

## Concise report

## Improving the feasibility of MRI in clinically suspect arthralgia for prediction of rheumatoid arthritis by omitting scanning of the feet

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## Abstract

**Objectives.** The use of MR-imaging is recommended for the early detection of RA. Next to the small joints of the hands, foot-joints are often involved. Therefore, imaging inflammation of the feet in addition to hands may be informative, but prolongs scan-time and leads to additional costs. We studied the value of MRI of the feet alone and complementary to MRI of the hands in patients with clinically suspect arthralgia (CSA).

**Methods.** 357 consecutively included CSA patients underwent contrast-enhanced 1.5T-MRI of hand (MCP2-5 and wrist) and foot (MTP1-5) joints at baseline. Scans were scored for synovitis, osteitis and tenosynovitis. After  $\geq 1$  year follow-up, the development of clinically apparent inflammatory arthritis (IA) was studied. Cox regression was performed and test characteristics were evaluated. Sensitivity analyses were performed for the outcome RA-development (2010-criteria).

**Results.** MRI-detected tenosynovitis of the feet was associated with IA-development, independently from synovitis and osteitis hazard ratio (HR) (95%CI) 4.75 (2.38; 9.49), and independently from ACPA and CRP, HR 3.13 (1.48; 6.64). From all CSA patients, 11% had inflammation in hands and feet, 29% only in hands and 3% only in feet. In line with this finding, the addition of MRI-feet to MRI-hands did not increase the predictive accuracy; the sensitivity remained 77%, while the specificity decreased from 66% to 62%. Sensitivity analyses with RA development as outcome showed similar results.

**Conclusion.** Tenosynovitis at the forefeet in CSA predicted IA and RA development. Addition of foot MRI to hand MRI did not increase the accuracy. Foot MRI can be omitted to reduce scan time and costs and increase the feasibility.

**Key words:** inflammation, early rheumatoid arthritis, MRI, feet

## Rheumatology key messages

- MRI-detected tenosynovitis at MTP joints is associated with an increased risk of RA development in CSA.
- Presence of MRI-detected subclinical inflammation in MTP joints, without concomitant subclinical inflammation of hand joints was infrequent.
- Addition of foot MRI to hand MRI did not increase the predictive accuracy of MRI in CSA.

## Introduction

In RA, imaging is recommended to aid the diagnostic process in case of doubt on the diagnosis [1]. Although treatment recommendations generally focus on the role of imaging in patients with clinically evident arthritis, several studies have shown that imaging can also be helpful in patients with symptoms at risk for RA that are in a

pre-arthritis phase due to the detection of MRI-detected subclinical joint inflammation [2, 3]. MRI in particular has shown to be sensitive and predictive in this setting, but is also costly. Thus far it is unknown if scan time and costs can be reduced by omitting the feet and scanning the hands only in these patients.

Patients with clinically suspect arthralgia (CSA) are identified based on their clinical presentation [4, 5]. Presence of CSA is associated with a risk of RA development of 18–20% in the next year. Results of additional investigations are required to arrive at higher positive predictive values. It has been shown in CSA patients, that presence of MRI-detected subclinical inflammation (i.e. presence of synovitis, osteitis, tenosynovitis more than observed in the general population of the same age) in

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hands or feet increased the risk of RA-development to ~35% [3].

While imaging was recommended by a EULAR taskforce in the diagnostic process of RA [1], it was not specified which joints should be imaged. The small joints of the feet are preferential locations of early RA and also in the phase of CSA [6]. Consequently, previous MRI studies in CSA scanned both extremities (hands and feet). However, there is no data whether scanning the feet in addition to the hands truly increases the prognostic accuracy of MRI; while, due to repositioning, it considerably increases scan time and thereby costs. Therefore, this study evaluated if MRI-detected inflammation of the feet had additional value to the hands in the early detection of patients at risk for RA development.

## Methods

### CSA cohort

The Leiden CSA cohort is a population-based inception cohort with the aim of studying the symptomatic phase of RA that precedes clinical arthritis. Inclusion required presence of arthralgia of small joints for <1 year which was, because of the character of the symptoms, considered as being suspected to progress to RA by a rheumatologist [3]. Its design is described elsewhere and supplementary [3]. The CSA cohort started before the EULAR definition for CSA was developed [5]. The requirements for this definition were recorded but were not required to be included in the CSA cohort.

The study was approved by the local Medical Ethical Committee. All participants signed for informed consent.

### Patient selection

Consecutively included patients between April 2012 and October 2017 in the CSA cohort that had  $\geq 1$  year follow-up (to allow time for IA development) were selected. This concerned 539 patients. A flowchart of the patient selection is provided (Supplementary Fig. S1, available at *Rheumatology* online). Patients without an MRI were excluded ( $n=32$ ), but baseline characteristics of patients with and without MRI did not differ (Supplementary Table S1, available at *Rheumatology* online). Furthermore, 73 patients were excluded because of participation in a placebo-controlled double-blind randomized trial (Treat Earlier (TE), trial registration number: NTR4853), because of a 50% chance on treatment with methotrexate, as described in the Supplementary methods, available at *Rheumatology* online. Finally, 357 patients were studied.

