

A clinical prediction rule combining routine assessment and power Doppler ultrasonography for predicting progression to rheumatoid arthritis from early-onset undifferentiated arthritis

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Abstract

Objectives

The ability to predict the development of rheumatoid arthritis (RA) in patients with an early-onset undifferentiated arthritis (UA) is highly required if the remission or an adequate response to the treatment are the main goal. The aim of the study was to develop a predictive rule combining clinical variables, serological biomarkers and power Doppler ultrasonography (PDUS) for the progression from an early-onset UA to RA in daily rheumatological practice.

Methods

A prediction rule was developed after a 12 months study of 149 adult patients with a recent-onset UA. The combination of routine assessment variables and PDUS findings was investigated. Logistic regression analysis was performed to identify the independent factors for the development of RA and global predictive score was calculated. The score of the predictive rule ranged from 0 to 10. The area under the receiver operating characteristic curve was used to evaluate the diagnostic performance of the rule. The post-test probability (post-TP) was evaluated using the Bayes theorem.

Results

Sixty-two patients (41.6%) developed a RA. The rule demonstrated excellent discriminative ability, with an AUC of 0.919 ($p=0.0001$). With the optimal cut-off point of 5, sensitivity was 89.9%, specificity was 88.6% and positive likelihood ratio was 7.89. If a threshold of 6.5 was applied a higher value of specificity (97.7%) was obtained, but sensitivity (47.6%) decreased. The post-TP value of the two different cut-off points mentioned above were 62% and 80%, respectively.

Conclusions

Our predictive rule, which includes PDUS assessment, revealed an excellent discriminative ability for assessing the likelihood of development of RA in patients with an early-onset UA. Further studies are required to confirm the results and to tailor a therapeutic approach in patients with an early-onset UA.

Key words

Rheumatoid arthritis, early-onset undifferentiated arthritis, prediction rule, ultrasonography, prognosis

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown origin with a prevalence of 0.5% in Italy (1). It is characterised by a chronic inflammation of the synovial joints, which leads to progressive joint erosions, physical disability and loss of quality of life (2). Treatment for RA has recently been dramatically improved. The advent of biological and conventional disease modifying antirheumatic drugs (DMARDs) with powerful anti-erosive effects, allowed to greatly reduce or even completely prevent joint damage and the risk of an adverse functional outcome (3). Therefore, it is desirable to find predictive factors at the onset of chronic arthritis to enable rheumatologists to define an individual prognosis. This may serve for stratification of patients in clinical trials and for selecting patients with poor prognosis at an early stage of the disease for more aggressive treatment with highly effective medications, which may often determine a higher incidence of more severe side effects. However, in rheumatology practices it is still difficult to predict who among the patients with recent-onset undifferentiated arthritis (UA) will have progression to RA.

Predictive models have been developed for use in clinical settings to estimate both diagnostic probability and prognosis (4). Recently, a model to predict disease course in patients with UA was proposed using prospective data from the "Leiden Early Arthritis Clinic" (5, 6). The model estimates the probability of progression from early-onset UA to RA using nine common clinical variables. Although most of these models have been applied in early arthritis cohorts, few data are available on the combined value of clinical variables and serological biomarkers such as rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies, with that of imaging modalities for evaluating the prognosis of UA in a routine diagnostic set up.

Interest has been directed towards new imaging modalities such as magnetic resonance imaging (MRI) and ultrasonography (US) for detecting and monitoring joint inflammation and

bone damage in patients early in their disease course. Increasing evidence supports the use of US, for its high sensitivity in revealing synovitis which was found higher than that of standard clinical joint assessment (7, 8). In particular, power Doppler ultrasonography (PDUS) estimates the activity of joint inflammation by detecting intra-articular abnormal blood flow at synovial tissue level (9, 10). The objective of this study was to develop a prediction rule that combined value of clinical variables and serological biomarkers with PDUS findings for predicting progression from early UA to RA in a routine diagnostic set up.

