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Risk of rheumatoid arthritis development in patients with unclassified arthritis according to the 2010 ACR/EULAR criteria for rheumatoid arthritis

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ABSTRACT

Objective

Early recognition and treatment of RA is associated with an improved outcome. The 2010 ACR/EULAR criteria for RA identify RA patients earlier than the 1987 ACR criteria. Nevertheless, we recently observed that 24% of the 2010 unclassified arthritis (UA) patients develop RA during follow-up. Here we studied this frequency in other cohorts and evaluated the prognostic accuracy of ACPA and the Leiden prediction rule in 2010 UA patients.

Methods

The 2010 UA patients from three Early Arthritis Clinics were studied: 776 from Leiden, 121 from Birmingham and 322 from Amsterdam. Fulfilment of the 1987 ACR criteria during follow-up was studied as the primary outcome. DMARD prescription during the year and having a persistent course of arthritis over 7 years were studied as secondary outcomes in one cohort. The presence of ACPA and the prediction score at baseline were evaluated in relation to these outcomes.

Results

In the three cohorts, 24%, 26% and 12%, respectively, of the 2010 UA patients fulfilled the 1987 criteria after 1 year. However, some of these patients already fulfilled the 1987 criteria at baseline. In 1987 and 2010 UA patients, 15%, 21% and 9%, respectively, developed RA (1987) at 1 year. In these patients, 0-6% of the patients were ACPA positive and 0-1% had high prediction scores. Consequently a large majority of the UA patients with an unfavorable outcome was not recognized by these prognostic tools.

Conclusion

A proportion of 2010 UA patients progress to RA. ACPA and the Leiden prediction rule are not useful in identifying these patients. These results imply that other predictive markers should be developed for 2010 UA patients.

INTRODUCTION

Persistence of inflammation and destruction of joints are hallmarks of RA. Several observational cohort studies and clinical trials demonstrate that early initiation of treatment is associated with more remission and less joint destruction.[1-3] In order to initiate treatment early, adequate referral strategies are required, as well as tools that identify RA patients among all patients with early unclassified arthritis (UA)[4] Several biomarkers have been identified, of which ACPAs are among the most potent. Combining several risk factors resulted in the construction of prediction models; of these the Leiden prediction rule is widely validated.[5,6] However, these studies were performed in patients with UA when RA was defined using the 1987 ACR criteria.

Recently, the 2010 ACR/EULAR criteria for RA were developed. A major reason to derive new criteria was to obtain criteria that are fulfilled at an early stage of RA.[7] Current data show that the 2010 criteria are indeed fulfilled earlier than the 1987 criteria.[8-10] Consequently the group of patients classified as UA when the 2010 criteria are applied has changed. The so-called 2010 UA patients have milder characteristics at disease onset and as a group also have a less severe disease outcome.[8,10] Nonetheless, not all patients who are eventually diagnosed with RA fulfil the 2010 criteria at first presentation. We recently observed that 24% of the early 2010 UA patients fulfilled the 1987 criteria during the first year of followup.[11] Ideally these patients should also be identified at initial presentation in order to achieve early and individualized treatment strategies.

This study aimed to evaluate (i) the proportion of 2010 UA patients who fulfil the 1987 criteria during the first year of the disease in other independent early arthritis cohorts and (ii) the prognostic value of available prognostic markers (ACPA and the Leiden prediction rule) in 2010 UA patients in all three cohorts.

PATIENTS AND METHODS

Patients

The study comprised early arthritis patients of three different cohorts. First, patients from the Leiden Early Arthritis Clinic (EAC) cohort were studied. This population-based longitudinal cohort started in 1993 and included patients with arthritis of at least one joint and symptom duration <2 years. At first visit, questionnaires were completed, physical examination performed, radiographs taken and blood obtained for determination of CRP, ESR, IgM-RF and ACPA. Follow-up visits were performed yearly.[12]

The second studied cohort comprised patients from the Birmingham very early arthritis clinic that started in 2000. Patients were included in cases of clinical synovitis of at least one joint and symptom duration (of any symptom attributed by the rheumatologist to inflam-

matory arthritis) of 43 months with no prior DMARD treatment. At baseline, demographic data, physical examination and radiographs were obtained and blood was obtained for determination of CRP, ESR, IgM-RF and ACPA. Follow-up visits were performed at 1, 2, 3, 6, 12 and 18 months.[9]