### MRI and scoring

To measure MRI-detected subclinical joint inflammation, contrast-enhanced MRI scans of MCP(2–5), wrist and MTP(1–5) joints were made of the most affected side (or dominant side in case of equally severe symptoms) on an musculoskeletal Extreme 1.5T-extremity MR system (GE, Wisconsin, USA). NSAIDs were stopped 24 h before the MRI scan. Scans were scored for MRI-detected inflammation in line with the OMERACT RAMRIS method

as described supplementary and previously published [3, 6].

Any MRI-detected inflammation was determined by summing synovitis, bone marrow oedema (BMO or osteitis) and tenosynovitis scores. Scans were scored by two independent readers. Inter- and intra-reader intraclass correlation coefficients were  $\geq 0.91$  and  $\geq 0.92$ , respectively (Supplementary Table S2, available at *Rheumatology* online). Mean MRI scores of both readers were calculated to obtain the total inflammation score (see Supplementary Methods, available at *Rheumatology* online). MRI scores were dichotomized as described previously [7]. They were considered positive if inflammation was scored by both readers and present in <5% of age-matched healthy volunteers [7].

### Outcomes

Patients were followed on IA development, confirmed as joint swelling at physical examination by a rheumatologist. The secondary outcome, fulfilment of the 2010 criteria, was also assessed.

### Analyses

Associations were tested with Cox proportional hazards regression using all available follow-up data. Multivariable analyses were adjusted for all types of local inflammation, and thereafter also for ACPA/RF positivity and elevated CRP. Test characteristics, predictive accuracies with corresponding 95% CI were assessed at 1-year follow-up. The added value was determined by comparing these values with and without scanning of the feet and by net reclassification indices (NRI).

Several sub-analyses were performed. First, analyses were repeated with RA development as outcome. Second, analyses were performed in the subset of CSA patients that fulfilled the EULAR definition; it has been shown that this is a slightly more homogeneous set of patients [5, 8]. Third, the additive value of the feet to the hand was evaluated without considering MTP1, as MTP1 is a preferential location for inflammation due to other causes such as degeneration or osteoarthritis. Although patients were included because of a clinical suspicion of imminent RA and evident other explanations for the joints symptoms (such as evident osteoarthritis) precluded the presence of CSA and were not studied, in sub-analyses data of MTP-1 was excluded to investigate if the results obtained were driven by eventual concomitant presence of other causes of inflammation in MTP1. Finally, the analyses were repeated with a restricted inclusion period (April 2012 to April 2015). In these analyses, all patients that were included at the time the randomized placebo-controlled trial was running were excluded. CSA patients with a positive MRI for inflammation were eligible; hence, in this time period, part of the patients with MRI-detected subclinical inflammation were excluded from the present study. Thus, to evaluate if the results of the total group were influenced, results were compared with a subgroup of patients that were included before the trial was running.

IBM SPSS v24 (IBM Corp, Armonk, NY) was used and *P*-values <0.05 were considered statistically significant.

## Results

### Patient characteristics

Patients with CSA had a mean age of 44 years and 78% were female; further characteristics are shown in Supplementary Table S3, available at *Rheumatology* online. Any subclinical MRI-detected inflammation in hands or feet was present in 43%. In more detail, 11% of CSA patients had any MRI-detected inflammation in hands and feet, 29% only in hands, and 3% only in feet. Thus, sole inflammation of the feet was infrequent (Supplementary Fig. S2, available at *Rheumatology* online).

### Associations between MRI-detected inflammation of feet and hands separately and IA development

For the feet, the highest association with IA development was observed with MRI-detected tenosynovitis (hazard ratio (HR) (95%CI) 6.64 (3.79; 1.63), Table 1). This association remained present in multivariable analyses after adjustment for osteitis and synovitis, HR 4.75 (2.38; 9.49) and also after additional adjustments for ACPA- and/or RF-positivity and elevated CRP, HR 3.14 (1.48; 6.64).

Similar findings were obtained for the hands. The highest association was found with MRI-detected tenosynovitis (HR 6.59 (3.92; 11.08)) in univariable analyses. The HR was 6.16 (3.58; 10.62) after adjusting for osteitis, synovitis and 5.36 (3.07; 9.37) after also adjusting for ACPA/RF and CRP (Table 1).

Thus, in both joint groups (hands and feet), tenosynovitis was associated with IA development, independently of other MRI-detected inflammation features and clinical factors.

