Arthritis & Rheumatology
Vol. 0, No. 0, Month 2025, pp 1–14
DOI 10.1002/art.43218

American College of Rheumatology
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EULAR/American College of Rheumatology Risk Stratification Criteria for Development of Rheumatoid Arthritis in the Risk Stage of Arthralgia

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This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the EULAR Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an independent data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

Classification criteria are essential in clinical and basic science research because they allow investigators to study relatively homogeneous populations of patients recruited from a single or multiple research sites. In clinical settings, diagnoses are made by health care professionals evaluating an individual patient's symptoms, signs, and results of laboratory and imaging studies in order to guide therapeutic recommendations. Patients diagnosed with a particular disease may or may not fulfill classification criteria for that disease. Classification criteria, in the hands of an experienced clinician with expertise in rheumatology, may inform a diagnostic evaluation, but improperly applied classification criteria may lead to misdiagnosis.

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Objective. The field of rheumatoid arthritis (RA) is moving towards identification of and intervention in people at risk of RA, but a validated risk stratification method is lacking. This work was undertaken to develop a risk stratification method for persons presenting with arthralgia considered to be at risk of RA.

Methods. A joint EULAR/American College of Rheumatology (ACR) expert committee was established. Risk factor and outcome data from 10 arthralgia cohorts (including clinically suspect arthralgia and autoantibody-positive arthralgia) were studied. The work focused on differentiating the risk of progression to clinically apparent inflammatory arthritis (IA) within 1 year, using clinical and serologic variables, without and with subclinical joint inflammation detected by ultrasound (US) or magnetic resonance imaging (MRI). Developing RA according to the 2010 EULAR/ACR criteria within 1 year was a secondary outcome. A set of validated risk stratification criteria was developed.

Results. Using data from 2,293 symptomatic at-risk individuals, a stratification method was derived consisting of 6 clinical and serologic variables (morning stiffness, patient-reported joint swelling, difficulty making a fist, C-reactive protein, rheumatoid factor, and anti-citrullinated peptide antibody) yielding an area under the curve (AUC) of 0.80 (95% confidence interval [CI] 0.77–0.83) for IA development. The inclusion of US variables did not increase the discriminative ability. When MRI-detected subclinical inflammation variables were included, the AUC was 0.87 (95% CI 0.82–0.90).

In the presence of clinical, serologic, and MRI variables, a sensitivity and specificity of >75% was achieved. For RA development, the AUC of the criteria with MRI was 0.93 (95% CI 0.90–0.97).

Conclusions. EULAR/ACR risk stratification criteria have been developed for people with arthralgia in secondary care who are considered at risk for RA. The criteria can be applied in the absence or presence of imaging data and have been developed to define homogeneous risk groups for future prevention trials.

INTRODUCTION

Rheumatoid arthritis (RA) is among the most common chronic autoimmune diseases. The presence of clinically apparent synovitis (swollen joints) is critical to diagnose and classify RA.[1] It has been established that early therapeutic interventions for RA improve clinical outcomes and reduce the progression of joint damage and disability.[2] Furthermore, it is well recognized that autoimmune processes may be aberrant long before clinical arthritis first develops.[3–5] This has led to a focus on the prearthritis stages of RA, under the hypothesis that these early stages are more amenable to disease-modifying interventions.

The transition from 'health' to RA has been divided into several stages: genetic and environmental risk factors, evidence of systemic autoimmunity, and symptoms, followed by clinically apparent inflammatory arthritis (IA) onset.[6] The symptomatic risk stage was defined using a data-driven approach with clinical expertise for reference, resulting in the EULAR definition of arthralgia suspicious for progression to RA.[7,8] This definition (consisting of symptoms and signs) is useful to distinguish arthralgia suspicious for progression to RA from other kinds of arthralgia. Many groups have initiated observational cohort studies of arthralgia at risk for RA, either in persons with clinically suspected arthralgia (CSA) or in persons with autoantibodies and arthralgia/musculoskeletal (MSK) symptoms. A recent EULAR taskforce summarized existing biomarker data and concluded that there was not yet consensus on which combination of predictors was most informative and that proper validation was lacking.[9,10] A uniform, accurate, and validated method for risk stratification in individuals with arthralgia is therefore warranted.

This article is simultaneously published in *Annals of the Rheumatic Diseases*.

Supported by EULAR and the American College of Rheumatology (ACR) (QoC 017).

Patient involvement: patient research partners from EULAR and ACR were part of the taskforce and included as authors on this work.

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Additional supplementary information cited in this article can be found online in the Supporting Information section (https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.43218).

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Submitted for publication May 1, 2025; accepted May 1, 2025.

This need is fueled by the results of recent randomized placebo-controlled trials that suggest that therapeutic interventions in CSA or autoantibody-positive arthralgia can modify the disease course.[11–13] To help design future trials efficiently, effective risk stratification is important to identify homogeneous groups when evaluating the effectiveness of interventions. In addition, at-risk individuals themselves have indicated that reliable risk information is pivotal for their interpretation of symptoms and decision-making.[14–16] Finally, accurate and accepted risk stratification is required by regulatory agencies. Therefore, to support and homogenize further studies in the pre-RA field, a EULAR and American College of Rheumatology (ACR) expert committee was formed to develop an accurate and validated risk stratification algorithm. An important consideration was that the method should be applicable regardless of the method used to identify symptomatic persons at risk (clinical grounds [CSA] or autoantibody-positive arthralgia) and regardless of the availability of imaging modalities for detecting subclinical joint inflammation. Second, it was considered important to ensure that the generated risk stratification criteria would not be misinterpreted as indicating the presence of a disease or as classification criteria. With these overarching principles, an expert committee developed EULAR/ACR risk stratification criteria.

METHODS

Expert committee. In 2020, a EULAR committee of experts in the field of 'arthralgia at risk of RA' was established. To pool existing cohort data and develop consensus, members were invited because they were the principal investigator of an arthralgia cohort or because of their expertise in this area. In 2023, it was decided by ACR and EULAR to include ACR experts and to continue as a joint EULAR/ACR initiative. The final expert committee consisted of 20 rheumatologists, 2 fellows, 1 EMEUNET representative, 4 patient research partners, 2 allied health professionals, 1 methodologist, and 2 statisticians, recruited from 10 European countries and North America.

Data sharing procedure. An inventory of available data in at-risk cohorts was made (including inclusion criteria, endpoints, and risk variables). At the first meeting (June 2021), consensus was reached on the variables to be shared and on the primary endpoint. At the second meeting (June 2022), data transfer agreements were signed and some data were shared. The final datasets were shared in October 2022. The principal investigators of the cohorts shared their cohort data for this project, but data will not be openly accessible to the general public.

