Clinically suspect arthralgia: unraveling the development of rheumatoid arthritis

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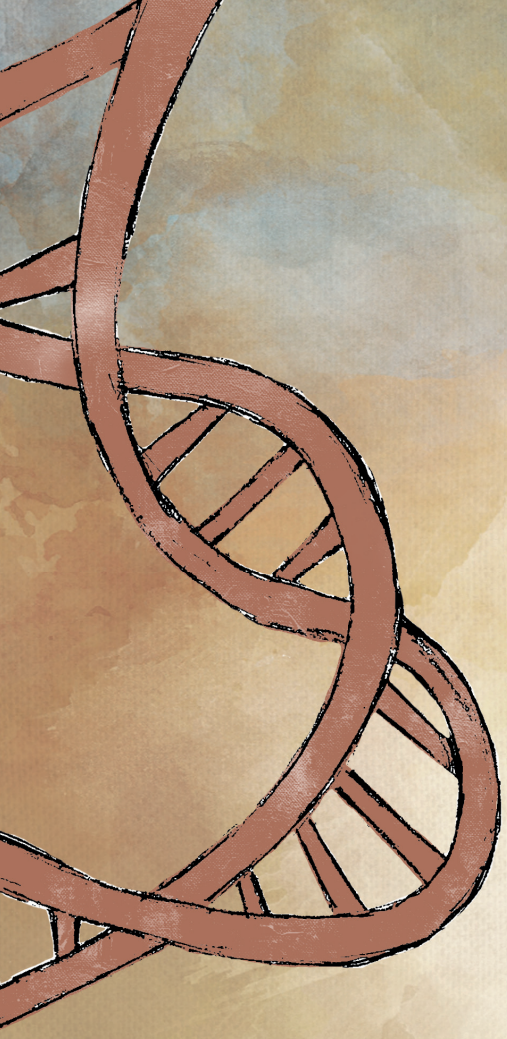

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Do magnetic resonance imaging-detected erosions predict progression to rheumatoid arthritis in patients presenting with clinically suspect arthralgia? A longitudinal study

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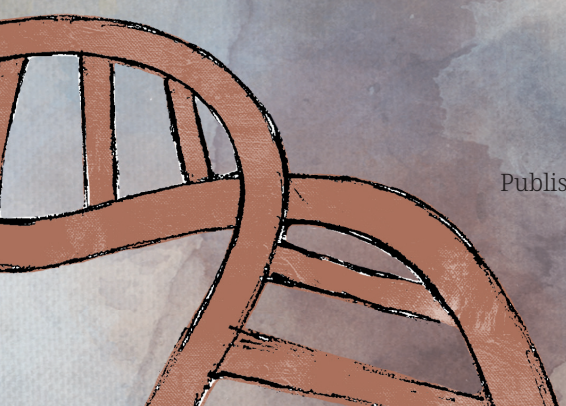

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Abstract

Objectives

Radiographic joint erosions are a hallmark of rheumatoid arthritis (RA). MRI is more sensitive than radiographs in detecting erosions. It is unknown if MRI-detected erosions are predictive for RA-development in patients with clinically suspect arthralgia (CSA). Therefore we investigated the prognostic value of MRI-detected erosions, defined as any MRI-erosion, or MRI-erosion characteristics that were recently identified as specific for RA in patients with evident arthritis.

Methods

Patients presenting with CSA (n=490) underwent contrast-enhanced 1.5T MRI of the wrist, metacarpophalangeal (MCP) and metatarsophalangeal (MTP) joints. MRIs were scored according to RAMRIS. Presence of any MRI-erosion (present in <5% of symptom-free controls) and RA-specific erosion characteristics as identified previously (grade ≥2 erosions, erosions in MTP5, erosions in MTP1 if aged <40) were studied with clinically apparent inflammatory arthritis development as outcome. Analyses were corrected for age and MRI-detected subclinical inflammation.

Results

Erosions were present in 20%. Presence of any MRI-erosion was not associated with arthritis development (HR multivariable analysis 0.97 (95% CI 0.59-1.59)). Also the different RA-specific erosion characteristics were not predictive (grade ≥2 HR 1.05 (0.33-3.34), erosions in MTP5 HR 1.08 (0.47-2.48) and MTP1 if aged <40 HR 1.11 (0.26-4.70)). Erosion scores were higher in ACPA-positive than in ACPA-negative patients (median 2.0 versus 1.0, p=0.002), and related to more subclinical inflammation. Within both subgroups, MRI-erosions were not predictive.

Conclusions

MRI-detected erosions in hands and feet were not predictive for inflammatory arthritis development. Therefore, evaluating MRI for erosions in addition to subclinical inflammation does not provide added clinical value in CSA.

Introduction

Rheumatoid arthritis (RA) is characterized by inflammation of synovial joints and subsequent bone damage. Bone erosions are frequently detectable at radiographs, even in an early disease phase.[1] Currently a lot of effort is undertaken to diagnose RA very early and imaging is increasingly used in prompt identification of RA. Moreover, a focus in research shifts towards identification of patients that will progress to RA already in the phase of arthralgia. Magnetic resonance imaging (MRI) is sensitive in detecting subclinical joint inflammation,[2] which is an established predictor for RA-development.[3] The value of different types of inflammatory features (synovitis, tenosynovitis and bone marrow edema (BME)) has been investigated; from these inflammatory features tenosynovitis has been shown to be most predictive for disease progression.[3] MRI also provides information on bone erosions. Thus far it is unknown if MRI-detected erosions are also predictive for progression to clinically apparent inflammatory arthritis (IA) and RA. However, we hypothesize that erosions might reflect previous episodes of early subclinical inflammation and hereby possibly provide additional value for prediction of IA- and RA-development.

