Genetics, autoantibodies and clinical features in understanding and predicting rheumatoid arthritis

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Chapter 16

A rule to predict disease outcome in patients with recent-onset undifferentiated arthritis to guide individual treatment decisions

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Submitted

ABSTRACT

Objectives. In patients with undifferentiated arthritis (UA) methotrexate is an effective drug to inhibit symptoms, structural damage, and progression towards rheumatoid arthritis (RA). However 40-50% of UA-patients remit spontaneously. Thus adequate treatment decision-making in early undifferentiated arthritis necessitates identification of the UA-patients that will develop RA.

Methods. A prediction rule was developed using data from the Leiden Early Arthritis Clinic, an inception cohort of patients with recent onset arthritis (n=1700). The patients that presented with UA were selected (n=570); progression to RA or other diagnosis was monitored after one-year follow-up. The clinical characteristics with independent predictive value for RA development were selected using logistic regression analysis. The diagnostic performance of the prediction rule was evaluated using the area under receiver operating characteristic curve (AUC). Cross-validation controlled for over-fitting of the data (internal validation). For external validation, an independent cohort of UA-patients was used.

Results. The prediction rule consists of nine clinical variables: gender, age, localization of symptoms, morning stiffness, tender and swollen joint count, C- reactive protein, rheumatoid factor and anti-CCP antibodies. Each prediction score varies between 0 and 14 and corresponds to a chance (percentage) RA development. For several cut-off values the positive and negative predictive values were determined. The AUC of the prediction rule, the prediction model after cross-validation and the external validation cohort were 0.89, 0.87 and 0.97 respectively.

Conclusions. In early undifferentiated arthritis the risk to develop RA can be predicted, thereby allowing individualized treatment decisions to initiate disease-modifying anti-rheumatic drugs in patients who present with UA.

INTRODUCTION

Individualized treatment decision-making is one of the most important challenges of medicine. To this end a number of studies have appeared that associated clinical variables or gene-expression profiles with disease outcome, thereby providing help for clinicians in treatment decisions in several diseases (e.g. breast cancer, Hodgkin disease, lymphoma 1-4). Treatment in rheumatoid arthritis (RA) is since the last decennium characterized by earlier and more aggressive treatment with disease-modifying antirheumatic drugs (DMARDs), as this treatment strategy prevents joint damage and functional disability (5-7). In rheumatological practice, the majority of patients that present with a recent onset arthritis have an undifferentiated arthritis (UA), arthritis in whom with the available classification criteria no diagnosis can be made. From several inception cohort studies it is known that about 40-50% of these UA-patients remit spontaneously, whereas one-third develops RA (8-10). Recent evidence indicates that treatment with methotrexate in patients with early UA hampers progression to RA and progression of joint damage (11), underscoring the need for guidance to start a clinically beneficial but potential harmful drug in UA. Ideally, only the UA-patients that develop RA are treated with DMARDs in contrast to those that remit spontaneously. At present, although several risk factors for the development of RA have been identified (8,12), a model that predicts the disease course specifically in patients with recent-onset UA is lacking. The present study aimed to develop a model that predicts the progression from UA to RA, using clinical variables that are easily assessed in daily clinical practice. The derived prediction rule was internally validated controlling for over-fitting of the data, and subsequently externally validated in an independent cohort of UA-patients.

METHODS

Patients

The prediction rule is derived using the Leiden Early Arthritis Clinic, an inception cohort containing more than 1900 patients with recent-onset arthritis of whom about 1700 have completed at least one-year follow-up. This cohort started in 1993 at the department of Rheumatology of the Leiden University Medical Center, the only referral center for rheumatology in a health care region of ~400,000 inhabitants in the Netherlands (13). General practitioners were encouraged to refer patients directly when arthritis was suspected; patients were included if physical examination revealed arthritis. At first visit various variables were collected. The rheumatologist answered a questionnaire inquiring about the initial symptoms as reported by the patient: type, localization and distribution of initial joint symptoms, symptom duration and course of start complaints. The smoking and family history were assessed. Patients rated the morning stiffness on a visual analogue

scale (0-100). For the present study, severity of morning stiffness was used instead of duration of morning stiffness as the first is proven to be a better discriminator (14,15). The Health Assessment Questionnaire (HAQ) yielded an index of disability. A 44-joint count for tender and swollen joint was performed, scoring each joint on a 0-1 scale (16). Compression pain of metacarpophalangeal and metatalohalangeal joints was recorded. Baseline blood samples were taken for determination of ESR, C-Reactive protein (CRP), IgM rheumatoid factor (RF, ELISA), and antibodies to cyclic-citrullinated peptide 2 (CCP; ELISA, Immunoscan RA Mark 2, Euro-Diagnostica, Arnhem, The Netherlands). The cut-off level for anti-CCP positivity was 25 arbitrary units. Radiographs of hands and feet were made and scored according to Sharp-van der Heijde (17). Patients gave their informed consent and the local Ethical Committee approved the protocol.

