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Original article

Hand and foot MRI in contemporary undifferentiated arthritis: in which patients is MRI valuable to detect rheumatoid arthritis early? A large prospective study

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Abstract

Objectives. Identifying patients that will develop RA among those presenting with undifferentiated arthritis (UA) remains a clinical dilemma. Although MRI is helpful according to EULAR recommendations, this has only been determined in UA patients not fulfilling 1987 RA criteria, while some of these patients are currently considered as RA because they fulfil the 2010 criteria. Therefore, we studied the predictive value of MRI for progression to RA in the current UA population, i.e. not fulfilling RA classification criteria (either 1987 or 2010 criteria) and not having an alternate diagnosis. Additionally, the value of MRI was studied in patients with a clinical diagnosis of UA, regardless of the classification criteria.

Methods. Two UA populations were studied: criteria-based UA as described above ($n = 405$) and expert-opinion-based UA ($n = 564$), i.e. UA indicated by treating rheumatologists. These patients were retrieved from a large cohort of consecutively included early arthritis patients that underwent contrast-enhanced MRI scans of hand and foot at baseline. MRIs were scored for osteitis, synovitis and tenosynovitis. Patients were followed for RA development during the course of 1 year. Test characteristics of MRI were determined separately for subgroups based on joint involvement and autoantibody status.

Results. Among criteria-based UA patients ($n = 405$), 21% developed RA. MRI-detected synovitis and MRI-detected tenosynovitis were predictive for progression to RA. MRI-detected tenosynovitis was independently associated with RA progression (odds ratio (OR) 2.79; 95% CI 1.40, 5.58), especially within ACPA-negative UA patients (OR 2.91; 95% CI 1.42, 5.96). Prior risks of RA development for UA patients with mono-, oligo- and polyarthritis were 3%, 19% and 46%, respectively. MRI results changed this risk most within the oligoarthritis subgroup: positive predictive value was 27% and negative predictive value 93%. Similar results were found in expert-opinion-based UA ($n = 564$).

Conclusion. This large cohort study showed that MRI is most valuable in ACPA-negative UA patients with oligoarthritis; a negative MRI could aid in preventing overtreatment.

Key words: rheumatoid arthritis, undifferentiated arthritis, magnetic resonance imaging, anti-citrullinated protein antibodies

Rheumatology key messages

- Within autoantibody-negative UA patients with mono-/oligo-/polyarthritis, the prior risk of RA development was 3%/19%/46%, respectively.
- Of inflammatory MRI features, MRI-detected tenosynovitis was the strongest predictor; post-test chances improved most within the oligoarthritis-subgroup (positive predictive value 27%, negative predictive value 93%).
- Within autoantibody-negative UA patients with oligoarthritis, a negative MRI largely excludes RA development (negative predictive value 93%); this may prevent overtreatment.

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CLINICAL SCIENCE

Introduction

Early treatment of RA is advocated because it is associated with improved outcomes [1]. However, early detection of patients who will develop RA among those presenting with undifferentiated arthritis (UA) is challenging. EULAR guidelines recommend use of imaging, which could be either US or MRI, as information about subclinical inflamed joints is presumed to be of prognostic relevance [2, 3]. However, this recommendation is based on early arthritis or UA defined as not fulfilling the 1987 RA criteria [4].

The UA population has changed since the introduction of the 2010 ACR/EULAR RA classification criteria [5–7]. Some patients that were diagnosed with UA according to the 1987 criteria in previous studies are currently classified as having RA, as they fulfil the 2010 criteria. This mainly concerns ACPA-positive patients. The opposite can be true for ACPA-negative patients; a proportion of patients that fulfilled the 1987 criteria do not fulfil the 2010 criteria, e.g. in the absence of positive autoantibodies, involvement of more than 10 joints is required [7–9]. These changes in classification criteria have affected the UA populations. Considering both criteria sets, the formal contemporary definition of UA is not fulfilling the 1987 or 2010 classification criteria and not having an alternate clinical diagnosis. Consequently, the current UA population decreased and reflects a different patient population from the previous UA population.

In clinical practice, rheumatologists identify UA patients based on expert opinion and experience, instead of routinely checking whether classification criteria (which were not designed as diagnostic criteria) are fulfilled. Hence, UA can be defined in two ways: formally as not fulfilling classification criteria for RA and pragmatically by the expertise of rheumatologists, whereby in both settings no clear alternative diagnosis should be present. For both UA populations (criteria based, expert opinion) there is little evidence on how to detect patients that will progress to RA. Likewise the value of MRI, in addition to other clinical variables, is unknown. We hypothesized that, in line with the formerly derived EULAR guidelines, MRI is also valuable in these contemporary UA populations and that the value will be different for patients with various other clinical characteristics that are generally assessed in daily clinical care. To achieve precision medicine and cost-effective use of additional investigations, it is important to identify the subgroup of patients in whom MRI can be helpful.

Therefore, we aimed to (i) determine the risk of RA development in the contemporary criteria-based UA population and in an expert opinion-based UA population, and (ii) determine the prognostic value of MRI in these populations, also in relation to generally assessed characteristics [i.e. swollen joint counts (SJC), acute-phase reactants, autoantibodies]. We performed a large prospective MRI study to this end, and aimed to provide an algorithm, useful in clinical practice, showing the value of MRI in clinically relevant subgroups of UA patients.