The sensitivity of MRI to depict erosions is higher than that of radiographs.[4] Recent studies revealed that small MRI-detected erosions in hand and foot joints are also present in symptom-free persons from the general population,[5] underlining the need to differentiate generally occurring bone erosions from disease associated bone erosions. A subsequent case-control study compared MRI-erosions of early RA-patients to MRI-erosions of symptom-free volunteers and patients with early arthritides other than RA. This study identified several erosion characteristics with a high specificity for RA as these almost never occurred in both reference groups; grade ≥2 erosions, erosions in metatarsophalangeal joint 5 (MTP5) and erosions in MTP1 in persons aged <40.[6]

With the ultimate aim to determine if the prognostic value of MRI could be improved by evaluating MRI-detected erosions, this study investigated if MRI-detected erosions are predictive for RA-development in patients with clinically suspect arthralgia (CSA) and if the prognostic accuracy of MRI could be improved by assessing MRI-detected erosions in addition to subclinical inflammation. We evaluated both the presence of any MRI-erosion and of MRI-erosion characteristics that were recently identified as RA-specific. Because it has been shown that erosions occur early in ACPA-positive patients in particular,[7-9] the analyses were stratified for ACPA.

Methods

Patients

Between April 2012-October 2018, 613 patients were included in the Leiden CSA cohort. CSA-patients had recent-onset (<1 year) arthralgia in the small joints, which was likely to progress to RA based on the clinical expertise of the rheumatologist. Per definition, patients were excluded if arthritis was detected upon physical examination or if a different explanation for the joint pain was more likely. Baseline visit consisted of physical examination, questionnaires, blood sampling and MRI. Follow-up visits were scheduled at 4, 12 and 24 months. When necessary, for instance in case of an increase of symptoms or when patients experienced joint swelling, additional visits were planned. Follow-up ended when patients developed arthritis, or else after 2-years. The cohort has been described in detail previously.[10]

All patients gave written informed consent. The study was approved by the local medical ethical committee.

MRI

Within two weeks after inclusion, CSA-patients underwent contrast-enhanced 1.5T MRI of wrist, 2nd-5th metacarpophalangeal (MCP) and 1st-5th MTP joints of the most painful side (in case of equally severe symptoms on both sides, the dominant side was scanned). For a detailed scanning protocol, see Supplementary File 1. Erosions, BME and synovitis were scored according to the RA MRI scoring system (RAMRIS),[11] tenosynovitis according to Haavardsholm.[12] Scoring was performed independently by two trained readers. Interreader and intrareader intraclass correlation coefficients were ≥0.91 and ≥0.92, respectively (Supplementary File 2).

MRI-erosion characteristics

Mean total erosion scores were studied, calculated by summation of mean erosion scores from both readers from all individual bones.

Next, as MRI-erosions also can be present in the general population, scores were dichotomized with MRI-erosion data of symptom-free controls as reference (n=193, as published previously).[5] Then patients were considered positive for MRI-erosions if ≥1 erosion that is uncommon in symptom-free controls, i.e. present in <5% of symptom-free controls in the same bone and in the same age category (<40, 40-59, ≥60), was present.

Lastly, erosion characteristics recently identified as RA-specific were evaluated; presence of grade ≥2 erosions, MTP5 erosions and MTP1 erosions when aged <40.

Outcome

The main outcome was development of inflammatory arthritis, determined by the rheumatologist at physical examination (66 swollen joint count ≥1). The secondary outcome was RA-development (fulfilment of 1987- or 2010-criteria).[13,14]

During follow-up (and before the main outcome was reached) treatment with disease-modifying antirheumatic drugs (DMARDs) (including steroids) was not allowed. Since April 2015, CSA-patients with MRI-detected subclinical inflammation could participate in a randomized double-blind placebo-controlled trial (RCT; TREAT EARLIER), studying the effect of Methotrexate in preventing RA-development. This RCT is still ongoing; patients enrolled in this trial (n=89) were excluded from the present study because of their 50% chance of DMARD-use.

Statistics

Total erosion scores and prevalence of MRI-erosions were evaluated with Mann-Whitney U and χ^2 tests. Cox proportional hazards regression was used to investigate predictive value. Multivariable models were adjusted for age and presence of MRI-detected subclinical inflammation (defined as synovitis, tenosynovitis and/or BME present in <5% of symptom-free controls in the same bone and in the same age category). Here all follow-up data was used. Analyses were stratified for ACPA. After 1-year follow the area under the curve (AUC) and the net reclassification index (NRI; the added value of MRI-detected erosions to subclinical inflammation) were determined.

Three subanalyses were performed. First, subanalyses were performed with the secondary outcome RA-development. Secondly, analyses were performed in the subgroup of CSA-patients that fulfilled the EULAR-definition of arthralgia suspicious for progression to RA (≥3/7 items present),[15] to study results in a more homogeneous CSA-population. Lastly, analyses were performed in patients included between April 2012-April 2015, i.e. before the start of the RCT, to investigate if excluding patients with subclinical inflammation affected the results.

P-values <0.05 were considered statistically significant. IBM SPSS Statistics Version 23 was used.

Results

Patients

Of 613 included patients, 123 were excluded (no MRI, participation in RCT; Supplementary File 3). Baseline characteristics are shown in Supplementary Table 1. 83 patients developed inflammatory arthritis after a median follow-up of 14 weeks (IQR 3-23). The median follow-up duration of patients that did not progress to inflammatory arthritis (n=407) was 103 weeks (IQR 51-113).

