The use of MRI in early inflammatory arthritis

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Evaluation of the diagnostic accuracy of hand and foot MRI for early Rheumatoid Arthritis

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Abstract

Objectives
To assess the diagnostic value of MRI for early RA. In some RA patients, a classifiable diagnosis cannot be made at first presentation; these patients present with unclassified arthritis (UA). The use of MRI for early diagnosis of RA is recommended, yet the evidence for its reliability is limited.

Methods
MRI of hand and foot was performed in 589 early arthritis patients included in the Leiden Early Arthritis Clinic (229 presented with RA, 159 with other arthritides and 201 with UA). Symptom-free controls provided a reference for defining an abnormal MRI. In preliminary investigations, MRI of patients who presented with RA was compared with MRI of symptom-free controls and of patients with other arthritides. Thereafter, the value of MRI in early RA diagnosis was determined in UA patients using the 1-year follow-up on fulfilling the 1987 RA criteria and start of disease-modifying drugs as outcomes.

Results
Preliminary investigations were promising. Of the UA patients, 14% developed RA and 37% started disease-modifying treatment. MRI-detected tenosynovitis was associated with RA development independent of other types of MRI-detected inflammation [odds ratio (OR) = 7.5, 95% CI: 2.4, 23] and also independent of age and other inflammatory measures (swollen joints, CRP) (OR = 4.2, 95% CI: 1.4, 12.9). Within UA patients, the negative predictive value of abnormal tenosynovitis was 95% (95% CI: 89%, 98%) and the positive predictive value 25% (95% CI: 17%, 35%). The performance was best in the subgroup of UA patients presenting with oligoarthritis (18% developed RA): the positive predictive value was 36% (95% CI: 23%, 52%), the negative predictive value was 98% (95% CI: 88%, 100%), the sensitivity was 93% (95% CI: 70%, 99%) and the specificity was 63% (95% CI: 51%, 74%).

Conclusion
MRI contributes to the identification of UA patients who will develop RA, mostly in UA patients presenting with oligoarthritis.

Introduction

Patients with RA should receive disease-modifying treat-ment (DMARDs) as soon as possible because this increases the chance of a better disease outcome.[1,2] In some RA patients, the classic phenotype has not yet completely developed at the first presentation, hampering prompt diagnosis of RA. To improve early identification, the 2010 ACR/EULAR classification criteria for RA have been developed.[3] These novel criteria do indeed identify RA patients earlier in time than the 1987 ACR classification criteria.[4] However, timely diagnosis is still impossible in some patients: up to 25% of patients presenting with recent-onset arthritis who cannot be classified by the 2010 criteria and have unclassified arthritis (UA) develop RA later on (typically within 1 year).[5] RA patients who initially present with UA have a disease course equally severe to that of RA patients who already fulfil the criteria at first presentation.[6] Thus, although prompt diagnosis is required, for some RA patients, accurate methods for this are lacking. These patients are mainly ACPA-negative[5]. It has been suggested that novel imaging modalities may be valuable in the early diagnosis of RA.[7]

MRI sensitively depicts inflammation; it visualizes synovitis, tenosynovitis and bone marrow oedema (BME). BME (also called osteitis in RA) is not depicted by other imaging modalities.[8–10] Hand and foot MRI is increasingly used as a measure of outcome in clinical trials.[11] Because MRI detects subclinical inflammation (not evident at physical examination) in patients presenting with early arthritis, and MRI-detected inflammation is associated with erosive progression,[12] it is thought that MRI may have a role in the diagnostic process of RA. The use of MRI for the early diagnosis of RA is recommended by a taskforce of the EULAR, but it was acknowledged that the evidence supporting this recommendation is low.[7] Previous studies on this subject included relatively low numbers of patients (n < 50),[13–21] used low-field-strength MRI scanners,[14,18,22,23] or studied selected groups of patients,[13–25] which hampered extrapolation of results to rheumatologic practice. Finally, the definition of an abnormal MRI varied between different studies;[13–25] no study considered using the findings for a symptom-free control population for defining a cut-off point to distinguish a normal MRI from an abnormal MRI.