Patients and methods

Patients

One hundred forty-nine adult patients (108 women, 41 men) with a mean age of 56.6 years (range from 18 to 77 years) and with UA of the hands and symptoms duration of less than 16 weeks (mean of 10.5 weeks), who were recruited through the rapid access to the Early Arthritis Clinic at the Department of Rheumatology of the Università Politecnica delle Marche, Ancona, Italy, were included in this study. General practitioners were encouraged to refer patients directly when inflammatory arthritis was suspected (11). UA was defined as those with one or more swollen wrists and finger joints with one or more of the following: positive IgM-RF, positive anti-CCP antibodies, early morning stiffness for more than 30 minutes or positive metatarsophalangeal joints (MTPj) squeeze test (12). Then, the patients were followed for a mean of 12 months (range from 11 to 14 months) by experienced rheumatologists and then assigned to their final diagnostic group. Patients had never undergone treatment with DMARDs or steroid.

Baseline clinical assessment

A standard diagnostic evaluation was performed at baseline by an experienced rheumatologist (FS), who started a treatment according to the guidelines developed by the Italian Society for Rheumatology (13). The data recorded were potentially diagnostic variables

Competing interests: none declared.

obtained from the patient's history, laboratory tests results, physical and PDUS evaluations. The demographic and clinical variables selected were age, gender, bilateral compression pain in the MTPj, global pain, patient global assessment (PGA), morning stiffness and physical disability. PGA and pain were assessed by an 11-point numerical rating scale (NRS), both scoring 0–10, whereas the duration of morning stiffness is rated in minutes. The Recent-Onset Arthritis Disability (ROAD) questionnaire was used to provide an index of disability (14, 15). All these patients gave their informed consent to be enrolled into this study according to the Declaration of Helsinki. The design of the study was approved by the local ethics committee.

US scanning technique and image interpretation

The US examinations were performed by a rheumatologist experienced in US and blinded to clinical findings in order to confirm the presence of synovitis of tender and/or swollen joints. The following US system workstation have been used: Logiq9 (GE Medical Systems, Waukesha, Wisconsin, U.S.A. with a 8-15 MHz linear probe). PDUS examination of both wrists and hands (second through the fifth metacarpophalangeal joints and second through the fifth proximal interphalangeal joints) were carried out from the dorsal aspect using a multiplanar scanning technique. These joints were selected on the basis of their likelihood of involvement in early RA as well as their easy accessibility with the US probe (16-17).

A proper amount of gel was placed on the skin in order to avoid compression on soft tissues under examination. Values of Doppler settings were set as follows: frequency 7.5 MHz, low wall filter, pulse repetition frequency (PRF) ranging from 700 to 1000 Hz and the maximal gain level not generating artifacts signal below the bony cortex. PDUS examination lasted 5 minutes per patient. We considered a joint positive if there was the contemporary presence of synovitis on grey scale and PDUS signal. Grey scale US assessment was

mandatory in order to confirm the intra-articular distribution of the PDUS signal. OMERACT definitions criteria for synovial fluid and synovial hypertrophy were applied (19). Positive intra-articular PDUS signal was reported only if a score higher than grade 1 according to Szkudlarek et al. (20) was found.

Laboratory investigations

Baseline blood samples were obtained for determination of the erythrocyte sedimentation rate (ESR) (normal values, ≤ 15 mm/h in men and ≤ 20 mm/h in female) the C-reactive protein (CRP) level, using standard laboratory methods (normal values, ≤ 0.80 mg/dl), the presence of IgM-RF, as determined by nephelometric method (Image Beckman) and the presence of anti-CCP antibodies as determined by ImmunoFluoroMetric Assay (IFMA) (EliA CCP, ImmunoCAP 250, Phadia S.r.l, Italy). The cut-off point for the anti-CCP antibodies positivity was >10 IU/ml, according to the manufacturer's instructions, whereas a titre of IgM-RF of 40 UI/ml was regarded as positive.

