Clinically suspect arthralgia and early rheumatoid arthritis: advances in imaging and impact on daily life

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The use of MRI-detected synovitis to determine the number of involved joints for the 2010 ACR/EULAR classification criteria for Rheumatoid Arthritis – is it of additional benefit?

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Abstract

Objective

To assess the value of MRI-detected synovitis to determine the number of involved joints on the performance of the 2010-ACR/EULAR classification criteria for rheumatoid arthritis (RA).

Methods

277 patients with a clinical suspicion of RA consecutively included in the Leiden Early Arthritis Clinic (EAC)-cohort underwent 1.5T MRI of MCP-, wrist- and MTP-joints. Test characteristics of the 2010-criteria were calculated when the number of involved joints was determined with and without including MRI-detected synovitis. Two outcomes were studied: disease modifying anti-rheumatic drug (DMARD)-initiation and 1987-criteria fulfilment during the first year.

Results

At baseline, 143 patients were classified as RA. When MRI-detected synovitis was considered, 14 patients additionally fulfilled the 2010-criteria. Of these, 64% (9/14) started DMARDs. When MRI-detected synovitis was also used to determine the number of involved joints the sensitivity changed from 62% to 67%, the specificity from 90% to 84% and the AUC from 0.76 to 0.75. The net reclassification index was -2.4%. When fulfilling the 1987-criteria was used as outcome, results were similar.

Conclusion

We found no scientific support that the use of MRI-detected synovitis is of additional benefit for the performance of the 2010 classification criteria.

Introduction

Because early classification is important in rheumatoid arthritis (RA), the 2010 ACR/EULAR classification criteria have been developed.[1] These criteria are more sensitive and slightly less specific than the 1987-criteria.[2] Differences between these criteria are amongst others a stronger weight of autoantibodies in the 2010-criteria. In addition, the 2010-criteria suggest the use of imaging tools to ascertain synovitis.[1] This addition seems reasonable as studies on Magnetic Resonance Imaging (MRI) have shown that synovitis in early arthritis patients can be present in a substantial amount of joints that were neither swollen nor tender at clinical examination.[3] Moreover, autoantibody-negative patients require the presence of > 10 involved joints to fulfil the criteria for RA.[4] The addition of advanced imaging modalities could substantially increase the number of involved joints and may therefore improve the accuracy of the criteria in the autoantibody-negative group in particular. Although the development of the 2010-criteria was primarily data-driven, the suggestion to also use advanced imaging modalities to detect synovitis was included in the criteria based on expert opinion.[5] Thus far there are no studies published in peer-reviewed journals that evaluated the effects of including information of synovitis detected by MRI on the performance of the 2010-criteria. Therefore, this study determined the effects of the inclusion of MRI-detected synovitis in the evaluation of the number of involved joints on the performance of the 2010-criteria.

Methods

Patients

We studied 277 patients with clinically evident inflammatory arthritis of ≥1 joint that were consecutively included in the Leiden Early Arthritis Clinic (EAC) cohort between 2013 and 2015, who when the results of regular laboratory investigations were known, had the clinical working diagnosis of RA or undifferentiated arthritis (UA) (Figure 3.1). The EAC is a population-based inception cohort of patients with recent-onset arthritis with a symptom duration <2 years that started in 1993 and is described in detail elsewhere.[6] At baseline 66-swollen and 68-tender joint counts (66-SJC and 68-TJC), laboratory investigations (including c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), immunoglobulin M-rheumatoid factor (RF) (positive if ≥3.5 IU/mL) and anti-citrullinated peptide antibody (ACPA, anti-CCP2, Eurodiagnostica, the Netherlands, positive if ≥25 U/mL; from 2009 EliA CCP, Phadia, the Netherlands, positive if ≥7 U/mL)) and an MRI were performed. Follow-up visits with standard clinical assessments were performed 3 months after the first presentation and yearly thereafter. The study was approved by the Ethics Committee. Written informed consent from each patient was obtained.