We set out to determine the accuracy of hand and foot MRI in identifying those UA patients who are in an early stage of RA. As preparatory work, we made MRI scans of hands and feet of 193 symptom-free persons from the general population and observed that MRI-detected inflammation was quite prevalent, especially at higher age and at preferred locations.[26] We hypothesized that including these findings in the definition of a positive MRI would reduce false-positive findings. Using a high-field-strength MRI scanner on an unselected early arthritis population visiting a rheumatologic outpatient clinic, this study aimed to (i) explore the discriminative value of MRI by comparing the MRI of patients with classifiable RA at presentation with MRI of symptom-free controls and patients with other arthritides and (ii) determine the value of MRI for the identification of those UA patients who are in an early phase of RA. UA patients were followed for RA development over 1 year. Because the differential diagnosis is slightly different for UA patients presenting with mono-, oligo- or polyarthritis, the diagnostic value of MRI was also explored in these subgroups of UA patients.

Methods

Setting and patients

The Leiden Early Arthritis Clinic is a longitudinal inception cohort including patients with clinically confirmed arthritis and symptom duration of <2 years who presented to the Leiden rheumatologic outpatient clinic. This is the only referral centre in a health care region of ~400 000 inhabitants. The cohort was initiated in 1993.[27] MRI was added to the study protocol in 2010. At first visit, questionnaires were completed by patients and rheumatologists, joint counts were performed, serum samples obtained and an MRI made. From August 2010 to October 2014, 598 consecutively included patients underwent MRI. Gadolinium chelate contrast was not administered in nine patients; those nine patients were excluded from this study. Two weeks after first presentation, when routine laboratory and radiographic results were known (but not MRI results), patients received their diagnosis; classification of RA was done according to the 2010 criteria.[3]

The symptom-free volunteers who served as a reference were recruited via advertisements in local newspapers and websites, and had no history of inflammatory rheumatic diseases, no joint symptoms during the last month and no evidence of arthritis at physical examination. A more detailed description of them is provided in reference.[26] This study was approved by the Leiden University Medical Center medical ethics committee, and all participants signed informed consent forms.

Outcomes

The study consisted of two parts. First, preliminary investigations were performed to explore the potential discriminative value of MRI. Patients who presented with RA were compared with symptom-free controls and with patients with other arthritides. Then the value of MRI was assessed in the target population of patients presenting with UA (flowchart in Supplementary (available at Rheumatology Online) Fig. S1). These patients were followed for 1 year. The primary outcome was RA development according to the 1987 criteria.[28] Although the 2010 criteria are fulfilled earlier in time, they have a lower specificity than the 1987 criteria, making them less suitable as long-term outcome measure.[4,29] Furthermore, ACPA-negative patients can only fulfill the 2010 criteria if >10 joints become involved; hence, they (and this reflects to the ACPA-negative patients) fulfill the 1987 criteria more easily. The secondary outcome was the initiation of DMARDs during the year of follow-up (see supplementary (available at Rheumatology Online) data, section DMARD therapy, for more detail). Rheumatologists may initiate DMARDs in UA patients if they anticipate that the patient will progress to RA. Early treatment may prevent progression to fulfilment of classification criteria. Compared with the natural course, this may result in an underestimation of the number of UA patients who progress to RA (the primary outcome). The secondary outcome, therefore, reflects the expert opinion of the rheumatologist on the presence of RA and may circumvent this underestimation.

MRI and scoring

At baseline, unilateral contrast-enhanced MRIs were made of the second to fifth MCPs, wrist and first to fifth MTP joints of the most painful side, or the dominant

side in the case of equally severe symptoms on both sides. MRI was performed on an Musculoskeletal Extreme 1.5 T extremity magnetic resonance (MR) system; see supplementary (available at Rheumatology Online) data, section detailed MRI protocol, for a detailed description of the protocol. Erosions, BME, synovitis and tenosynovitis were scored as described in the supplementary (available at Rheumatology Online) data, section MRI scoring and dichotomizing,[30,31] by two trained readers (W.P.N. and E.C.N., both having scored >800 MRIs), blinded to any clinical data. Within-reader intraclass correlation coefficients for the total RA MRI scoring system (RAMRIS) inflammation scores, based on 40 MRIs scored twice, were, respectively, 0.98 and 0.93; the betweenreader intraclass correlation coefficient, based on all 598 scans, was 0.95. The total inflammation score per patient was calculated by summing all BME, synovitis and tenosynovitis scores. The mean for both readers was used for analyses on continuous scores.