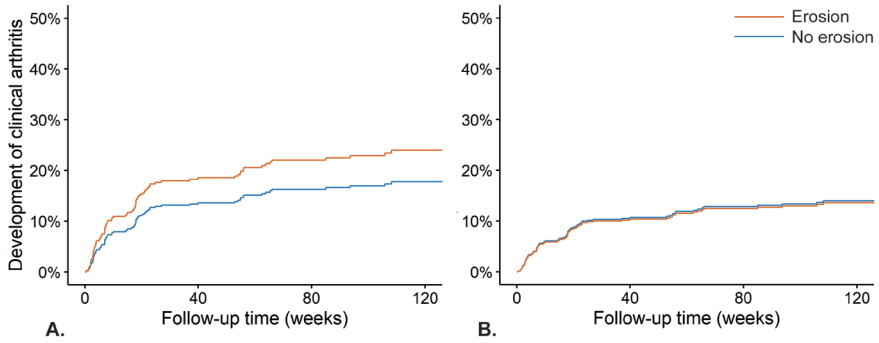
Total erosion scores and arthritis development

The median total erosion score in patients who progressed to inflammatory arthritis was 1.5 versus 1.0 in patients that did not progress. Erosion scores were associated with arthritis development in univariable analysis (HR 1.12 (95% CI 1.01-1.23)), but not after adjustments for age and subclinical inflammation (HR 0.97 (0.85-1.10)) (Table 1).

Presence of MRI-erosion and arthritis development

Next, only those erosions present in <5% of the general population in the same bone and age category were considered. These MRI-erosions were present in 20% of CSA-patients. In 60% of these patients subclinical inflammation was also present, in 40% there was no subclinical inflammation. Presence of MRI-detected erosions was not associated with arthritis development in univariable (HR 1.40 (0.86-2.28)) and multivariable analysis adjusted for age and subclinical inflammation (HR 0.97 (0.59-1.59)) (Table 1, Figure 1).

Figure 1. Development of inflammatory arthritis in presence/absence of erosions in univariable (A) and multivariable (B) analyses



Erosions were considered present if the MRI-erosion was uncommon in symptom-free controls, i.e. present in <5% of symptom-free controls at the same location and in the same age category (<40, 40-59, ≥60). Multivariable models were adjusted for presence of subclinical inflammation. The HR (95% CI) for univariable and multivariable analyses were 1.40 (0.86-2.28) and 0.97 (0.59-1.59), respectively. HR: hazard ratio, CI: confidence interval

Table 1. Erosion scores, prevalence and association with development of inflammatory arthritis in patients with CSA

	No arthritis (n=407)	Arthritis (n=83)	Univariable Cox regression		Multivariable Cox regression[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	1.0 (0.5-2.5)	1.5 (0.5-3.5)	1.12 (1.01-1.23)	0.033	0.97 (0.85-1.10)	0.61
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	78 (19.2)	22 (26.5)	1.40 (0.86-2.28)	0.18	0.97 (0.59-1.59)[b]	0.90
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	7 (1.7)	3 (3.6)	1.84 (0.58-5.84)	0.30	1.05 (0.33-3.34)	0.94
MTP5 erosion	23 (5.7)	6 (7.2)	1.28 (0.56-2.95)	0.56	1.08 (0.47-2.48)	0.86
MTP1 erosion if age <40 (n=192)	11 (6.7)	2 (7.4)	1.16 (0.28-4.92)	0.84	1.11 (0.26-4.70)[b]	0.89

[a] Adjusted for age and presence of subclinical inflammation
[b] Adjusted for presence of subclinical inflammation
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint

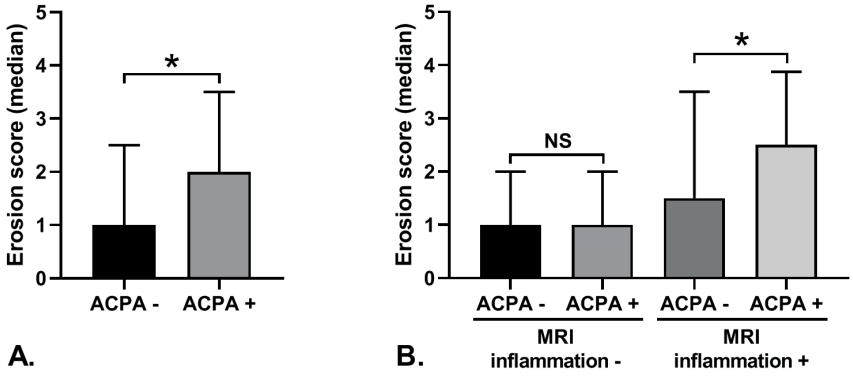
RA-specific erosion characteristics and arthritis development

Subsequently we studied the predictive value of erosion characteristics previously defined as RA-specific. Grade ≥2 erosions, MTP5 erosions, and MTP1 erosions in patients aged <40 were not associated with progression to inflammatory arthritis (multivariable HR 1.05 (0.33-3.34), 1.08 (0.47-2.48) and 1.11 (0.26-4.70), respectively) (Table 1).

Analyses of ACPA-positive and ACPA-negative patients

As ACPA-positive and ACPA-negative RA are different subsets, analyses were stratified for ACPA. ACPA-positive patients had significantly higher erosion scores than ACPA-negative patients (median 2.0 versus 1.0, p=0.002) (Figure 2A). However, when subclinical inflammation was also considered, this difference was only seen in patients with subclinical inflammation but not in ACPA-positive CSA-patients without subclinical inflammation (Figure 2B). Thus presence of ACPA without inflammation did not result in a higher erosion-score.