Methods

Patients

The Early Arthritis Clinic (EAC) is a population-based inception cohort, started in 1993 by the department of Rheumatology of the Leiden University Medical Center. Patients with recent onset arthritis of at least one joint and a symptom duration of <2 years were consecutively included. This cohort is described in detail elsewhere [10]. From August 2010 onwards baseline MRI was added to the protocol. Therefore, patients consecutively included since August 2010 are the basis of this study.

At baseline, swollen and tender joint counts and laboratory procedures were performed, including: ACPA [EliA CPP (anti-CCP2), Phadia, Nieuwegein, The Netherlands, considered elevated if $\geq$10 U/ml], IgM RF (in-house ELISA, considered elevated if $\geq$5.0 IU/ml), CRP (elevated if $\geq$10 mg/l) and ESR. In addition, a hand-and-foot MRI was obtained, as described below. Follow-up assessments were performed after 4 and 12 months, and yearly thereafter. UA treatment was provided in line with international recommendations.

Patients consecutively included in the Leiden EAC between August 2010 and March 2020 were evaluated (Fig. 1). Two UA populations were selected from the total dataset: (i) criteria-based UA, defined as not fulfilling the 1987 or the 2010 criteria and not having an alternative diagnosis, and (ii) expert-opinion based UA, which was defined as a clinical diagnosis of UA according to the treating rheumatologists. Both the 1987 and the 2010 RA classification criteria were considered in the definition of criteria-based UA, because the 2010 RA classification criteria identify autoantibody-positive RA patients earlier compared with the 1987 criteria, but autoantibody-negative RA can be classified earlier with the 1987 criteria than with the 2010 criteria, since the latter require $>$10 involved joints in the absence of autoantibodies [8, 9]. The expert-opinion based UA population is partly different from the criteria-based UA population as the classification criteria are not diagnostic criteria, and the classification criteria are generally not routinely checked when making a diagnosis in clinical practice. Per definition patients with an alternative diagnosis (e.g. PsA, inflammatory OA, gout) or with a high suspicion of another diagnosis were not included in either UA population. Joint involvement was based on clinical joint examination only; imaging results were not considered. UA patients with a missing MRI scan (mainly due to logistic reasons), who had a postponed MRI while DMARD treatment was already started or who concomitantly participated in a clinical trial (and were thus not routinely treated) were excluded from analyses.

Ethics approval and consent to participate

Approval was received from 'Commisie Medische Ethiek' of the Leiden University Medical Centre (B19.008). Consent for publication was not applicable.

MRI scans and scoring

Since August 2010, MCP (2–5), wrist and MTP (1–5) joints were scanned using a 1.5 Tesla MRI. MCP and wrist joints were scanned after administration of i.v. gadolinium and from June 2013 onwards MTP joints were scanned after contrast administration as well. Joints were scanned unilaterally at the most affected side, or the dominant side in case of equally affected joints. Patients were asked to stop NSAIDs 24 h before the scan, conforming to hospital policy. Three pairs of experienced readers scored MRI scans for erosions, osteitis and synovitis according to the RA MRI Scoring (RAMRIS) method, and scored tenosynovitis according to Haavardsholm *et al.* [11–13]. Readers were blinded to any clinical data. Intraclass correlation coefficients were excellent ($\geq$0.95 for total RAMRIS score; supplementary Table S1, available at *Rheumatology* online). Total MRI inflammation score was calculated by combining the scores of MRI-detected osteitis, synovitis and tenosynovitis. Dichotomized MRI features (osteitis, synovitis, tenosynovitis or any inflammation defined as MRI scan abnormal for one of these features) were corrected for prevalence in the general population. MRI features were considered abnormal if this score at this particular location was present in $<$5% of symptom-free controls within the same age category ($<$40, 40–59 and $\geq$60 years) [14, 15]. Further details about scanning and scoring are described in supplementary Table S1 and Supplementary Data S2, available at *Rheumatology* online. As MRI scans were evaluated for research purposes, clinicians and patients did not have access to MRI scans and were blinded for both the MRI images and scoring results.

Outcome

The primary outcome was RA development, defined as fulfilment of either 1987 and/or 2010 RA classification criteria after 1 year of follow-up [4, 5]. Since the 2010 criteria are less accurate in early identification of autoantibody-negative RA, both 1987 and 2010 RA classification criteria were used as the primary outcome [8, 9]. The secondary outcome was fulfilment of either 1987 and/or 2010 RA classification criteria or initiation of DMARD treatment. This secondary outcome was evaluated since patients might have received DMARD treatment during follow-up while not yet fulfilling RA classification criteria. DMARD treatment could prevent fulfilment of RA classification criteria, although DMARD start does reflect the strong suspicion of (imminent) RA by rheumatologist. Whereas the primary outcome may be an underestimation of the natural disease course and the frequency of RA development, the secondary outcome could be an overestimation of the frequency of RA development. Although this distorting effect of DMARD treatment on RA development cannot be prevented, both outcomes were studied to circumvent this.

Analyses

Associations between the MRI inflammation features (osteitis, synovitis, tenosynovitis and all three features summed into total MRI inflammation score) and RA development within 1 year were analysed using univariable and multivariable logistic regression. EULAR guidelines recommend taking the number of swollen joints (mono-, oligo-, polyarthritis: 1, 2–4, $>$4 swollen joints, respectively), acute-phase reactants (CRP) and autoantibodies (ACPA, RF) into consideration in undifferentiated arthritis [2]. These factors are also generally considered in the diagnostic process, and were therefore included in multivariable analyses. Model performance was calculated using c-statistics, area under the curve (AUC) and calibration slopes. To account for potential overfitting, bootstrapping (random sample with replacement, 200 replications) was used to calculate optimism-corrected performance. Thereafter, the value of MRI was analysed within various subgroups of UA patients. Subgroups were stratified based on MRI features and clinically relevant variables that were independently associated with RA development. Test characteristics and predictive values were determined. To estimate the additional value of MRI the net reclassification indices (NRI) for events (RA) and non-events (non-RA) were calculated. IBM SPSS Statistics version 25 was used for statistical analyses.

