Defining erosive disease typical of RA in the light of the ACR/EULAR 2010 criteria for rheumatoid arthritis; results of the data driven phase

Rachel Knevel, Cédric Lukas, Désirée van der Heijde, et al.

Ann Rheum Dis 2013 72: 590-595 originally published online February 7, 2013
doi: 10.1136/annrheumdis-2012-202778

Notes

EXTENDED REPORT

Defining erosive disease typical of RA in the light of the ACR/EULAR 2010 criteria for rheumatoid arthritis; results of the data driven phase

Rachel Knevel,[1] Cédric Lukas,[2] Désirée van der Heijde,[1] Nathalie Rincheval,[2] Bernard Combe,[2] Annette H M van der Helm-van Mil[1]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2012-202778).

[1]Department of Rheumatology, Leiden University Medical Center, Leiden,The Netherlands
[2]Department of Rheumatology, Lapeyronie Hospital, UMR 5534, Montpellier I University, Montpellier, France

Correspondence to
Dr Annette H M van der Helm-van Mil, Department of Rheumatology, Leiden University Medical Center, P.O. Box 9600, Leiden 2300RC, The Netherlands; AvdHelm@lumc.nl

RK and CL contributed equally.

Received 4 October 2012
Accepted 14 January 2013
Published Online First
7 February 2013

ABSTRACT

Background According to the 2010 criteria, rheumatoid arthritis (RA) can be classified in the presence of ≥6 points on the criteria or 'typical' erosive disease. RA-specific erosiveness however has not been defined yet. This study reports the results of the data driven phase of a European League Against Rheumatism (EULAR) taskforce aiming to define RA-specific erosiveness.

Methods Baseline radiographs of hands and feet of 980 Dutch and 811 French early arthritis patients were studied on the number and site of erosive joints. Test characteristics were determined, with the outcome measures being initiation of methotrexate (MTX) therapy or any disease modifying antirheumatic drug (DMARD) therapy within the first year of disease and arthritis persistency over 5 years. Analyses were repeated in the patients with <6 points on the American College of Rheumatology/EULAR 2010 criteria.

Results In both cohorts comparable test characteristics were observed for the outcomes MTX therapy, any DMARD therapy and arthritis persistency. Test characteristics were not influenced by the site of erosiveness. The specificity observed was >50% for ≥1 erosive joint, >80% for ≥3 erosive joints and >90% for ≥5 erosive joints. When analysing the patients not fulfilling the 2010 criteria (n=308 and 149), specificity was >60% for ≥1 erosive joint, >90% for ≥3 erosive joints and >95% for ≥5 erosive joints. Few of these patients fulfilled the radiological criterion; 27–36 patients had ≥3 erosive joints and 13–14 patients had ≥5 erosive joints.

Conclusions RA-specific erosiveness can be defined with high specificity at several cut-offs for the number of erosive joints in two independent cohorts with multiple different outcomes. The final radiological criterion will be established in the next phase.

INTRODUCTION

Recently, the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) developed new criteria to classify rheumatoid arthritis (RA).[1] These new criteria are valuable as they facilitate the inclusion of patients with early RA in clinical trials. Until recently, the large majority of randomised clinical trials included patients who fulfilled the 1987 ACR criteria. Since the 1987 ACR criteria are adequate for classifying RA in a more advanced stage but are not appropriate to classify early stage RA, most clinical trials have not included the spectrum of early RA patients. Fortunately, the 2010 criteria have shown to be fulfilled earlier in disease than the 1987 criteria.[2 3]

According to the 2010 classification criteria, a patient can be classified with RA in two ways. First, RA is considered when ≥6 out of 10 points are obtained in four items: number and size of involved joints, serology, acute phase reactants and duration of symptoms. Second, a patient can be classified as RA when 'RA typical erosiveness' is present. Thus, while erosiveness was one of the seven items of the 1987 ACR criteria, in the 2010 criteria patients with typical erosions can be classified as having RA without fulfilling the other criteria. Since in this way erosiveness can be the sole requirement for the classification of RA, the question is raised what number or site of erosions are sufficiently characteristic for RA. At the time of the publication of the 2010 ACR/EULAR criteria, a description of RA-specific erosiveness was not available and it was decided that it would be a subject for further studies to identify these specific features.