Figure 2. Erosion scores in ACPA-positive and ACPA-negative patients with and without concurrent subclinical inflammation



Graphs show total erosion scores in ACPA-positive and ACPA-negative patients (A), also stratified for presence of MRI-detected subclinical inflammation (B). *p<0.05, NS: non-significant, ACPA: anti-citrullinated protein antibody

Subsequently the predictive value of presence of MRI-erosions was assessed within each ACPA subset, and neither presence of any MRI-erosion, nor RA-specific erosions, were predictive for arthritis development in univariable and multivariable analyses (Supplementary Table 2 and 3).

Prognostic accuracy of MRI-erosions when added to MRI-inflammation

After 1-year follow-up (n=434) the AUC of any MRI-erosion to predict inflammatory arthritis development was 0.54. For comparison, the AUC of MRI-detected subclinical inflammation was 0.73. The AUC of both erosions and subclinical inflammation was

also 0.73. To determine if MRI-erosions improved the prognostic accuracy, the NRI was also determined. When erosion-data was added to the presence of subclinical inflammation, 35 patients (8.1%) were reclassified, 2 correctly, 33 incorrectly. This resulted in an NRI of -5.8, revealing no improved prognostic accuracy. Thus, the prognostic accuracy of MRI-detected subclinical inflammation did not improve, but in fact created a high number of false-positive predictions, when MRI-detected erosions were also assessed.

Subanalyses

MRI-erosions were not predictive with the outcome RA-development (n=490), within CSA-patients that fulfilled the EULAR-definition (n=317), and in patients included before the start of the RCT (n=225) (Supplementary Table 4-6).

Discussion

This study investigated if MRI-detected erosions in CSA-patients are predictive for development of inflammatory arthritis or RA. No association was found and MRI-detected erosions did not improve prognostic accuracy of MRI-detected subclinical inflammation. This implies that evaluating MRI-erosions of CSA-patients is superfluous if MRI-detected subclinical inflammation is assessed.

Until now the predictive value of MRI-detected erosions in CSA has not been studied longitudinally. A recent longitudinal study in patients presenting with undifferentiated arthritis (UA) showed that also in these patients MRI-erosions were not predictive for RA-development.[16] Interestingly, frequencies of any MRI-erosion or RA-specific erosions found in UA were quite similar as currently observed in CSA. Although we did not determine the frequency of presence of any MRI-erosions during IA-development, the finding of similar prevalence in UA and CSA suggests that the frequency of erosions did not increase over time. This would be in line with results from a previous study showing that the total MRI-erosion score did not increase during progression from CSA to RA.[17] Most importantly, the data together demonstrate that MRI-erosions in CSA and UA are not predictive for progression to the disease stage of RA. This result is different from previous findings on radiographic erosions in early RA, that are highly predictive for further radiographic progression.

Previous studies identified 'RA-specific erosions' by comparing patients with RA with other early arthritides. The present study revealed that 'RA-specific erosions' (that were identified in the phase of clinically apparent arthritis) are infrequent in the phase CSA and not prognostically valuable.

Even though MRI-detected erosions were not associated with RA-development, higher erosion scores were present in ACPA-positive compared to ACPA-negative patients; which is similar to our previous finding, done in the same cohort.[7] In our view these data suggest that presence of subclinical inflammation in ACPA-positive arthralgia is mediating the development of erosions. Whether ACPA can directly induce erosions, without an intermediary effect of inflammation, remains questionable and our data could not find support for this notion. Furthermore, this study added novel data to the field by demonstrating that MRI-erosions were not associated with progression to RA within ACPA-positive CSA-patients or within ACPA-negative CSA-patients.

Mouse models have suggested that osteoclast formation occurs early in the preclinical phase and before the development of inflammatory arthritis.[18] In the present cohort, of the CSA-patients with erosions (20%), 40% had no concomitant subclinical inflammation. Interestingly, this concerned both ACPA-positive and ACPA-negative patients (Figure 2). It can be speculated that erosions in these patients were the result of preceding subclinical inflammation. However, in absence of subclinical inflammation, RA-development was low.[3] This suggests that the presence of grade 1 MRI-detected erosions, without subclinical inflammation, is often not a feature of imminent RA. Perhaps additional stimuli needed for progression were lacking.

Since April 2015, CSA-patients with MRI-detected subclinical inflammation could participate in an RCT studying Methotrexate. Patients that entered this trial were excluded from analyses (Supplementary File 3). The group of patients in the present study that was included after April 2015 had less often subclinical inflammation than patients included before April 2015 (33% versus 51%); demonstrating that part of the patients with subclinical inflammation, a risk factor for arthritis development, was excluded. This might have resulted in over- or underestimation of the association between erosions and arthritis development. Although the frequency of subclinical inflammation was lower since the start of the RCT, the ratio of erosion presence within strata of patients with or without subclinical inflammation generally remains unchanged. Additionally, known risk factors for arthritis development were comparable for patients with subclinical inflammation who did and did not participate in the RCT. Hence, a possible influence on the effect in the total cohort can be eliminated by stratifying for subclinical inflammation; also then MRI-erosions were not predictive (Supplementary Table 7 and 8). Furthermore, subanalyses evaluating only patients included before April 2015, revealed similar results. Therefore we consider it unlikely that exclusion of patients because of the RCT caused false-negative results.

In conclusion, this large longitudinal study showed that MRI-detected erosions in

hands and feet of patients with CSA are not predictive for arthritis development. Therefore, evaluating MRI for erosions in addition to subclinical inflammation does not provide added prognostic value in CSA.

References

1. van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. Br J Rheumatol. 1995;34 Suppl 2:74-8.

2. Krabben A, Stomp W, Huizinga TW et al. Concordance between inflammation at physical examination and on MRI in patients with early arthritis. Ann Rheum Dis. 2015;74:506-12.