Patients and public involvement

Patient partners were involved in the design of the Leiden Early Arthritic Clinic.

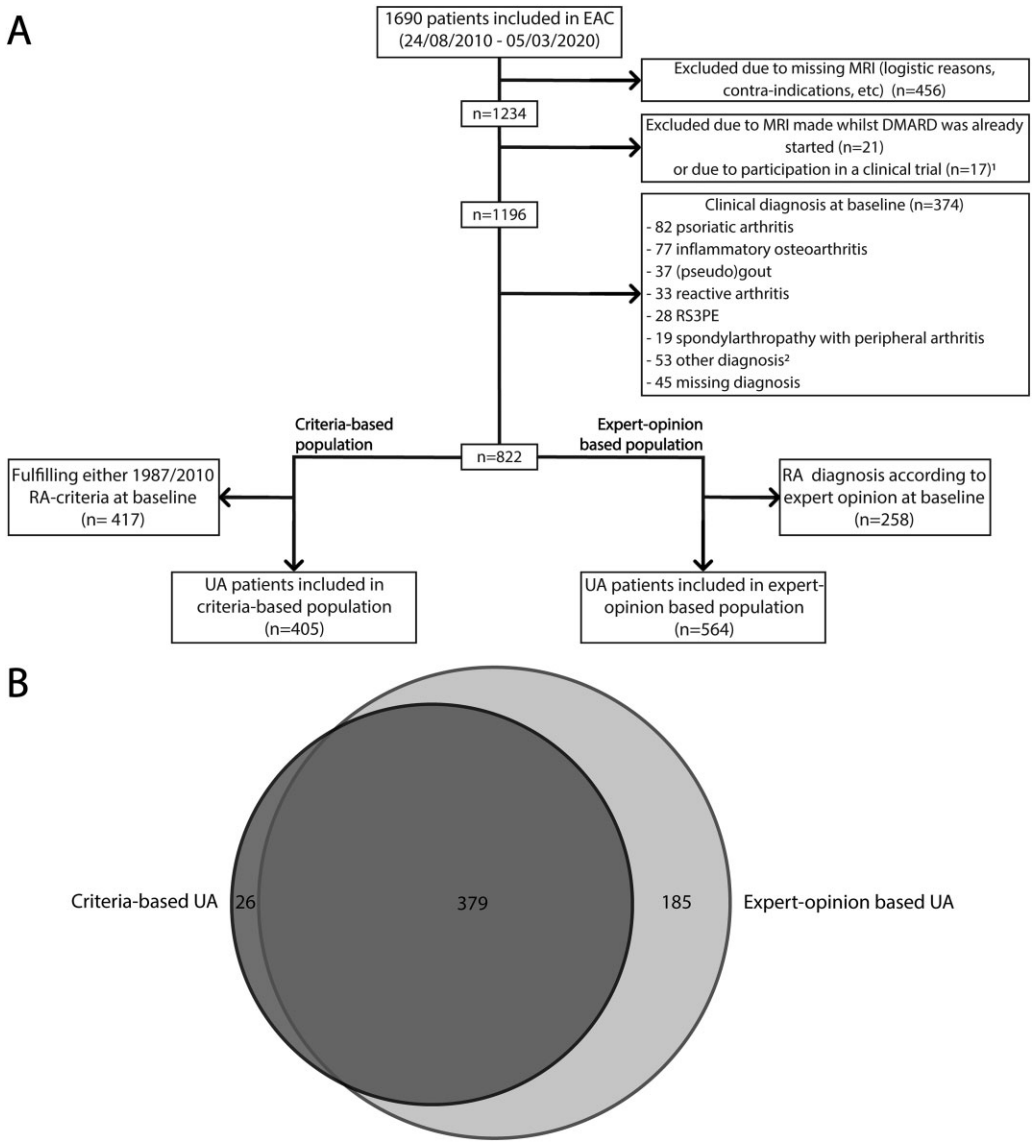
Results

Baseline characteristics

From 1690 consecutively included patients in the EAC cohort between August 2010 and March 2020, 1234 patients had an MRI at baseline (Fig. 1A). Some (n = 456) patients had no baseline MRI, due to logistic reasons such as MRI maintenance or contraindications for MRI. Baseline characteristics were comparable for both groups (supplementary Table S2, available at *Rheumatology* online). Thirty-eight patients were excluded due to DMARD use while the MRI was taken or concomitant participation in clinical trials, and 374 patients were excluded due to having another distinct diagnosis at baseline. Among the remaining patients, 405 patients had criteria-based UA and 564 patients had expert-based UA (379 UA patients had both criteria-based UA and expert-opinion UA, Fig. 1B).