A EULAR taskforce was initiated to define erosiveness for the use in the 2010 ACR/EULAR criteria. The aim was to derive a definition for a type of erosiveness that can be used to classify RA and that is easy to apply. To achieve this, a two staged approach, composed of a data driven and a consensus phase, was used. The current manuscript reports on the first, data driven phase. The working group on the 2010 ACR/EULAR classification criteria for RA stated that there is a need for the definition of erosive disease in patients who may have clinical RA but who do not meet current classification. This could include patients with longstanding but inactive disease, and patients with (frequently early) undiagnosed disease in whom radiographs are available. Since in daily practice the challenges are generally concentrated on the early stages of the disease, and not on advanced stages, it was decided to focus here on the latter situation, thus on patients with early arthritis. In two large early arthritis cohorts, the quantity and locations of erosive lesions in hand and foot joints were studied in relation to three different outcomes: the use of methotrexate (MTX), any disease modifying antirheumatic drug (DMARD) in the first year of the disease and arthritis persistency over 5 years.

▶ http://dx.doi.org/10.1136/annrheumdis-2012-202779

METHODS

Patients

Early arthritis patients who were formerly classified with unclassified arthritis or RA (according to the 1987 ACR criteria) and had scored data of radiographs of hands and feet at baseline were studied. Early arthritis patients who at baseline fulfilled criteria for other diagnoses were excluded. Two cohorts were studied.

The first cohort is the Dutch Leiden-Early Arthritis Clinic (Leiden-EAC), an inception cohort that was started in 1993.[4] Patients were included when arthritis of ≥1 joint was confirmed at physical examination and symptom duration was <2 years. At the first visit, patients and rheumatologists completed questionnaires, physical examination was performed, hands and feet radiographs were performed and blood was collected. Follow-up visits were performed yearly. Between 1993 and 2006 (allowing a follow-up period of at least 5 years), 1116 patients with unclassified or RA were included. Unclassified arthritis patients who participated in randomised clinical trials (n=55) were excluded as it was unsure whether they would have been prescribed DMARD treatment by their treating rheumatologist if they had not participated in a trial. Patients who had no baseline x-ray (n=125) or no data on medication usage were also excluded (n=34). Consequently, 902 patients were left for analyses. The x-rays were scored by two experienced readers, who both scored approximately half of the cohort. The intraclass correlation coefficient of all scorers was >0.90.

The second cohort is the French ESPOIR (Étude et Suivi des POlyarthrites Indifférenciées Récentes) cohort.[5] Between 2002 and 2005, 811 patients were enrolled. Inclusion criteria were the presence of inflammatory arthritis lasting for 6 weeks up to 6 months, involvement of >2 joints and the diagnosis by the rheumatologist as RA or RA-like (ie, a high suspicion of RA). Patients were excluded if they had other clearly defined inflammatory rheumatic diseases according to the rheumatologist. Regular and standardised follow-up was performed and included clinical, biological and radiographic data collection; data on the prescribed treatments were systematically compiled. A total of 700 patients had clinical and radiographic data available. The x-rays were scored by one experienced reader.

Definition of erosiveness

Baseline radiographs of bilateral hands and feet were scored using the Sharp-van der Heijde scoring method.[6] The unit of analysis in this study, however, does not relate to a number of Sharp-van der Heijde points but to an erosive joint, defined as a joint with at least one erosion. Erosion was defined as an interruption of the cortex of the bone. The scoring data were used to group patients according to the number of erosive joints; the categories were one, two, three, four, or five or more erosive joints. The CMC-bone with the os trapezium was considered as one joint. The radial and ulna bone together with the os scaphoid and the os lunatum were considered one joint as well (the wrist).

For subanalyses, patients were grouped per location of the erosions. The tested groups were: erosions only in PIPs, MCPs, MTPs or wrist. Combinations of groups were also considered; these were erosions in MCPs or MTPs; in MCPs, MTPs or PIPs; and in MCPs, MTPs, PIPs or wrist.