3. van Steenbergen HW, Mangnus L, Reijnierse M et al. Clinical factors, anticitrullinated peptide antibodies and MRI-detected subclinical inflammation in relation to progression from clinically suspect arthralgia to arthritis. Ann Rheum Dis. 2016;75:1824-30.

4. Ejbjerg BJ, Vestergaard A, Jacobsen S et al. Conventional radiography requires a MRI-estimated bone volume loss of 20% to 30% to allow certain detection of bone erosions in rheumatoid arthritis metacarpophalangeal joints. Arthritis Res Ther. 2006;8:R59.

5. Mangnus L, van Steenbergen HW, Reijnierse M et al. Magnetic Resonance Imaging-Detected Features of Inflammation and Erosions in Symptom-Free Persons From the General Population. Arthritis Rheumatol. 2016;68:2593-602.

6. Boeters DM, Nieuwenhuis WP, van Steenbergen HW et al. Are MRI-detected erosions specific for RA? A large explorative cross-sectional study. Ann Rheum Dis. 2018;77:861-8.

7. Ten Brinck RM, Toes REM, van der Helm-van Mil AHM. Inflammation functions as a key mediator in the link between ACPA and erosion development: an association study in Clinically Suspect Arthralgia. Arthritis Res Ther. 2018;20:89.

8. Kleyer A, Finzel S, Rech J et al. Bone loss before the clinical onset of rheumatoid arthritis in subjects with anticitrullinated protein antibodies. Ann Rheum Dis. 2014;73:854-60.

9. Berglin E, Johansson T, Sundin U et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Ann Rheum Dis. 2006;65:453-8.

10. van Steenbergen HW, van Nies JA, Huizinga TW et al. Characterising arthralgia in the preclinical phase of rheumatoid arthritis using MRI. Ann Rheum Dis. 2015;74:1225-32.

11. Ostergaard M, Peterfy C, Conaghan P et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003;30:1385-6.

12. Haavardsholm EA, Ostergaard M, Ejbjerg BJ et al. Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Ann Rheum Dis. 2007;66:1216-20.

13. Arnett FC, Edworthy SM, Bloch DA et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315-24.

14. Aletaha D, Neogi T, Silman AJ et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62:2569-81.

15. van Steenbergen HW, Aletaha D, Beaart-van de Voorde LJ et al. EULAR definition of arthralgia suspicious for progression to rheumatoid arthritis. Ann Rheum Dis. 2017;76:491-6.

16. Boeters DM, Boer AC, van der Helm-van Mil AHM. Evaluation of the predictive accuracy of MRI-detected erosions in hand and foot joints in patients with undifferentiated arthritis. Ann Rheum Dis. 2019;78:144-6.

17. Ten Brinck RM, van Steenbergen HW, van der Helm-van Mil AHM. Sequence of joint tissue inflammation during rheumatoid arthritis development. Arthritis Res Ther. 2018;20:260.

18. Hayer S, Redlich K, Korb A et al. Tenosynovitis and osteoclast formation as the initial preclinical changes in a murine model of inflammatory arthritis. Arthritis Rheum. 2007;56:79-88.

Supplementary File 1 – MRI scanning and scoring protocol

Detailed MRI scan protocol

MRI was performed on a MSK-extreme 1.5T extremity MRI system (GE, Wisconsin, USA) using a 145mm coil for the foot and a 100mm coil for the hand. The patient was positioned in a chair beside the scanner, with the hand or foot fixed in the coil with cushions.

In the hand (metacarpophalangeal (MCP) joints 2-5 and wrist) the following sequence was acquired before contrast administration: T1-weighted fast spin-echo (FSE) sequence in the coronal plane (repetition time (TR) 575 ms, echo time (TE) 11.2 ms, acquisition matrix 388×288, echo train length (ETL) 2). After intravenous injection of gadolinium contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1 mmol/kg) the following sequences were obtained: T1-weighted FSE sequence with frequency selective fat saturation (fatsat) in the coronal plane (TR/TE 700/9.7ms, acquisition matrix 364×224, ETL 2), T1-weighted FSE fatsat sequence in the axial plane (wrist: TR/TE 540/7.7 ms; acquisition matrix 320x192; ETL 2 and MCP-joints: TR/TE 570/7.7 ms; acquisition matrix 320x192; ETL 2).

The obtained sequences of the forefoot (metatarsophalangeal (MTP) joints 1-5) were for the first 77 patients before contrast administration: T1-weighted FSE sequence in the axial plane (TR/TE 650/17ms; acquisition matrix 388x288, ETL 2); and T2-weighted FSE fatsat sequence in the axial plane (TR/TE 3000/61.8; acquisition matrix 300x224, ETL 7). Imaging of the foot was initially limited to pre-contrast axial sequences. For the latter 413 patients post-contrast sequences were included: T1-weighted FSE fatsat sequence in the axial plane (TR/TE 700/9.5ms; acquisition matrix 364x224, ETL 2) and: T1-weighted FSE fatsat sequence in the coronal plane (perpendicular to the axis of the metatarsals) (TR/TE 540/7.5ms; acquisition matrix 320x192, ETL 2).

Field-of-view was 100mm for the hand and 140mm for the foot. Coronal sequences of the hand had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. Coronal sequences of the foot had 20 slices with a slice thickness of 3mm and a slice gap of 0.3mm. All axial sequences had a slice thickness of 3mm and a slice gap of 0.3mm with 20 slices for the wrist, 16 for the metacarpophalangeal-joints and 14 for the foot.