Study population. Some cohorts included persons defined as being at risk for RA because of autoantibody positivity with any arthralgia/MSK symptoms; others were selected based on the rheumatologists' expert opinion that the person had arthralgia characteristics that put them at high risk of progressing to RA (ie, CSA). The expert committee agreed to include both approaches. Additionally, it was decided to exclude cohorts in which at least some individuals were treated with disease-modifying antirheumatic drugs in the phase of arthralgia/MSK symptoms. The cohorts are described in Supplemental Tables S1 and S2. By definition, all at-risk individuals studied did not have clinically apparent IA at inclusion in the cohorts. Ethical approval was ensured by the individual cohorts.

Endpoint. The primary endpoint was the development of clinically apparent IA, identified by physical examination by rheumatologists, at 1-year follow-up. This was collected across all cohorts. Secondary endpoints were fulfilling of the 2010 EULAR/ACR criteria for RA[1] at 1 year and developing IA at 2 years follow-up.

Risk variables. Three categories of predictor variables were studied: clinical and serologic (available in all cohorts), and, where available, subclinical inflammation detected by ultrasound (US) or magnetic resonance imaging (MRI) (Supplemental Table S1). Clinical variables were studied as available (31 variables, Supplemental Figure S1A). The presence of CSA, based on clinical opinion or EULAR definition,[7] was not included as a variable because it was missing from autoantibody-positive arthralgia cohorts. However, data on several clinical items from the EULAR definition were available and examined. Imaging protocols differed between the cohorts (Supplemental Table S3 for US, Supplemental File S1 for MRI). Anatomical sites and characteristics that were reasonably similar across cohorts were included (92 variables for US and 62 for MRI, Supplemental Figure S1B and S1C). The presence of subclinical inflammation by US was defined as grey scale (GS) ≥2 (except for metatarsophalangeal [MTP] joints 1–3, where a threshold of ≥3 was chosen because of the prevalence of GS ≤2 in healthy persons[17]) or power Doppler ≥1. For MRI, subclinical inflammation was considered present if the Rheumatoid Arthritis Magnetic Resonance Imaging Score at a joint/bone/tendon sheath was present in <5% of age-matched symptom-free persons at the same location.[18,19]

Statistics. A statistical analysis plan was developed and approved.

Derivation. Missing variables were imputed using the total dataset (including available clinical, serologic, imaging, and outcome data). Twenty completed datasets were created using multiple imputation by chained equation.

Because of a high number of variables in relation to the number of events, the number of variables was reduced prior to the main analyses to prevent overfitting. Thirty-one clinical items were present. Some were not included, eg, because of absence of

association in univariable logistic analyses of the primary endpoint, leaving 24 clinical and serologic variables for the main analyses (Supplemental Figure S1A). For US, data from 92 variables were present across the cohorts (Supplemental Figure S1B). Summation reduced this to 10 US variables without loss of discriminatory capacity (area under the receiver operating characteristic curve [AUC]) (Supplemental Figure S1B). Similarly, 62 MRI variables were summed into 12 variables (Supplemental Figure S1C).

For the main analyses, least absolute shrinkage and selection operator (Lasso) penalized regression was used. First, a Lasso logistic regression model was built with 24 clinical and serologic variables and the primary endpoint as outcome in the total dataset of all cohorts for application in the absence of imaging data. The regression coefficients of the selected variables were fixed into a linear predictor (ie, clinical and serologic variables with fixed coefficients). Subsequently, this linear predictor was included in 2 other analyses, including 10 baseline US or 12 MRI variables. These analyses assessed the incremental value of US-/MRI-detected inflammation added to the information from the clinical and serologic variables.

Cohort heterogeneity was evaluated by adding a cohort variable as an adjustment variable. Two cohort variables were studied: grouped in 2 categories (identification of being at risk based on autoantibody-positive arthralgia/MSK symptoms or CSA) or 5 categories (grouping by geography/region and identification method).

A risk stratification algorithm was derived by summing the coefficients of the identified items with scaling and rounding for better applicability. This consisted of a section with clinical and serologic variables, and if US or MRI data were available, these additional variables could be used. The predicted risks were plotted against the risk scores. Test characteristics (sensitivity and specificity) and predictive values (positive and negative predictive values) were determined for different cutoffs of risk scores.

Discriminatory capacity of the 3 models (clinical and serologic, +US, and +MRI) was assessed primarily by the AUC, with higher AUCs indicating better performance. We evaluated whether a sensitivity and specificity of ~80% (a priori selected criterion) was achieved.

We assessed whether risk stratification could be simplified without loss of performance (AUC). Additionally, we compared the percentage of participants with low, intermediate, or high risk where risk categories were arbitrarily defined (low risk <25% development of clinically apparent IA; intermediate risk 25%–75%; high risk ≥75%). The goal was to have as few people as possible in the intermediate risk group. Statistical methods are further described in Supplemental File S2.

Validation. We applied a cross-validation procedure with 200 bootstrap replications. In addition, the total dataset was split into 2 sets comprising two-thirds and one-third; the split was performed at the cohort and outcome levels. Finally, the performance per each of 5 groups of cohorts was evaluated.

Final consensus. The results were presented at the third meeting (in-person, at EULAR congress 2023) and at the final online meeting (June 2023). Consensus was then assessed by voting according to the EULAR standardized operating procedures.[20]

RESULTS

Population. Of the 14 cohorts in the inventory phase, 10 cohorts generated data from a total of 2,583 symptomatic at-risk persons (Supplemental Figure S2, Supplemental Table S1). These data came from observational cohorts from Amsterdam (The Netherlands), Birmingham (UK), Erlangen (Germany), Leeds (UK), Leiden (The Netherlands), Rotterdam (The Netherlands), Rome (Italy), and Vienna (Austria) and the placebo arm of the Dutch multicenter TREAT EARLIER trial. Two cohorts were excluded because of disease-modifying antirheumatic drug treatment, leaving 2,293 persons for analysis (Table 1, Supplemental File S2).

Primary endpoint. Clinically apparent IA developed in 389 persons (17%) (282 anti-citrullinated peptide antibody [ACPA]-positive, 107 ACPA-negative persons) within 1 year. Clinical, serologic, and imaging factors were studied in relation to this endpoint.

Clinical and serologic risk factors. From the 24 variables, 7 were strongly associated with the primary endpoint (Table 2). These were difficulty to make a fist, patient-reported joint swelling, increased C-reactive protein (CRP), rheumatoid factor (RF), and ACPA, and the cohort variable that was included to adjust for cohort heterogeneity (2-category variable, being at risk based on autoantibody-positive arthralgia/CSA). The AUC was 0.80. When the 5-category cohort variable (5 groups based on geography and autoantibody-positive arthralgia/CSA) was used to adjust for cohort heterogeneity, the results were similar (Supplemental Table S4). The 2-category cohort variable was used as an adjustment factor in further analyses.

US-detected subclinical joint inflammation. A model with only the 10 aggregated US variables (n = 835 with US data) yielded an AUC of 0.63 (Supplemental Table S5). Including these to the panel of fixed clinical and serologic variables identified 5 US variables that were associated with the endpoint (Table 2). This model had an AUC of 0.80.