The MRI findings in 193 symptom-free persons, who were scanned according to same protocol,[26] were used as a reference for dichotomizing the MRI scores: a bone/joint/tendon was considered abnormal for BME/ synovitis/tenosynovitis if, according to both readers, the score for that finding was above the 95th percentile of scores at the same location in symptom-free persons of the same age category (18-40, 40-60 or >60 years).[26]

The locations that showed inflammation in >5% of controls are presented in supplementary (available at Rheumatology Online) Table S1. Subsequently, at the patient level, an MRI was considered abnormal if one (or more) bone/joint/tendon was considered abnormal. (See the supplementary (available at Rheumatology Online) data, section MRI scoring and dichotomizing, for an example.) In sub-analyses, a bone/joint/tendon was considered abnormal if the score was higher than all scores (100th percentile) of the symptom-free persons of the same age category at the same location.[26]

Analyses

Logistic regression analysis was used to assess the predictive value of MRI in UA patients. The additional value of MRI-detected inflammation to the swollen joint count (SJC) and CRP was evaluated using multivariable logistic regression analyses. Here, an elevated CRP was defined as 510 mg/l and the SJC was categorized into clinically relevant categories, because of high-leverage outliers. Test characteristics and predictive values were determined. Analyses were repeated after stratification for the number of swollen joints. Decision curve analysis[32] was performed to explore the additive value of MRI, also weighting the harms of over- and underprediction of RA development, comparing the predicted probabilities of models with and without MRI (supplementary (available at Rheumatology Online) data, section decision curve analysis). Statistical analyses were performed in IBM SPSS ver. 20 and Stata ver. 14. $P < 0.05$ were considered significant.

Results

Study population

Table 1 Baseline characteristics of all early arthritis patients and those presenting with RA and with unclassified arthritis

	All early arthritis patients n=589	Subgroup RA patients n=229	Subgroup UA patients n=201
Age, mean(SD)	54.8 (15.5)	55.9 (14.4)	54.1 (15.8)
Female, n(%)	363 (61.6%)	155 (67.7%)	123 (61.2%)
Symptom duration, in weeks, median (IQR)	12 (5-26)	15 (8-28)	9 (4-24)
Swollen joint count, median (IQR)	3 (2-7)	6 (2-11)	2 (1-4)
CRP (mg/L), median (IQR)	6 (3-17)	9 (3-22)	4 (3-10)
RF positive, n(%)	195 (33.1%)	151 (65.9%)	19 (9.5%)
ACPA positive, n(%)	137 (23.3%)	124 (54.1%)	8 (4%)
Diagnosis at presentation			
Rheumatoid arthritis	229		
Unclassified arthritis	201		
Psoriatic arthritis or spondyloarthritis	39		
Inflammatory osteoarthritis	35		
Reactive arthritis	25		
Crystal arthropathy	15		
RS3PE	10		
SLE+MCTD	6		
Other diagnoses	29		

SD, standard deviation; IQR, Inter quartile range; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; RF, rheumatoid factor; ACPA, anti-citrullinated-peptide-antibody; RS3PE, remitting seronegative symmetrical synovitis with pitting edema; SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease

A total of 589 early arthritis patients were studied: 229 had RA at presentation, 201 UA and 159 other arthritides. Baseline characteristics are shown in Table 1. The continuous RAMRIS scores in RA patients and UA patients are shown in Table 2.

Preliminary investigations

Patients presenting with RA (n = 229) were first compared with symptom-free controls (n = 193) and with early arthritis patients with other arthritides (n = 360). The continuous MRI inflammation scores were higher in RA patients than in symptom-free controls (supplementary (available at Rheumatology Online) Table S2). High continuous MRI inflammation scores were not only observed in RA, but also in some other arthritides, for example, RS3PE, SLE and MCTD (supplementary (available at Rheumatology Online) Fig. S2). The discriminative value of an abnormal MRI is shown in Table 3. Compared with synovitis and BME, tenosynovitis had the best discriminative accuracy (Table 3). In sub-analyses, a

Table 2 Continous RA MRI scores of patients who presented with RA or unclassified arthritis

	RA	UA	UA subgroups		
			Mono-arthritis	Oligo-arthritis	Poly-arthritis
Total RAMRIS score, median (IQR)	16.50 (9.00-32.00)	11.00 (4.00-19.50)	7.50 (3.00-15.50)	12.00 (5.00-20.00)	14.00 (6.50-24.00)
Inflammation Score, median (IQR)	13.50 6.50-26.00)	7.50 (2.50-15.50)	5.00 (1.50-10.50)	8.00 (3.50-15.00)	12.00 (4.50-21.00)
BME score, median (IQR)	3.75 (1.25-8.50)	2.00 (0.50-5.00)	1.50 (0.50-4.00)	2.50 (0.50-6.00)	1.50 (0.50-4.50)
Synovitis score, median (IQR)	5.00 (2.50-9.00)	3.00 (1.00-6.00)	2.00 (0.50-5.50)	3.50 (1.00-6.50)	4.00 (1.50-9.00)
Tenosynovitis score, median (IQR)	4.00 (1.50-7.50)	1.50 (0.00-5.00)	1.00 (0.00-3.00)	1.50 (0.00-4.50)	2.00 (0.50-8.00)
Erosion score, median (IQR)	3.00 (1.50-6.00)	2.50 (1.00-5.00)	2.00 (1.00-4.50)	3.00 (1.00-5.50)	2.50 (1.50-5.50)