Third, early arthritis patients from the EAC at the Jan van Breemen Research Institute/ Reade in Amsterdam, The Netherlands, which started in 1995, were studied. Patients were included with at least two swollen joints, symptom duration of <2 years and no prior DMARD treatment. Patients with OA, crystal arthropathy, SpA, SLE, SS and infectious arthritis were excluded. At baseline, demographic data were collected, physical examination was performed, radiographs were taken and blood was obtained for determination of CRP, ESR, IgM-RF and ACPA. Follow-up visits were performed at 3 month intervals during the first year (Table 1).[8]

Table 1: Baseline characteristics of '2010-UA-patients' in the three cohorts

Characteristic	Leiden-EAC* (n=776)	Birmingham-EAC** (n=121)	Amsterdam-EAC*** (n=322)
Age, mean±SD, years	50.3±17.2	47.9±18.3	50.1±15.0
Female sex, n (%)	443 (57.1)	65 (53.7)	197 (61.2)
Morning stiffness, median (IQR), min	30 (0-60)	30 (0-120)	30 (8-60)
Swollen joint count (66 joint count), median (IQR)	2 (1-5)	2 (1-3)	3 (1-5)
Tender joint count (68 joint count), median (IQR)	2 (1-6)	2 (1-4)	3 (1-5)
Localisation of affected joints			
Small joints hands/feet, n (%)	492 (66.1)	92 (76.0)	135 (41.9)
Symmetrical, n (%)	328 (47.7)	20 (16.5)	243 (75.5)
Upper extremities, n (%)	468 (69.8)	75 (62.0)	98 (30.4)
CRP, median (IQR), mg/l	8 (3-23)	17 (<5-45)	7 (3-21)
ACPA positive, n (%)	61 (9.6)	1 (0.8)	15 (4.7)
RF positive, n (%)	76 (9.9)	3 (2.5)	14 (4.3)

Except where indicated otherwise, values are the number (%) of patients. IQR = interquartile range, SD = standard deviation. Localisation of affected joint: 'upper extremities' stands for upper joints with or without involvement of the lower joints, whereas 'small joints' stands for smaller joints with or without involvement of the large joints.

*In the Leiden-EAC cohort, some data were missing, as follows: for morning stiffness, n=37; for swollen joint count (SJC), n=22; for tender joint count (TJC), n=337; for small joints involved, n=32, for symmetrical joint involvement, n=89; for upper extremity joints involved, n=106; for C-reactive protein (CRP), n=58; for anti-citrullinated-peptide antibodies (ACPA), n=143; for rheumatoid factor (RF), n=10.

**In the Birmingham-EAC, some data were missing, as follows: for morning stiffness, n=1, for CRP, n=4, for ACPA, n=3, for RF, n=8.

***In the Amsterdam-EAC cohort, some data were missing, for morning stiffness, swollen joint count (SJC), tender joint count (TJC), symmetrical joint involvement and upper extremity joints involvement, n=8.

In all three cohorts, the baseline diagnosis was assessed. First, other diagnoses were excluded, such as ReA, PsA, crystal arthropathy, SpA, SLE and sarcoidosis. Subsequently, RA was classified according to the 2010 criteria where radiologic information was not taken into account.[9,10] Then the remaining patients were classified as 2010 UA and were studied here. Furthermore, we evaluated which of the 2010 UA patients fulfilled the 1987 criteria at baseline. Patients who were classified as UA according to both the 1987 and 2010 criteria (1987 and 2010 UA patients) were also studied (see supplementary Fig. S1 for an overview, available at Rheumatology Online). All three cohorts obtained written informed consent from the participants. The studies were approved by the local medical ethic committees.

Outcome

Fulfilling the 1987 criteria during the first year of follow-up was the outcome measure studied. The 1987 criteria could be fulfilled cumulatively during follow-up. Although fulfilling the 1987 criteria may not be an early phenomenon, these criteria still reflect the core phenotype of RA. Since it can be argued that this outcome is subject to some degree of circularity, two other outcomes were studied in the Leiden dataset, DMARD initiation during the first year and disease persistency over 7 years of follow-up. Patients treated according to a randomized trial were not studied for the outcome DMARD initiation during the first year. Arthritis persistency was defined as the absence of a sustained DMARD-free remission, which was described as the absence of synovitis for at least 1 year after cessation of eventual DMARD therapy.[13]

