

## MARKERS OF PROGRESSION TO RHEUMATOID ARTHRITIS: DISCRIMINATIVE VALUE OF THE NEW ACR/EULAR RHEUMATOID ARTHRITIS CRITERIA IN A PORTUGUESE POPULATION WITH EARLY POLYARTHRITIS

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### Abstract

**Objectives:** Our goal was to test the performance of the new American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for the classification of rheumatoid arthritis (RA) in a cohort of patients with very recent onset polyarthritis.

**Patients:** Untreated polyarthritis patients with less than 6 weeks of duration were enrolled. All patients were followed-up in order to establish a definitive diagnosis.

**Results:** Thirty-seven patients were included. During the follow up 57% of the patients evolved to RA. The median age of the RA-group patients was similar to the median age of the non-RA group (median (IQR) 47 (31-58.5) vs 43 (34-69) years,  $p=0.74$ ). At the initial visit the DAS 28 in the RA group was significantly higher than in the non-RA group, as well as the visual analogue scale (VAS), the HAQ and the number of swollen joints. Among the 21 RA patients, 43% presented RF and 28.6% presented anti-citrullinated protein antibody (ACPA) in the first visit. RF and ACPA were not detectable in any of the patients who did not evolve to RA. According to the new ACR/EULAR criteria, the mean total score of the RA group at baseline was significantly higher than the non-RA group (median (IQR) 6 (4.5-8) vs 4.5 (2.2-6),  $p=0.007$ ).

**Conclusion:** In our cohort high DAS28, swollen

joint count, VAS and HAQ and the presence of RF or ACPA were eventually associated with the evolution into RA. The new ACR/EULAR criteria for the classification of RA seem to perform well in very early RA.

**Keywords:** Rheumatoid Arthritis; Very Early Polyarthritis; ACR/EULAR Classification criteria.

### Introduction

Up to 30% to 50% of the patients attending a rheumatology clinic present arthritis of recent onset<sup>1</sup>. The definition of early arthritis is not precisely clear and, consequently, recent-onset arthritis cohorts differ in disease duration at entry (between 4 weeks and 24 months)<sup>2-5</sup>. Moreover, recent-onset arthritis exhibits considerable clinical and prognostic variability, as it may progress to established rheumatoid arthritis (RA), evolve to other inflammatory arthropathies, remain undifferentiated or, in opposite, it may also enter spontaneous remission. To achieve the best possible outcome, patients with early arthritis must be identified and treated aggressively<sup>6-11</sup>. In fact, European League Against Rheumatism (EULAR) recently recommended that patients presenting with arthritis of more than one joint should be referred to and observed by a rheumatologist, ideally within 6 weeks after the onset of symptoms<sup>12</sup>. Due to the current lack of reliable methods of differentiating between RA and other inflammatory joint diseases during the first weeks of symptoms<sup>13</sup>, the diagnosis of these early arthritis patients is often uncertain in clinical practice<sup>14</sup>.

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It is well known that the 1987 American College of Rheumatology (ACR) classification criteria for RA<sup>15</sup>, which were developed based on patients with established RA, are weak predictors for the development of RA in early polyarthritis patients<sup>16</sup>. Thus, a taskforce constituted by rheumatologists from Europe and North America developed new classification criteria for RA that allows earlier identification of cases, focusing in variables that predict evolution to a chronic arthritis. The final goal was the early beginning of an adequate treatment to prevent progression of the disease<sup>17</sup>. Another relevant point was that the criteria were aimed to be useful and understandable for primary care physician's referral and not just for specialists.

The new criteria for the classification of RA<sup>17</sup> focus on some parameters that were absent from the previous criteria, such as anti-citrullinated protein antibody (ACPA) testing. The criteria are mainly based on 4 topics: number and localization of joints affected, disease duration, acute phase response (erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)), and presence and level of rheumatoid factor (RF) and ACPA. These criteria were developed based on 6 European cohorts: Netherlands (Amsterdam and Rotterdam), Austria, France, United Kingdom (Manchester) and Norway, and validated in 3 additional populations (Leeds, Leiden and Toronto). As described, the large majority of the cohorts were originated from North Europe, and three even came from the same country (Netherlands). As the authors emphasized these criteria need to be tested in other populations. Moreover publications applying the criteria are useful for its divulgation and increase worldwide use. It is also necessary to test them in cohorts with different inclusion criteria. In this study we applied the new RA classification criteria to a Portuguese untreated polyarthritis cohort with less than 6 weeks of disease duration, representing the characteristics of a Southern European population.

