for latent variable interactions with incomplete indicators. *Multivariate Behav Res* 2017;52:12–30.
30 Muthén LK, Muthén BO. *Mplus User's Guide*Eighth Edition. Los Angeles, CA: Muthén & Muthén, 1998.
31 van der Helm-van Mil AHM, Verpoort KN, Breedveld FC, *et al*. Antibodies to Citrullinated proteins and differences in clinical progression of rheumatoid arthritis. *Arthritis Res Ther* 2005;7:R949–58.
32 Rydell E, Forslind K, Nilsson J-Å, *et al*. Predictors of radiographic erosion and joint space narrowing progression in patients with early rheumatoid arthritis: a cohort study. *Arthritis Res Ther* 2021;23:27.
33 Nzeusseu Toukap A, Galant C, Theate I, *et al*. Identification of distinct gene expression profiles in the Synovium of patients with systemic lupus erythematosus. *Arthritis Rheum* 2007;56:1579–88.
34 Lewis MJ, Barnes MR, Blighe K, *et al*. Molecular portraits of early rheumatoid arthritis identify clinical and treatment response phenotypes. *Cell Rep* 2019;28:2455–70.
35 Jenkinson C, Coulter A, Wright L. Short form 36 (Sf36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993;306:1437–40.
36 Krishnan E, Sokka T, Häkkinen A, *et al*. Normative values for the health assessment questionnaire disability index: Benchmarking disability in the general population. *Arthritis Rheum* 2004;50:953–60.
37 Molto A, Sieper J. Peripheral Spondyloarthritis: concept, diagnosis and treatment. *Best Pract Res Clin Rheumatol* 2018;32:357–68.