### Test characteristics of MRI-detected inflammation of the feet, the hands and combined

MRI-detected tenosynovitis in the feet had a sensitivity of 29% and specificity of 95%; the area under the curve (AUC) was 0.62. Any MRI-detected inflammation of the feet had a sensitivity of 38%, a specificity of 89% and AUC of 0.64. The moderate-low sensitivity reflects that CSA patients that developed IA often did not present with MRI-detected subclinical inflammation at the feet joints.

For the hands, tenosynovitis had a sensitivity of 65% and specificity of 80%, the AUC was 0.73. Any MRI-detected inflammation had a sensitivity of 77%, specificity of 66% and AUC of 0.71.

Assessing both hands and feet for tenosynovitis resulted in a sensitivity of 67%, specificity of 79% and AUC of 0.73. Thus, these test characteristics were comparable to those of MRI of the hands alone. Also, when any MRI-detected inflammation was assessed, no improved test characteristics were observed. Assessing hands and feet had a sensitivity of 77% and specificity of 62% and the AUC was 0.69, which were not better than those of scanning the hands alone (Table 2).

### Net reclassification index

The NRI when assessing tenosynovitis of hands only vs hands and feet MRI was 0.6%. When assessing 'any MRI-detected inflammation' the NRI was -3.9%. Thus, also with this method, no benefit of adding feet MRI to the hands was demonstrated.

### Sub-analyses

Analyses were repeated with RA development as outcome (Supplementary Table S4, available at *Rheumatology* online). Similar findings were obtained for associations (Supplementary Table S5, available at *Rheumatology* online) and test characteristics (Supplementary Table S6, available at *Rheumatology* online). Sensitivity analyses were also performed in CSA patients that also fulfilled the EULAR definition (Supplementary Table S7, available at *Rheumatology* online); these results were also similar to the main findings, for associations (Supplementary Table S8, available at *Rheumatology* online) and test characteristics (Supplementary Table S9, available at *Rheumatology* online). We repeated the analyses on the added value of foot MRI to hand MRI while excluding MTP1. Again, test characteristics of hands and feet were not superior to those of hand alone (Supplementary Table S10, available at *Rheumatology* online). The NRI was -2.6%.

Finally, the test characteristics were determined in the part of the cohort that was collected before the start of the placebo-controlled double-blind trial, thus before part of the patient with MRI-detected subclinical inflammation were excluded from the present study; similar findings were obtained (Supplementary Table S11, available at *Rheumatology* online).

## Discussion

This longitudinal MRI study in patients with CSA assessed the predictive value of MRI of the feet alone as well as the additional value of the foot MRI to hand MRI for predicting IA or RA development. We observed that tenosynovitis at the MTPs was independently predictive for RA development. However, tenosynovitis was predictive also for the hands and adding foot to hand MRI did not result in an increased predictive accuracy, either when tenosynovitis or any MRI-detected inflammation was assessed. This can presumably be explained by the low percentage of patients that had inflammation of the feet but not of the hands (3%).

Previous studies in CSA scanned hands and feet and did not assess them separately. Furthermore, in these studies synovitis and osteitis were scored in hands and feet but tenosynovitis was scored in the hands only [3, 9, 10]. Thus, the previous finding that tenosynovitis in CSA was predictive for RA development concerned only tenosynovitis of the hands [3, 11]. The current study is the first in CSA to demonstrate that tenosynovitis of the feet predicts RA development [3].

We did not examine the value of MRI-detected erosions, and focused solely on MRI-detected inflammation.

TABLE 1 Associations with inflammatory arthritis development

	All patients (n = 357)	Arthritis (n = 63)	No Arthritis (n = 294)	HR <sup>a</sup> (95% CI)	P-value	HR <sup>b</sup> (95% CI)	P-value	HR <sup>c</sup> (95% CI)	P-value
MRI features									
Feet (MTP 1–5)									
Tenosynovitis, n (%)	29 (8)	17 (27)	12 (4)	6.64 (3.79; 11.63)	<0.001	4.75 (2.38; 9.49)	<0.001	3.14 (1.48; 6.64)	0.003
Synovitis, n (%)	34 (10)	16 (25)	18 (6)	4.46 (2.53; 8.88)	<0.001	2.48 (1.18; 5.23)	0.017	2.15 (0.98; 4.68)	0.06
BMO, n (%)	21 (6)	7 (11)	14 (5)	2.57 (1.17; 5.64)	0.019	0.66 (0.25; 1.69)	0.38	0.67 (0.25; 1.76)	0.41
Hands (MCP 2–5 and wrist)									
Tenosynovitis, n (%)	95 (27)	41 (65)	54 (18)	6.59 (3.92; 11.08)	<0.001	6.16 (3.58; 10.62)	<0.001	5.36 (3.07; 9.37)	<0.001
Synovitis, n (%)	60 (17)	19 (30)	41 (14)	2.35 (1.37; 4.02)	0.002	1.06 (0.60; 1.87)	0.85	1.12 (0.63; 2.01)	0.69
BMO, n (%)	57 (16)	18 (29)	39 (13)	2.39 (1.39; 4.14)	0.002	1.94 (1.11; 3.38)	0.019	2.33 (1.31; 4.14)	0.004
Clinical features									
Elevated CRP, n (%)	71 (21)	21 (33)	50 (18)	2.22 (1.31; 3.75)	0.003				
ACPA and/or RF Positive, n (%)	69 (21)	30 (48)	39 (14)	4.37 (2.65; 7.19)	<0.001				