Subgroups of UA patients are based on the number of inflamed joints at presentation: BME: bone marrow oedema; monoarthritis: 1 clinically swollen joint; oligoarthritis: 2-4 clinically swollen joints; polyarthritis:>4 clinically swollen joints; RAMRIS: RA MRI score; UA: unclassified arthritis.

Table 3 Preliminary investigations: test characteristics for an abnormal MRI to identify patients clinically presenting with RA

MRI abnormal for	Sensitivity, % (95%CI)	Specificity, % (95%CI)	AUC
RA versus symptom-free controls			
Any Inflammation	88% (83%-91%)	71% (64%-77%)	0.79
Bone marrow edema	61% (55%-67%)	78% (72%-83%)	0.70
Synovitis	66% (59%-71%)	93% (88%-96%)	0.79
Tenosynovitis	75% (69%-80%)	95% (91%-97%)	0.85
RA versus early arthritis patients with other arthritides			
Any Inflammation	88% (83%-91%)	33% (28%-38%)	0.60
Bone marrow edema	61% (55%-67%)	57% (52%-62%)	0.59
Synovitis	66% (59%-71%)	58% (52%-63%)	0.62
Tenosynovitis	75% (69%-80%)	56% (50%-61%)	0.65

Test characteristics of an abnormal MRI for discriminating patients who clinically present with RA from symptom-free controls and patients presenting with other arthritides. MRI abnormal for any inflammation indicates the presence of abnormal bone marrow oedema, synovitis or tenosynovitis. AUC: area under the receiver operating characteristic curve.

stricter definition for an abnormal MRI was used; these showed similar results (supplementary (available at Rheumatology Online) Table S3).

Accuracy of MRI in identifying those UA patients who developed RA within 1 year

The clinical characteristics of the UA patients are shown in supplementary (available at Rheumatology Online) Table S4. During the 1-year follow-up, 29 of 201 UA patients (14%) progressed to RA and 75 (37%) were prescribed DMARD therapy. Patients who progressed to RA were older and presented

with a higher SJC and higher CRP levels than patients who did not progress (supplementary (available at Rheumatology Online) Table S4). The total MRI inflammation, synovitis and tenosynovitis scores at baseline were higher in the UA patients who developed RA than in those who did not develop RA (all P < 0.001, supplementary (available at Rheumatology Online) Fig. S3); the BME scores were similar (P = 0.72). An abnormal MRI for any type of inflammation had an odds ratio (OR) for RA development of 7.2 (95% CI: 1.6, 31.2). The ORs of the individual inflammation types were 6.7 (95% CI: 2.4, 18.3) for tenosynovitis, 2.3 (95% CI: 1.0, 5.2) for synovitis and 0.9 (95% CI: 0.4, 2.1) for BME (Table 4). UA patients frequently had an abnormal MRI for several types of inflammation: 24% had tenosynovitis, synovitis and BME, 21% had two types of inflammation, 24% had only tenosynovitis, synovitis or BME and 62 patients (31%) had a normal MRI (supplementary (available at Rheumatology Online) Fig. S4). Multivariable logistic regression showed that tenosynovitis was associated with RA development, independent of synovitis and BME (OR = 7.5, 95% CI: 2.4, 23.1; Table 4). Also after adjusting for age, SJC and CRP, an abnormal MRI for tenosynovitis was associated with RA development (OR = 4.2, 95% CI: 1.4, 12.9; Table 4). Similar results were observed with the start of DMARD therapy as outcome (Table 4; supplementary (available at Rheumatology Online) Fig. S3) and when using a stricter definition for an abnormal MRI (supplementary (available at Rheumatology Online) Table S5). In addition to MRI inflammation, MRI-detected erosions were evaluated. These were not associated with RA development in univariable or multivariable analyses (supplementary (available at Rheumatology Online) Table S6).