Analysis

Analyses were done both on 2010 UA patients and 1987 and 2010 UA patients using SPSS version 17.0. The proportion of 2010 UA patients and 1987 and 2010 UA patients who progressed to RA was determined. ACPA positivity and the Leiden prediction score (grouped as score 46, >6 and <8 and 58) were evaluated in relation to the development of RA. The Leiden prediction model consists of nine items. Each prediction score varied from 0 to 14 and corresponded to the percent chance of developing RA. The higher the score, the higher the chance of progressing to RA. A score of 46 is associated with a negative predictive value (NPV) of 91% and a score 58 with a positive predictive value (PPV) of 84%. The area under the receiver operator characteristic curve (AUC) was determined; the prediction score was analyzed as continuous variable.

RESULTS

In total, 1219 2010 UA patients, originating from three different early arthritis clinics, were studied: 776 from Leiden, 121 from Birmingham and 322 from Amsterdam (see supplementary Fig. S1 for an overview, available at Rheumatology Online). In these three cohorts, 24%, 26% and 12% of the 2010 UA patients, respectively, fulfilled the 1987 ACR criteria during the first year of follow-up.

As a proportion of the 2010 UA patients fulfilled the 1987 criteria at baseline (103, 7, 86 patients in the three cohorts, respectively), progression to RA was subsequently studied in the subgroup of patients who were classified as UA according to both sets of criteria. Now 673, 114 and 236 1987 and 2010 UA patients were studied, of whom 15%, 21% and 9%, respectively, progressed to RA.

Next, we evaluated the extent to which UA patients who fulfil the 1987 criteria during follow-up could be identified at baseline using ACPA or the Leiden prediction rule. First, 2010 UA patients were studied. The frequency of ACPA positivity in the different cohorts with 2010 UA patients varied between 0% and 7%. When evaluating the prediction scores, it was observed that a prediction score of 58 was seldom obtained. The AUC of ACPA ranged between 0.49 and 0.60 and that of the prediction score between 1.59 and 0.81.

Subsequently, the 1987 and 2010 UA patients were evaluated. The frequency of ACPA positivity or high prediction scores was even lower here (Table 2). This prohibited determination of PPVs and reduced the clinical utility of these markers in these patients. The NPVs of ACPA were 83%, 79% and 91%, respectively. The NPVs of prediction scores 46 were 88%, 81% and 90%, respectively. Although these NPVs seem adequate, these chances were comparable to the prior chances of not developing RA, which were 85%, 79% and 91%, respectively. The AUCs of both predictive markers ranged between 0.49 and 0.55 for the ACPA and between 0.53 and 0.78 for the prediction score (supplementary Table S1, available at Rheumatology Online).

Since we observed that the majority of 1987 and 2010 UA patients who progressed to RA within the first year of follow-up were ACPA negative and had low prediction scores, we studied the baseline characteristics of these patients in more depth. This revealed an overall milder phenotype at baseline of 1987 and 2010 UA patients who did not progress to RA compared with those who did (supplementary Table S2, available at Rheumatology Online).

The main outcome studied was fulfilling the 1987 ACR criteria after 1 year of follow-up. DMARD initiation during year 1 and disease persistency over 7 years (absence of sustained DMARD-free remission) were also assessed as secondary outcomes. During the first year, 39% of the 2010 UA patients and 34% of the 1987 and 2010 UA patients initiated a DMARD. Over the 7-year follow-up in the Leiden dataset, 54% of the 2010 UA patients

Table 2: Stratification of ACPA positivity and the Leiden prediction score in relation to the development of RA in '2010-UA-patients' as well as in '2010-UA-and-1987-UA-patients' in three different cohorts.