MRI

From 2010 onwards an MRI was made at baseline and from June 2013 onwards not only the MCP- and wrist-joints, but also the MTP-joints were imaged after gadolinium enhancement. As contrast enhancement is beneficial for the evaluation of synovitis,[7] patients were selected from June 2013 onwards at the time contrast enhancement

of the MTP-joints was added to the protocol. Patients studied here were included between June 2013 and December 2015. A 1.5T MRI was made at the most severely affected symptomatic side or at the dominant side if symptoms were equal at both sides (see online supplementary methods). According to the protocol the MRI was made before disease modifying anti-rheumatic drug (DMARD)-initiation (including glucocorticoids) and patients were asked to stop NSAIDs 24hours before the scan. The scans were scored according to RA MRI Scoring (RAMRIS) method by two experienced readers (intraclass correlation coefficients (ICC) for synovitis 0.96). More details on the scanning and scoring method are provided supplementary *(online available)*. Mean

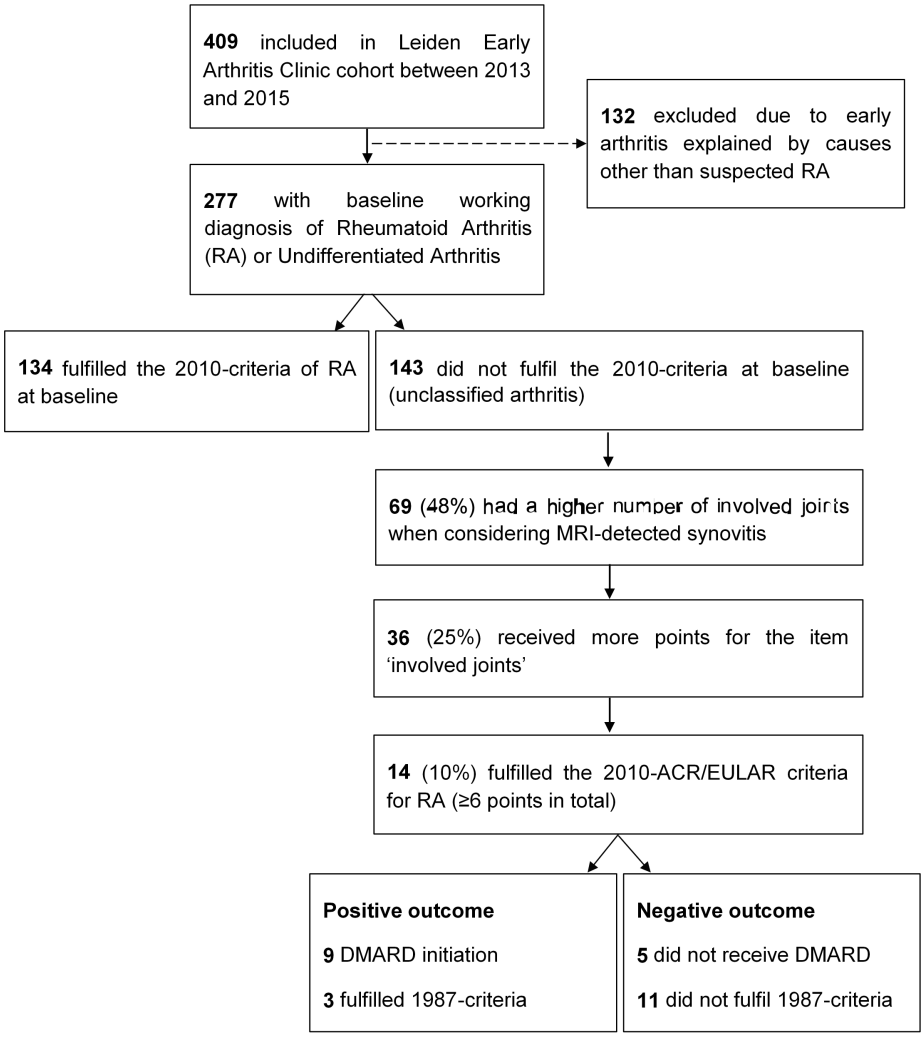

Figure 3.1: Flowchart of patient selection from the Leiden Early Arthritis Clinic cohort.

scores of two readers were calculated and in case of a mean score of ≥1, the MRI was considered positive for MRI-detected inflammation (synovitis, tenosynovitis or bone marrow oedema (BMO)). The MRI reading results were not communicated to the clinicians at any time point.[6, 8]