Table 1 presents the baseline characteristics. Criteria-based UA patients were mainly ACPA negative (96%)

FIG. 1 Overview of patient selection within the EAC cohort and the overlap between both study populations



(**A**) An overview of patients selected within the EAC cohort. (i) From patients treated with DMARDs before MRI, five patients had another clear diagnosis at baseline. (ii) Other diagnosis: composed of multiple groups, including sarcoidosis ($n = 7$), paramalignant ($n = 4$), SLE ($n = 5$), MCTD/vasculitis ($n = 5$), Lyme disease ($n = 3$), post-traumatic ($n = 1$), septic arthritis ($n = 1$), other systemic disease ($n = 10$) and other diagnosis ($n = 17$). (**B**) Overview of the overlap between both study populations (criteria-based UA and expert-opinion based UA). EAC: Early Arthritis Cohort; UA: undifferentiated arthritis; RS3PE: remitting seronegative symmetrical synovitis with pitting edema.

and RF negative (94%), and patients had mild disease activity with a median SJC of 2. Expert-opinion-based UA patients had roughly similar characteristics: 88% were ACPA negative and 82% RF negative, and had a median of three swollen joints.

Prior risks of RA-development in criteria-based UA

In total 21% ($n = 87$) of criteria-based UA patients developed RA. This strongly depended on autoantibody status: 80% of ACPA-positive patients developed RA, while only 19% of ACPA-negative UA patients developed RA. Similarly, 38% of RF-positive (but ACPA-negative) patients progressed to RA and only 19% of autoantibody-negative UA developed RA. The frequency of RA development within autoantibody-negative patients was also dependent on the number of joints with arthritis: 3% of monoarthritis patients, 19% of oligoarthritis patients and 46% of polyarthritis patients developed RA.

Table 1 Baseline characteristics of UA patients from both study populations

	Criteria-based UA population, $n = 405$	Expert-opinion UA population, $n = 564$
Age at inclusion (years), mean (S.D.)	56.0 (15.8)	56.7 (15.7)
Female gender, *n* (%)	226 (56)	339 (60)
Symptom duration (days), median (IQR)	59 (30–136)	68 (34–176)
Swollen joint count at baseline (68–joints), median (IQR)	2 (1–4)	3 (1–5)
Tender joint count at baseline (71–joints), median (IQR)	3 (1–6)	4 (2–9)
ACPA positivity (≥10 U/ml), *n* (%)	15 (4)	67 (12)
RF positivity (≥5.0 IU/ml), *n* (%)	23 (6)	104 (18)
CRP (mg/l), median (IQR)	4.0 (3–12)	5.5 (3–16)
Elevated CRP (≥10 mg/l), *n* (%)	116 (29)	196 (35)
MRI features		
Positive for any inflammation, *n* (%)	304 (75)	437 (77)
Positive for osteitis, *n* (%)	198 (49)	288 (51)
Positive for synovitis, *n* (%)	195 (48)	298 (53)
Positive for tenosynovitis, *n* (%)	227 (56)	345 (61)
DMARD treatment		
Treatment with DMARD (glucocorticoids excluded), *n* (%)	168 (42)	239 (42)
MTX, *n* (%)	112 (28)	167 (30)
HCQ, *n* (%)	34 (8)	49 (9)
SSZ, *n* (%)	20 (5)	21 (4)
LEF, *n* (%)	1 (0.2)	1 (0.2)
Rituximab, *n* (%)	1 (0.2)	1 (0.2)
Glucocorticoids, *n* (%)	25 (6)	50 (9)

Some data were missing within the criteria-based study population, for symptom duration ($n = 42$), for total tender joint count ($n = 12$), for CRP ($n = 14$), for MRI synovitis ($n = 1$), for MRI-detected tenosynovitis ($n = 1$) and for (type of) DMARD treatment ($n = 1$). Some data were missing within the expert-opinion-based study population: for symptom duration ($n = 46$), for total tender joint count ($n = 12$), for CRP ($n = 16$), for MRI-detected synovitis ($n = 1$), for MRI-detected tenosynovitis ($n = 1$) and for (type of) DMARD treatment ($n = 24$). UA: undifferentiated arthritis; IQR: interquartile range.

Associations with RA development in criteria-based UA

Univariable analyses showed that SJC (both continuous and categorized in mono-/oligo-/polyarthritis), CRP, RF and ACPA were associated with RA development (Table 2). Presence of any MRI inflammation (MRI scan abnormal for osteitis, synovitis and/or tenosynovitis) was univariably associated with RA development [odds ratio (OR) 2.73; 95% CI 1.39, 5.37]. Osteitis, synovitis and tenosynovitis were also studied separately to examine whether all three MRI inflammation features are essential in predicting RA or whether fewer features can be assessed, in order to make the process more time-efficient. MRI-detected synovitis and MRI-detected tenosynovitis were univariably associated with RA development, while MRI-detected osteitis was not. From these two, only MRI-detected tenosynovitis was independently associated (OR 3.19; 95% CI 1.74, 5.86). Table 2 shows that after correction for the clinically relevant variables (number of swollen joints, CRP, ACPA positivity) MRI-detected tenosynovitis remained independently associated with RA development (OR 2.79; 95% CI 1.40, 5.58). Therefore, further analyses in clinically relevant subgroups focused on MRI-detected tenosynovitis.

Value of MRI-detected tenosynovitis in subgroups of criteria-based UA

Since autoantibodies and SJC were strongly associated with RA development, in contrast to CRP, subgroups were determined based on these variables. As only 15 patients were ACPA positive, and the majority (80%) of these patients developed RA, uni- and multivariable analysis were not performed in this subgroup. Within ACPA-negative UA, MRI-detected tenosynovitis was associated with RA development, similar to the total UA population (Table 2). The AUC was 0.795, as shown in supplementary Fig. S1, available at *Rheumatology* online. The optimism-corrected performance was almost similar, AUC 0.791. The calibration plot showed that observed *vs* predicted risks were also similar.