Statistical analysis

The data recorded were entered into a database (Microsoft Office Excel 2007; Microsoft, Redmond, WA, USA). Analysis were conducted in MedCalc[®] version 10.1.2.0. (MedCalc Software, Mariakerke, Belgium). Continuous data were presented as means with standard deviations (SDs) or medians with interquartile range (IQR), depending on the distribution of the data (tested with the Kolmogorov-Smirnov test). Patients with UA who developed RA (21) were compared with those who did not evolved into RA, using Mann-Whitney U-test for continuous variables or Chi-square test with Yates' correction or Fisher's exact test for nominal variables and for comparison of percentages. Subsequently, the diagnostic variables recorded at the first visit were entered as possible explanatory variables in a logistic regression model, with disease outcome (no progression to RA or progression to RA) at 1 year of follow-up as possible dependent variable. The independent

variables were selected from univariate analyses if $p < 0.05$. To investigate the value of PDUS as a predictor variable three groups were created based on the number of joints with intra-articular PDUS signal at the hands and wrists level: a first group with a single joint involved, a second group with two to three joints involved and a third group with more than three joints involved. Moreover the presence of IgM-RF (≥ 40 UI/ml) and anti-CCP antibodies (≥ 10 UI/ml) and of acute phase reactants has been considered and implemented into the predictive rule (Table I). According to the new American College of Rheumatology (ACR) criteria recently proposed for the diagnosis of RA (Annual Congress of ACR 2009, Philadelphia, USA, unpublished data)¹, the positivity of IgM-RF or anti-CCP antibodies have been dichotomised in low titre (defined as more but not higher than three times the upper limit of normal value) and higher titre (defined as more than three times the upper limit of normal value). With regards to acute phase reactants abnormal values of ESR or CRP have been considered. Using a backward selection procedure, the most significant independent variables were identified, using a p -value greater than 0.10 as the removal criterion. To obtain a simplified rule, the regression coefficients of the predictive variables were rounded to the nearest number ending in 0.5 or 0.0, resulting in a weighted score. Subsequently, these values were summed. The final resulting model was then evaluated using the area under the curve (AUC) the receiver operating characteristic (ROC) analysis. Sensitivities, specificities and likelihood ratios (LRs), were computed for multiple levels of scoring. LRs were calculated for multiple levels of score system. In literature have been reported that the percentage of patients with UA who progressed to RA one year after baseline evaluation is ranging from 17% to 55% (5, 22-24). According to these data, a more restrictive estimated prevalence of 17% was assumed as pre-test probability (pre-TP). Furthermore, we

¹ Conference Proceedings, website link/URL: <http://acr.confex.com/acr/2009/webprograms/lababus/start.html>

Table I. Independent predictive variables associated with an unfavourable outcome of RA, based on results of logistic regression model*.

Variables	Disease outcome		Coefficient β	Std. Error	<i>p</i> -value	Odds ratio	95% CI	Points
	Progression to RA (n=62)	No progres- sion to RA (n=87)						
Laboratory markers:								
anti-CCP or IgM-RF positivity at high titre	13 (37.1)	7 (8.0)	2.1332	0.6392	0.0012	10.9483	2.571 to 46.6162	2
anti-CCP or IgM-RF positivity at low titre	18 (29.0)	13 (14.9)	1.5595	0.6644	0.0086	5.8095	1.5797 to 21.3646	1.5
abnormal CRP or abnormal ESR	50 (80.6)	42 (48.3)	1.5767	0.6088	0.0058	5.3477	1.6216 to 17.6362	1.5
Power Doppler ultrasound (PDUS) involvement of the wrists and hands:								
involvement of 1 joint	14 (22.6)	14 (16.1)	2.1972	0.7464	0.0020	9.9463	2.3031 to 42.9544	2
involvement of 2 to 3 joints	26 (41.9)	25 (28.7)	2.9655	0.6717	0.00001	17.5572	4.7063 to 65.4990	3
involvement of more than 3 joints	22 (35.5)	17 (19.7)	4.0361	0.8769	0.000001	48.7186	8.7352 to 271.7161	4
Symptoms duration (6 weeks or longer)	23 (37.1)	13 (14.9)	1.6049	0.6525	0.0139	4.9772	1.3855 to 17.8804	1.5
Morning stiffness (for more than 30 minutes)	46 (74.2)	29 (33.3)	1.1508	0.5591	0.039	3.1607	1.0564 to 9.4567	1