Outcome measures

RA is at present identified using phenotypic characteristics and not based on pathophysiological characteristics. Consequently, the 'gold standard' for RA is related to the phenotype and this implies elements of circularity. It was therefore decided to evaluate three outcome measures. In accordance with the data driven phase of the derivation of the 2010 criteria,[7] initiation of MTX therapy within the first year of follow-up was used as outcome measure. The other two outcomes were: use of any DMARD within the first year of follow-up and arthritis persistency over 5 years of disease. Initiation of any DMARD was studied since MTX was not the anchor drug in the Leiden-EAC before 2000; then hydroxychloroquine, penicillamine and sulfasalazine were more frequently prescribed. Consequently, studying only MTX initiation may give rise to misclassification. Arthritis persistency was defined by the absence of a sustained DMARD-free remission. This remission was present in case after cessation of eventual DMARD therapy no synovitis was detected for at least 1 year.[8] This outcome was chosen as persistency of the disease is a core feature of RA. Persistency data were available in 868 and 538 early arthritis patients (Leiden-EAC and ESPOIR, respectively).

Analyses

The sensitivity, specificity, positive and negative likelihood ratios, and the positive and negative predictive values, PPV and NPV, were determined. The discriminative ability was expressed using the area under the receiver operating characteristic curve. The specificity was the main test characteristics of interest as a high value reflects a low frequency of false positives. Second, the PPV may be informative as it reflects the chance of a correct classification in case of an individual with a positive test result.

Patients were grouped based on the number of erosive joints, using different cut-off values. Thus, patients who had a number of erosive joints equal to or above the cut-off were compared with patients with less erosive joints. Analyses were done for all three outcome measures. As MTX was not the anchor drug before 2000 in the Leiden-EAC, in this cohort a subanalysis was performed, evaluating the early arthritis patients who were included before or after 2000 separately, to determine the influence on the change in treatment strategy on the results.

The analyses were repeated on the early arthritis patients who had not fulfilled the 2010 ACR/EULAR criteria by having six points as this allows evaluation of the test characteristics in the patients in whom classification is entirely dependent on the radiological criterion. In the Dutch dataset, five patients had insufficient data to calculate the 2010 criteria and were therefore excluded.

Finally, it was determined what number of patients would additionally be classified with RA when evaluating radiological data in addition to the existing 2010 criteria for RA. The outcomes of these patients (frequency of MTX or any DMARD use in the first year and arthritis persistency over 5 years) were also evaluated.

RESULTS

Patients

The characteristics of the early arthritis patients of both cohorts are presented in table 1.

From the 902 patients in the Leiden-EAC, 352 (38%) received initial MTX therapy within the first year of the disease and 604 (65%) received any DMARD during the first year. Of the patients included before 2000, 73 (14%) were treated with MTX and 276 (53%) with any DMARD. Of the patients included from 2000 onwards, in contrast, 277 (73%) were

Table 1 Characteristics of the early arthritis patients studied who were included in the Dutch Leiden-Early Arthritis Clinic (Leiden-EAC) and Étude et Suivi des POlyarthrites Indifférenciées Récentes (ESPOIR)

Baseline	Leiden-EAC	ESPOIR
N	902	700
Age (mean±SD)	54±17	48±12
Female n(%)	596 (64)	538 (77)
SJC mean±SD	8±8	7±5
1 medium/large joint, n (%)	189 (21%)	125 (17.9%)
2–10 medium/large joints, n (%)	407 (45%)	398 (39.8%)
1–3 small joints, n (%)	183 (20)	91 (13%)
4–10 small joints, n (%)	292 (33)	256 (36.6%)
>10 joints, n (%)	321 (36)	407 (58.1%)
Anti-CCP2+ n (%)	350 (37)	280 (40)
IgM-RF+ n (%)	390 (42)	330 (47)
CRP (mg/l) mean±SD	27±34	20±33
Symptom duration at first presentation (mean±SD weeks)	26±34	31±37
ESR mean±SD	35±27	29±25

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; SJC, swollen joint count.

treated with MTX and 323 (85%) were treated with any DMARD. In all, 78% of the patients studied had persistent arthritis after 5 years of follow-up.

From the 700 patients in the French cohort, 473 (68%) received initial MTX therapy and 622 (89%) received any DMARD within the first year of the disease. In addition, 459 (85%) of the 538 early arthritis patients with data after 5 years of follow-up had persistent arthritis at that time.