Incorporation of MRI-detected inflammation for the classification of RA-patients

The 2010-criteria were applied to all 277 patients with clinical synovitis of at least one joint that had no alternative explanation for their complaints and were considered as at risk for RA by their treating rheumatologist. Joint counts were performed with and without the addition of MRI-detected inflammation. For example, in case a joint was neither tender nor swollen, but was positive for MRI-detected synovitis (mean score ≥1 per joint by 2 separate independent readers) it resulted in a positive joint for the calculation of the 2010 ACR/EULAR classification criteria with MRI-detected synovitis. Although the 2010-classification criteria stated that synovitis detected by advanced imaging modalities might be assessed to determine the number of involved joints, MRI also depicts tenosynovitis and BMO. Therefore we also explored if adding information of these features increased the accuracy of the criteria. Patients that fulfilled ≥6 points of the classification criteria were considered 2010-criteria positive RA.[1]

Analyses

After 1-year follow-up patient files were assessed on two outcomes that were used as a proxy of RA. The primary outcome was the initiation of a DMARD (including the start of oral, intra-articular or intramuscular glucocorticoids); this outcome was also used in the data-driven phase of the derivation of the 2010-criteria. The secondary outcome was fulfilment of the 1987-criteria. We calculated test characteristics for the 2010-criteria without and with the addition of MRI-detected synovitis. The net reclassification index was calculated.

Results

At baseline 143 out of the total of 277 patients studied did not fulfil the 2010-criteria when the number of involved joints was determined at clinical evaluation only (Figure 3.1) and 134 did. Table 3.1 shows the baseline characteristics; in line with previous observations the patients that did not fulfil the criteria were mostly auto-antibody negative. When MRI-detected synovitis was also considered to count the number of involved joints, 69 patients had increased joint counts. Subsequently we determined the number of patients that received more points for the item 'number of involved joints'; this concerned 36 patients. Then we counted the additional number of patients in whom the total points had become 6 or higher. A total of 14 additional patients now fulfilled the 2010-criteria for RA. Thus, when data on MRI-detected synovitis were included 10% of patients that were formally classified as UA were now additionally classified as having RA.

Then the 1-year follow-up data were studied. When MRI-detected synovitis was not

considered, the sensitivity (95% CI) of the 2010-criteria was 62% (55; 69) and the specificity 90% (82; 95) for DMARD initiation as outcome (Table 3.2). Nine of the 14 additionally classified patients (64%) were started on DMARDs and were considered as true positives, whereas the other five patients (36%) were not treated with DMARDs. These five patients developed alternative clinical diagnoses during the first year (gout (n=2), inflammatory osteoarthritis (n=1), paraneoplastic inflammatory arthritis (n=1)) or had spontaneous resolution of arthritis in the first year (n=1). With the addition of MRI-detected synovitis the sensitivity increased to 67% (60; 73) and the specificity decreased to 84% (73; 90). The area under the receiver operating characteristic curve (AUC) changed from 0.76 to 0.75. The net reclassification index -2.4% (Supplementary table 3.3).

Results for the secondary outcome, fulfilment of the 1987-criteria after 1-year, were similar (Table 3.2). The sensitivity changed from 79% (71; 85) to 81% (74; 87) and the specificity from 78% (71; 84) to 71% (63; 78). The net reclassification index was -5.1% (Supplementary table 3.4).

To investigate whether the additionally classified patients with MRI-detected synovitis could be explained by the definition of MRI-detected synovitis, we also applied a cut-off based on findings from symptom-free volunteers, as previously published,[9] instead of a cut-off of mean ≥1. Then MRI-detected synovitis was considered present in a joint if this was seen in <5% of age matched healthy controls. This caused less UA-patients to fulfil the 2010-criteria and also resulted in both an increase in falsely and correctly additionally classified RA-patients (data not shown). The area under the receiver operating characteristic curve (AUC) remained 0.76.

Since MRI does not only depict synovitis, but also tenosynovitis and BMO, it was explored if incorporation of these inflammatory findings changed the results. As depicted in Table 3.2, the test characteristics and AUC were almost similar to that of

Table 3.1: Baseline characteristics of 277 patients studied and for those that did not fulfil the 2010-criteria when MRI results were not considered (Undifferentiated Arthritis, UA).