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

anti-CCP: anti-cyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

used the LRs to estimate post-test probabilities (post-TP) associated with an unfavorable outcome of RA, together with their 95% confidence intervals (95% CI), using Bayes theorem. The post-TP was graphically evaluated using the Fagan's nomogram (25) which is available at the following website address: <http://araw.mede.uic.edu/cgi-alansz/testcalc.pl>.

Results

Assessment status after 1 year

At prospective follow-up of 12 months, 62 patients (41.6%) were found to have progressed to RA on the 1987 ACR criteria (21) while the remainder 87 (58.4%) were non-progressor. Of these, 18 (12.1%) developed another non-RA arthropathy (5 were diagnosed with inflammatory osteoarthritis, 5 patients were diagnosed with psoriatic arthritis due to subsequent development of skin psoriasis, 3 with undifferentiated spondyloarthropathy, 2 with reactive arthritis, 2 with Sjögren's syndrome and one with systemic lupus erythematosus), while the largest group of non-progressors remained undifferentiated at follow-up, with 22 of those who were free of symptoms and in natural remission. After all, only 53.4% of the patients could be diagnosed with a specific rheumatic disease after a 12-month follow-up. During the study if an inflammatory arthritis was suspected, patients started a DMARD therapy with or without a steroid bridging. Therefore, the percent-

age of patients receiving DMARDs and steroid was much higher in 62 patients with UA who progressed to RA than in 87 who did not. In this regard, 49 patients (79%) of the progressors were treated with DMARDs, including 22 patients with methotrexate, 13 patients with hydroxychloroquine, 6 patients with methotrexate and sulfasalazine 5 with methotrexate and hydroxychloroquine, 2 patients with methotrexate and etanercept, and 1 patient with methotrexate and adalimumab, whereas only 16 patients (18.4%) received DMARDs among 87 patients with UA who did not progress to RA ($p < 0.0001$). As regards steroid treatment, 34 patients (54.8%) with UA who progressed to RA, received a mean dose of 6-metilprednisolone of 3.8 mg/once a day whereas, among 87 patients who did not progress to RA, 21 patients (24.1%) received a mean dose of 6-metilprednisolone of 2.6 mg/once a day ($p < 0.0001$).

Univariate analysis

The laboratory markers, PDUS involvement of the hands, symptoms duration, morning stiffness and female gender were the variables significantly associated with progression to RA in univariate analysis. The variable with the highest statistical significance ($p < 0.0001$) was the presence of involved joints on PDUS. Among the laboratory variables, the anti-CCP and IgM-RF positivity at higher titre (3 times more than the reference's value)

were significantly associated with progression to RA (both at $p < 0.0001$). None of the following variables were significantly different between the two groups: age, VAS pain, PGA, squeeze test of the MTF joints and ROAD disability score.

Multivariate analysis of independent predictors of disease outcome

Only the baseline variables with a $p < 0.05$ were included in a multiple logistic regression model in which disease outcome (no progression to RA or progression to RA) at 1 year of follow-up was the dependent variable (Table I). The PDUS positivity in the wrists and hands appeared to be the strongest independent predictor of an unfavourable outcome of RA. The contemporary presence of synovitis on grey scale and PDUS signal at level of one single joint significantly increased the probability of progression to RA (odds ratio of 9.94). Moreover, the positivity of 2-3 joints or more than 3 joints at PDUS evaluation significantly increased the odds ratio of progression to RA to 17.55 and 48.71, respectively (Table I). Among the biomarkers, the high titre positivity (defined as more than three times the upper limit of normal) of anti-CCP antibodies or RF appeared to be the strongest ($p = 0.0012$) independent predictor (OR 10.94, 95% CI 2.57 to 46.61). Symptoms duration of more than 6 weeks (OR 4.97, 95% CI 1.38 to 17.88), and morning stiffness of more