The goal of our work was to test the performance of the new ACR/EULAR criteria for the classification of RA in a cohort of patients with a very recent onset polyarthritis (less than 6 weeks of arthritis).

## Patients and Methods

Patients presenting with more than 4 tender and/or swollen joints with less than 6 weeks of disease duration coming from the Emergency Room and

from the Rheumatology outpatient clinic of Santa Maria Hospital were consecutively enrolled in this study during a period of 5 years (2005-2009). They were not exposed previously to corticosteroids or disease modifying anti rheumatic drugs (DMARDs). All the patients with very early arthritis were prospectively followed during the study period, in order to establish a definitive clinical diagnosis. The minimum follow-up time for each patient was 10 months.

Patients were excluded if the disease presentation was monoarthritis or oligoarthritis, if disease duration exceeded 6 weeks at the recruitment date and if they were already medicated with corticosteroids or DMARDs.

A protocol was applied (PMAR)<sup>18</sup>, including demographic and clinical data, the number of swollen and tender joints using the 66/68 joint assessment, the visual analogue scale (VAS) of global health as assessed by the patient and ESR to calculate the disease activity score of 28 joints (DAS28).

The health assessment questionnaire (HAQ)<sup>19</sup> was also completed at the first visit. A blood sample was collected to assess laboratorial parameters, namely ESR, RF and ACPA levels, before any treatment was started. During follow up, patients were divided in two groups, according to the final diagnosis: RA (defined both by the clinician opinion and by the 1987 ACR criteria) *vs* non-RA group. After the initial visit (first visit), patients were observed 4-6 weeks after starting low dose prednisone (5-10 mg) (2<sup>nd</sup> visit) and, if applicable, 4 months after reaching the minimum effective dose of MTX (3<sup>rd</sup> visit) Patient's management was done in accordance with the standard practice. At the end of the study period all the included patients were submitted to a final clinical evaluation (final visit).

This study was approved by the local Ethics committee and all patients gave written informed consent to participate. The follow-up was performed in accordance with the Helsinki declaration.

## Statistical analysis

The continuous variables were described as median and interquartile range, whereas categorical variables were presented as frequencies. Univariate analysis and statistical differences between continuous RA and non-RA variables groups were determined by the non-parametric Mann-Whit-

**Table I. Baseline differences between patients who latter evolved to RA (RA-group), comparing to who did not (non-RA group)**

Parameter	RA	Non-RA	p-value
n	21	16	
DAS28	6.2 (5.2-7.3)	5.1 (4.3-6.1)	0.018*
VAS	60 (50-89.5)	46 (30-60)	0.045*
Swollen joints	8 (3-20)	2 (0-9.7)	0.024*
Tender joints	10 (4.5-20)	5.5 (4-17.7)	0.191
Total involved joints	12 (8-19)	11 (4-18)	0.580
CRP	2.74 (1.7-4.3)	2.1 (0.1-4.8)	0.810
ESR	37 (26.5-63.5)	25 (19.5-60)	0.419
HAQ	1.9 (1-2)	0.87 (0.25-1)	0.020*

\*p-value <0.05 in univariate analysis performed using Mann-Whitney test; n: number of patients; DAS28: Disease Activity Score 28; VAS: Visual Analogue Scale; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RA: Rheumatoid arthritis. Values are expressed as median and interquartile range: median (IQR).

ney test. Generalized linear model (GLM) for repeated measures was used to detect differences between the follow-up visits within the RA group. Contingency tables with discrete variables were analysed by the Fisher's exact test. Sensitivity and specificity using the cut-off criteria of 6 and of 7 points in our population was calculated. All the analysis was done using GraphPad Prism (Graph-Pad, San Diego, CA). Differences were considered statistically significant for  $p < 0.05$ .