MRI-detected subclinical joint inflammation. MRI data were analyzed in a similar way as US data. MRI data alone resulted in a model with an AUC of 0.76 (Supplemental

Table 1. Characteristics at baseline and frequency of the primary endpoint*

	Total population (n = 2293)	Population with US (n = 835)	Population with MRI (n = 730)	Population without imaging (n = 728)
Baseline characteristics				
Female, n (%)	1,733 (76)	630 (75)	558 (76)	545 (75)
Age, y, mean (SD)	47 (13)	49 (13)	44 (12)	49 (12)
Symptom duration, wk, median (IQR)	43 (19-104)	51 (26-110)	21 (11-46)	52 (28-156)
Presence of hand symptoms, n (%)	987 (84)	327 (80)	582 (86)	78 (83)
Morning stiffness ≥60 min, n (%)	521 (26)	180 (22)	234 (34)	107 (21)
TJC44, median (IQR)	2 (0-6)	2 (0-6)	4 (2-9)	0 (0-3)
Increased CRP, n (%)	372 (17)	113 (14)	163 (22)	96 (14)
RF positivity, n (%)	949 (41)	357 (44)	150 (20)	431 (61)
Low-positive	455 (20)	155 (19)	59 (8)	241 (34)
High-positive	483 (21)	202 (25)	91 (12)	190 (27)
ACPA positivity, n (%)	1,103 (48)	531 (65)	102 (14)	470 (66)
Low-positive	391 (17)	188 (23)	17 (2)	186 (26)
High-positive	712 (31)	343 (42)	85 (12)	284 (40)
Primary identification method for RA risk, n (%)	1,242 (54)	597 (71)	0	645 (89)
Autoantibody positivity with arthralgia/MSK symptoms				
CSA	1,051 (46)	238 (29)	730 (100)	83 (11)
Primary endpoint				
Clinically apparent inflammatory arthritis within 1 y, n (%)	389 (17)	153 (18)	102 (14)	134 (18)

* ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CSA, clinically suspect arthralgia; IQR, interquartile range; MRI, magnetic resonance imaging; MSK, musculoskeletal; RA, rheumatoid arthritis; RF, rheumatoid factor; TJC, tender joint count; US, ultrasound.

Table S6). Combining the aggregated 12 MRI variables with the fixed clinical and serologic risk factors revealed that 6 MRI variables were incrementally associated with the endpoint (Table 2). The AUC of this model was 0.87.

Development of extended risk stratification. Based on these results, an algorithm was derived using the 6 clinical and serologic variables, the cohort variable, and with the 5 US or 6 MRI variables (Figure 1). The possible scores ranged between 0 and 28 (clinical and serologic data), 0 and 40 (with US data), or 0 to 45 (with MRI data). The predicted risks per score are presented in Figure 1. Additionally, the test characteristics and predictive values for various cutoffs are presented.

Performance. The main statistics for performance were the AUC values, which were 0.80, 0.80, and 0.87 for the clinical and serologic data only, with additional US data, and with additional MRI data, respectively (Table 2). Sensitivity and specificity ~80% was only possible when including MRI data and with a risk score ≥12 (sensitivity 79%, specificity 78%) (Figure 1).

Validation. Internal validation showed little variability in the AUC (Table 3). Analyses in two-thirds and one-third of the population also showed only minor changes in AUC. Analysing the 5 groups of cohorts separately showed AUCs ranging from 0.75 to 0.84 (Supplemental Table S7).

Secondary endpoints. Of the individuals, 12% (209 of 1708) developed RA at 1 year according to the 2010 EULAR/ACR classification criteria. The AUC for this secondary endpoint was 0.85 for the clinical and serologic data, 0.84 when US data were added, and 0.93 when MRI data were added (Table 3). Of the individuals, 21% (441 of 2055) developed clinically apparent IA within 2 years. The AUC values were roughly similar to those with this endpoint at 1 year follow-up (Table 3).

Simplified risk stratification. For ease of use, simplifications were applied for the algorithm with the primary endpoint. The cohort variable was omitted because it is an 'artificial variable' that was used to adjust risk estimates for cohort heterogeneity. US-detected inflammation data were omitted as their contribution was negligible in this analysis. For MRI, only tenosynovitis was included because the contribution of the other combined MRI variables was negligible.

Therefore, the clinical and serologic variables in the final criteria were morning stiffness, presence of patient-reported joint swelling, difficulty making a fist, and increased CRP, RF, and ACPA status (Table 4). For imaging, the presence of tenosynovitis of the flexors of the wrist, the extensors of the wrist, the extensors of the metacarpophalangeal joints and the extensors of the MTP joints were included (Table 4). The clinical and serologic score ranged from 0 to 26; when MRI data was added, the score ranged from 0 to 42 (Table 4). The predicted risks were

Table 2. Results from Lasso regression including clinical and serologic variables plus additional ultrasound- or MRI-detected subclinical joint inflammation*

Variable	Clinical and serologic (n = 2,293)	Clinical and serologic + ultrasound (n = 835)	Clinical and serologic + MRI (n = 730)
Morning stiffness			
30-60 min	1.5	1.5	1.5
≥60 min	2.2	2.2	2.2
Patient-reported joint swelling	2.5	2.5	2.5
Difficulty making a fist	3.7	3.7	3.7
Increased CRP	1.3	1.3	1.3
RF			
Low-positive	1.5	1.5	1.5
High-positive	2.4	2.4	2.4
ACPA			
Low-positive	2.9	2.9	2.9
High-positive	8.2	8.2	8.2
2-category cohort variable[a]	1.7	1.7	1.7
Ultrasound			
PD synovitis PIPs	–	2.8	–
PD tenosynovitis	–	1.7	–
PD synovitis MTPs	–	1.4	–
GS synovitis wrist	–	1.2	–
GS tenosynovitis	–	1.2	–
MRI			
Tenosynovitis flexors wrist	–	–	3.3
Tenosynovitis extensors MCPs	–	–	2.7
Tenosynovitis extensors MTPs	–	–	1.9
Tenosynovitis extensors wrist	–	–	1.3
Osteitis wrist	–	–	1.1
Synovitis MCPs	–	–	1.1
AUC (95% CI)	0.80 (0.77-0.83)	0.80 (0.75-0.84)	0.87 (0.82-0.90)

* Values are the OR derived from the regression coefficient. The regression coefficient was used to derive the weights per variable in Figure 1. As Lasso shrinks the coefficient to zero, measures of variations are not informative. The AUC of the clinical and serologic Lasso model in the n = 835 and n = 730 groups were 0.78 (95% CI 0.72–0.83) and 0.84 (95% CI 0.79–0.88), respectively. ACPA, anti-citrullinated peptide antibody; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; CSA, clinically suspect arthralgia; GS, grey scale; Lasso, least absolute shrinkage and selection operator; MCP, metacarpophalangeal joint; MRI, magnetic resonance imaging; MTP, metatarsophalangeal joint; OR, odds ratio; PD; power Doppler; PIP, proximal interphalangeal joint; RA, rheumatoid arthritis; RF, rheumatoid factor.
[a] Identification of RA risk based on CSA or autoantibody-positive arthralgia/musculoskeletal symptoms.

plotted per risk for RA score, both for the criteria without and with imaging (Figure 2). Test characteristics were presented for several cutoffs for the risk for RA score (Figure 2; Supplemental Tables S8 and S9).