Disease Outcome

570 patients had two weeks after inclusion (when results on laboratory and radiological investigations were known) an arthritis that could not be classified according to the ACR-criteria and were documented as undifferentiated arthritis (UA). After 1-year follow-up the disease status of all UA-patients was examined to determine whether they had developed RA or other diagnosis according to the ACR-criteria. Inherent to the design of an inception cohort the duration of follow-up differed within the study population and at the moment of analysis (July 2005) the majority of UA-patients (94%) had been followed for more than one year (mean follow-up 8 years, SD 3 years).

External validation cohort

Patients included in the placebo-arm of the PROMPT-trial, a double-blind placebo-controlled randomized trial in which patients with recent onset UA were treated with either methotrexate or placebo, were used for validation (n=55) (11). Exclusion of the UA-patients that were also included in the EAC cohort resulted in 36 independent UA-patients. Two of these were lost to follow-up. For each patient the progression score at baseline was calculated and the development of RA after 1-year follow-up was assessed (11).

Statistical analysis

The UA-patients that did or did not develop RA were compared using the Chi-square test for nominal variables and the student's t-test for continuous variables. Symptom duration was categorized. Subsequently all clinical variables were entered as possible explanatory variables in a logistic regression analysis with the disease outcome (RA or non-RA) at one-year follow-up as dependent variable. Using a backward selection procedure, the most significant independent variables were identified, using $p>0.10$ as removal criteria. In the logistic regression model the predicted probability on RA is related to the covariates via the prognostic index: $B_1*x_1+B_2*x_2+B_3*x_3...B_k*x_k$. The B (regression coefficient) of the covariate indicates an estimate

of the relative magnitude of the prognostic power of the concerning variable. Using the prognostic index, for every subject the predicted probability on RA development was calculated. For continuous variables (age, VAS-score, tender and swollen joint count, CRP) the effect was studied both as continuous variable and categorized. Categories were made using clinically applied cut-off levels and percentiles. Categories were pooled if corresponding regression coefficients were similar. Data on VAS morning stiffness were missing in 160 subjects, data on anti-CCP antibodies in 64 subjects and data on disease duration in 22 subjects. To prevent that these subjects were excluded from the logistic regression analysis, the median value was imputed. The multivariate regression analysis was performed using 562 UA patients as in 8 patients one or more of the following variables were missing: rheumatoid factor (n=1), CRP (n=1), tender joint count (n=5), swollen joint count (n=4). To get a simplified prediction rule, the regression coefficients of the predictive variables were rounded to the nearest number ending in .5 or .0 resulting in a weighted score; subsequently the independent predictive variables were summed. The calculated prediction scores were compared with the observed percentage progression to RA. The positive and negative predictive values were determined for several cut-off values of the prediction scores. To evaluate the diagnostic performance, a receiver-operating characteristic (ROC) curve was constructed. The area under the ROC curve (AUC) provided a measure of the overall discriminative ability of a model. For internal validation, cross-validation was performed to control for over-fitting (18). Cross-validation mimics the prediction situation and yields for each observation a prediction score based on the other (n-1) observations (18). To validate the model a ROC-curve was made using the cross-validated predictions as well as the external validation cohort. The Statistical Package for Social Sciences (SPSS), version 10.0 (SPSS, Chicago, IL) was used.

RESULTS

Disease outcome

Of 570 UA-patients, 177 developed RA during the first year of follow-up, 94 patients developed other rheumatological diseases, 149 patients remained unclassified and 150 patients achieved clinical remission defined as discharge from the outpatient clinic because of absence of arthritis without DMARDs. For further analysis, the patients with other rheumatological diagnosis, unclassified arthritis and remission were assembled as the non-RA group (n= 393).