We used the contrast enhanced T1-weighted fat suppressed sequence to assess BME in the MCP-joints of all patients. In the MTP-joints BME was assessed on T2-weighted fatsat sequences in the first 77 patients and on the contrast enhanced T1-weighted

fat suppressed sequence in the latter patients. According to the RAMRIS-method, T2-weighted fat suppressed sequences, or when this sequence is not available a short tau inversion recovery (STIR) sequence, should be used to assess BME. However, three previous studies have demonstrated that a contrast enhanced T1-weigthed fat suppressed sequence has a strong correlation with T2-weighted fat suppressed sequences.[1-3] Furthermore, the arthritis subcommittee of the European Society of Musculoskeletal Radiology (ESSR) also recommends the use of contrast enhanced T1-weighted fat suppressed sequences for depicting BME.[4] The T2-weighted image shows increased water signal and a contrast-enhanced T1-weighted sequence shows increased water content and the increased perfusion and interstitial leakage. A strong correlation has been shown in arthritis patients and in patients without inflammatory diseases such as bone bruises, intraosseous ganglions, bone infarcts and even nonspecific cases.[2,3] Based on these results BME was assessed on contrast enhanced T1-weighted fat suppressed sequences as it has a higher signal to noise ratio and allowed a shorter scan time for patients. In addition, because T2-weighted fat suppressed sequences could be omitted, coronal sequences of the foot could be added. In total this resulted in a shorter total scan time and more information.

MRI scoring

All bones, joints and tendons were scored semi-quantitatively according to the validated RA MRI scoring system (RAMRIS). All bones were scored separately for erosions on a scale 0-10, based on the proportion of eroded bone (0: no erosion, 1: 1-10% of bone eroded, 2: 11-20%, etc.). BME was scored on a scale 0-3 based on the affected volume of the bone (no BME, >0-33%, >33-66%, >66%) and synovitis was scored on a range 0-3 based on the volume of enhancing tissue in the synovial compartment (none, mild, moderate, severe).[5] Similar to methods described by Haavardsholm et al the tenosynovitis-score was based on the thickness of peritendinous effusion or synovial proliferation with contrast enhancement (normal, <2mm, 2-5mm, >5mm (range 0-3)).[6]

References

1. Stomp W, Krabben A, van der Heijde D et al. Aiming for a shorter rheumatoid arthritis MRI protocol: can contrast-enhanced MRI replace T2 for the detection of bone marrow oedema? Eur Radiol. 2014;24:2614-22.

2. Schmid MR, Hodler J, Vienne P et al. Bone marrow abnormalities of foot and ankle: STIR versus T1-weighted contrast-enhanced fat-suppressed spin-echo MR imaging. Radiology. 2002;224:463-9.

3. Mayerhoefer ME, Breitenseher MJ, Kramer J et al. STIR vs. T1-weighted fat-suppressed gadolinium-enhanced MRI of bone marrow edema of the knee: computer-assisted quantitative comparison and influence of injected contrast media volume and acquisition parameters. J Magn Reson Imaging. 2005;22:788-93.

4. Sudol-Szopinska I, Jurik AG, Eshed I et al. Recommendations of the ESSR Arthritis Subcommittee for the Use of Magnetic Resonance Imaging in Musculoskeletal Rheumatic Diseases. Semin Musculoskelet Radiol. 2015;19:396-411.

5. Ostergaard M, Peterfy C, Conaghan P et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003;30:1385-6.

6. Haavardsholm EA, Ostergaard M, Ejbjerg BJ et al. Introduction of a novel magnetic resonance imaging tenosynovitis score for rheumatoid arthritis: reliability in a multireader longitudinal study. Ann Rheum Dis. 2007;66:1216-20.

Supplementary File 2 – Inter- and intrareader correlation

MRI scans of CSA-patients and symptom-free controls were scored by two readers according to the RAMRIS. A total of nine readers was available and different combinations of readers were used. All readers were trained in the same way, and interreader intraclass correlation coefficients (ICC) were ≥0.91. All intrareader ICCs were ≥0.92. See the Tables below for an overview of all ICC values.

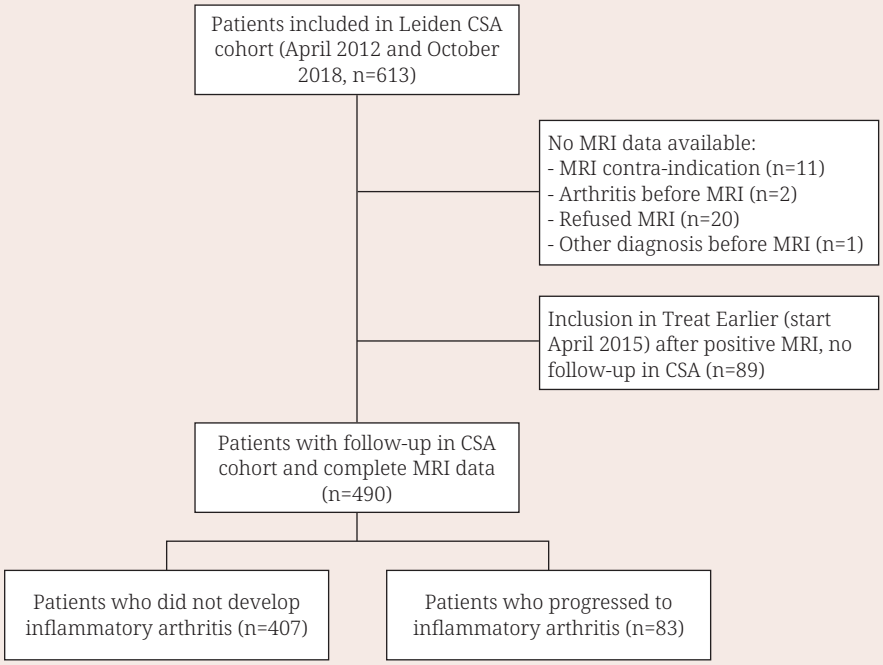
Interreader intraclass correlation coefficients