			Leiden EAC*						Birmingham EAC**		Amsterdam EAC***	
			RA-1987 at 1 yr		DMARD initiation at 1 yr		Persistent disease 7 yr		RA-1987 at 1 yr		RA-1987 at 1 yr	
			-	+	-	+	-	+	-	+	-	+
2010-UA	ACPA positivity	-	439 *(69%)*	133 *(21%)*	263 *(62%)*	141 *(33%)*	168 *(44%)*	200 *(52%)*	87 *(74%)*	30 *(25%)*	268 *(83%)*	39 *(12%)*
		+	18 *(3%)*	43 *(7%)*	9 *(2%)*	12 *(3%)*	4 *(1%)*	14 *(4%)*	0 *(0%)*	1 *(1%)*	14 *(4%)*	1 *(0%)*
	Prediction rule score	≤6	547 *(70%)*	110 *(14%)*	311 *(58%)*	176 *(33%)*	180 *(43%)*	206 *(49%)*	79 *(69%)*	21 *(18%)*	213 *(68%)*	28 *(9%)*
		>6 and <8	42 (5%)	49 *(6%)*	18 *(3%)*	26 *(5%)*	11 *(3%)*	17 *(4%)*	4 *(4%)*	10 *(9%)*	60 *(19%)*	11 *(4%)*
		≥8	1 *(0%)*	27 *(3%)*	1 *(0%)*	3 *(1%)*	1 *(0%)*	3 *(1%)*	0 *(0%)*	0 *(0%)*	1 *(0%)*	0 *(0%)*
2010-UA & 1987-UA	ACPA positivity	-	425 *(79%)*	84 *(16%)*	259 *(67%)*	113 *(29%)*	159 *(46%)*	176 *(51%)*	87 *(78%)*	23 *(21%)*	202 *(86%)*	20 *(8%)*
		+	17 *(3%)*	13 *(2%)*	8 *(2%)*	7 *(2%)*	3 *(1%)*	9 *(3%)*	0 *(0%)*	1 *(1%)*	13 *(6%)*	1 *(0%)*
	Prediction rule score	≤6	524 *(78%)*	69 *(10%)*	301 *(61%)*	148 *(30%)*	168 *(43%)*	187 *(48%)*	79 *(74%)*	18 *(17%)*	170 *(75%)*	18 *(8%)*
		>6 and <8	47 *(7%)*	26 *(4%)*	22 *(4%)*	21 *(4%)*	15 *(4%)*	15 *(4%)*	4 *(4%)*	6 *(6%)*	36 *(16%)*	2 *(1%)*
		≥8	1 *(0%)*	6 *(1%)*	2 *(0%)*	0 *(0%)*	0 *(0%)*	2 *(1%)*	0 *(0%)*	0 *(0%)*	1 *(0%)*	0 *(0%)*

*Leiden-EAC: 2010-UA n=776 (ACPA status n=633), 2010-UA&1987-UA n=673 (ACPA status n=539). Persistent disease: 2010-UA n=418 (ACPA status n=386), 2010-UA&1987-UA n=387 (ACPA status n=347)

**Birmingham-EAC: 2010-UA n=121 (ACPA status n=118, prediction rule n=114), 2010-UA&1987-UA n=114 (ACPA status n=111, prediction rule n=107).

***Amsterdam-EAC: 2010-UA n=322 (prediction rule n=313), 2010-UA&1987-UA n=236 (prediction rule n=227).

Except where indicated otherwise, values are the number (%) of patients.

and 53% of the 1987 and 2010 UA patients had persistent disease. However, with these outcomes the majority of patients with DMARD initiation and/or persistent arthritis were not recognized by ACPA or the prediction model, which was due to the low prevalence of ACPA and high prediction scores in these UA patients (Table 2).

DISCUSSION

This study evaluated the frequency of development of RA (1987 criteria) in 2010 UA patients in three independent cohorts and showed that a large number of 2010 UA patients fulfil the 1987 criteria during follow-up. Second, it was evaluated whether ACPA or a previously derived prediction rule is useful in identifying which 2010 UA patients will progress to RA (1987). Analyses on 2010 UA patients from three clinics consistently revealed that the majority of patients were ACPA negative and had low prediction scores, indicating that they are not relevant prognostic markers in UA (2010 criteria).

The very low frequency of ACPA positivity or of high prediction scores may be explained by the fact that ACPA and the majority of variables composing the prediction rule are also included in the 2010 criteria and hence have already been used for classification. Apparently, after having been used for risk estimation via the 2010 criteria, neither ACPA nor the prediction rule is able to subsequently identify the individual patients who are missed by the 2010 criteria.

It was observed that some of the 2010 UA patients already fulfil the 1987 criteria at baseline. These data confirm previous reports, showing that not all 1987 RA patients are classified as RA according to the 2010 criteria[9, 10]. This may suggest that it is appropriate to use both the 2010 and 1987 criteria in individual patients. Finally, we studied 1987 and 2010 UA patients; the findings regarding ACPA and the prediction rule in these patients were comparable to those in the 2010 UA patients.