Within UA patients, an abnormal MRI for tenosynovitis had better test characteristics for RA development than BME and synovitis [area under the receiver operating characteristic curve (AUC) of 0.70, vs 0.49 and 0.60]. The positive predictive value of tenosynovitis for RA development was 25% and the negative predictive value 95% (supplementary (available at Rheumatology Online) Table S7). Since the association of an abnormal MRI for tenosynovitis with RA development was stronger than that of an abnormal MRI for synovitis or BME, further analyses were confined to tenosynovitis. Similar results for tenosynovitis were seen using DMARD initiation as the outcome (supplementary (available at Rheumatology Online) Table S7).

Accuracy of MRI in subgroups of UA patients presenting with mono-, oligo and polyarthritis

The differential diagnoses for UA patients presenting with monoarthritis (1 swollen joint), oligoarthritis (2-4 joints) and polyarthritis (>4 joints) can differ. Because the value of MRI might also differ in these patients, the value of MRI was explored in these three subgroups. RA development was rare in UA patients presenting with monoarthritis (3%); of the UA patients presenting with oligo and polyarthritis, 18% and 29%, respectively, developed RA (Table 5). The continuous RAMRIS scores of the three subgroups are shown in Table 2. In UA patients with mono- and polyarthritis, an abnormal MRI for tenosynovitis was not associated with RA development (Table 5). In UA patients with oligoarthritis, in contrast, an abnormal MRI for tenosynovitis was associated with RA development (P < 0.001), the sensitivity was 93%, specificity 63%, positive predictive value 36% and negative predictive value 98%. Similar results were found when using initiation of DMARD

Table 4 Results of logistic regression analyses for RA development and DMARD initiation in unclassified arthritis patients

	Univariable analyses		Multivariable analysis: types of MRI-inflammation		Multivariable analysis: abnormal tenosynovitis adjusted for age, SJC, and CRP	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Outcome: RA						
Constant/Intercept			0.06 (-)	<0.001	0.01 (-)	<0.001
MRI abnormal for						
any inflammation	7.2 (1.6-31.2)	0.009				
BME	0.9 (0.4-2.1)	0.87	0.5 (0.2-1.2)	0.14		
synovitis	2.3 (1.0-5.2)	0.04	1.2 (0.5-3.2)	0.68		
tenosynovitis	6.7 (2.4-18.3)	<0.001	7.5 (2.4-23.1)	<0.001	4.2 (1.4-12.9)	0.01
Age, per year	1.03 (1.00-1.06)	0.02			1.01 (0.97-1.04)	0.68
Swollen joints,						
1 joint	ref				ref	
2-4 joints	8.3 (1.8-37.5)	0.006			7.5 (1.6-34.8)	0.01
2-4 joints	15.5 (3.3-73.6)	0.001			10.4 (2.1-51.5)	0.004
Elevated CRP	3.8 (1.7-8.5)	0.001			2.2 (0.9-5.4)	0.10
Outcome: DMARD initiation						
Constant/Intercept			0.30 (-)	<0.001	0.09 (-)	<0.001
MRI abnormal for						
any inflammation	2.3 (1.2-4.6)	0.01				
BME	1.1 (0.6-2)	0.70	0.7 (0.3-1.3)	0.27		
synovitis	2.1 (1.2-3.7)	0.01	1.2 (0.6-2.4)	0.67		
tenosynovitis	4.2 (2.3-7.8)	<0.001	4.4 (2.2-9.0)	<0.001	3.0 (1.5-6.0)	0.003
Age, per year	1.03 (1.01-1.05)	0.006			1.01 (0.98-1.03)	0.55
Swollen joints,						
1 joint	ref				ref	
2-4 joints	2.5 (1.2-5.1)	0.01			2.3 (1.1-4.9)	0.03
>4 joints	6.6 (2.9-15.3)	<0.001			5.2 (2.1-12.7)	<0.001
Elevated CRP	3.0 (1.6-5.7)	0.01			2 (1.0-4.2)	0.06

MRI abnormal for any inflammation indicates the presence of abnormal bone marrow oedema, synovitis or tenosynovitis; OR: odds ratio; SJC: swollen joint count.

therapy as the outcome (supplementary (available at Rheumatology Online) Table S8). When a stricter definition of an abnormal MRI was used, the results were similar (supplementary (available at Rheumatology Online) Table S9).