## Results

Thirty-seven patients with untreated early polyarthritis with less than 6 weeks duration were included. The mean age of the group was  $48 \pm 18$  years [median: 47, inter-quartile range (IQR) 32-62 years], and 68% (25 out of 37) were females. All the patients were Caucasian from European origin. The mean follow-up time was  $33.2 \pm 11.2$  (10-48) months. During the follow up period most of the patients evolved to RA (twenty-one individuals, 57%) (Table I). The remaining patients evolved to other diseases as can be detailed in Table II.

### RA vs NON-RA PATIENTS

The median age of the patients who evolved to RA

**Table II. Diagnosis of the patients included in the non-RA group**

Diagnosis	Number of patients
Self-limited arthritis	5
Gouty arthritis	3
Paraneoplastic arthritis	2
Systemic lupus erythematosus	2
Psoriatic arthritis	2
Polymialgia rheumatica	1
HIV-related arthritis	1
<b>Total</b>	<b>16</b>

(the RA-group) was similar to the median age of the patients who developed other diagnosis (non-RA group) [median (IQR) 47 (31-58.5) vs 43 (34-69) years, respectively,  $p = 0.74$ ].

The majority of patients in the RA group were females (81%), as opposed to the non-RA group (50% females) ( $p = 0.077$ ).

The global initial mean DAS 28 was  $5.8 \pm 1.4$ . At the initial visit the median DAS 28 in patients who have latter evolved to RA was significantly higher than in the non-RA patients [median (IQR) 6.2 (5.2-7.3) vs 5.1 (4.3-6.1), respectively;  $p = 0.018$ ] (Table I). VAS was also higher in the RA group [median (IQR) 60 (50-89.5) vs 46 (30-60), respectively;  $p = 0.045$ ], as well as the number of swollen joints [median (IQR) 8 (3-20) vs 2 (0-9.7);  $p = 0.024$ ], when compared to the non-RA group.

We did not find significant differences in the number of tender joints in both groups [median (IQR) 10 (4.5-20) vs 5.5 (4-17.7), respectively;  $p = 0.19$ ]. The involvement of hands and wrists (pain or swelling of finger joints or wrists) was also similar in the RA and non-RA groups (*data not shown*).

Among the 21 RA patients, 21 were evaluated for RF and 17 for ACPA in the first visit. Of these, 9 (43%) presented RF and 6 (28.6%) presented ACPA in the serum. Importantly, RF and ACPA were not detectable in any of the patients who did not evolve to RA ( $p = 0.0019$  and  $p = 0.0177$ , respectively).

The initial ESR values did not differ significantly between RA and non-RA groups [median (IQR) 37 (26.5-63.5) vs 25 (19.5-60),  $p = 0.419$ ] (Table I).

At baseline ESR was normal (<20 mm/h) in 20% patients.

At the first visit, the RA group had a higher functional impairment when compared to the non-RA group, as it was shown by the HAQ values [median

(IQR) 1,87 (1-2) *vs* 0,87 (0.25-1), respectively;  $p=0.020$ ] (Table I).