To guide decision making in clinical practice, the pre-test chances of RA development, as well as the chances of RA in the presence/absence of MRI-detected tenosynovitis, were determined, for autoantibody-positive and autoantibody-negative patients. The latter group was further subdivided into mono-, oligo- and polyarthritis (Fig. 2A). Within monoarthritis patients, RA development was highly unlikely (97% did not develop RA). This was not considerably increased in the absence of

TABLE 2 Results of univariable and multivariable-analyses for RA development in all criteria-based UA patients ($n = 405$) and multivariable analysis for ACPA-negative criteria-based UA patients ($n = 390$)

	Univariable analysis		Multivariable analysis in all UA patients: MRI-detected tenosynovitis adjusted for SJC, CRP and ACPA		Multivariable analysis in ACPA negative UA-patients: MRI-detected tenosynovitis adjusted for SJC and CRP	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Outcome RA						
SJC (continuous)	1.34 (1.21, 1.48)	<0.001				
SJC (categorized)						
1 joint (monoarthritis)	Reference		Reference		Reference	
2–4 joints (oligoarthritis)	2.75 (1.43, 5.28)	0.002	3.79 (1.60, 8.99)	0.002	3.61 (1.51, 8.60)	0.004
>4 joints (polyarthritis)	8.38 (4.10, 17.13)	<0.001	11.49 (4.60, 28.69)	<0.001	11.01 (4.41, 27.47)	<0.001
Elevated CRP (≥10 mg/l)	2.63 (1.58, 4.36)	<0.001	1.72 (0.96, 3.10)	0.070	1.74 (0.95, 3.17)	0.071
RF positivity (≥5.0 IU/ml)	5.41 (2.28, 12.82)	<0.001				
ACPA positivity (≥10 IU/ml)	16.80 (4.63, 61.03)	<0.001	55.14 (11.55, 263.23)	<0.001		
Abnormal MRI feature						
Any inflammation	2.73 (1.39, 5.37)	0.004				
Osteitis	1.38 (0.87, 2.22)	0.187				
Synovitis	2.04 (1.26, 3.32)	0.004				
Tenosynovitis	3.56 (2.04, 6.19)	<0.001	2.79 (1.40, 5.58)	0.004	2.91 (1.42, 5.96)	0.003

The association between routinely assessed variables in clinical practice and several MRI features with RA development is shown via univariable analysis for all criteria-based UA patients. MRI-detected tenosynovitis is the most strongly associated MRI inflammation feature. The middle column shows that MRI-detected tenosynovitis is independently associated with RA development, even after correction for SJC, CRP and ACPA. The far-right column shows that this association remains similar within ACPA-negative patients. Some data are missing: within all UA patients for CRP ($n = 14$), for MRI synovitis ($n = 1$, no contrast administration during MRI) and for MRI-detected tenosynovitis ($n = 1$, no contrast administration during MRI); within the ACPA-negative UA patients, for CRP ($n = 11$), for MRI synovitis ($n = 1$, no contrast administration during MRI), for MRI-detected tenosynovitis ($n = 1$, no contrast administration during MRI). UA: undifferentiated arthritis; OR: odds ratio; SJC: 68-swollen joint count; Swollen joints: Swollen joint count based on a 68-joint swollen joint count.

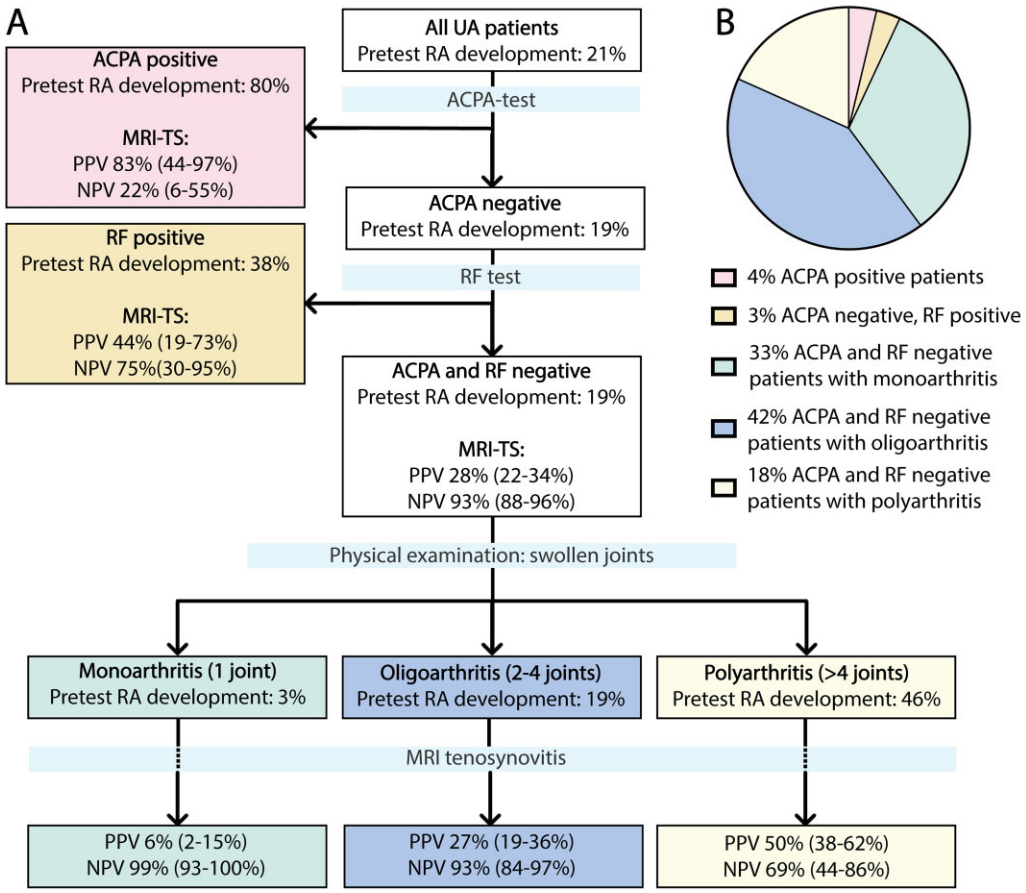
abnormal tenosynovitis on MRI (99%), showing that an MRI was not of additional value within this subgroup. A positive MRI in autoantibody-negative oligoarthritis patients increased the pre-test risk of 19% to a post-test risk of 27%. The pre-test risk of not developing RA (81%) increased to 93% in the presence of a negative MRI for tenosynovitis. The pre- and post-test risks of developing and not developing RA in polyarthritis (respectively 46% and 50%) improved slightly, but less than for oligoarthritis (Fig. 2A). ORs, sensitivities and specificities for mono-, oligo- and polyarthritis groups are presented in Table 3. As shown in Fig. 2B, most autoantibody-negative patients presented with oligoarthritis. Within this population, MRI-detected tenosynovitis was of the highest additional value. The non-event NRI was 36% (calculated via 64/177), indicating that 36% of the patients were correctly reclassified as not having RA (supplementary Table S3, available at *Rheumatology* online). The event NRI was −7.6%, indicating that only 7.6% patients were incorrectly reclassified while having RA (calculated via 5/66). For illustrative purposes two examples of MRI scans of autoantibody-negative oligoarthritis patients are presented in supplementary Fig. S2, available at *Rheumatology* online.