Variables		Points
1. What is the symptoms duration?	• If ≥ 6 weeks	1.5
2. What is the length of the morning stiffness?	• If ≥ 30 minutes	1
3. Are the ESR or CRP abnormal?	• If yes	1.5
4. Are the anti-CCP or IgM-RF positive?	• If at least one of these two tests are positive at low titer	1.5
	• If at least one of these two tests are positive at high titer	2
5. What is the number of involved joints on PDUS?	• If 1 joint	2
	• If 2-3 joints	3
	• If more than 3 joints	4
Total score		-----

Fig. 1. Form used to calculate a patient's prediction rule. The range of possible score is 0–10, with higher scores indicating a greater risk of developing RA.

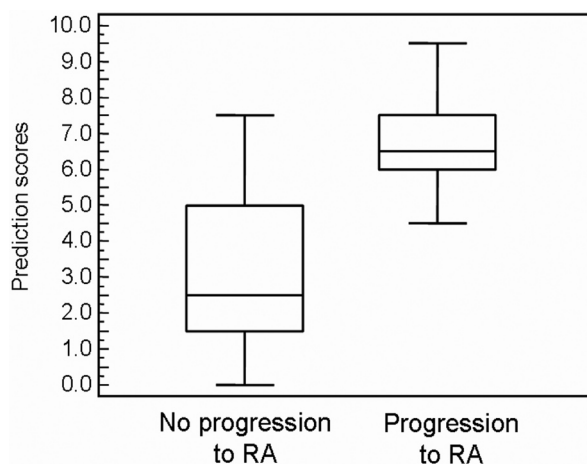


Fig. 2. Prediction scores for the progression from UA to RA. The box plots provide information of the symmetry of a distribution, of the numerical measures of central tendency, and of the variability and spread of data in the tails of a distribution. The box contains the median values (represented by a horizontal line within the box), 25th and 75th percentiles, and 90th percentiles. The Mann-Whitney U-test for continuous variables was carried out to compare patients with UA who developed RA and those who did not evolve into RA ($p < 0.001$).

than 30 minutes (OR 3.16, 95% CI 1.05 to 9.45) were also independent predictors of unfavorable outcome of RA. The significant association to progression to RA of the female gender variable in the univariate analyses was not maintained in the multivariate analysis ($p = 0.184$). Applying a logistic analysis (Table I) the coefficients β and correspondent weights were calculated. The form that can be used to calculate the prediction score is showed in Figure 1. The range of the prediction scores is from 0 to 10 and a higher score indicates a greater risk of progression to RA.

Discriminative ability

The graphical representation of prediction scores for the progression from UA to RA are shown in Figure 2. Among patients with UA who progressed to RA the median prediction score was 6.5 (IQR, 6.0 to 7.0) whilst, among patients who did not develop a RA the median prediction score was 2.5 (IQR,

2.0 to 3.5) ($p < 0.001$). The AUC-ROC curve was used to evaluate the diagnostic performance of the rule for discrimination between patients with UA in whom RA developed and those in whom RA did not developed. The rule demonstrated excellent discriminative ability ($p = 0.0001$), with an AUC of 0.919 (95% CI 0.863 to 0.957) for discrimination between patients with UA and future development of RA, and patients with UA without future development of RA. From the ROC curve we computed the optimal cut-off point (Table II). For the model an optimal cut-off point of 5 comes close to maximising both sensitivity and specificity. With this optimal cut-off point, sensitivity was 89.9% (95% CI 79.5% to 95.3%), specificity was 88.6% (95% CI 77.2% to 93.8%), and positive likelihood ratio (+LR) was 7.89. If a threshold of 6.5 was applied a higher value of specificity (97.7%) was obtained, but sensitivity (47.6%) decreased. By

the Fagan's nomogram we calculated post-TP (Fig. 3). If a likelihood ratio of 20.48 was applied the test gained predictivity with a post-TP of 80%.