Univariate analyses

Characteristics of UA-patients that did and did not develop RA are compared in Table 1. In univariate analysis, all variables except smoking were significantly associated with progression to RA.

Table 1. Characteristics at inclusion of UA-patient that did not and did progress to RA.

Patient characteristic	Non-RA N=393	RA N=177	P
Age, mean (SD)	48.6 (17.0)	56.3 (15.3)	<0.001
Female, n (%)	208 (53)	121 (68)	0.001
Positive family history for RA, n (%)	81 (21)	54 (31)	0.01
Course start complaints, n (%)			
acute <24 hr	116 (30)	36 (20)	
subacute > 24 hr	123 (31)	51 (29)	
creping	141 (36)	86 (49)	
intermittent	13 (3)	4 (2)	0.02
Symptom duration at inclusion, n(%)			
< 6 weeks	103 (27)	18 (11)	
6 weeks – 3 months	80 (21)	43 (25)	
3- 6 months	89 (23)	47 (28)	
> 6 months	107 (28)	61 (36)	<0.001
Localisation affected joints, n(%)			
small hand/feet	171 (44)	95 (54)	
big joints	165 (42)	32 (18)	
both	57 (15)	50 (28)	<0.001
Localisation affected joints, n(%)			
symmetric	147 (37)	118 (67)	<0.001
Localisation affected joints, n(%)			
upper extremities	177 (45)	71 (40)	
lower extremities	139 (35)	22 (12)	
both	77 (20)	84 (47)	<0.001
Morning stiffness (VAS), mean (SD)	35.5 (30.0)	53.3 (30.1)	<0.001
Compression pain MCP joints, n(%)	159 (40)	116 (66)	<0.001
Compression pain MTP joints, n(%)	134 (34)	103 (58)	<0.001
Number tender joints, median (IQR)	3 (2-7)	8 (4-12)	<0.001
Number swollen joints, median (IQR)	2 (1-4)	4 (2-7)	<0.001
CRP level (mg/L), median (IQR)	8 (3-21)	14 (7-43)	<0.001
ESR level (mm1st hr), median (IQR)	17 (8-38)	32 (19-53)	<0.001
Rheumatoid factor positive, n (%)	56 (14)	84 (47)	<0.001
Anti-CCP positive, n(%)	38 (11)	83 (51)	<0.001
HAQ score, mean (SD)	0.7 (0.6)	1.0 (0.7)	<0.001
Smoking, n(%)	187 (48)	84 (47)	1.0
Erosiveness, n(%)	29 (7)	29 (16)	0.001

Multivariate analyses, derivation of prediction rule

In a logistic regression analysis the independent predictive variables for RA development were: age, gender, localization of joint complaints (small/big joints, symmetric/asymmetric, upper/lower extremities), morning stiffness, tender and swollen joint count, CRP-level, RF and anti-CCP antibodies (Table 2). Age as continuous variable was more predictive than categorized; the other continuous variables were categorized. The resulting model had a fraction of explained variation (Nagelkerke R^2) of 0.57 and, when taking a predicted

probability of 0.5 as cut off value, predicted 83% of patients correctly. The coefficients for the simplified prediction score are listed in Table 2. Figure 1a presents a form to easily calculate the prediction score. The prediction score ranges between 0 and 14; a higher score indicates a higher risk to develop RA. For every UA-patient the prediction score was calculated. Figure 1b shows the predicted risk on RA as function of the prediction score (obtained from a logistic model with score as independent variable). Table 3 presents the observed percentage with progression to RA in relation to the calculated score. All UA-patients with a prediction score ≤3 did not progress to RA during the one-year follow-up, and all UA-patients with a score ≥11 had progressed to RA. The patients with intermediate scores (4-10) had progressed to RA in increasing frequency at rising scores. Table 3 also shows the percentage of the patients that progressed to RA for several cut-off values of the prediction score. For example if the scores 5.0 and 9.0 were chosen as cut-off values, 97% of UA-patients with a score a score ≤5.0 did not develop RA and a score ≥9.0 was associated with progression to RA in 84% of patients. If the cut-off values were 6.0 and 8.0,

Table 2. Independent predictive variables for RA development resulting from multivariate regression analysis