The simplified clinical and serologic model had an AUC of 0.80; when adding MRI data, the AUC was 0.86. Calibration graphs are presented in Supplemental Figure S3. Sensitivity and specificity ≥75% was only possible with the criteria with MRI data; a risk score of ≥10 points corresponded to a sensitivity of 75% and specificity of 79%.

The percentages of participants classified as low, intermediate, and high risk (<25%, 25%–75%, and ≥75%, respectively) based on clinical and serologic data are shown for those who did and did not reach the endpoint (Figure 3). Patients who did not develop clinically apparent IA were almost exclusively in the low-risk group. Patients who developed the endpoint were in all 3 groups. Exploration revealed that the convertors classified as low risk were ACPA-positive with few symptoms or ACPA-negative with little subclinical joint inflammation (Supplemental Table S10). Importantly, the intermediate risk group, which should ideally be as small as possible, contained 18% of all studied at-risk individuals. This intermediate risk group was the smallest, 11%, when MRI data were included (Figure 3).

Consensus. During voting in the final meeting, 96% of task force members approved the stratification criteria. It was agreed to present both the extended and simplified versions, and agreement was reached on the target population defined in the eligibility criteria (Table 4).

DISCUSSION

We present EULAR/ACR risk stratification criteria for the development of clinically apparent IA and RA, representing the culmination of an international collaborative effort that

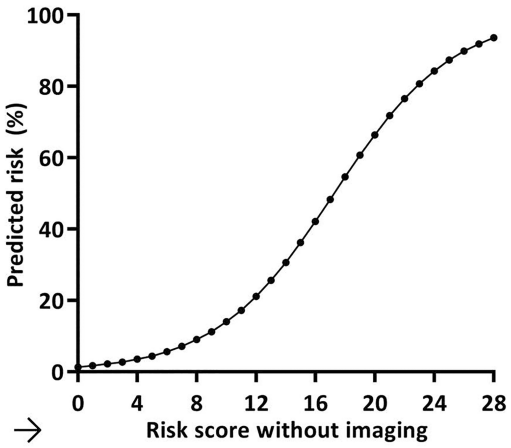
A

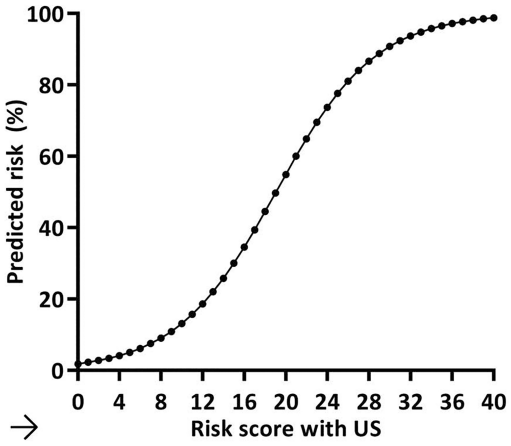
Clinical & serological factors:	
Morning stiffness, 30-60 min	2
≥ 60 min	4
Patient-reported joint swelling	4
Difficulty with making fist	5
Increased CRP	1
RF, Low-positive	2
High-positive	4
ACPA, Low-positive	4
High-positive	8
2-category cohort variable CSA as primary identification method for RA-risk	2
Total score:	...

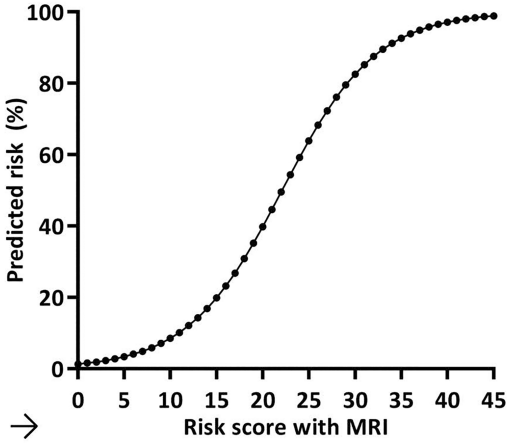
If ultrasound:	
Score Clinical & serological factors	...
PD synovitis PIPs	5
PD tenosynovitis	3
PD synovitis MTPs	2
GS synovitis wrist	1
GS tenosynovitis	1
Total score:	...

If MRI:	
Score Clinical & serological factors	...
Tenosynovitis flexors wrist	6
Tenosynovitis extensors MCPs	5
Tenosynovitis extensors MTPs	3
Tenosynovitis extensors wrist	1
Synovitis MCPs	1
Osteitis wrist	1
Total score:	...

B







C

Cutoff	Sens	Spec	PPV	NPV	% persons
≥5 points	97%	24%	21%	98%	80%
≥8 points	84%	43%	30%	95%	63%
≥10 points	73%	63%	36%	93%	45%
≥12 points	56%	77%	44%	90%	31%
≥14 points	42%	80%	50%	89%	19%
≥16 points	28%	93%	59%	87%	12%
≥19 points	14%	98%	64%	85%	5%
≥21 points	8%	99%	76%	84%	3%
≥23 points	2%	99.7%	77%	83%	1%

Cutoff	Sens	Spec	PPV	NPV	% persons
≥6 points	97%	21%	23%	97%	83%
≥9 points	84%	50%	30%	94%	57%
≥12 points	64%	70%	41%	91%	38%
≥14 points	52%	84%	49%	89%	24%
≥16 points	41%	90%	60%	88%	17%
≥19 points	22%	97%	64%	84%	7%
≥21 points	14%	98%	71%	84%	5%
≥24 points	4%	99.5%	74%	82%	1%

Cutoff	Sens	Spec	PPV	NPV	% persons
≥5 points	98%	21%	17%	98%	81%
≥8 points	94%	47%	23%	98%	89%
≥10 points	84%	61%	32%	96%	46%
≥12 points	79%	78%	38%	96%	30%
≥14 points	73%	85%	44%	95%	23%
≥16 points	67%	90%	52%	94%	18%
≥20 points	43%	96%	68%	91%	11%
≥23 points	29%	98%	80%	90%	5%
≥26 points	21%	99%	85%	89%	4%

Figure 1. Risk stratification for development of inflammatory arthritis within 1 year using clinical and serologic data and with additional US- or MRI-detected subclinical joint inflammation in arthralgia at risk for RA (A), with predicted risks per risk scores (B), and test characteristics and predictive values for different risk score cutoffs (C). The risk score without imaging ranges from 0 to 28, the risk score with US from 0 to 40, and the risk score with MRI from 0 to 45. The cohort variable was included to adjust for heterogeneity between the cohorts. This was classified in a 2-category variable based on the primary identification method for RA risk, namely identification of being at risk based on autoantibody-positive arthralgia/musculoskeletal symptoms or CSA. ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CSA, clinically suspect arthralgia; GS, grey scale; MCP, metacarpophalangeal joint; MRI, magnetic resonance imaging; MTP, metatarsophalangeal joint; NPV, negative predictive value; PD, power Doppler; PIP, proximal interphalangeal joint; PPV, positive predictive value; RA, rheumatoid arthritis; RF, rheumatoid factor; Sens, sensitivity; Spec, specificity; US, ultrasound.