	1	2	3	4	5	6	7	8	9
1	x	0.97	0.97	0.98	0.97	0.96	0.95	0.97	0.93
2	0.97	x	0.99	0.95	0.94	0.95	0.94	0.96	0.93
3	0.97	0.99	x	0.95	0.95	0.95	0.96	0.96	0.94
4	0.98	0.95	0.95	x	0.97	0.96	0.94	0.95	0.91
5	0.97	0.94	0.95	0.97	x	0.95	0.94	0.95	0.92
6	0.97	0.95	0.95	0.96	0.95	x	0.95	0.96	0.95
7	0.95	0.94	0.96	0.94	0.94	0.95	x	0.98	0.98
8	0.97	0.96	0.96	0.95	0.95	0.96	0.98	x	0.96
9	0.93	0.93	0.94	0.91	0.92	0.95	0.98	0.96	x

Intrareader intraclass correlation coefficients

1	2	3	4	5	6	7	8	9
0.99	0.98	0.94	0.92	0.96	0.94	0.98	0.99	0.96

Supplementary File 3 – Patient selection flowchart



Patients that progressed to inflammatory arthritis had a median follow-up of 14 weeks (IQR 3-23). The median follow-up duration of patients that did not progress was 103 weeks (IQR 51-113).

Supplementary Table 1. Baseline characteristics of CSA patients

	All CSA patients (n=490)	ACPA negative (n=425)	ACPA positive (n=65)
Age in years, mean (SD)	43.6 (12.7)	43.0 (12.6)	47.6 (12.7)
Female, n (%)	379 (77.3)	326 (76.7)	53 (81.5)
Symptom duration in weeks, median (IQR)	19 (9-43)	18 (9-41)	22 (13-53)
68-TJC, median (IQR)	5 (2-10)	5 (2-11)	3 (2-7)
ACPA positivity (≥7 U/mL), n (%)	65 (13.3)	NA	NA
RF positivity (≥3.5 IU/mL), n (%)	97 (19.8)	47 (11.1)	50 (76.9)
Increased CRP (≥5 mg/L), n (%)	98 (21.1)	78 (19.3)	20 (33.3)
Presence of local subclinical inflammation[a], n (%)	202 (41.2)	154 (36.2)	48 (73.8)

[a] Presence of MRI-detected subclinical inflammation that is uncommon in symptom-free controls, i.e. present in <5% of the symptom-free controls at the same location and in the same age category (<40, 40-59, ≥60).
CSA: clinically suspect arthralgia, ACPA: anti-citrullinated protein antibody, SD: standard deviation, IQR: interquartile range, TJC: tender joint count, RF: rheumatoid factor, CRP: c-reactive protein, NA: not applicable

Supplementary Table 2. Erosion scores, prevalence and association with development of inflammatory arthritis in ACPA-negative patients with CSA

	No arthritis (n=378)	**Arthritis (n=47)**	**Univariable Cox regression**		**Multivariable Cox regression**[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	1.0 (0.5-2.0)	1.5 (0.5-3.0)	1.08 (0.93-1.24)	0.33	0.95 (0.79-1.14)	0.59
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	70 (18.5)	9 (19.1)	0.98 (0.48-2.03)	0.96	0.72 (0.35-1.50)[b]	0.38
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	7 (1.9)	0 (0.0)	0.048 (0.00-416)	0.51	NA	NA
MTP5 erosion	20 (5.3)	3 (6.4)	1.19 (0.37-3.83)	0.77	1.12 (0.35-3.63)	0.85
MTP1 erosion if age <40 (n=173)	10 (6.4)	1 (6.3)	1.05 (0.14-7.97)	0.96	0.99 (0.13-7.53)[b]	0.99

[a] Adjusted for age and presence of subclinical inflammation
[b] Adjusted for presence of subclinical inflammation
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint, ACPA: anti-citrullinated protein antibody, NA: not applicable

Supplementary Table 3. Erosion scores, prevalence and association with development of inflammatory arthritis in ACPA-positive patients with CSA

	No arthritis (n=29)	**Arthritis (n=36)**	**Univariable Cox regression**		**Multivariable Cox regression**[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	2.0 (0.5-3.5)	2.3 (0.8-3.5)	1.01 (0.88-1.17)	0.84	0.93 (0.79-1.10)	0.39
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	8 (27.6)	13 (36.1)	1.16 (0.59-2.29)	0.67	0.91 (0.46-1.81)[b]	0.78
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	0 (0.0)	3 (8.3)	3.26 (0.97-10.95)	0.056	2.91 (0.86-9.83)	0.085
MTP5 erosion	3 (10.3)	3 (8.3)	0.93 (0.28-3.02)	0.90	0.62 (0.18-2.10)	0.45
MTP1 erosion if age <40 (n=19)	1 (12.5)	1 (9.1)	0.86 (0.11-6.74)	0.88	2.16 (0.23-20.12)[b]	0.50

[a] Adjusted for age and presence of subclinical inflammation
[b] Adjusted for presence of subclinical inflammation
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint, ACPA: anti-citrullinated protein antibody

Supplementary Table 4. Erosion scores, prevalence and association with RA-development (1987- or 2010-criteria) in patients with CSA