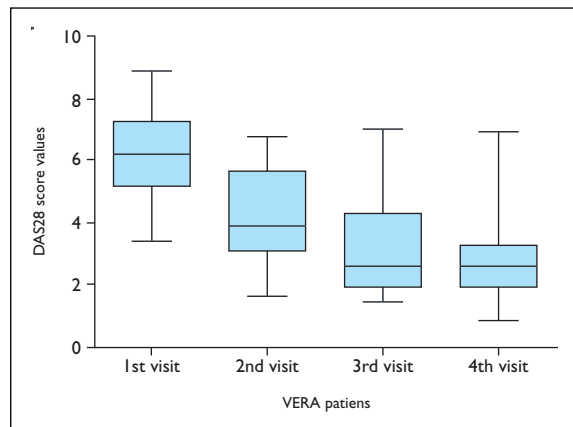
## EARLY RA-group EVALUATION

In the RA cohort, at the initial visit the median (IQR) DAS 28 was 6.2 (5.2-7.3). We found no differences in DAS 28 between patients with or without detectable serum RF [median (IQR) 6.2 (4.8-6.6) *vs* 6.7 (4.9-7.8), respectively;  $p=0.436$ ], and between ACPA positive or negative patients [median (IQR) 5.7 (3.8-6.8) *vs* 6.7 (4.9-7.8), respectively;  $p=0.313$ ]. We also compared the mean value of HAQ of these groups, however no differences were found between RF positive and RF negative patients [median (IQR) 1.6 (1.1-1.8) *vs* 1.2 (0.75-1.8), respectively;  $p=0.495$ ], or when comparing ACPA positive and ACPA negative patients [median (IQR) 2.0 (1.5-2.0) *vs* 1.6 (0.8-2.0), respectively;  $p=0.333$ ].

The DAS28 after starting prednisone (2<sup>nd</sup> visit) was significantly lower than that at the initial visit [median (IQR) 3.8 (3.1-5.7) *vs* 6.1 (5.2-7.3), respectively;  $p=0.0008$ ]. Between the initial visit and the visit after starting prednisone treatment, five patients had an EULAR good response, five patients had an EULAR moderate response and eight patients did not reach an EULAR response<sup>20</sup>.

After 4 months of a stable dose of MTX (3<sup>rd</sup> visit) the mean DAS28 was significantly lower when comparing to DAS28 before starting MTX treatment [median (IQR) 2.6 (1.9-4.3) *vs* 3.8 (3.1-5.7);  $p=0.021$ ] (Figure 1) and only 3 patients maintained a DAS28 >3.2. An EULAR good response (20) occurred after starting MTX treatment in eight patients, in two patients a moderate response occurred and two patients had no EULAR response. The 3 patients that still had a DAS28>3.2 received combination therapy with sulphasalazine and hydroxychloroquine, with further reduction of DAS28 below 3.2. In the 4<sup>th</sup> visit, after a mean follow up of 33 months, the mean DAS28 was of  $2.84 \pm 1.39$ . The majority of our RA patients responded with a moderate or good EULAR response to low dose corticosteroids and MTX (in monotherapy or combined DMARD therapy). At the final visit, the mean DAS28 was significantly lower when compared to baseline evaluation [median (IQR) 2.6 (1.9-3.2) *vs* 6.2 (5.2-7.3), respectively;  $p=0.0003$ ]. The mean DAS28 reduction between all the visits was always statistically significant.

The presence of RF or ACPA did not influence



**Figure 1.** Median values of DAS28 in early RA cohort at the different time-points evaluated

Legend – DAS28: Baseline (1st visit), 4-6 weeks after starting prednisone (2nd visit), 4 months after MTX (3rd visit) and at the final evaluation (4th visit) after a mean follow up of 33 months of the RA-group of patients. At the final visit, the mean DAS28 was significantly lower when compared to baseline evaluation ( $p=0.0004$ ). The mean DAS28 reduction between all the visits was always statistically significant.

the final DAS28: we found no difference when comparing RF positive and RF negative patients [median (IQR) 2.9 (1.9-4.2) *vs* 2.5 (1.9-2.8), respectively;  $p=0.464$ ], or when comparing ACPA positive and ACPA negative patients [median (IQR) 2.4 (1.8-3.6) *vs* 2.6 (2.3-3.1), respectively;  $p=0.859$ ].

## Discriminative value of the new ACR/EULAR Criteria for the classification of rheumatoid arthritis in a very early arthritis population

The new ACR/EULAR criteria for the classification of RA are mainly based on 4 items: number and localization of affected joints, disease duration, levels of acute phase reactants (ESR and CRP), and presence and title of RF and ACPA.

As previously observed the total number of involved joints (tender and/or swollen joints) was not significantly higher in the RA group [median (IQR) 12 (8-19) *vs* 11 (4-18),  $p=0.58$ ] when compared with the non RA group. Taking into consideration the median joint counts, the two groups scored 5 in the joint involvement category and individually there were 12 (57.1%) patients scoring 5 in the RA group and 8 (50%) patients reaching the same score in the non RA group.