Table 3. Performance of validation using bootstrapping and data split and for secondary endpoints*

Included variables	Internal validation			Secondary endpoints	
	Bootstrapping AUC (95% CI)	Data $^{2}/_{3}$ AUC (95% CI)	split $^{1}/_{3}$ AUC (95% CI)	Clinical arthritis within 2 y AUC (95% CI)	RA (2010 criteria) within 1 y AUC (95% CI)
Clinical and serologic	0.80 (0.77-0.83)	0.80 (0.77-0.83)	0.80 (0.77-0.83)	0.79 (0.77-0.82)	0.85 (0.83-0.88)
Clinical and serologic + US	0.79 (0.74-0.84)	0.80 (0.76-0.83)	0.79 (0.74-0.82)	0.78 (0.75-0.81)	0.84 (0.78-0.90)
Clinical and serologic + MRI	0.86 (0.81-0.89)	0.84 (0.81-0.86)	0.83 (0.80-0.85)	0.85 (0.81-0.89)	0.93 (0.90-0.97)

* A total of 2,055 persons had 2-year follow-up data; of these, 441 (21.5%) progressed to clinical arthritis within 2 years. A total of 1,708 persons had data on development of clinical arthritis and fulfilled the 2010 EULAR/ACR classification criteria for RA; of these, 209 (12.2%) developed RA within 1 year. Derived models were evaluated after a two-third to one-third split that was performed at the cohort and outcome levels. ACR, American College of Rheumatology; AUC, area under the curve; CI, confidence interval; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; US, ultrasound.

Table 4. EULAR/ACR risk stratification criteria (after simplification) for individuals with arthralgia at risk for RA, to be used in presence or absence of imaging*

Target population (who should be tested?): persons with arthralgia in secondary care without clinical arthritis with the arthralgia not better explained by another disease/condition		
Clinical and serologic characteristics		Score
Morning stiffness[a]	0-30 min	0
	30-60 min	2
	30-60 min	4
Patient-reported joint swelling[b]	No	0
	Yes	4
Difficulty making a fist[c]	No	0
	Yes	5
Increased CRP[d]	No	0
	Yes	1
RF[e]	Negative	0
	Low-positive	2
	High-positive	4
ACPA[e]	Negative	0
	Low-positive	4
	High-positive	8
Clinical and serologic sum score		*See* Figure 2 *for risk*
Imaging characteristics if also MRI		
Tenosynovitis flexors wrist[f]	Absent	0
	Present	6
Tenosynovitis extensors wrist[g]	Absent	0
	Present	2
Tenosynovitis extensors MCPs[h]	Absent	0
	Present	5
Tenosynovitis extensors MTPs[i]	Absent	0
	Present	3
Subscore MRI		
Clinical, serologic, and imaging sum score		*See* Figure 2 *for risk*

* The sum risk score without imaging ranges from 0 to 26 and with imaging from 0 to 42. Predicted risks and test characteristics for several cut-offs of risk scores are presented in Figure 2, with a more extensive list in Supplemental Table S8. The AUC of the criteria without imaging is 0.80 and with MRI data is 0.85. A sensitivity and specificity of ≥75% was only possible with the risk stratification criteria with imaging data and a score of ≥10 points. ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; IU, international unit; MCP, metacarpophalangeal joint; MRI, magnetic resonance imaging; MTP, metatarsophalangeal joint; RAMRIS, Rheumatoid Arthritis Magnetic Resonance Imaging Score; RF, rheumatoid factor; ULN, upper limit of normal.

[a] Morning stiffness refers to patient-reported duration of joint stiffness in the morning.

[b] Patient-reported joint swelling refers to presence of a swollen joint as reported by the patient.

[c] Difficulty with making a fist is defined as inability of ≥1 fist with incomplete closure (fingertips do not touch the palm at active closing).

[d] Increased CRP defined as above the local laboratory reference.

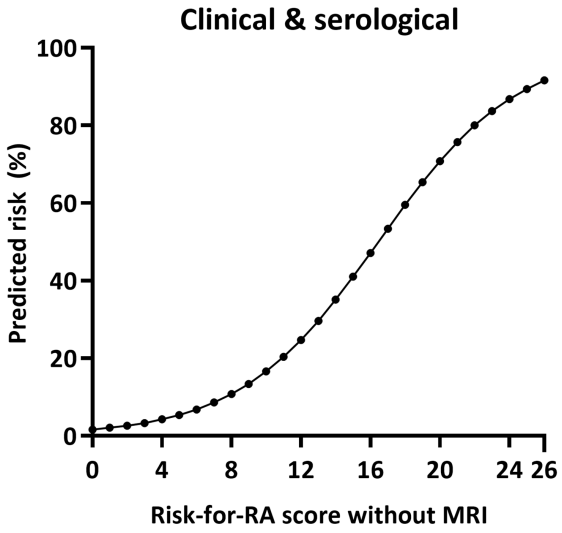
[e] For RF and ACPA, negative refers to IU values less than or equal to the ULN for the laboratory and assay; low-positive refers to IU values that are greater than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay.

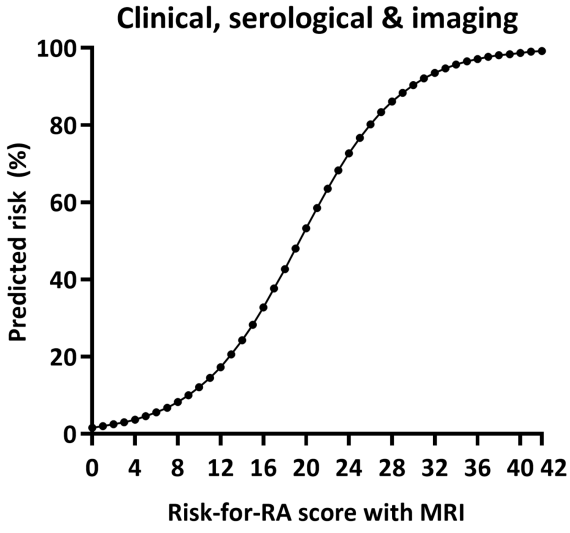
[f] Tenosynovitis of the wrist flexors: presence (RAMRIS ≥1) Of any tenosynovitis of the following: flexor carpi ulnaris, ulnar bursa including flexor digitorum profundus and superficialis tendon quartets, flexor pollicis longus (tendon) in radial bursa, or flexor carpi radialis.