	No RA (n=430)	**RA (n=60)**	**Univariable Cox regression**		**Multivariable Cox regression**[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	1.0 (0.5-2.5)	2.0 (0.5-3.5)	1.13 (1.00-1.27)	0.042	0.94 (0.81-1.09)	0.39
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	83 (19.3)	17 (28.3)	1.54 (0.88-2.69)	0.13	1.03 (0.58-1.82)[b]	0.92
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	8 (1.9)	2 (3.3)	1.71 (0.42-6.99)	0.46	0.89 (0.22-3.69)	0.88
MTP5 erosion	24 (5.6)	5 (8.3)	1.50 (0.60-3.74)	0.39	1.23 (0.49-3.07)	0.66
MTP1 erosion if age <40 (n=192)	12 (6.9)	1 (5.9)	0.91 (0.12-6.86)	0.93	0.84 (0.11-6.37)[b]	0.87

[a] Adjusted for age and presence of subclinical inflammation
[b] Adjusted for presence of subclinical inflammation
RA: rheumatoid arthritis, CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, MTP: metatarsophalangeal joint

Supplementary Table 5. Erosion scores, prevalence and association with development of inflammatory arthritis in CSA-patients fulfilling EULAR-definition[a]

	No arthritis (n=257)	**Arthritis (n=60)**	**Univariable Cox regression**		**Multivariable Cox regression[b]**	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	1.0 (0.5-2.5)	1.5 (0.5-3.5)	1.09 (0.96-1.25)	0.18	0.96 (0.82-1.13)	0.61
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	53 (20.6)	16 (26.7)	1.27 (0.72-2.25)	0.41	0.92 (0.52-1.64)[c]	0.78
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	6 (2.3)	1 (1.7)	0.69 (0.095-4.98)	0.71	0.45 (0.062-3.27)	0.43
MTP5 erosion	15 (5.8)	6 (10.0)	1.65 (0.71-3.84)	0.25	1.52 (0.65-3.54)	0.33
MTP1 erosion if age <40 (n=135)	8 (7.1)	1 (4.5)	0.70 (0.094-5.19)	0.73	0.57 (0.076-4.21)[c]	0.58

[a] Patients fulfilled the EULAR-definition of arthralgia suspicious for progression to RA if ≥3/7 items were present
[b] Adjusted for age and presence of subclinical inflammation
[c] Adjusted for presence of subclinical inflammation
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint

Supplementary Table 6. Erosion scores, prevalence and association with development of inflammatory arthritis in CSA-patients included before 2015

	No arthritis (n=182)	**Arthritis (n=43)**	**Univariable Cox regression**		**Multivariable Cox regression**[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	1.5 (0.5-3.5)	1.5 (0.5-3.5)	1.01 (0.87-1.17)	0.92	0.93 (0.78-1.11)	0.42
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	49 (26.9)	12 (27.9)	1.01 (0.52-1.97)	0.98	0.72 (0.37-1.42)[b]	0.34
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	6 (3.3)	2 (4.7)	1.43 (0.34-5.90)	0.63	1.01 (0.24-4.24)	0.99
MTP5 erosion	15 (8.2)	4 (9.3)	1.15 (0.41-3.22)	0.79	1.06 (0.38-2.97)	0.91
MTP1 erosion if age <40 (n=84)	5 (7.2)	0 (0.0)	0.045 (0.00-391)	0.50	NA	NA

[a] Adjusted for age and presence of subclinical inflammation
[b] Adjusted for presence of subclinical inflammation
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint, NA: not applicable

Supplementary Table 7. Erosion scores, prevalence and association with development of inflammatory arthritis in CSA-patients without subclinical inflammation

	No arthritis (n=271)	**Arthritis (n=17)**	**Univariable Cox regression**		**Multivariable Cox regression**[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	1.0 (0.0-2.0)	1.0 (0.5-2.0)	1.01 (0.76-1.34)	0.96	1.04 (0.76-1.14)	0.80
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	37 (13.7)	3 (17.6)	1.23 (0.35-4.30)	0.74	NA	NA
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	2 (0.7)	1 (5.9)	7.67 (1.01-58.09)	0.049	8.13 (1.06-62.37)	0.044
MTP5 erosion	11 (4.1)	2 (11.8)	2.28 (0.51-10.10)	0.28	2.31 (0.52-10.29)	0.27
MTP1 erosion if age <40 (n=120)	7 (6.3)	0 (0.0)	0.045 (0-14854)	0.63	NA	NA

[a] Adjusted for age
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint, NA: not applicable

Supplementary Table 8. Erosion scores, prevalence and association with development of inflammatory arthritis in CSA-patients with subclinical inflammation

	No arthritis (n=136)	**Arthritis (n=66)**	**Univariable Cox regression**		**Multivariable Cox regression**[a]	
Continuous MRI-erosion data	*Erosion score, median (IQR)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Total erosion score	2.0 (0.5-3.5)	2.0 (1.0-3.5)	1.02 (0.91-1.15)	0.73	0.94 (0.82-1.09)	0.42
Dichotomized MRI-erosion data	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Presence of ≥1 erosion with symptom-free controls as reference	41 (30.1)	19 (28.8)	0.93 (0.54-1.58)	0.78	NA	NA
Erosion characteristics previously determined as RA-specific	*Prevalence, n (%)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Grade ≥2 erosion	5 (3.7)	2 (3.0)	0.79 (0.19-3.24)	0.75	0.71 (0.17-2.90)	0.63
MTP5 erosion	12 (8.8)	4 (6.1)	0.86 (0.31-2.36)	0.77	0.83 (0.30-2.29)	0.72
MTP1 erosion if age <40 (n=72)	4 (7.5)	2 (10.5)	1.52 (0.35-6.62)	0.57	NA	NA

[a] Adjusted for age
CSA: clinically suspect arthralgia, IQR: interquartile range, HR: hazard ratio, CI: confidence interval, RA: rheumatoid arthritis, MTP: metatarsophalangeal joint, NA: not applicable