All patients had zero points in the “disease duration” category of the criteria, as all included pa-

**Table III. Performance characteristics for different cut-points of 6 and 7 in our cohort**

Total score	RA	Non-RA		RA	Non-RA
≥ 6 points	15 (71.4%)	7 (43.8%)	≥ 7 points	14 (66.7%)	0 (0%)
< 6 points	6 (28.6%)	9 (56.2%)	< 7 points	7 (33.3%)	16 (100%)
RR	1.7			3.3	
Sensitivity(%)	71			67	
Specificity(%)	56			100	
PPV (%)	68			100	
NPV (%)	60			69	

RA: Rheumatoid arthritis, RR: relative risk of evolving to RA, Sensitivity: measures the proportion of actual positives which are correctly identified as such (e.g. the percentage of RA patients who are correctly identified as having RA), Specificity: measures the proportion of negatives which are correctly identified (e.g. the percentage of non-RA patients who are correctly identified as not having RA), PPV: positive predictive value (proportion of patients with positive test results who are correctly diagnosed as RA), NPV: negative predictive value (proportion of patients with negative test results who are correctly diagnosed as non-RA).

tients had less than 6 weeks of disease duration (one of the inclusion criteria).

The analysis of the acute phase reactants showed that the initial ESR values did not differ significantly between RA and non-RA patients [median (IQR) 37 (26.5-63.5) *vs* 25 (19.5-60),  $p=0.419$ ] as well as the initial CRP values [median (IQR) 2.74 (1.7-4.3) *vs* 2.1 (0.1-4.8),  $p=0.810$ , respectively], thus the two groups scored 1 in this parameter. At an individual basis 19 (90.5%) patients scored 1 in the RA group and 12 (75%) patients attained the same score in the non RA group.

Regarding the presence and title of RF and ACPA, the mean score in this item was significantly different between the groups ( $1.05 \pm 1.28$  in the RA group *vs*  $0 \pm 0$  in the non-RA group,  $p<0.05$ ). Of notice, RF and ACPA were not detectable in any of the patients who did not evolve to RA. Therefore, the non-RA group score zero and 9 (43%) of the patients in the RA group scored at least 2 [4 (19%) patients scored 3].

Globally, according to the new RA classification criteria, the median total score of the RA group at baseline was significantly higher than the non-RA group [median (IQR) 6 (4.5-8) points in the RA group *vs* 4.5 (2.2-6) points in the non-RA group,  $p=0.007$ ]. Only 6 (28.6%) of the 21 RA's patients had baseline scores lower than 6 comparing to 9 (56.3%) of the 16 patients that did not evolve to RA. Interestingly, the highest score reached in the non-RA patients was 6 points, the cut off point to classify patients as having RA. These results prompted us to test a cut off point of 7 (Table III) in order to improve the specificity of the criteria in our very

early arthritis population. As expected, the relative risk of evolving to RA in patients who have 7 or more points is higher than with the original cut off point of 6 (1.7 *vs* 3.3, respectively). The specificity and positive predictive value improve dramatically to 100% when applying the cut point 7 in our cohort, without a significant decrease in the sensitivity of the criteria (71% to 67%, respectively).

## Discussion

In a cohort of untreated polyarthritis patients with less than 6 weeks of evolution we have assessed the performance of the new ACR/EULAR RA classification criteria. We have identified baseline RF and ACPA positivity, the initial disease activity and functional impairment as predictors of evolution to RA. In addition, our data suggest that in this particular setting of a very early polyarthritis cohort, a cut off of 7 points increases the specificity without significantly affecting the sensitivity of the new ACR/EULAR classification criteria.

In order to understand which factors influence the persistence of arthritis, it is crucial to study patients very early in their disease course, preferentially without any exposure to treatments. However, studies enrolling this type of patients are hindered by delay on referral from the general practitioners or delay in reaching a rheumatology clinic, and in most of the cases cohorts include patients exceeding 6 weeks of disease duration. The herein work recruited only untreated polyarthritis patients with less than 6 weeks of disease duration,

which enriched the interest of this analysis but restricted the number of patients included.