[g] Tenosynovitis of wrist extensors: presence (RAMRIS ≥1) Of any tenosynovitis of the 6 extensor compartments: (I) extensor pollicis brevis, abductor pollicis longus; (II) extensor carpi radialis brevis, extensor carpi radialis longus; (III) extensor pollicis longus; (IV) extensor digitorum communis, extensor indicus proprius; (V) extensor digiti quinti proprius; (VI) extensor carpi ulnaris.

[h] Tenosynovitis of the extensors of the MCPs: presence (RAMRIS ≥1) Of any tenosynovitis of the extensors of MCP2-5.

[i] Tenosynovitis of the extensors of the MTPs: presence (RAMRIS ≥1) Of any tenosynovitis of the extensors of MTP1-5.





Cutoff	Sens	Spec	PPV	NPV
≥4 points	95%	14%	23%	97%
≥6 points	90%	38%	26%	96%
≥8 points	78%	50%	33%	94%
≥10 points	66%	71%	38%	92%
≥12 points	51%	80%	46%	90%
≥14 points	37%	91%	53%	88%
≥16 points	24%	94%	60%	86%
≥18 points	13%	98%	64%	85%
≥20 points	7%	99%	71%	84%

Cutoff	Sens	Spec	PPV	NPV
≥5 points	94%	41%	22%	98%
≥8 points	83%	61%	34%	95%
≥10 points	75%	79%	41%	95%
≥12 points	70%	85%	47%	95%
≥15 points	55%	93%	61%	93%
≥18 points	47%	96%	69%	92%
≥20 points	34%	98%	74%	90%
≥22 points	28%	99%	82%	89%
≥24 points	20%	99%	84%	88%

Figure 2. Predicted risks (graph) and test characteristics and predictive values for several score cutoffs (table) for the risk stratification criteria with- out or with imaging. Predicted risks for the sum scores obtained in Table 4. Test characteristics and predictive values for several cutoffs of risk scores are shown; an extensive list of cutoffs with test characteristics and data on the percentage of persons with these cutoffs is presented in Supplemental Table S8. The area under the curve of the criteria without imaging is 0.80 and with MRI data is 0.85. MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; RA, rheumatoid arthritis; Sens, sensitivity; Spec, specificity.

included researchers curating arthralgia cohorts, expert rheumatologists, health care professionals, and patient research partners across Europe and North America. The risk stratification criteria consist of symptoms (morning stiffness, patient-reported joint swelling), a sign (difficulty making a fist), serologic markers (CRP, RF, and ACPA), and MRI-detected tenosynovitis. This product has been developed with the key aim of supporting the inclusion of homogeneous risk groups in future prevention trials with individuals with arthralgia in secondary care in whom imminent RA is considered more likely than other causes of arthralgia. Importantly, risk of a disease is not the same as having a disease and therefore, the product is not described as classification criteria.

We aimed to derive an algorithm that is broadly applicable both in settings in which imaging modalities are available to detect subclinical joint inflammation and where such modalities are lacking. The statistical methodology was adapted accordingly, aiming to take maximum advantage of the information from clinical and serologic variables. Most importantly, the information from clinical and serologic data was fixed and prioritized. In the presence of both imaging-detected subclinical inflammation and clinical data, whereby the latter was related to inflammation (eg, morning stiffness is known to be related to subclinical synovitis[21] and difficulty making a fist to subclinical tenosynovitis[22]), multivariable analyses will generally select the imaging variable as the best predictor for RA development because of the most direct relationship. However, for practical application, clinical variables were given priority (set as fixed in the analyses). Consequently, the effect sizes of the clinical and serologic variables were larger than if such an approach had not been applied. In contrast, the effect sizes of imaging variables were lower than would have been the case without this prioritization, and with this approach only revealed the incremental value of adding imaging to what was already known through the clinical and serologic variables. The value of imaging is therefore also lower than previously reported in studies in symptomatic at-risk individuals. This method led to an algorithm that is applicable also in the absence of imaging modalities. The criteria without imaging perform well because they use the underlying correlation of clinical with imaging variables in this