<sup>a</sup>HR of univariable analyses. <sup>b</sup>HR of multivariable analyses including the three inflammatory MRI features; multivariable analyses were performed for the MTP, MCP and wrist separately. <sup>c</sup>Multivariable analyses including also CRP, positivity for ACPA and/or RF.

**TABLE 2** Test characteristics of subclinical inflammation and inflammatory arthritis development within 1 year

	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC
<b>Feet (MTP 1-5)</b>						
Tenosynovitis	29 (18; 42)	95 (92; 97)	52 (34; 69)	89 (85; 92)	86 (82; 89)	0.62
Synovitis	37 (25; 50)	83 (78; 86)	26 (18; 38)	88 (84; 92)	76 (71; 80)	0.60
BMO	27 (17; 40)	85 (81; 89)	24 (15; 36)	87 (83; 91)	77 (72; 81)	0.56
Any inflammation	38 (26; 52)	89 (85; 92)	38 (26; 51)	89 (86; 92)	82 (77; 85)	0.64
<b>Hands (MCP 2-5 and wrist)</b>						
Tenosynovitis	65 (52; 77)	80 (75; 84)	36 (27; 46)	93 (89; 96)	78 (73; 82)	0.73
Synovitis	29 (18; 42)	85 (81; 89)	25 (16; 37)	88 (83; 91)	77 (72; 81)	0.57
BMO	29 (18; 42)	86 (82; 90)	26 (17; 39)	88 (83; 91)	78 (73; 82)	0.58
Any inflammation	77 (64; 86)	66 (60; 71)	28 (21; 36)	94 (90; 97)	68 (62; 72)	0.71
<b>Hands and feet</b>						
Tenosynovitis	67 (54; 78)	79 (74; 83)	35 (26; 45)	93 (90; 96)	77 (72; 81)	0.73
Synovitis	42 (30; 56)	81 (77; 85)	28 (19; 39)	89 (85; 92)	76 (71; 80)	0.62
BMO	48 (35; 61)	64 (58; 69)	18 (13; 26)	88 (83; 91)	61 (56; 66)	0.56
Any inflammation	77 (64; 86)	62 (56; 67)	26 (19; 33)	94 (90; 97)	64 (59; 69)	0.69

Test characteristics and their corresponding 95% intervals are shown. All values are percentages, except for the AUC. NPV: negative predictive value; PPV: positive predictive value.

The value of MRI-detected erosions was studied recently, and it was shown that MRI-detected erosions in hand and feet were not predictive of RA development in patients with CSA [12].

Several studies on MRI in arthralgia or early arthritis scanned the hands but not the feet. Some studies did scan the feet but did not explore the value of the feet [3, 6, 9, 10, 13–16]. Therefore, the (additional) value of the feet is largely unknown. One recent study did explore the added value of foot MRI to hand MRI in patients presenting with undifferentiated arthritis (UA) [17]. Also here, the predictive accuracy did not increase when data of the feet were added to the hands, which is in line with the present results obtained in the phase of CSA.

The added value was determined by comparing test characteristics and using the NRI. Similar conclusions were drawn by both methods, which illustrates the robustness of the findings. Also, the fact that current results in CSA are similar to previous findings obtained in UA strengthens the notion that scanning of the feet can be omitted when the hands are imaged for the early detection of RA [17].

In the present study, a contrast-enhanced 1.5 T-MRI was used. The implications of our findings are presumably also relevant for other field-strength MRI machines, such as 3 T-MRI, as repositioning is also required for the feet here.

We are aware of the fact that the OMERACT-RAMRIS was not developed for diagnostic purposes, but for outcome measures in clinical trials. This is a limitation, but no other validated method is available. Because scoring according to OMERACT is time consuming, other evaluation methods might be required to facilitate MRI reading for diagnostic purposes. Based on the present results, if such methods would be developed, this could be restricted to hand joints.

In conclusion, the current study showed the prognostic value of MRI-detected tenosynovitis of the feet in patients with arthralgia at risk for RA. Further, although MRI-detected tenosynovitis was associated with IA development, addition of foot MRI to hand MRI did not increase the predictive accuracy. Therefore, in light of time management and cost efficiency, MRI of the feet can be omitted.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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