Number of erosive joints in relation to MTX and DMARD initiation

The test characteristics were obtained with the patients with no or less erosive joints than the cut-off as reference group. The specificity increased with a higher number of erosive joints as cut-off value for RA-specific erosiveness (table 2). In the Dutch cohort, the specificity increased from 57% in the presence of ≥1 erosive joint to 88% in the presence of ≥5 erosive joints using MTX as outcome, and from 75% to 97% using any DMARD as outcome. The specificity obtained with MTX initiation as outcome was lower than the specificity obtained with any DMARD as outcome. To explore whether this was due to a lower MTX prescription before 2000, analyses were repeated on patients included before and after 2000 separately (see online supplementary table S1). Indeed, considerably higher specificity on the MTX analyses in the patients included after 2000 was observed, suggesting that initiation of any DMARD is a more appropriate outcome than MTX initiation when studying the entire Dutch cohort. The PPVs also increased with increasing cut-off values for RA-specific erosiveness; for instance, with any DMARD as outcome the PPV for ≥1 erosive joint was 75% and for ≥5 erosive joints 94% (table 2). Likewise, the LR+ increased from 2.90 in the presence of ≥1 erosive joint to 8.51 in the presence of ≥5 erosive joints.

In the French cohort, similar results were observed (table 2). For MTX use and any DMARD use as outcomes, the specificity was 51% and 57% for ≥1 erosive joint and 90% and 95%, respectively, in the presence of ≥5 joints. Similarly, the PPVs were 67% and 87% in the presence of ≥1 erosive joint; this increased till 73% and 94% for presence of ≥5 erosive joints for usage of MTX and DMARD as outcomes, respectively (table 2).

Table 2 Test characteristics of different cut-offs for the number of erosive joints with initiation of MTX or any DMARD during the first year as well as arthritis persistency over 5 years as outcome, in all early arthritis patients studied

		Leiden-EAC (n=902)*								ESPOIR (n=700)†							
Outcome	N erosive joints	N patients (%)‡	Sens	Spec	PPV	NPV	LR+	LR-	AUC	N patients (%)*	Sens	Spec	PPV	NPV	LR+	LR-	AUC
MTX	None	395			311												
	≥1 joint	507 (56)	0.77	0.57	0.53	0.79	1.78	0.41	0.67	389 (56)	0.60	0.51	0.67	0.43	1.23	0.78	0.56
	≥2 joints	387 (43)	0.64	0.71	0.58	0.76	2.19	0.51	0.68	261 (37)	0.41	0.69	0.69	0.41	1.35	0.84	0.55
	≥3 joints	307 (34)	0.51	0.77	0.58	0.71	2.19	0.63	0.64	177 (25)	0.29	0.80	0.71	0.40	1.48	0.88	0.55
	≥4 joints	227 (25)	0.40	0.84	0.62	0.69	2.51	0.72	0.62	133 (19)	0.21	0.85	0.71	0.39	1.44	0.92	0.53
	≥5 joints	179 (20)	0.32	0.88	0.64	0.67	2.74	0.77	0.60	96 (14)	0.16	0.90	0.73	0.39	1.61	0.93	0.53
DMARD	None	395						311									
	≥1 joint	507 (56)	0.72	0.75	0.85	0.57	2.90	0.37	0.74	389 (56)	0.58	0.57	0.87	0.21	1.34	0.74	0.57
	≥2 joints	387 (43)	0.57	0.86	0.89	0.50	4.03	0.50	0.72	261 (37)	0.40	0.75	0.88	0.20	1.56	0.81	0.57
	≥3 joints	307 (34)	0.46	0.89	0.89	0.45	4.09	0.61	0.67	177 (25)	0.28	0.86	0.91	0.19	2.04	0.84	0.57
	≥4 joints	227 (25)	0.35	0.93	0.91	0.42	5.21	0.70	0.64	133 (19)	0.21	0.90	0.91	0.19	2.04	0.88	0.55
	≥5 joints	179 (20)	0.28	0.97	0.94	0.40	8.51	0.74	0.62	96 (14)	0.15	0.95	0.94	0.18	3.04	0.89	0.55
PERSISTENCY	None	395				234											
	≥1 joint	473 (54)	0.60	0.64	0.85	0.31	1.67	0.62	0.62	304 (56)	0.59	0.56	0.85	0.25	1.34	0.73	0.58
	≥2 joints	358 (41)	0.47	0.80	0.89	0.30	2.41	0.65	0.64	202 (37)	0.40	0.74	0.87	0.23	1.55	0.81	0.57
	≥3 joints	283 (33)	0.38	0.85	0.90	0.28	2.63	0.72	0.62	135 (25)	0.27	0.85	0.88	0.22	1.78	0.86	0.56
	≥4 joints	209 (24)	0.29	0.92	0.92	0.27	3.45	0.78	0.60	98 (18)	0.20	0.90	0.90	0.21	2.10	0.88	0.55
	≥5 joints	169 (19)	0.24	0.95	0.94	0.26	4.55	0.81	0.59	70 (13)	0.15	0.96	0.94	0.21	3.95	0.88	0.56