Discussion

The prognosis of patients with UA may vary from self-limited to severe destructive RA. The decision to treat UA patients depends on the likelihood ratio to develop RA. It is therefore advantageous to stratify patients in terms of prognostic indicators prior to starting treatment for an optimal management of the therapeutic approach.

From the literature, the proportion of patients with UA who progressed to RA one year after inclusion varied considerably and range between 6% and 55%. However, in the cohorts that required arthritis to be present at inclusion and that defined RA according to the ACR 1987 criteria (21) the proportions range from 17% to 46.2% (5, 22-24). In a Dutch cohort of UA patients the priori risk of developing RA was 35%, which increased to 66% in patients who were anti-CCP antibodies positive (26). These differences may be explained by the discrepancy in referral and recruitment procedures, inclusion criteria and, most notably, disease criteria between the various cohorts. Our data show a relatively higher percentage of patients (41.6%) with UA who develop a RA after 12 months of follow-up. This can be explained by the high percentage of patients showing a clinically evident synovitis in more than one or two small joints at baseline examination. A great deal of research has already been carried out to try to identify one or multiple features or a combination of these factors to use as predictive criteria for the development of RA in patients with UA. Different methods exist to construct such prediction models or classification rules (5, 6, 27).

The literature of recent years confirms that among all variables the presence of IgM-RF and/or anti-CCP antibodies, in patient with a recent-onset UA, are the most predictive factors for developing RA (28-32). For instance, Visser *et al.* (33) found that among patients seen at an early arthritis clinic with less than 2 years of signs and symptoms,

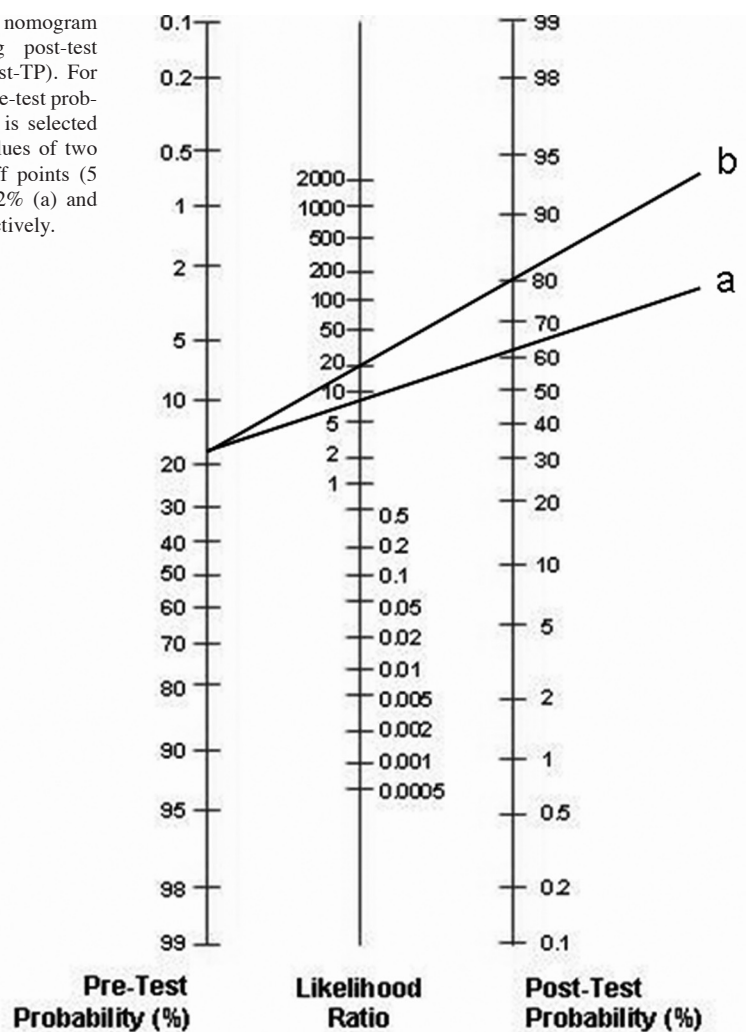
Table II. Criterion values and coordinates of the ROC curve. Sensitivities, specificities, likelihood ratios (LRs) and post-test probabilities (post-TP), together with their 95% confidence intervals (95% CI) were computed considering Bayes theorem.