The value of MRI in expert-opinion based UA

Forty percent of expert-opinion-based UA patients developed RA within the first year of follow-up. Results were similar to the criteria-based UA population: MRI-detected tenosynovitis was independently associated with RA development, in both the total group (OR 2.00; 95% CI 1.23, 3.25) and the ACPA-negative subgroup (OR 1.98; 95% CI 1.20, 3.26) (supplementary Table S4, available at *Rheumatology* online). The value of MRI within clinical subgroups was similar to the criteria-based UA patients (Fig. 3).

Sensitivities and specificities in all autoantibody negative UA patients and in subgroups are shown in supplementary Table S5, available at *Rheumatology* online. The overall sensitivity was 78% and the specificity was 50%.

FIG. 2 Flowchart for criteria-based UA patients showing pre-test and post-test predictive value for RA development and percentages of patients within these subgroups



(**A**) Flowchart with NPV and PPV for MRI-detected tenosynovitis within the specified groups. Pre-test probability of developing RA is shown as a percentage of patients fulfilling 1987 and/or 2010 RA criteria. (**B**) A total of 404 patients were studied: 15 patients were ACPA positive (4%), 13 patients were ACPA negative and RF positive (3%), and 376 patients were ACPA and RF negative (93%), of which 133 patients had monoarthritis (1 swollen joint, 33%), 169 patients had oligoarthritis (2–4 swollen joints, 42%) and 74 patients had polyarthritis (>4 swollen joints, 18%). One patient is missing in this analysis due to missing outcome for MRI-detected tenosynovitis; this patient belonged in the oligoarthritis group. UA: undifferentiated arthritis; ACPA: considered positive if ≥10 U/ml; RF: considered positive if ≥5.0 IU/ml; MRI-TS: MRI-detected tenosynovitis; NPV: negative predictive value; PPV: positive predictive value; swollen joints: based on a 68-swollen joint count.

Sensitivity analysis with secondary outcome

Fulfilment of RA classification criteria after 1 year might be an underestimation of the natural outcome due to DMARD treatment (Table 1) and its influence on disease progression. Because DMARD therapy was presumably started in patients in whom rheumatologists were most concerned about RA development even though they might not fulfil RA criteria, a sensitivity analysis was performed where, as a secondary outcome, RA was defined as fulfilment of criteria or start of DMARD treatment within 1 year. Notably, compared with the criteria-based outcome, the percentage of RA development increased by adding start of DMARD treatment (21% to 45%, respectively), meaning that DMARD treatment was initiated in patients who have not fulfilled RA criteria. Nonetheless, this secondary outcome showed similar results: MRI-detected tenosynovitis remained independently associated with RA development and MRI-detected tenosynovitis was particularly associated in the autoantibody-negative UA population presenting with oligoarthritis (supplementary Table S6 and Fig. S3, available at *Rheumatology* online).