A strength of the present study is that three different early arthritis cohorts were studied. These cohorts had slightly different inclusion and exclusion criteria, which can be seen as a limitation. Despite this heterogeneity, the observed findings were remarkably similar between cohorts, strengthening the validity of the findings and the conclusion that ACPA and the Leiden prediction rule are not accurate prognostic tools in 2010 UA patients.

There are several caveats to this study. A potential drawback is that the replication cohorts were smaller than the first cohort. On the other hand, as mentioned, the trend in the data is comparable in all three cohorts, suggesting that the results regarding ACPA and the prediction rule are not false negatives. Second, a majority of the patients studied were enrolled when aggressive DMARD treatment of UA was uncommon. Nonetheless, we cannot exclude that some of the patients who were classified as not fulfilling the 1987 criteria during follow-up are misclassified due to DMARD treatment. This implies that the

actual proportion of UA patients who have an early form of RA is even higher. However, in this scenario, the conclusions regarding the studied predictive markers would not change. Third, in a portion of the Leiden patients, ACPA data were not available, especially on those UA patients who did not progress to be 1987 criteria positive over time. Theoretically some of the patients may have been falsely classified as 2010 UA at baseline. However, considering the similarity in results between the cohorts, this influence is probably small.

In conclusion, a proportion of 1987 RA patients were not identified at baseline by the 2010 criteria. Assuming also that in UA patients who fulfil the RA criteria later in time a window of opportunity effect is present, these patients are preferably identified at baseline to this end. The ACPA test and the Leiden prediction rule are also not useful in identifying these patients. Hence other prognostic markers are needed with significantly different sensitivity and specificity characteristics to clinical examination; these may include imaging modalities such as ultrasound or extremity MRI.[14,15]

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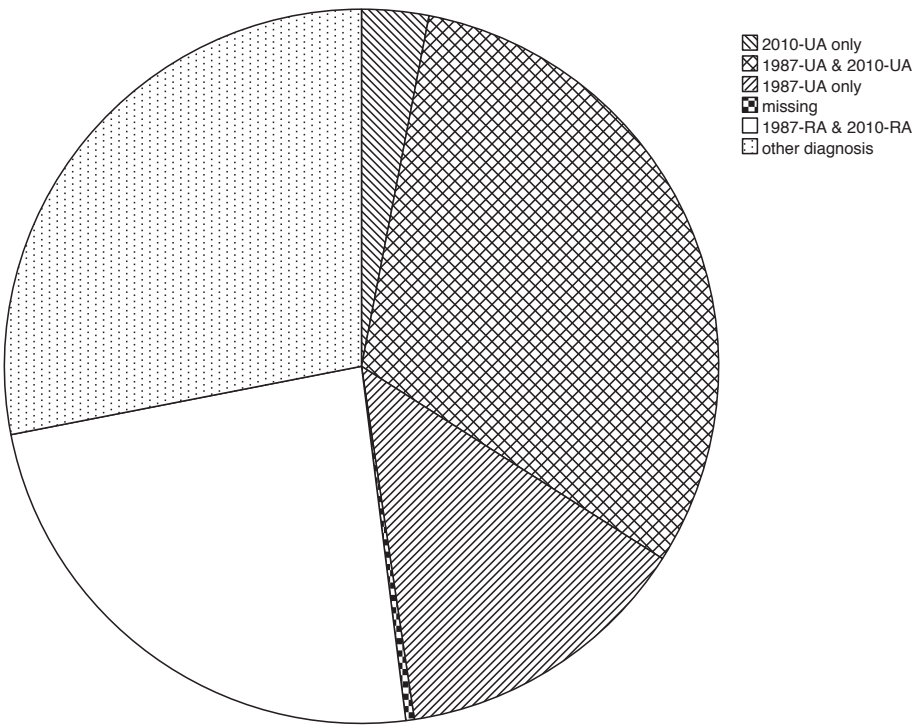
Supplementary table 1: The area under the receiver operator characteristic curve (AUC) of anti-CCP antibodies and the prediction score in '2010-UA-patients' and '1987-and-2010-UA-patients' from each of the three cohorts

	Leiden-EAC		Birmingham-EAC		Amsterdam-EAC	
	2010-UA (n=776)	1987-UA & 2010-UA (n=673)	2010-UA (n=121)	1987-UA & 2010-UA (n=114)	2010-UA (n=322)	1987-UA & 2010-UA (n=236)
Anti-CCP-positivity	0.60±0.03	0.55±0.03	0.52±0.06	0.52±0.07	0.49±0.05	0.49±0.07
Prediction rule score	0.81±0.02	0.76±0.02	0.81±0.04	0.78±0.05	0.59±0.04	0.53±0.06

Expressed are AUC +/- standard error (SE). The AUC of anti-CCP positivity was dichotomously evaluated. The AUC of the prediction rule was evaluated on the full range of scores (not categorized).