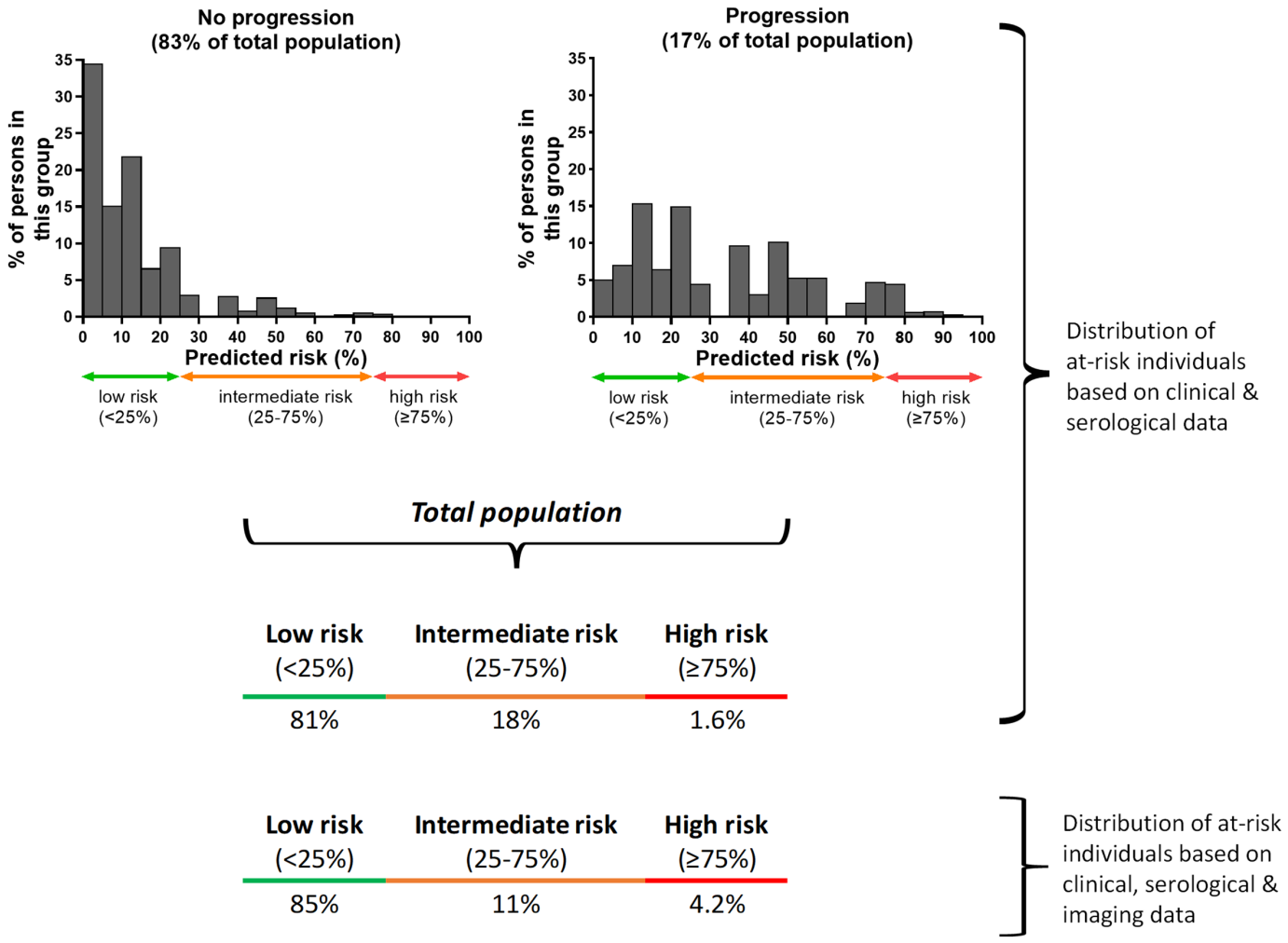


Figure 3. Distribution of subjects who did not and did reach the endpoint based on the predicted risks using the risk stratification criteria with clinical and serologic data in Table 4. Subsequently, risk categories were defined as low (<25% risk), intermediate (25%-75%) and high (≥75%) in the total population based on clinical and serologic data (n = 2,293). The same was done when additionally using MRI data (n = 703). Characteristics of per- sons who developed the endpoint and were categorized as low risk (8% of the total population) are presented in Supplemental Table S10, both for the setting without and with imaging data. MRI, magnetic resonance imaging.

population. Because this is a derivative, the criteria with imaging may be preferred for optimal trial design.

Importantly, the risk stratification criteria are derived from data collected in secondary care and as such are based on the correlation structure between the variables that exist in arthralgia patients in secondary care. For example, patient-reported swelling is related to subclinical joint inflammation in arthralgia at risk for RA.[23] In other situations, eg, the general population in which hand osteoarthritis is more prevalent than imminent RA, this relationship may be different. Consequently, this method cannot be extrapolated for trials in other populations (eg, primary care-based populations) or for triaging referrals from primary to secondary care. The developed criteria are expected to be widely applicable, but only in persons seen with arthralgia in secondary care, where impending RA is more likely than other causes of arthralgia.

The criteria were derived with the idea that the accuracy of data-driven risk stratification performs better than risk stratification by expert opinion of individual rheumatologists. Whether this assumption is true needs to be verified in future studies.

Performance was evaluated using the AUC (combining sensitivity and specificity). In line with the aim of promoting the inclusion of homogeneous risk groups in future studies, this metric evaluates performance for groups of persons. At the design of the project, the intention was to achieve both specificity and sensitivity of ~80%. The algorithm using clinical and serologic data achieved a 'best combination' of sensitivity and specificity of approximately 65% to 70% (Figures 1 and 2). When MRI data were available, a specificity and sensitivity of almost 80% was achieved by a score ≥12 in the expanded version or ≥10 in the simplified version. Therefore, if a sensitivity and specificity of both >75% are desired, the imaging criteria and a cutoff of ≥10 points

are appropriate. However, the expert committee did not choose one cutoff point because, depending on the clinical situation or intervention (with different risks of side effects), either a (very) high sensitivity or specificity may be preferred. With the current presentation, investigators can choose the test characteristics and corresponding cutoff that is felt acceptable by their team of rheumatologic and patient experts.

Importantly, it was not the intention to develop an instrument for individual patients in clinical practice. Absolute risk estimates are more difficult to generalize (than test characteristics) because they depend on prior risks of a disease (context-dependent prevalence). Interestingly, the prior risk of developing clinical arthritis within 1 year was quite similar in all at risk populations studied here (ranging from 14%–18%). Nonetheless, this may be different in other places, and the developed criteria are therefore not suitable for decision-making in individual patients.

Subclinical joint inflammation (particularly tenosynovitis) is a known predictor of clinical arthritis and RA development,[24] and data collected via US and MRI were assessed. MRI-detected subclinical joint inflammation showed some incremental value compared to clinical and serologic data alone. This was demonstrated by an increase in AUC and a higher combination of sensitivity and specificity. This did not occur for subclinical inflammation detected with US. This difference may be explained by previous findings that tenosynovitis is a powerful imaging predictor missed by US in up to 80% of tenosynovitis lesions compared to MRI.[25,26] Additionally, US scanning protocol and gradings that were used in the cohorts were different and could not be standardized in retrospect. The available US data also included less tenosynovial sites than MRI (Supplemental Table S3). US-detected erosions were shared from 1 dataset (Rotterdam SONAR cohort) and were found to be nonpredictive. The taskforce had extensive discussions about the US results, and it was agreed that the data would be presented as they are, with the US in the extended algorithm. Furthermore, the US results presented here apply to the setting of individuals with arthralgia at risk for RA and are not relevant to the value of US in a broader context in the field of RA.

MRI also has disadvantages. Some subtle synovitis and osteitis is present when using contrast-enhanced MRI in the general symptom-free population, especially in older age and in specific joints and bones.[18] These variations need to be considered when defining an abnormal MRI result to prevent false-positive tests.[19] In contrast, tenosynovitis has been found to be rare in the general population[18] and was the only variable that remained in the simplified risk stratification criteria. Tenosynovitis is also relatively easy to detect reliably on MRI. Although MRI is already used for the classification of other rheumatic diseases,[27] MRI may be considered impractical due to the need for intravenous contrast agents, long scan times, and resulting high costs. Recent data have emerged suggesting that a short modified Dixon MRI sequence correlates well with conventional contrast-enhanced MRI for scanning of hands/forefeet.[28] With a scan time of 5 minutes without the need for intravenous contrast, this could make MRI more feasible. The value of this short MRI sequence and its cost-effectiveness are subjects for further research. If positive, this could have a significant impact on the assessment of the burden and costs of MRI compared to the incremental value in risk stratification.

The method for identifying persons at risk of RA varies between centers and countries. In some, the presence of a positive autoantibody test is the starting point, and the presence of any MSK symptom increases the risk. Alternatively, individuals can be identified by a combination of symptoms and signs that resemble RA but where clinical IA is absent, ie, by having CSA. Both identification methods alone have proven to be insufficient. Risk stratification, as shown previously[29–31] and also here, requires a combination of clinical and serologic features combined with imaging of joints. Although all participants in the CSA cohorts were reported to have CSA by their rheumatologists, for participants in the autoantibody-positive cohorts, it was unknown whether they had CSA (according to their rheumatologist), and data from some items of the EULAR definition of CSA[7] were absent/incomplete. Therefore, having CSA at an individual level could not be included in the analyses, but several clinical items that are part of the EULAR definition of CSA have entered the risk stratification criteria (morning stiffness and difficulty making a fist).