	All patients (n=277)	UA patients (n=143)
Age, mean (SD)	57 (16)	56 (17)
Female, n (%)	176 (64)	85 (59)
68-Tender joint count, median (IQR)	6 (9)	3 (5)
CRP (mg/L), median (IQR)	7 (18)	5 (11)
Symptom duration in days, median (IQR)	73 (166)	59 (156)
RF positive (≥3.5 IU/mL), n (%)	97 (36)	11 (8)
ACPA positive (≥7 U/mL), n (%)	97 (36)	22 (16)
Either RF or ACPA positive, n (%)	127 (46)	29 (20)

ACPA, anti-citrullinated peptide antibody; RF, rheumatoid factor; CRP, c-reactive protein; SD, standard deviation; IQR, Inter quartile range.

MRI-detected synovitis.

Discussion

This study provided evidence on the value of the inclusion of MRI-detected synovitis in addition to the evaluation of tender and swollen joints for the classification of RA. Our data show that the accuracy as measured by the AUC did not improve. This conclusion is similar to that reported in two abstracts that to our knowledge did not proceed to papers published in peer-reviewed journals.[10, 11] We observed that almost 50% of patients had MRI-detected synovitis in joints that were neither swollen nor tender at physical examination. However this resulted in a positive classification for the 2010-criteria in a minority of patients. Furthermore one-third of additionally classified patients did not have RA with DMARD-treatment as reference and could be considered as false-positives.

A meta-analysis on the performance of the 2010-criteria by Radner *et al* reported a

Table 3.2: Test characteristics of the 2010 EULAR/ACR criteria for RA without and with considering MRI-detected inflammation for the primary outcome (initiation with DMARDs in the first year) and secondary outcome (fulfilment of the 1987-criteria at year one).

Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
DMARD initiation in the first year as outcome					
2010-RA without considering MRI					
62 (55; 69)	90 (82; 95)	95 (90; 97)	46 (38; 54)	70 (64; 75)	0.76
2010-RA with considering MRI-detected synovitis					
67 (60; 73)	84 (73; 90)	92 (86; 95)	47 (39; 56)	71 (66; 76)	0.75
2010-RA with considering MRI-detected tenosynovitis					
66 (59; 72)	86 (77; 92)	93 (88; 96)	47 (39; 56)	71 (66; 76)	0.76
2010-RA with considering MRI-detected bone marrow oedema					
64 (57; 70)	86 (77; 92)	93 (87; 96)	46 (38; 54)	70 (64; 75)	0.75
2010-RA with considering any MRI-detected inflammation					
68 (61; 74)	82 (72; 89)	91 (86; 95)	48 (39; 57)	72 (66; 77)	0.75
1987-criteria fulfilment in the first year as outcome					
2010-RA without considering MRI					
79 (71; 85)	78 (71; 84)	76 (68; 83)	81 (74; 87)	79 (74; 83)	0.79
2010-RA with considering MRI-detected synovitis					
81 (74; 87)	71 (63; 78)	71 (63; 78)	81 (74; 87)	76 (70; 80)	0.76
2010-RA with considering MRI-detected tenosynovitis					
81 (74; 87)	74 (66; 80)	73 (65; 80)	82 (75; 88)	77 (72; 82)	0.78
2010-RA with considering MRI-detected bone marrow oedema					
81 (73; 87)	76 (68; 82)	74 (66; 81)	82 (74; 87)	78 (73; 82)	0.78
2010-RA with considering any MRI-detected inflammation					
82 (75; 88)	69 (61; 76)	70 (62; 76)	82 (74; 87)	75 (70; 80)	0.76

Test characteristics are shown in percentages with a 95% CI except for the AUC, area under the receiver operating characteristic curve. PPV, positive predictive value; NPV, negative predictive value. Any MRI-detected inflammation consists of either synovitis, tenosynovitis or bone marrow oedema.

sensitivity and specificity for DMARD initiation of 65% and 80% respectively. Our findings are in line with these data.