Variable	B *	OR	95%CI	P	Points #
Gender	0.8	2.1	1.3-3.6	0.003	1
Age	0.02	1.02	1.01-1.04	0.011	0.02/yr
Localisation small joints hand/feet	0.6	1.8	1.1-3.1	0.024	0.5
Localisation symmetric	0.5	1.6	1.0-2.8	0.075	0.5
Localisation upper extremities	0.8	2.1	1.1-4.4	0.04	1
upper and lower extremities	1.3	3.5	1.7-7.5	0.001	1.5
VAS morning stiffness					
0-25	-	-	-	-	-
26-50	0.9	2.4	1.2-4.5	0.009	1
51-90	1.0	2.7	1.3-5.6	0.006	1
>90	2.2	9.3	3.0-28.7	<0.001	2
Number tender joints					
0-3	-	-	-	-	-
4-10	0.6	1.8	0.9-3.3	0.082	0.5
>10	1.2	3.3	1.5-7.0	0.003	1
Number swollen joints					
0-3	-	-	-	-	-
4-10	0.4	1.5	0.8-2.7	0.18	0.5
> 10	1.0	2.8	1.1-7.6	0.038	1
CRP level					
0-4	-	-	-	-	-
5-50	0.6	1.6	0.9-3.0	0.13	0.5
>50	1.6	5.0	2.0-12.1	0.00	1.5
RF positive	0.8	2.3	1.2-4.2	0.009	1
Anti-CCP positive	2.1	8.1	4.2-15.8	<0.001	2

***** B means regression coefficient

Points for the simplified prediction rule derived from the regression coefficient

1. What is the age in years?	Multiply with 0.02		_____
2. What is the gender?	In case female:	1 point	_____
3. How is the distribution of involved joints?			
	In case small joints hands / feet:	0.5 point	_____
	In case symmetric:	0.5 point	_____
	In case upper extremities	1 point	
	or in case upper & lower extremities:	1.5 points	_____
4. What is the length of the VAS morning stiffness (range 0-100 mm)?			
	In case 26-90 mm:	1 point	
	In case > 90 mm:	2 points	_____
5. What is the number of tender joints?			
	In case 4-10:	0.5 point	
	In case 11 or higher:	1 point	_____
6. What is the number of swollen joints?			
	In case 4-10:	0.5 point	
	In case 11 or more:	1 point	_____
7. What is the C-reactive protein level (mg/L)?			
	In case 5-50:	0.5 point	
	In case 51 or higher:	1.5 points	_____
8. Is the Rheumatoid factor positive?	If yes:	1 point	_____
9. Are the anti-CCP antibodies positive?	If yes:	2 points	_____
		Total score	_____

Figure 1a. Form to calculate a patient's prediction score

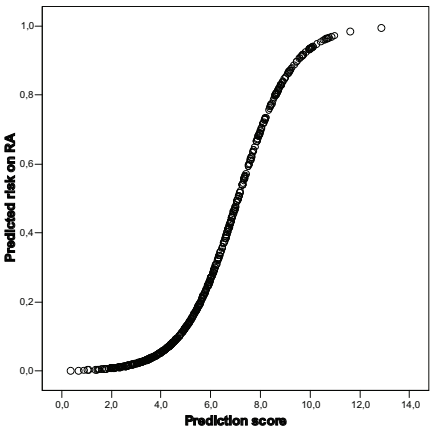

Figure 1b. The subjects' prediction scores plotted versus the predicted risk to develop RA.

91% of UA-patients with a score ≤ 6.0 did not develop RA (negative predictive value 91%, 95%CI 88-94%) and a score ≥8.0 corresponded with progression to RA in 84% (positive predictive value 84%, 95%CI 75-91%). With these cut-off values 145 UA-patients (25%) had a score between 6.0 and 8.0, indicating that for these patients no adequate prediction could be made. Twenty-five UA-patients did not fulfill the 1987 ACR-criteria for RA after one-year follow-up, but developed RA later in the disease course. These patients had a median prediction score of 5.7 (IQR 4.8-6.2); this value is in-between the scores of the UA-patients that did and did not develop RA during the first year of follow-up (median score 7.7, IQR 6.6-8.8 and median score 4.6, IQR 3.3-5.9 respectively).

Discriminative ability

The discriminative ability of the logistic regression model and the prediction rule were evaluated with a ROC curve (Figure 2). Both had an AUC of 0.89 (SE 0.014). The finding that the AUC of the logistic regression model and the prediction rule were equal, indicates that the derivation of the prediction rule from the logistic regression model had not introduced a loss in discriminative ability.