The proportion of patients that evolved to RA in our cohort was about 60%, much higher than it was expected according to the published literature of European early arthritis clinics<sup>2,4,5</sup>, which describes progression to RA in about 33.3% of the patients presenting with early arthritis. However, we have to emphasize that most of those cohorts also included patients presenting with mono and oligoarthritis, increasing the probability of developing other diseases. This might had also an effect on another observation, in fact, we were expecting that initial involvement of hands and wrists would be significantly higher in RA patients, but this was not the case. Again, this involvement may be more important in differentiating RA from non-RA patients when lower limbs oligoarthritis and monoarthritis cases are included.

In our very early polyarthritis cohort the comparison of the patients that evolved to RA *vs* those that were latter classified as having other conditions revealed that RF and ACPA were highly specific but had a low sensitivity to very early RA. In our study the presence of both antibodies (RF and ACPA) conferred a high risk of progression to RA. In addition, patients that evolve to RA tend to present a more severe onset of the disease when compared to non-RA patients, as it is shown by the higher baseline values of DAS28, swollen joints, VAS and HAQ.

The application of the new ACR/EULAR criteria for classification of RA to our population showed that patients evolving to RA presented a significantly higher score than patients who evolved to other diseases. Moreover, the application of the new criteria in our cohort identified the majority of patients that evolved to RA: 15 (71.4%) of the 21 RA's patients had scores higher or equal to 6 comparing to 7 (43.7%) of the 16 patients that did not evolve to RA. However, in our population, about 30% of patients who progressed to RA did not meet the new criteria for RA in the first evaluation, a higher proportion than would be expected. Of notice, all patients included in the study had arthritis with less than 6 weeks of duration (one of the study inclusion criteria). This restriction on disease duration lowers by one point the total score of every patient included in our cohort. The effect of treatment on acute phase reactants and on joint counts precluded further application of the criteria at latter time points.

The new ACR/EULAR RA classification criteria have determined the cut off point of 6, to classify patients as definite RA in order to maximise the sensitivity of the criteria. In our cohort of patients with less than 6 weeks of disease duration, all of the non-RA patients had 6 points or less, which motivated our intention to test a higher cut-point (7 points) in order to improve the specificity of the criteria in our population. Applying the new cut point to our cohort, we found this cut point of 7 to be much more specific for patients evolving to RA, comparing to the original cut off point of 6 (Table III): none of the patients that did not progress to RA had a score equal or higher than 7, comparing to 7 (43.8%) non-RA patients who scored 6. Despite a dramatic effect on the specificity, the sensitivity of the criteria with the new cut off point of 7 was similar when compared to the original cut off point of 6 (67% *vs* 71%, respectively), which means that in our very early arthritis population the cut off point of 7 highly improves specificity without compromising the original sensitivity of the criteria. Our sample size hinders the generalization of this finding, but these results indicate that the cut off point of 7 might be used in polyarthritis patients with less than 6 weeks of disease duration.

The aim of the working group of the new RA classification criteria was to provide a standardized approach for discriminating, from a population of individuals presenting with arthritis, the subgroup with the highest probability of persistence and joint damage, who may benefit from DMARD intervention. In fact the high criteria performance in addition to a very good outcome of the patients classified as RA in our cohort consubstantiate this strategy.

In conclusion, we have shown that in a cohort of polyarthritis patients with less than 6 weeks of disease duration a high DAS28 score, a high number of swollen joints, a low functional status assessed by HAQ and the presence of RF or ACPA are eventually associated with the evolution to RA. In this cohort, 71.4% of the patients that latter progressed to RA, when initially assessed (with less than 6 weeks of symptoms), scored the 6 points needed to be classified as RA. Thus, the new ACR/EULAR criteria for the classification of RA showed, even in very early arthritis, a good sensitivity for the identification of patients that are likely to evolve to RA. However, the specificity was rather low as 43.7% of the patients that evolved to non-RA conditions also scored 6 points. By raising

the cut off point, in this very early arthritis cohort to 7, it was possible to increase specificity while keeping sensitivity.

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