This table describes the test characteristics when the cut-off of erosiveness was set at different number of erosive joints. Patients with equal or more number of erosive joints as specified were compared with patients with less erosive joints as specified. The predictive ability of each cut-off was tested against the initiation of MTX, any DMARD during the first year or disease persistency over 5 years.

*868 patients had sufficient follow-up to define persistency in the Leiden-EAC.

†538 patients had sufficient follow-up to define persistency in ESPOIR.

‡Number and percentage of patients positive in this analysis.

AUC, area under the receiver operating characteristic curve; DMARD, disease modifying antirheumatic drug; ESPOIR, Étude et Suivi des POlyarthrites Indifférenciées Récentes; Leiden-EAC, Dutch Leiden-Early Arthritis Clinic; MTX, methotrexate; NPV, negative predictive value; PPV, positive predictive value.

Number of erosive joints in relation to disease persistency over 5 years

In the Dutch cohort, the specificity of ≥1 erosive joint was 64% when evaluating disease persistency as outcome. This increased to 95% in the presence ≥5 erosive joints. Likewise, the PPV increased from 85% to 94%. Again, similar trends were observed in the French cohort; the specificity (≥1 till ≥5 erosive joints) ranged between 56% and 96% and the PPV between 85% and 94% (table 2).

Effect of site of erosive joints

The test characteristics were determined for the number of erosive joints in hands and feet separately; no tangible differences were observed (see online supplementary table S2). Next, every joint group (wrist, MCPs, PIPs or MTPs) was studied individually; different combinations of joint groups were also studied (see online supplementary table S3). The specificity, sensitivity and PPV observed were rather comparable with those obtained when both hands and feet were evaluated. Because the sites of the erosive joints did not affect the test characteristics or predictive values, further analyses were done evaluating both hands and feet combined.

Analyses in patients who did not meet six points

Next, the ACR/EULAR 2010 criteria were applied as previously described.[2] In the Dutch dataset, 66% of the patients met the ACR/EULAR 2010 criteria for RA. In the French data, 78% of the patients fulfilled the 2010 ACR/EULAR criteria by having at least six points. The analyses described above were repeated on the remaining 308 and 149 patients who did not meet the ACR/EULAR 2010 criteria (table 3). Also here specificity for each of the three outcome definitions (MTX use, DMARD use and persistent disease) increased with increasing number of erosive joints as cut-off to define RA-specific erosiveness. In the Dutch and French cohorts the specificity was 81% and 64% for ≥1 erosive joint, which values gradually increased till 99% and 98% in the presence of ≥5 erosive joints, with any DMARD use during the first year as outcome (see table 4).

The number of patients who would be additionally classified as RA based on the radiological criterion solely was evaluated and differed depending on the cut-off. When 'RA-specific erosiveness' would be defined as one erosive joint, 93 Dutch and 61 French patients would meet this criterion. However, when the cut-off would be three or five erosive joints, the numbers of patients were 36 and 14 in the Dutch cohort and 27 and 13 in the French cohort, respectively (table 3).

Finally, the outcomes of the patients who would be classified as RA based on the erosion criteria solely were studied. Only with the cut-off of ≥5 erosive joints, 100% of patients had persistent arthritis over 5 years. With lower cut-offs, this frequency decreased (table 3). Also here the results were similar in both cohorts.