Table 5 Test characteristics of an abnormal MRI for tenosynovitis for RA development in unclassified arthritis patients

		RA	no-RA	p	Sens. , % (95%CI)
All UA-patients, n (%)		29 (14)	172 (86)		
	MRI-TS +	24	72	<0.001	83%
	MRI-TS -	5	100		(65%-92%)
	CRP +	15	38	0.001	52%
	CRP -	14	134		(34%-69%)
CRP +	MRI-TS +	15	22	0.002	100
	MRI-TS -	0	16		(80%-100%)
CRP -	MRI-TS +	9	50	0.05	64%
	MRI-TS -	5	84		(39%-84%)
Subgroup: Monoarthritis, n (%)		2 (3)	75 (97)		
	MRI-TS +	1	29	0.99	50%
	MRI-TS -	1	46		(9%-91%)
Subgroup: Oligoarthritis, n (%)		15 (18)	68 (82)		
	MRI-TS +	14	25	<0.001	93%
	MRI-TS -	1	43		(70%-99%)
	CRP +	8	14	0.020	53%
	CRP -	7	54		(30%-75%)
CRP +	MRI-TS +	8	8	0.051	100%
	MRI-TS -	0	6		(68%-100%)
CRP -	MRI-TS +	6	17	0.009	86%
	MRI-TS -	1	37		(49%-97%)
Subgroup: Polyarthritis, n (%)		12 (29)	29 (71)		
	MRI-TS +	9	18	0.49	75%
	MRI-TS -	3	11		(47%-91%)

Mono-, oligo- and polyarthritis, respectively: swollen joint count of 1, 2-4 and>4; RA, fulfilment of the 1987 RA criteria within the first year; P: P-values of Chi-square test (or Fisher's exact test when appropriate); Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR-: negative likelihood ratio; AUC: area under the receiver operating characteristic curve; MRI-TS: abnormal MRI-detected tenosynovitis; MRI-TS +: presence of abnormal MRI-detected tenosynovitis; MRI-TS-: absence of abnormal MRI-detected tenosynovitis; CRP+: elevated CRP; CRP-: normal CRP.

Spec. , % (95%CI)	PPV, % (95%CI)	NPV, % (95%CI)	LR+, % (95%CI)	LR-, % (95%CI)	AUC
58%	25%	95%	1.98	0.30	0.70
(51%-65%)	(17%-35%)	(89%-98%)	(1.55-2.52)	(0.13-0.66)	
78%	28%	91%	2.34	0.62	0.65
(71%-83%)	(18%-42%)	(85%-94%)	(1.49-3.67)	(0.42-0.91)	
42%	41%	100	1.73	-	0.71
(28%-58%)	(26%-57%)	(81%-100%)	(1.32-2.27)	-	
63%	15%	94%	1.72	0.57	0.63
(54%-70%)	(8%-27%)	(88%-98%)	(1.10-2.70)	(0.28-1.16)	
61%	3%	98%	1.29	0.82	0.56
(50%-72%)	(1%-17%)	(89%-100%)	(0.31-5.32)	(0.20-3.30)	
63%	36%	98%	2.54	0.11	0.78
(51%-74%)	(23%-52%)	(88%-100%)	(1.81-3.57)	(0.02-0.71)	
79%	36%	89%	2.59	0.59	0.66
(68%-87%)	(20%-57%)	(78%-94%)	(1.33-5.04)	(0.34-1.02)	
43%	50%	100%	1.75	-	0.71
(21%-67%)	(28%-72%)	(61%-100%)	(1.11-2.75)	-	
69%	26%	97%	2.72	0.21	0.77
(55%-79%)	(13%-46%)	(87%-100%)	(1.66-4.47)	(0.03-1.29)	
38%	33%	79%	1.21	0.66	0.56
(23%-56%)	(19%-52%)	(52%-92%)	(0.78-1.86)	(0.22-1.95)	

Decision curve analyses

In all UA patients and in the subgroup of UA patients presenting with oligoarthritis, models with and without abnormal MRI tenosynovitis were compared (supplementary (available at Rheumatology Online) Table S10). This showed a higher net benefit for the model with MRI in both analyses (Fig. 1).