Internal validation

Cross-validation was used to control for over-fitting. This procedure yielded for every patient a predicted probability on RA, based on the model fitted on the other patients

Table 3. Prediction score and number (%) of patients that did not or did progress to RA, as well as several cut-off values for prediction scores with corresponding chances on RA development

Score*	Non-RA n (%)	RA n (%)
0	1 (100)	0 (0)
1	8 (100)	0 (0)
2	42 (100)	0 (0)
3	58 (100)	0 (0)
4	78 (93)	6 (7)
5	73 (85)	13 (15)
6	63 (74)	22 (26)
7	37 (49)	38 (51)
8	16 (33)	33 (67)
9	6 (14)	36 (86)
10	5 (23)	17 (77)
11	0 (0)	8 (100)
12	0 (0)	1 (100)
13	0 (0)	1 (100)
14	0	0
Total	387	175
Score ≤ 4.0	145 (99)	1 (1)
4.0 -10.0	240 (60)	159 (40)
≥10.0	2 (12)	15 (88)
Score ≤ 5.0	223 (97)	8 (3)
5.0-9.0	157 (55)	131 (46)
≥ 9.0	7 (16)	36 (84)
Score ≤ 6.0	296 (91)	28 (9)
6.0-8.0	76 (52)	69 (48)
≥8.0	15 (16)	78 (84)

* Prediction scores were rounded to the nearest number ending in .5 or.0. (i.e. scores ≤0.5 are in the category 0, >0.5 and ≤1.5 in the category 1, etc)

(18). The AUC of the cross-validated predictions nearly equaled the AUC of the prediction score: 0.87 (SE 0.015, Figure 2), indicating that over-fitting is not a major problem.

External validation

In the validation cohort 47% of UA-patients had progressed to RA after one-year follow-up. The prediction scores of the UA-patients that did not and did develop RA are presented in Figure 3. The UA-patients who had progressed to RA had a median prediction score of 8.0 (IQR 6.1-9.1) and the patients who did not develop RA had a median prediction score of 4.6 (IQR 3.5-5.5). 94% of the patients with a prediction score ≤6.0 had not progressed to RA and RA-development was observed in 83% of patients with a score >6. All patients with a score ≥8.0 had progressed to RA and 78% of patients with a score <8 did not develop RA. 17% of the UA-patients in the validation cohort had a prediction score

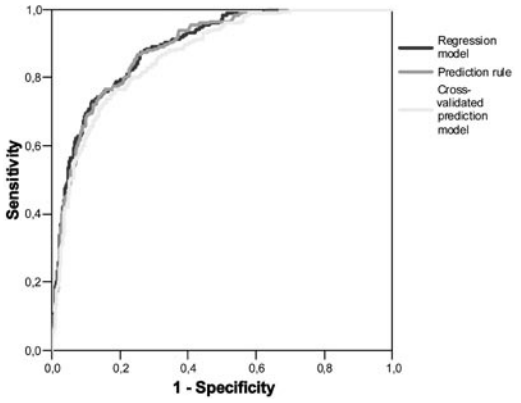

Figure 2. Receiver operator curve of logistic regression model, prediction rule and cross-validated prediction model. The AUC of the logistic regression model, prediction rule and cross-validated prediction model were respectively 0.89, 0.89 and 0.87.

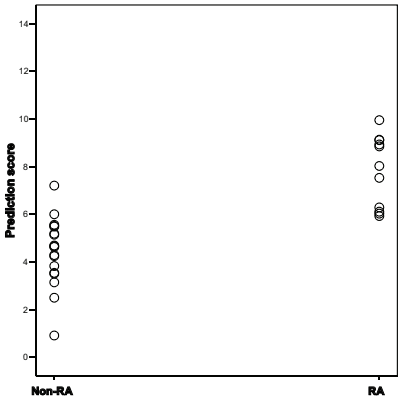

Figure 3. The prediction scores of the patients included in the external validation cohort that did not and did develop RA.

between 6 and 8; two-third of them had not developed RA and one-third had developed RA. When treatment decisions were based on the prediction rule using the cutoff level ≥8 for initiating treatment and ≤6 for withholding treatment, only 6% of the patients should have been inaccurately withheld from treatment and no patients should have been inaccurately treated. The AUC of the validation cohort was 0.97 (SE 0.024).