Supplementary Figure 1. In total 2,472 early arthritis patients from the Leiden EAC were studied. 772 patients were diagnosed other than unclassified arthritis or RA. Subsequently, RA was classified according to the 2010 criteria and the remaining patients were classified as 2010-UA. This resulted in 776 2010-UA patients from the Leiden EAC. 673 of these 2010-UA patients were also classified as UA according to the 1987 criteria; the '1987-UA & 2010-UA patients'. In the 4 'missing' patients only one serological test and one acute-phase response measure was obtained and therefore they could not be classified according to the 2010 criteria. The same classification was performed in the other two cohorts and resulted in 121 2010-UA patients in the Birmingham cohort and 322 2010-UA patients in the Amsterdam cohort.

Supplementary Table 2: Baseline characteristics of patients with undifferentiated arthritis by both 1987-criteria and 2010-criteria who either eventually fulfilled (RA) or did not fulfill (non-RA) the 1987-criteria during one year follow-up, in three different cohorts.

Characteristic	Leiden-EAC (n=673)		Birmingham-EAC (n=114)		Amsterdam-EAC (n=236)	
	RA (n=101)	Non-RA (n=572)	RA (n=24)	Non-RA (n=90)	RA (n=21)	Non-RA (n=215)
Morning stiffness, median (IQR) in minutes	60 (20-120)#	15 (0-60)#	90 (15-180)†	30 (0-60)†	10 (3-53)	15 (5-60)
Swollen joint count (66 joint count), median (IQR)	4 (2-6)#	2 (1-3)#	4 (2-5)†	2 (1-2)†	2 (1-4)*	2 (1-4)*
Tender joint count, median (68 joint count) (IQR)	5 (3-8)#	3 (1-5)#	4 (2-6)†	2 (1-3)†	2 (1-3)*	2 (1-5)*
ESR, median (IQR) mm/hour	24 (8-41)†	14.5 (7-32)†	18 (7.5-54)	17 (6.0-39.0)	14 (5-32)	19 (6-35)
CRP, median (IQR) mg/liter	8 (3-35.3)	7 (3-20)	14 (3-42.5)	16 (<5-47)	9 (2-23)	6 (2-21)
RF positive	11 (11)†	30 (5.3)†	2 (0.9)	1 (0.0)	2 (9.5)	12 (5.6)
ACPA positive	13 (13.4)#	17 (3.8)#	1 (0.4)	0	1 (4.8)	13 (6.0)
HAQ, mean ± SD	0.9±0.7#	0.7±0.6#	n.a.	n.a.	0.6±0.5	0.7±0.6
2010-criteria score, mean ± SD	4±1.1#	3±1.4#	4.1±0.7#	2.6±1.2#	4±0.8	4±1.1

*Leiden-EAC: 2010-UA n=776 (ACPA status n=633), 2010-UA&1987-UA n=673 (ACPA status n=539). Persistent disease: 2010-UA n=418 (ACPA status n=386), 2010-UA&1987-UA n=387 (ACPA status n=347)

**Birmingham-EAC: 2010-UA n=121 (ACPA status n=118, prediction rule n=114), 2010-UA&1987-UA n=114 (ACPA status n=111, prediction rule n=107).

***Amsterdam-EAC: 2010-UA n=322 (prediction rule n=313), 2010-UA&1987-UA n=236 (prediction rule n=227).

Except where indicated otherwise, values are the number (%) of patients. IQR = interquartile range, SD = standard deviation. *28 joint count. Characteristics were tested between RA and non-RA, per cohort. A chi-square test was used for nominal variables and the Student's t-test or Mann-Whitney U-test for continuous variables. Student's t-test was performed when variables are presented as mean and a Mann-Whitney U-test was performed when variables are presented as median. †p-value <0.05 and #p-value <0.001.