Discussion

This study determined the risk of RA development in the two UA populations, the contemporary criteria-based UA and expert-opinion-based UA, and assessed the prognostic value of MRI within these populations. Previously, UA was defined as not fulfilling 1987 criteria,

TABLE 3 Test characteristics for MRI-detected tenosynovitis and chances of RA development within autoantibody-negative criteria-based UA patients and within subgroups

	RA development, *n* (%)	OR (95% CI)	*P*-value	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
All autoantibody negative UA patients, $n = 376$	70 (19)	5.36 (2.71, 10.60)	<0.001	84 (74, 91)	50 (44, 56)	28 (22, 34)	93 (88, 96)
Subgroup: monoarthritis, $n = 133$	4 (3)	4.59 (0.46, 45.33)	0.192	75 (30, 95)	60 (52, 68)	6 (2, 15)	99 (93, 100)
Subgroup: oligoarthritis, $n = 169$	32 (19)	4.73 (1.72, 13.02)	0.003	84 (68, 93)	46 (39, 55)	27 (19, 36)	93 (84, 97)
Subgroup: polyarthritis, $n = 74$	34 (46)	2.20 (0.68, 7.13)	0.189	85 (70, 94)	28 (16, 43)	50 (38, 62)	69 (44, 86)

RA development is defined as fulfilment of either 1987 or 2010 RA classification criteria. Monoarthritis is specified as 1 swollen joint, oligoarthritis 2–4 swollen joints and polyarthritis >4 swollen joints. Within all autoantibody-negative UA patients, 212 patients (56%) had an MRI positive for tenosynovitis, within mono-, oligo- and polyarthritis patients, MRI-detected tenosynovitis was found within 54 (41%), 100 (59%) and 58 (78%) patients, respectively. UA: undifferentiated arthritis; OR: odds ratio; PPV: positive predictive value; NPV: negative predictive value.

however with the introduction of the 2010 RA criteria, RA was recognized earlier and the remaining UA-population decreased [2, 7]. Little is known about the risk of RA in this group and the value of regularly assessed markers in the contemporary UA populations. This knowledge gap prompted us to perform this study.

Both UA definitions have advantages and disadvantages. Classification criteria are not diagnostic criteria, and may not be applied during the diagnostic process in clinical practice. The expert-opinion-based definition, in contrast, reflects clinical practice. However, this expertise-based definition may be found subjective and may result in a more heterogeneous patient population. Furthermore, the treating rheumatologist could diagnose patients with UA while they fulfil RA classification criteria. Per definition, the criteria-based UA population does not suffer from this, may be more homogeneous and facilitates comparison of study results internationally. Hence the two UA populations studied differed. Despite these different definitions of UA, the same predictive variables were observed and the value of MRI was similar in both groups. This shows the robustness of the findings and implies that the results of this study may be used to promote personalized decision making in UA patients in both daily clinical practice and future studies where risk stratification is used.

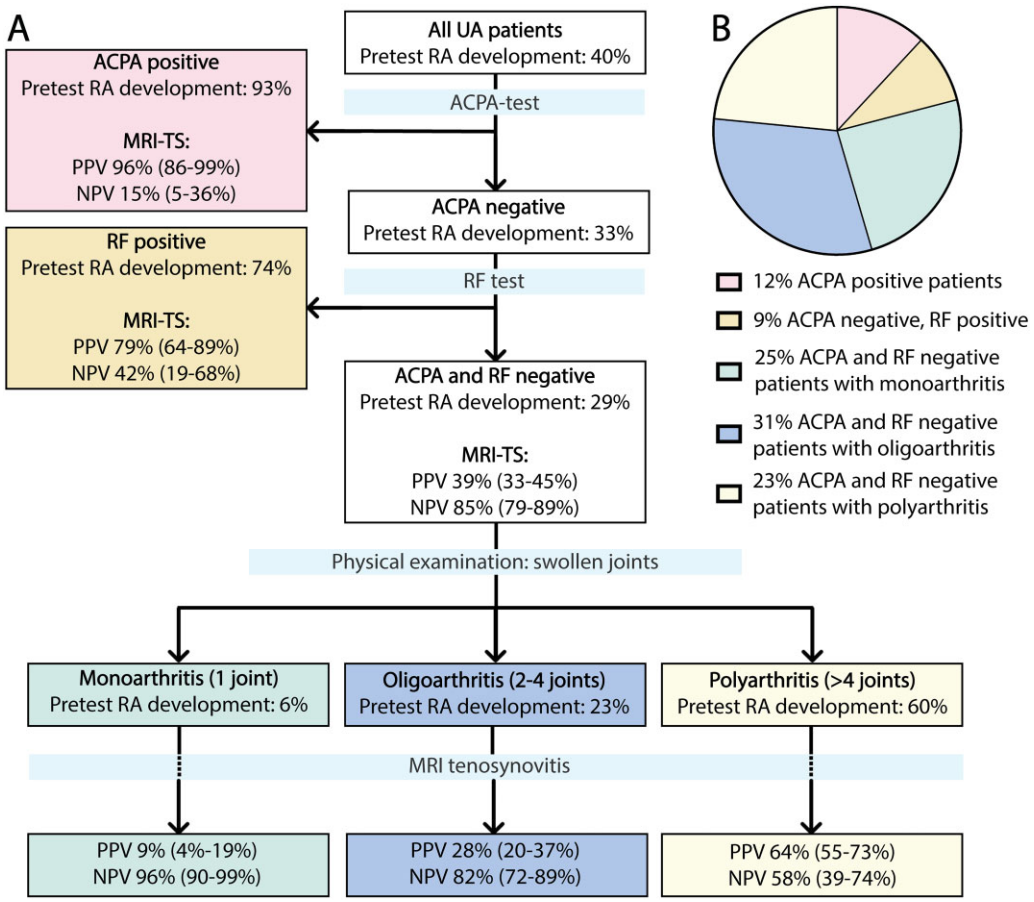
From all MRI inflammation features, MRI-detected tenosynovitis associated most strongly with RA development. Although synovitis is a well-established RA feature, it was not the strongest predictor for RA development. This could be explained by the fact that all patients required arthritis, and thus possibly indirectly synovitis, at inclusion. However, the value of MRI-detected tenosynovitis observed here is in line with previous studies that also reported on the predictive accuracy of MRI-detected tenosynovitis [16, 17]. Moreover, the finding that MRI-detected tenosynovitis alone is as predictive as the total inflammation score suggests that in practice only MRI-detected tenosynovitis can be assessed, rather than evaluating all features. This contributes to a time-efficient evaluation of MR images.