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR	Post-test probability (post-TP %)
0	100.00	94.3 – 100.0	12.79	6.6 – 21.7	1.15	0.00	19
1	98.41	91.4 – 99.7	18.60	11.0 – 28.4	1.21	0.08	20
1.5	98.41	91.4 – 99.7	36.05	26.0 – 47.1	1.54	0.04	24
2	98.41	91.4 – 99.7	40.70	30.2 – 51.8	1.66	0.03	25
2.5	98.41	91.4 – 99.7	51.16	40.1 – 62.1	2.02	0.03	29
3	96.83	89.0 – 99.5	60.47	49.3 – 70.8	2.45	0.05	33
3.5	95.24	86.7 – 99.0	65.12	54.1 – 75.1	2.73	0.07	36
4	95.24	86.7 – 99.0	72.09	61.4 – 81.2	3.41	0.06	41
4.5	92.06	82.4 – 97.3	74.42	63.9 – 83.2	3.60	0.11	42
5*	89.90	79.5 – 95.3	88.62	77.2 – 93.8	7.89	0.15	62
5.5	82.11	72.3 – 89.5	89.93	81.1 – 95.1	8.17	0.23	63
6	61.90	48.8 – 73.9	93.02	85.4 – 97.4	8.87	0.41	65
6.5	47.62	34.9 – 60.6	97.67	91.8 – 99.7	20.48	0.54	80
7	31.75	20.6 – 44.7	98.84	93.7 – 99.8	27.30	0.69	84
7.5	19.05	10.3 – 30.9	98.93	95.8 – 100.0	29.82	0.81	85
8	11.11	4.6 – 21.6	99.21	95.8 – 100.0	33.01	0.89	87
8.5	7.94	2.7 – 17.6	99.48	95.8 – 100.0	40.20	0.92	89
9	6.35	1.8 – 15.5	99.77	95.8 – 100.0	53.31	0.94	92
9.5	4.76	1.0 – 13.3	99.98	95.8 – 100.0	64.04	0.95	93
10	0.00	0.0 – 5.7	100.00	95.8 – 100.0	/	1.00	/

*Optimal cut-off point, corresponding with the maximum sum of sensitivity and specificity.

the strongest associations for persistent self-limiting arthritis were symptom duration of ≥ 6 months, with an OR of 5.49, and anti-CCP positivity, with an OR of 4.58. In another study, Jansen *et al.* (34) showed that values of IgM-RF >40 or anti-CCP antibodies >50 in patients with early arthritis can predict, with a sensitivity of 55.4% and a specificity of 96.7%, those who will be diagnosed of RA. Subsequent studies gave an indication of the relative importance of these factors in prediction of development of RA (24, 26). Recently there have been reported the prediction value of anti-CCP antibodies for the development of RA in patients with early UA (35). These and other data clearly show that beside the presence of biomarkers such as anti-CCP antibodies and/or IgM-RF, the number of swollen joints is another important and independent prognostic factor for development of RA in patients with UA (5, 9). A prospective study in patients with early inflammatory arthritis in France (ESPOIR cohort study) further demonstrated that involvement of more than 3 joint groups of the hands, and the presence of anti-CCP antibodies were also the most relevant aspects for the final decision to start DMARDs treatment (36). The above prediction rule

Fig. 3. Fagan’s nomogram for calculating post-test probability (post-TP). For example, if a pre-test probability of 17% is selected the post-TP values of two different cut-off points (5 and 6.5) are 62% (a) and 80% (b), respectively.



and the Leiden Early Arthritis Cohort prediction rule (5, 6) indicate that clinical evaluation is still the gold standard in detecting synovitis. However, the sensitivity of clinical assessment of synovitis is known to be lower to that of new imaging modalities, especially early in the disease course (7-9, 20, 36, 37). Technological advances and the increasing availability of new imaging techniques, such as MRI and US have provided exciting new possibilities for the assessment of early inflammatory arthritis (38-41).