The primary endpoint, development of clinically apparent IA, was ascertained by consensus and was a pragmatic choice because data on the 2010 classification criteria for RA were missing in 25%. RA was most likely the final diagnosis in the event of the development of clinical arthritis because at-risk individuals were selected based on RA-related autoantibodies or CSA. Previous studies of cohorts that are included here have demonstrated that diagnoses other than RA or undifferentiated arthritis are indeed rare.[11,29,30] Moreover, the performance for the development of RA was comparable to that for the primary endpoint. Thus, risk stratifications were made for developing IA, an acceptable proxy for RA in this setting.

Heterogeneity between cohorts (eg, individual characteristics, outcomes) poses a challenge when combining datasets.[32,33] Sex, age, and endpoint frequency were similar between the datasets, but there were also differences in clinical and serologic characteristics arising from the method of identifying individuals at risk (eg, the cohorts that included individuals with CSA had higher frequencies of tender joints and the cohorts that selected for autoantibodies showed a higher frequency of ACPA positivity). Unmeasured factors related to geography or other factors may also differ between the cohorts. Cohort heterogeneity was taken into account by including a cohort variable. This had an independent association with the endpoint, suggesting an influence. Although this may suggest some impact on generalizability, exclusion of the cohort variable in the simplification step did not affect performance.

Validation was performed with bootstrapping and a data split. The similarity in AUCs demonstrated robustness. Data from European populations were shared in the taskforce. We did not find cohorts of arthralgia patients from the US, Canada, or Asia who were willing to share data. External validation in non-European populations should be conducted.

A limitation is that the selection of risk variables was based on consensus and availability. Some risk factors previously shown to be predictive in some cohorts (eg, human leukocyte antigen-shared epitope alleles,[29,30,34] functional disability,[35] and T cell subsets[30]), were not assessed in many cohorts and thus not included here. The additional value of these variables can be evaluated in future studies. Including additional variables would be valuable if, for example, the ACPA-negative progressing individuals that are currently classified as low risk would be recognized as high risk. This will not be easy because included ACPA-negative individuals with arthralgia had a prior risk of 9%, and posttest risks depend on prior risks. The high AUC also suggests that there is little room for improvement.

Patient research partners were involved during all phases of the project. Based on their advice, further research into the patients' perspective is needed. Understanding how risk information is perceived and relates to willingness to participate in trials is essential to inform future trials. Perceived risk status has been shown to affect tolerance for side effects of preventive treatments.[16,36] Furthermore, the proportion of at-risk individuals with 'intermediate' risk of RA was relatively small (11%), but their views of risk classification would need further investigation.

In conclusion, risk stratification criteria for arthralgia at risk for RA have been developed based on international cohort data and expert consensus. The developed risk stratification criteria are validated and intended to support the inclusion of homogeneous risk groups in future prevention trials.

ACKNOWLEDGMENTS

The authors are grateful to all the cohorts that shared their data. Daniel Aletaha, Andrew Filer, Georg Schett, and Paul Emery are acknowledged for allowing access to at-risk cohorts. Daniel Aletaha, Duncan Porter, and Iain McInnes are acknowledged for advice. Professor Saskia le Cessie is acknowledged for statistical advice. The authors also wish to thank EULAR and ACR for their financial support, Simona Lupatin from EULAR, and Amy Turner from ACR for administrative support, and EMEUNET for providing a representative (Ilfita Sahbudin).

AUTHOR CONTRIBUTIONS

All authors have contributed to this work, drafted the work or revised it critically and approved the final version. Drs van Steenbergen and van der Helm-van Mil confirm that all authors have provided the final approval of the version to be published and take responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

DISCLOSURES

The authors reported the following competing interests, outside the submitted work. SA–grants or contracts: Novartis, AbbVie; payment for lectures: AbbVie, Eli Lilly, Sandoz. CC –payment or honoraria for lectures: AbbVie, Amgen, Boehringer Ingelheim, Ewopharma, Lilly, Novartis, Pfizer, Sobi; leadership or fiduciary role in other board: President-elect of Romanian Society of Rheumatology, President of Romanian Registry of Rheumatic Diseases. SBC–grants or contracts: investigator and consultant Amgen, AbbVie, BMS, Pfizer; consulting fees: Amgen, AbbVie, BMS, Pfizer; payment or honoraria for lectures: Pfizer; participation on a data safety monitoring board (DSMB): Gilead. APC–grants or contracts: BMS, UCB; consulting fees: BMS, Galvani, Janssen, UCB, Lilly; payment or honoraria for lectures: BMS, Galapagos; leadership or fiduciary role in other board: chair EULAR Research Centre Clinical Research subcommittee. KD–payment or honoraria for lectures: Werfen, ThermoFisher; receipt of equipment, materials: Werfen. BE–grants or contracts: Boehringer Ingelheim; consulting fees: Boehringer Ingelheim. AK–consulting fees: Novartis Deutschland GmbH, Eli Lilly Deutschland GmbH, Gilead Sciences, Medac GmbH. KM–grants or contracts: Gilead, Lilly, Serac Healthcare, Astra Zeneca; consulting fees: Galapagos, Lilly, Serac Healthcare, Deepcure, Zura Bio; payment or honoraria for lectures: AbbVie, Galapagos; sup- port for attending meetings and/or travel: Lilly; participation on a DSMB: Galapagos. LJON–consulting fees: Fresenius Kabi, UCB; payment or honoraria for lectures: AbbVie. AS–grants or contracts: FOREUM; consulting fees: AbbVie, UCB, Novartis; payment of honoraria for lectures: Lilly, AbbVie; support for attending meetings and/or travel: Janssen, Lilly; leadership of fiduciary role in other board: editor in chief ARP Rheumatology, associate editor RMD Open. JAPdS–consulting fees: Amgen, Fresenius Kabi; payment or honoraria for lectures: UCB, Amgen; participation on a DSMB: Fresenius Kabi. JAS–grants or con- tracts: National Institute of Arthritis and Musculoskeletal and Skin Diseases, Rheumatology Research Foundation, R. Bruce and Joan M. Mickey Research Scholar Fund, Gordon and Llura Gund Foundation, BMS, Boehringer Ingelheim, Sonoma Biotherapeutics; consulting fees: AbbVie, Amgen, Boehringer Ingelheim, BMS, Gilead, Inova Diagnostics, Johnson & Johnson, MustangBio, Optum, Pfizer, ReCor, Sana, Sobi, UCB. PS–grants or contracts: FOREUM, Horizon/HADEA, AAL, EUREKA, Jubil€aumsfond der Stadt Wien; consulting fees: AbbVie; payment or honoraria for lectures: AstraZeneca; support for attending meetings and/or travel: Janssen, Galapagos. RL–payment or honoraria for lectures: AbbVie, UCB, Pfizer, Galapagos, Janssen Pharma, Novartis, Lilly; participation on a DSMB: UCB SLE trial; leadership or fiduciary role in other board: ASA board; other financial or nonfinancial interests: director of Rheumatology Consultancy BV, director of Joint Imaging BV. KR –grants or contracts: BMS.

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