Our current findings show that MRI had little value in autoantibody-negative monoarthritis, as RA development was rare in this group, and had little value in autoantibody-negative polyarthritis. MRI had the highest additional value in autoantibody-negative oligoarthritis patients. In particular, an MRI negative for tenosynovitis was helpful, as this could largely exclude RA development. This subgroup with autoantibody-negative UA with oligoarthritis is the largest subgroup among contemporary UA patients. The risks of RA, both pre- and post-test, are summarized in an algorithm (Fig. 2) that can be helpful to fill the diagnostic gap in a population where predicting RA development is difficult.

Although the sensitivity was rather good, the specificity was moderate, indicating that at group level the population of UA patients that did not develop RA was not accurately characterized by absence of MRI-detected tenosynovitis.

The outcome of RA used was fulfilment of classification criteria. This was chosen as all evidence on the efficacy of early DMARD treatment derived from patients that fulfilled classification criteria for RA. Other outcomes, such as persistency of arthritis, are also important, but patients that fulfil classification criteria generally have a persistent course of arthritis [18]. From patients' perspectives, symptoms (pain or fatigue) may be more reflective of the disease burden than fulfilment of classification criteria. However, as DMARD efficacy is based on data from RA (defined as criteria positivity), this was

FIG. 3 Flowchart for expert-opinion UA patients showing pre-/post-test predictive values for RA development and percentages of patients within subgroups



(**A**) Flowchart with NPV and PPV for MRI-detected tenosynovitis within the specified groups. Pre-test probability is shown as a percentage of patients fulfilling 1987 and/or 2010 RA criteria. (**B**) A total of 563 patients were studied: 67 patients were ACPA positive (12%), 51 patients were ACPA negative and RF positive (9%), and 445 patients were ACPA and RF negative (79%), of which 138 patients had monoarthritis (1 swollen joint, 25%), 175 patients had oligoarthritis (2–4 swollen joints, 31%) and 132 patients had polyarthritis (>4 swollen joints, 23%). One patient is missing in this analysis due to missing outcome for MRI-detected tenosynovitis, this patient belonged in the oligoarthritis group. UA: undifferentiated arthritis; ACPA: considered positive if ≥10 U/ml; RF: considered positive if ≥5.0 IU/ml; MRI-TS: MRI-detected tenosynovitis; NPV: negative predictive value; PPV: positive predictive value; swollen joints: based on a 68-swollen joint count at physical examination.

chosen as the primary outcome of our study. A possible limitation is that the criteria-based RA outcome can be underestimated due to concurrent DMARD treatment. Indeed, when adding start of DMARD treatment to the outcome, an increase in the percentage of patients with this outcome was found. The sensitivity analyses in which DMARD treatment and a clinical diagnosis of RA were also considered as RA showed similar results.

Another limitation is that the MTPs were imaged with a less optimal scan protocol before June 2013, and MRI-detected tenosynovitis of MTP joints was therefore not assessed and included in the analyses. However, previous research has shown that MRI of the foot has no additional value in early identification of RA, as MRI-detected tenosynovitis of the feet was highly correlated with simultaneous presence of MRI-detected tenosynovitis of the hand [19, 20]. Finally, a known limitation of predictive research is the risk of overfitting. While it was not the intention of this research to create a full prediction model, we performed bootstrapping to account for potential overfitting. We acknowledge that external validation in data from another cohort would be ideal and remains a subject for further research.

A strength of this study is the large sample size of patients that were consecutively included over 10 years, which allowed us to select UA patients. Secondly, imaging results were not known in clinical practice and did not influence treatment decisions. The imaging results

were also not considered in assessment of joint involvement when applying the 2010 criteria. This prevented possible false-positive RA classifications, which have been reported when considering imaging results to define joint-involvement [21]. This way the additional role of MRI in predicting RA could be properly investigated.

We studied the value of MR imaging in detecting joint inflammation. US is currently used more frequently than MRI. To our best knowledge no US studies of this magnitude, and with consecutively included UA patients (according to the contemporary definition) that underwent systematic US investigation, are available. The fact that we found that MRI-detected tenosynovitis to be the best predictor and previous studies showed that US has a poor sensitivity for tenosynovitis compared with MRI (∼19–50%) suggests that US would be less accurate than MRI [22, 23]. However, formal studies would be needed to determine this.

The high costs of MRI prevent its implementation in clinical practice. However, new MRI sequences with short scan time and which do not require contrast enhancement are under development and may facilitate application of MRI in clinical practice in due course [24]. Cost-effectiveness analyses have not been performed yet and are a relevant subject for future research, especially since early diagnosis and treatment may be helpful in shortening the disease duration and thus reducing the need for use of expensive treatments.

In conclusion, this large prospective MRI study determined the risk of RA development in the contemporary UA populations. The risk of developing RA for clinically relevant subgroups was established. MRI had the highest additional value in autoantibody-negative UA patients presenting with oligoarthritis, in whom a negative MRI for tenosynovitis almost excluded imminent RA. The results of this study could be helpful in achieving precision medicine in patients with UA and in preventing overtreatment.

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Data availability statement

All data relevant to the study are included in the article or uploaded as supplementary information. Additional data are available upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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