It has been suggested that the incorporation of MRI signs of synovitis in the ACR criteria of RA (21) would increase their accuracy leading to an earlier diagnosis of some RA patients (42). In addition, Tamai *et al.* (43) recently found that the gadolinium-diethylenetriamine-enhanced MRI findings, in conjunction with anti-CCP antibodies and/or IgM-RF is efficient in predicting progression from UA to RA. Similar results has been reported by Eguchi (44), demonstrating that the presence of anti-CCP antibodies and/or IgM-RF, symmetric synovitis and bone marrow edema and/or bone erosion at entry could discriminate patients with RA from UA or other than RA. A total score of two or more of the three objective measures allowed the prediction for RA with 83% sensitivity and 85% specificity, respectively (44). However, MRI is an expensive and time consuming technique and, therefore, cannot be used routinely. US provides for a non-invasive, safe, reproducible and relatively inexpensive method for detecting joint inflammation. Many studies have highlighted the ability of US to detect early synovial disease in both large and small joints and its higher sensitivity with respect to clinical examination (7, 8, 35-37, 45). Power Doppler US allows for a sensitive assessment of synovial perfusion and it was found to be helpful in evaluating the inflammatory activity and efficacy of different therapeutic regimens (46-49) and predicts short-term relapse (8). Pascual-Ramos *et al.* (50) have investigated if serial clinical and US evaluations differ between early RA patients who develop erosive disease identifying outcome

predictors of erosions. In particular, they showed that serial PDUS-assessed synovitis was greater in patients who developed erosions than in those who did not. Freeston *et al.* (51), in a recent pilot study, showed that the probability of inflammatory arthritis in patients presenting with very early hand symptoms \pm signs can be predicted according to the presence or absence of certain clinical features, laboratory tests and PDUS findings of sub-clinical synovitis. Apart from this study, we are unaware of data on the importance of PDUS findings with respect to evolution of UA to RA (*i.e.* indicating the prognostic value of PDUS in UA). Some indirect evidence to support the possible predictive value of PDUS is also provided by its high level of agreement with MRI-proven synovitis in RA (19, 38) and the concordance between the presence of a Doppler signal within the pannus and the histologic identification of vessels within the same pannus (10).

In our study the PDUS positivity of more than 3 joints in the wrists and hands, documented in a recent onset UA, significantly increased the probability of progression to RA from 17% (pre-TP) to 41% (post-TP). Moreover, the contemporary presence of more than 3 joints of wrist and hands positive at PDUS evaluation and IgM-RF or anti-CCP antibodies at higher titre, increased the above mentioned probability to 65% (post-TP).

While gaining and maintaining competency in musculoskeletal US require time devoted to getting trained and scanning, a dedicated learning program focused on acquiring skills necessary to examine small joints for identifying sonographic signs of joint inflammation is relatively shorter and should be considered within the reach of all rheumatologists (52-54).

Conclusions

The predictive rule that we are proposing is, to our knowledge, the first that combined routine assessment variables (symptoms duration, morning stiffness, ESR, CRP, anti-CCP antibodies and IgM-RF) with the presence of intra-articular PDUS signal in the wrists and the small joints of the hands to be

used in patients with recent-onset UA. Based on our findings, this predictive rule revealed an excellent discriminative ability for assessing the likelihood of development of RA in patients with an early-onset UA. This set of prognostic markers contributes to providing evidence in favour of starting a DMARD treatment earlier in the course of disease, and it should facilitate the development of personalised medicine in this clinical context. Since our internal validation cohort is relatively small, the proposed current predictive rule requires confirmation in wider independent cohorts of patients with UA.

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