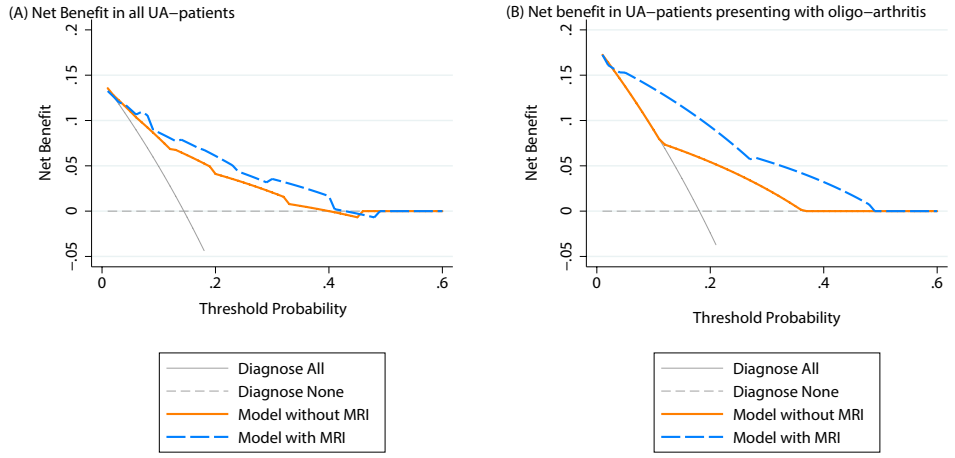

Figure 1 Decision curve analysis comparing models with and without MRI-detected tenosynovitis for identification of RA progression in unclassified arthritis patients

Decision curve analysis demonstrating the net benefit of different diagnostic models (supplementary (available at Rheumatology Online) Table S10) for identifying the patients who progress to RA among all unclassified arthritis (UA) patients (A) and among the subgroup of UA patients who presented with oligoarthritis (B). The net benefit (y-axis) is measured as the rate of correctly diagnosed patients developing RA within the first year without additional false-positive identified patients. The threshold probability (x-axis) represents the probability at which the benefit of early diagnosis is considered equivalent to the harm of overdiagnosis.

Discussion

It is recommended by the EULAR that treatment of RA should be initiated as soon as possible.[33] Early treatment requires early identification of RA. This is difficult if patients present with UA. It is inextricably linked to early recognition that the phenotype may not yet be completely matured; additional tests are therefore needed. When using the 2010 criteria, UA patients are mainly ACPA-negative, as was also shown here.[5,34] The regular predictors such as CRP and the number of swollen joints also have a limited predictive value. As it has been advocated that MRI-detected inflammation is valuable for the early identification of RA,[7] this study determined the diagnostic accuracy of hand and foot MRI in 2010 UA patients. Although an abnormal MRI did not yield high absolute risks for RA, the data showed that MRI contributed to the identification of UA patients that will progress to RA. Of all types of inflammation, tenosynovitis had the best accuracy and, of all UA patients, the test characteristics were highest in the subgroup of UA patients who presented with oligoarthritis. Furthermore, the absence of MRI-detected inflammation made progression to RA highly unlikely.

Generally, the development of a diagnostic tool starts with comparing established

patients with controls. This allows testing of the chosen cut-off value. The disadvantage is that this generally results in accuracies that are misleadingly high.[35,36] Subsequently, the test needs to be evaluated in clinically relevant settings. We set out to use this approach. We used information on MRIs of symptom-free persons from the general population to define an abnormal test and compared the MRI findings for patients who presented with RA with those of symptom-free controls and with patients with other arthritides. Indeed, we observed that the test characteristics were lower when comparing RA with other arthritides than with healthy controls; this is also in line with a smaller previous study that showed that early arthritis patients with other arthritides also show inflammation of the hands and feet on MRI.[37] After these explorative studies, the value of MRI was assessed in the clinically relevant setting of UA.

At baseline, RA was defined according to the 2010 criteria, and UA patients did not fulfil these criteria. Ninety-six percent of 2010 UA patients were ACPA-negative and only 4% was ACPA-positive. This is in line with the composition of the 2010 criteria, where ACPA-positive patients can fulfil the criteria with one (or more) swollen joint and ACPA-negative patients require >10 swollen joints.[3] This suggests that the 2010 criteria are less sensitive for the early detection of ACPA-negative RA. Indeed, a recent study proved that ACPA-negative RA patients had more extensive inflammation than ACPA-positive RA patients.[38] Consequently, ACPA-negative patients are nowadays more frequently classified as UA; this was also shown in our data.

Fulfilling the 1987 criteria was the primary outcome because these criteria had a higher specificity than the 2010 criteria[4,29] and because ACPA-negative UA patients can only become 2010-positive when they develop >10 involved joints; also, DMARDs may be initiated before the disease is as advanced. Intuitively it feels contradictory not to use the 2010 criteria as the outcome, but we balanced up the characteristics of the different criteria (the 2010 criteria being sensitive and fulfilled earlier than the 1987 criteria, the 1987 criteria being more specific over time). In our data only 5% of ACPA-negative patients fulfilled the 2010 criteria after 1-year, whereas 14% fulfilled the 1987 criteria and 36% were treated with DMARDs. Hence, our data confirm the observation that ACPA-negative patients fulfil the 1987 criteria more easily than the 2010 criteria. Still, in both ACPA-negative and ACPA-positive patients, treatment may have resulted in a decreased percentage of patients developing RA. Therefore DMARD initiation was also studied as outcome.