DISCUSSION

The 2010 ACR/EULAR criteria were derived in order to classify RA at an earlier stage than with the 1987 ACR criteria. Several characteristics of the 1987 ACR criteria, such as erosions and nodules, made that these criteria are more characteristic of advanced RA than early RA. During the data driven phase of the derivation of the 2010 criteria, radiological information was explicitly not assessed, in order to prevent that baseline erosiveness would emerge again in the renewed criteria for RA. Nevertheless, in the later phases of the process it was agreed that presence of erosions in patients with a history compatible with RA could be used as prima facie evidence of RA. The present study describes our efforts to characterise such RA-specific radiographic aspects. The performance of the independent assessment of radiographs of hands and feet in predicting either the initiation of a specific treatment (ie, MTX or any DMARD) or the long-term persistency of the rheumatic disease, which can both be regarded as a surrogate for the diagnosis of RA, is presented. Obtaining a high sensitivity is relevant for the complete criteria set, when six points are required to fulfil the classification of the patient as having RA, because it is crucial that only a limited number of patients are inappropriately missed. Since it was intended that the radiological criterion would be used as an add-on to the existing criteria, sensitivity is not the main issue and it is most important to have a highly specific criterion to reduce the risk on false positive classification. This study reports the first, data driven approach of defining RA-specific erosiveness using long-term data from two independent early arthritis cohorts.

There exists no definitive standard which defines RA. To partly overcome this problem, the present study evaluated

Table 3 Characteristics and outcomes of patients who did not fulfil the 2010 ACR/EULAR criteria at baseline

		Baseline			1 year			5 years
Erosive joints (exact number)	N	N (%) female	N (%) ACPA+	Median number of points of 2010 criteria (min–max)*	N (%) MTX prescription within 1 year	N (%) DMARD prescription within 1 year	N (%) RA (1987) at 1 year†	N (%) persistent disease*
Leiden-EAC (n=308)								
2 erosive joints	14	9 (64)	0 (0)	4.0 (3–5)	4 (29)	9 (64)	6 (43)	8/14 (57)
3 erosive joints	14	11 (79)	3 (21)	4.0 (2–5	3 (21)	7 (50)	6 (43)	10/12 (83)
4 erosive joints	8	5 (63)	0 (0)	4.5 (1–5)	1 (13)	7 (50)	5 (63)	3/6 (50)
≥5 erosive joints	14	8 (57)	0 (0)	4.0 (1–5)	4 (29)	11 (79)	12 (86)	13/13 (100)
ESPOIR (n=149)								
2 erosive joints	11	10 (91)	0	5.0 (3–5)	3 (27)	5 (45)	5 (45)	3/7 (43)
3 erosive joints	11	5 (45)	0	4.0 (3–5)	5 (45)	7 (64)	7 (64)	4/6 (67)
4 erosive joints	3	1 (33)	1 (33)	5.0 (5–5)	2 (67)	2 (67)	2 (67)	1/3 (33)
≥5 erosive joints	13	8 (61)	0	4.0 (3–5)	5 (42)	11 (92)	7 (54)	9/9 (100)

*Persistency data were present of 299 patients in Leiden-EAC and of 101 patients in ESPOIR. Therefore, the total number of patients in this group was added. So 8/14 means that from the 14 patients who had two erosive joints, eight had persistent disease.
†Percentage of patients who fulfilled the diagnostic criteria for Rheumatoid Arthritis 1987 at 1-year follow-up.
ACR, American College of Rheumatology; DMARD, disease modifying antirheumatic drug; ESPOIR, Étude et Suivi des POlyarthrites Indifférenciées Récentes; EULAR, European League Against Rheumatism; Leiden-EAC, Dutch Leiden-Early Arthritis Clinic; MTX, methotrexate; RA, rheumatoid arthritis.

Table 4 Test characteristics of different cut-offs for the number of erosive joints with initiation of MTX or any DMARD during the first year as well as arthritis persistency over 5 years as outcome in the patients who did not fulfil the 2010 ACR/EULAR criteria at baseline by having six points