We also did not identify studies or trials stating that imaging modalities were used for the application of the classification criteria. Hence we are unfamiliar with how often novel imaging modalities are currently used to this end. The value of ultrasound for the classification criteria has been studies previously.[12–15] All studies were differently designed. In two studies the presence of clinically evident inflammatory arthritis was not required for inclusion.[12, 14] Another study showed associations between ultrasound-detected synovitis and fulfilment of the 2010-criteria, but test characteristics with and without the use of ultrasound were not provided.[15] One study calculated test characteristics and showed that the use of ultrasound resulted in an increased sensitivity at the cost of specificity, which is in line with our findings.[13] Also these ultrasounds studies showed, similarly to our study, an increase of both correctly and incorrectly classified RA-patients.[15]

The method how MRI-detected synovitis should be incorporated in the 2010-criteria was not thoroughly explained.[1] We used MRI additionally to clinical evaluation of joints. However, the study of Nakagomi *et al* that used ultrasound, included patients without clinical synovitis and determined the number of involved joints solely by imaging.[12] This resulted in patients fulfilling the criteria for RA without any clinically detectable synovitis.

Importantly, concerning the type of inflammation assessed, our main focus was the addition of MRI-detected synovitis, as this was explicitly stated in the table by Aletaha *et al.*[1] To further examine the impact of other types of MRI-detected inflammation, we seperately analysed the value of tenosynovitis, BMO and the presence of any type of inflammation as an addition to the criteria. These results were similar to the outcomes of MRI-detected synovitis.[8]

The definition of the presence of synovitis on imaging was not explicated in the 2010-criteria. Several previous studies showed low-grade synovitis in small joints of asymptomatic persons, especially at higher age.[16–18] Although the nature of this phenomenon remains indefinite, not considering this may possibly result in an overestimation of affected joints. Therefore we analysed an alternative definition for synovitis-positivity and investigated the effects if a joint was considered positive when this was present in <5% of age matched healthy controls. This also resulted in an increase in falsely and correctly classified RA-patients. Consequently, we think that the presence of low-grade synovitis in the general population does not explain the lack of increased accuracy when using MRI-detected synovitis in the criteria.

In this study we observed an increased sensitivity at the cost of the specificity. It could be discussed that classification criteria should be sensitive and therefore incorporation of imaging into the 2010-criteria for RA could be considered favourable. At the other hand, here this also resulted in a substantial increase of false positives.

In addition to the outcome studied here, it would also be interesting to evaluate more a long-term outcome like disease persistence. Further, the present findings require external validity in other cohorts of early RA patients to assess if these results are generalizable.

In conclusion, we did not find an increased accuracy of the 2010 ACR/EULAR classification criteria when MRI-detected synovitis was incorporated. Further research on this subject in other longitudinal cohorts is needed. At present there is no scientific proof that MRI-detected synovitis is of additional benefit for classification of RA.

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Supplementary data

Supplementary methods are online available at *Annals of the Rheumatic Diseases Online*.

Supplementary tables

Table 3.3: Reclassification of patients fulfilling the ACR/EULAR 2010-criteria for RA at baseline, without and with MRI-detected synovitis at baseline and outcome initiation with DMARDs within one year.

	Start with DMARD within 1 year		
	No DMARD	DMARD	Total
Baseline RA (2010-criteria)			
No RA	116	27	143
RA	32	102	134
Baseline RA (2010-criteria) including synovitis detected by MRI			
No RA	105	24	129
RA	43	105	148
Total	148	129	227

The net increase in correct classifications was 4.4% (9/204) and incorrect classifications with MRI-detected synovitis 6.8% (5/73), the net reclassification index was -2.4%.

Table 3.4: Reclassification of patients fulfilling the ACR/EULAR 2010-criteria for RA at baseline, without and with MRI-detected synovitis at baseline and outcome fulfilment of the 1987-criteria within one year.

	1987-criteria fulfilment		
	No RA	RA	Total
Baseline RA (2010-criteria)			
No RA	116	27	143
RA	32	102	134
Baseline RA (2010-criteria) including synovitis detected by MRI			
No RA	105	24	129
RA	43	105	148
Total	148	129	227

The net increase in correct classifications was 2.3% (3/129) and incorrect classifications with MRI-detected synovitis 7.4% (11/148), the net reclassification index was -5.1%.