DISCUSSION

The currently developed rule predicts in UA-patients the risk to develop RA using nine clinical variables that are all commonly assessed during the first visit: gender, age, localization of joint symptoms, morning stiffness, counts for tender and swollen joints, CRP, rheumatoid factor and anti-CCP antibodies. The resulting prediction score corresponds with a chance on progression to RA. The positive and negative predictive values of the prediction score depend on the chosen cut-off values. The discriminative ability was excellent with an AUC of 0.89, and 0.87 after internal validation correcting for over-fitting. The subsequent validation in a small independent cohort revealed an AUC of 0.97. As the developed prediction rule is accurate and easily assessed in daily clinical practice, the present model is an important step forward in achieving individualized treatment in patients with recent-onset UA.

As current evidence on treatment of RA is based on large trials using patients fulfilling the 1987 ACR-criteria for RA, fulfilment of these criteria was used as outcome. Alternative

outcome measurements such as disease persistence or remission can be considered, but no generally accepted definitions for these disease states are present and there are no trials of patients with these disease states providing guidance in treatment decisions. Nevertheless, the use of fulfilment of the ACR-criteria as outcome may lead to circularity as the items of the ACR-criteria are expected to result as predictive variables. However, several studies have shown that the ACR-criteria themselves have low discriminative value in patients with UA (12, 19-23) and only part of the variables of the present prediction rule are items of the ACR-criteria. In the end it will most likely not make a large difference whether the outcome of a prediction rule is the diagnosis RA or disease persistence, as the ACR-criteria are formulated based on RA-patients with longstanding/persistent disease (mean disease duration 8 years) and the reported remission rate in these patients is low: 10-15% (24,25).

Misclassification may have occurred when patients who presented with UA were treated with any drug that has hampered the progression to RA. In case of misclassification, patients that normally had progressed to RA are now classified as non-RA. Exclusion of these eventual misclassified patients, with supposedly high prediction scores as they were prone to develop RA, will result in an increased discriminative ability of the current prediction rule.

The presence of erosions on radiographs of hands and/or feet is reported to have a high specificity (but low sensitivity) for discriminating between self-limiting and persistent disease (23). Although in univariate analysis erosions were significantly more present in the UA-patients that developed RA compared to the UA-patients that did not (16% vs. 7%), multivariate regression analysis revealed that the presence of erosions was not an independent prognostic variable. The presence of erosions appeared to be associated with a higher age (median 64 years in erosive versus 49 years in non-erosive disease), number of swollen joints (median 5 joints in erosive versus 2 joints in non-erosive disease) and presence of rheumatoid factor (46% in erosive versus 23% in non-erosive disease). As the presence of erosions was not identified as a variable with an independent predictive value, data on erosions were not included in the prediction rule.

A model for the prediction of a self-limiting, persisting or erosive arthritis exists (23). For this model's development all consecutive patients referred with arthritis were incorporated, including the patients in whom during the first weeks a definite diagnosis was made. Decisions on initiation of DMARDS are seldom problematic in these patients. At present, support in treatment decisions is needed in patients with recent onset UA (26), as the disease outcome in these patients is variable. The present study therefore selected the patients with UA from a total number of 1700 consecutive patients and developed a prediction rule specifically for UA.

The positive and negative predictive values of the prediction score depend on the chosen cut-off level. If the upper and lower cut-off values were 8.0 and 6.0, the corresponding positive predictive value and negative predictive value were respectively 84% and 91%. In the original cohort 25% of patients had a prediction score between 6.0 and 8.0; these patients had an equal chance to develop RA or not. Apparently, clinical characteristics are in these patients insufficient to predict the disease outcome. In the validation cohort, the prediction score discriminated even better: a hundred percent of patients with a score of 8.0 or higher had progressed to RA and 94% of patients with a score of 6.0 or lower did not develop RA. This indicates that when treatment decisions were based on the prediction rule using the cutoff level ≥8 for initiating treatment and ≤6 for withholding treatment, only 6% of the patients should have been inaccurately withheld from treatment and no patients should have been inaccurately treated. In the validation cohort 17% of patients had a prediction score between 6.0 and 8.0; for treatment decisions in these patients the observed risk to progress to RA can be weighted against the individual risk profile for treatment toxicity. Although the validation cohort is relatively small and the current prediction rule should be evaluated in other early arthritis cohorts, we feel that the current model allows physicians and patients an evidence-based choice whether or not to initiate DMARDs in the majority of patients presenting with UA.

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