		Leiden-EAC n=308*								ESPOIR n=149†							
Outcome	**N erosive joints**	**N patients (%)‡**	**Sens**	**Spec**	**PPV**	**NPV**	**LR+**	**LR-**	**AUC**	**N patients(%)‡**	**Sens**	**Spec**	**PPV**	**NPV**	**LR+**	**LR-**	**AUC**
MTX	None	215		88													
	≥1 joint	93 (30)	0.64	0.73	0.19	0.95	2.40	0.49	0.69	61 (41)	0.48	0.63	0.44	0.67	1.32	0.82	0.56
	≥2 joints	50 (16)	0.43	0.86	0.24	0.94	3.16	0.66	0.65	37 (25)	0.27	0.76	0.40	0.63	1.13	0.96	0.51
	≥3 joints	36 (11)	0.29	0.90	0.23	0.93	2.96	0.79	0.60	26 (17)	0.21	0.85	0.46	0.64	1.42	0.92	0.53
	≥4 joints	21 (7)	0.18	0.94	0.24	0.92	3.13	0.87	0.56	15 (10)	0.12	0.91	0.47	0.63	1.45	0.96	0.52
	≥5 joints	14 (5)	0.14	0.97	0.31	0.92	4.44	0.89	0.56	12 (8)	0.08	0.92	0.42	0.63	1.19	0.98	0.51
DMARD	None	215		88													
	≥1 joint	93 (30)	0.57	0.81	0.55	0.82	2.99	0.53	0.69	61 (41)	0.44	0.64	0.66	0.43	1.25	0.86	0.54
	≥2 joints	50 (16)	0.35	0.91	0.62	0.78	4.01	0.71	0.63	37 (25)	0.28	0.80	0.67	0.42	1.36	0.91	0.54
	≥3 joints	36 (11)	0.25	0.94	0.61	0.75	3.87	0.80	0.59	26 (17)	0.22	0.90	0.77	0.43	2.18	0.86	0.56
	≥4 joints	21 (7)	0.17	0.97	0.71	0.74	6.15	0.85	0.57	15 (10)	0.14	0.97	0.87	0.42	4.26	0.88	0.55
	≥5 joints	14 (5)	0.12	0.99	0.85	0.74	13.53	0.88	0.56	12 (8)	0.12	0.98	0.92	0.42	7.21	0.89	0.55
PERSISTENCY	None	214		60													
	≥1 joint	85 (28)	0.30	0.76	0.57	0.50	1.23	0.93	0.53	41 (41)	0.46	0.66	0.63	0.48	1.34	0.82	0.56
	≥2 joints	45 (15)	0.20	0.91	0.70	0.51	2.19	0.88	0.56	25 (25)	0.30	0.82	0.68	0.47	1.64	0.86	0.56
	≥3 joints	31 (10)	0.15	0.95	0.77	0.51	3.14	0.89	0.55	18 (18)	0.24	0.91	0.78	0.48	2.70	0.83	0.58
	≥4 joints	19 (6)	0.09	0.98	0.82	0.50	4.28	0.93	0.53	12 (12)	0.17	0.95	0.83	0.47	3.86	0.86	0.56
	≥5 joints	13 (4)	0.07	1.00	1.00	0.50	/	0.93	0.54	9 (8.9)	0.16	1	1	0.48	/	0.84	0.58

*299 patients had data on disease persistency in Leiden-EAC.
†101 patients had data on disease persistency in ESPOIR.
‡Number and percentage of patients positive for erosiveness in this analysis.
ACR, American College of Rheumatology; AUC, area under the receiver operating characteristic curve; DMARD, disease modifying antirheumatic drug; ESPOIR, Étude et Suivi des POlyarthrites Indifférenciées Récentes; EULAR, European League Against Rheumatism; Leiden-EAC, Dutch Leiden-Early Arthritis Clinic; MTX, methotrexate; NPV, negative predictive value; PPV, positive predictive value.

three outcome measures. The first outcome was initiation of MTX therapy, which is similar to the derivation of the 2010 criteria. This outcome was suboptimal in the Dutch dataset where a large proportion of the patients was included and treated at a time when MTX was not the anchor drug. Therefore, use of any DMARD may be the most appropriate outcome measure in this cohort. The potential disadvantages of MTX use and any DMARD use as outcome are that they may include some level of circularity with the former RA criteria. In addition, these medications can also be prescribed for other chronic inflammatory diseases, such as psoriatic arthritis. In the present dataset, 10 Dutch patients and eight French patients were diagnosed with psoriatic arthritis during the first year after inclusion. Exclusion of these patients did not affect the results substantially (data not shown). The third outcome measure was disease persistency. Arthritis persistency over 5 years relates to chronicity and hence to a crucial feature of RA. It is known that about 10%–15% of RA patients achieve a sustained DMARD-free remission over time, on average after about 43 months of disease.[8] Nonetheless, despite the possible drawbacks of the individual outcome measures, the results of the present study are supported by the fact that comparable findings were observed in both cohorts and for different outcome measures.

Clinical data of 213 Leiden patients and 796 French patients were also used in the data driven phase of the derivation of the 2010 criteria.[7] Hence, the characteristics of the patients used to derive the clinical criteria resemble the characteristics of the patients used to derive the radiological criterion. However, the clinical criteria were derived on a much larger number of early arthritis patients (n=3315 in total).