The present data emphasize that MRI is valuable in (APCA-negative) UA, especially in ACPA-negative UA patients presenting with oligoarthritis. Only 3% of ACPA-negative patients presenting with monoarthritis progressed to RA; with this low prior risk a predictive effect of MRI could not be detected. Also, in ACPA-negative patients presenting with polyarthritis, a predictive effect of MRI was not found; presumably in patients who presented with polyarthritis already, information on MRI-detected local joint inflammation was not of additional value.

The present finding that tenosynovitis was most discriminative is in line with previous studies.[14,20,22,23] Interestingly, tenosynovitis was also an early phenomenon in mice models of induced arthritis[39] and has recently also been shown to be predictive for the development of clinically apparent arthritis in patients who

present with clinically suspect arthralgia.[40] Tenosynovitis is also detectable with US. Although some studies suggested that US is less sensitive than MRI in detecting tenosynovitis, the question of whether MRI can be replaced with US in UA patients when identifying patients with impending RA remains to be answered.[20,41,42]

Importantly, the early arthritis patients studied were consecutively seen at the outpatient clinic and included in the cohort without further selection other than recent-onset arthritis;[27] this allows extrapolation of findings. Other strong elements are the comprehensive approach and the sample size. This study contains by far the largest number of consecutive included early arthritis patients with MRI data thus far. High-quality MRI data were obtained; we used a superconductive 1.5 T system with powerful gradients, allowing small acquisition matrices with relatively high SNR and frequency-selective fat suppression.

BME was assessed on contrast-enhanced T1-weighted fat-saturated sequences; RAMRIS suggests STIR/T2-sequences (see supplementary (available at Rheumatology Online) data, section detailed MRI protocol).[30] Previous studies, in diverse patient populations, have shown high similarities for BME between these sequences,[43–45] and both sequences are recommended by the European Society of Skeletal Radiology (ESSR).[46]

Previously, both in our study and the research of others, BME has been shown to be predictive for erosive progression in RA patients.[47–50] In the present study, BME and erosions were not predictive for RA development in UA patients. Possibly, this is related to the fact that most UA patients were ACPA-negative, or to the fact that predictors for erosive progression are different from those predicting RA development. Apparently, different markers perform differently when used in slightly different types of patients, in different disease phases, and with respect to different outcomes.

Our study has several limitations. First, the sample set: although we studied a large group of 201 UA patients, only 29 of these patients developed RA. This also resulted in a low number of cases in the subgroups of mono-, oligo- and polyarthritis. In general, low numbers of cases lead to a higher probability of a type II error. The RAMRIS method was used to score the MRIs. This method is the only validated method for evaluating hand and foot MRIs and is suitable for research, but it was not designed for diagnostic purposes. RAMRIS scoring is time-consuming, rheumatologists and radiologists are generally not experienced with the method, and the reproducibility may be moderate if readers are insufficiently trained. This may hamper direct clinical implementation. After showing the continuous MRI scores, the most important analyses were done by comparing abnormal with normal MRI results. Dichotomization generally leads to loss of information and possibly loss of discriminative value. However, using continuous scores would have hampered the use of findings done in symptom-free controls. More work is needed in order to make MRI feasible for diagnostic use. As in other fields of radiology, a small set of well-defined imaging parameters are needed to allow the use of MRI in the differential diagnostic process in a subjective clinical environment.

We did not address the cost-effectiveness of MRI. Although MRI is relatively

expensive, the possible benefits of an early RA diagnosis could be a multitude when resulting in reduced disability and reduced use of biologics. We also did not evaluate to what extent it is required to scan hand and foot joints, or if a limited region would be equally informative. These are subjects for further research.

In conclusion, this study revealed that MRI-detected inflammation contributes to the identification of UA patients who will develop RA. MRI-detected tenosynovitis was most helpful, and the accuracy was the highest in UA patients who presented with oligoarthritis. Furthermore, RA was unlikely to develop in UA patients with a normal MRI. This comprehensive study therefore indicates that MRI is of help in the diagnostic process of RA.

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