The number of patients with high numbers of erosive joints was substantial; 20% (n=179) of the early arthritis patients included in the Dutch cohort and 14% (n=96) of the patients included in the French cohort had ≥5 erosive joints. However, the majority of these patients also met the 2010 ACR/EULAR criteria by having six or more points. Only 14 Dutch or 13 French patients would be classified with RA based on the radiological criterion only when defined as ≥5 erosive joints. When the cut-off would be ≥3 erosive joints, these numbers would be 36 and 27, respectively. Intriguingly, the majority of these patients were ACPA-negative. An advantage of the ≥5 erosion joint cut-off is that it was associated with 100% arthritis persistency in both cohorts; when lower cut-offs were chosen part of the patients achieved a sustained DMARD-free remission in the first 5 years of the disease. On the other hand, the specificity of the cut-off ≥3, ≥4 and ≥5 erosive joints were all above 90% in both cohorts.

A possible limitation is that the radiographs were scored by (experienced) readers who were not trained together and originated from different cohorts and countries. On the other hand, this adds to the generalisability of the results as the results are not dependent on one observer. Radiographs were initially scored according to the Sharp-van der Heijde method; these data were available and used to retrieve the number of erosive joints. This latter measure was studied as evaluation of the number of erosive joints is easily applicable in daily clinical practice.

A strength is the similarity of the results on the two datasets. Despite the completely independent collection of clinical and radiographic data, therapeutic strategies and radiographic scoring conducted in the Dutch and French cohorts, a remarkable consistency in data and interpretations was found for the numerous analyses that were conducted. Also the frequency of patients classified as RA being similar and the percentage of patients tending to reach remission are strong forces towards homogeneity in both cohorts.

In conclusion, a large amount of data on test characteristics and predictive values for different numbers of erosive joints on

radiographs of hands and feet were derived from two early arthritis cohorts. These data form the basis for the second phase in which a team of international expert rheumatologists has to obtain consensus on the definition of RA-specific erosiveness as a part of the 2010 ACR/EULAR criteria for RA.

Acknowledgements ESPOIR cohort: An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Abbott, Pfizer and Roche also supported the ESPOIR cohort study. We also wish to thank all the investigators who recruited and followed the patients (F Berenbaum, Paris-Saint Antoine, MC Boissier, Paris-Bobigny, A Cantagrel, Toulouse, B Combe, Montpellier, M Dougados, Paris-Cochin, P Fardenolonne et P Boumier Amiens, B Fautrel, Paris-La Pitié, RM Flipo, Lille, Ph Goupille, Tours, F Liote, Paris-Lariboisière, X Le Loet et O Vittecoq, Rouen, X Mariette, Paris Bicetre, O Meyer, Paris Bichat, A Saraux, Brest, Th Schaeverbeke, Bordeaux, J Sibilia, Strasbourg).

Contributors RK, CL, NR, BC and AHMvdH-vM collected the data. RK and CL performed the analyses. DvdH, BC and AHMvdH-vM supervised the project. All authors wrote and approved the manuscript.

Funding Leiden-EAC: The work of RK is supported by the Dutch Arthritis Association. The work of AHMvdH-vM is supported by The Netherlands Organization for Health Research and Development.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Aletaha D,** Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;**69**:1580–8.
2. **van der Linden MP,** Knevel R, Huizinga TW, *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.
3. **Cader MZ,** Filer A, Hazlehurst J, *et al*. Performance of the 2010 ACR/EULAR criteria for rheumatoid arthritis: comparison with 1987 ACR criteria in a very early synovitis cohort. *Ann Rheum Dis* 2011;**70**:949–55.
4. **de Rooy DP,** van der Linden MP, Knevel R, *et al*. Predicting arthritis outcomes—what can be learned from the Leiden Early Arthritis Clinic? *Rheumatology (Oxford)* 2011;**50**:93–100.
5. **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.
6. **van der Heijde D**. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000;**27**:261–3.
7. **Funovits J,** Aletaha D, Bykerk V, *et al*. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. *Ann Rheum Dis* 2010;**69**:1589–95.
8. **van der Woude D,** Young A, Jayakumar K, *et al*. Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts. *Arthritis Rheum* 2009;**60**:2262–71.