# Diagnostic outcomes associated with ankle synovitis in early inflammatory arthritis: a cohort study

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## Abstract

### Objective
To examine the diagnostic outcomes associated with clinical ankle synovitis in an early inflammatory arthritis cohort.

### Methods
Data from the Birmingham early inflammatory arthritis cohort (BEACON) were used to obtain information about baseline disease and demographic variables and diagnostic outcomes at 18 month follow-up. The prevalence of clinical ankle synovitis (defined as joint swelling on examination) was calculated. Relative risk (RR) and 95% confidence interval (95% CI) were used to estimate whether clinical ankle synovitis at baseline predicts diagnostic outcomes independent of age, sex, baseline 66-joint swollen joint count, and presence of either rheumatoid factor (RF) or anti-CCP antibody.

### Results
324 patients (52% women) were included. 103 had clinical ankle synovitis at the first clinic visit. Patients with bilateral ankle synovitis were more likely to be classified as having acute sarcoid arthritis (aRR (95%CI) 10.15 (1.13–90.89)). Among patients presenting with oligoarthritis and seronegative for RF and anti-CCP antibodies those with ankle synovitis were significantly more likely to be classified as having seronegative spondyloarthritis (RR (95%CI) 6.15 (1.58–23.88) and unclassified arthritis (RR (95%CI) 4.07 (1.05–15.81)) than RA.

### Conclusion
Current predictive algorithms for patients with early arthritis focus on the prediction of RA or persistent arthritis. This alternative approach focused on a specific joint shows that baseline ankle synovitis predicts specific diagnostic outcomes besides RA. Future work should address the development of models to predict the totality of potential outcomes based on clinical phenotype and the results of routinely available investigations and clinical data.

### Key words
sarcoidosis, ankle synovitis, early inflammatory arthritis.

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## Introduction

Approximately one third of inflammatory arthritis patients have ankle synovitis at initial presentation (1). Ankle involvement is more common in those presenting with oligoarthritis (43.5%) than in those presenting with mono- (18.9%) or polyarthritis (33.7%) (1, 2). It is the most common involved joint in those presenting with oligoarthritis (1). Despite a high frequency of ankle involvement, the full range of diagnostic outcomes associated with ankle synovitis has not been examined in an early inflammatory arthritis cohort. Understanding the potential diagnostic outcomes associated with specific clinical presentations provides a powerful resource for decision making in clinical practice. The objectives of this study were to examine the diagnostic outcomes associated with ankle synovitis in patients with early inflammatory arthritis.

## Methods

### Patients

This was a single centre, hospital-based, prospective cohort study of patients referred to the Birmingham rapid access early inflammatory arthritis clinic with clinically apparent synovitis of at least one joint, and musculoskeletal symptoms attributed to inflammatory arthritis for ≤3 months. The study was approved by the research and ethics committee, and all patients gave written informed consent. Information about age, sex, duration of symptoms, duration of early morning stiffness, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor (RF) and anti-CCP antibody status were recorded. Participants underwent a baseline 66-swollen and 68-tender joint count. Radiographs of hands and feet were performed. A chest radiograph was performed if clinically indicated. Follow-up visits occurred at 1, 2, 3, 6, 12 and 18 months.

### Outcome variable

The eventual diagnosis at the end of an 18-month follow-up period was the outcome of interest. Participants were classified as RA if they met the 1987 American Rheumatism Association (ARA) classification criteria in a cumulative fashion in the absence of any other cause of inflammatory arthritis (3). Similarly, participants were classified as having psoriatic arthritis (4), reactive arthritis (5), and systemic lupus erythematosus (6) if they met the relevant classification criteria. Gout and calcium pyrophosphate crystal arthritis were diagnosed if there was a history consistent with crystal arthritis (*e.g.* classical podagra), or there was microscopic and/or radiographic (*e.g.* chondrocalcinosis) evidence of crystal deposition. Definite acute sarcoid arthritis was defined as clinically apparent arthritis, erythema nodosum, and intra-thoracic involvement (*i.e.* bilateral hilar lymphadenopathy, and/or interstitial lung disease) confirmed by imaging. Possible acute sarcoid arthritis was defined as clinically apparent arthritis and erythema nodosum in the absence of intra-thoracic involvement. For the purpose of this study, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, and inflammatory bowel disease associated arthritis were grouped together as seronegative spondyloarthritis (SpA) (7). Patients who did not meet the 1987 ARA classification criteria for RA, and in whom an alternative musculoskeletal diagnosis could not be reached were regarded as having unclassified arthritis (UA). Patients were further classified as having resolving or persistent arthritis. Resolving arthritis was defined as the absence of clinically apparent joint swelling attributed to inflammatory arthritis at final assessment with no DMARDs or corticosteroid having been administered in the previous 3 months.

### Predictive variables

Ankle synovitis was the principal predictive variable, defined as ankle joint swelling, attributed to synovitis on clinical examination at the baseline clinical assessment performed by a rheumatologist (AF or KR). For the purpose of this study, ankle joint tenderness alone was disregarded when deciding whether clinical ankle synovitis was present or not. Age at first presentation (in years), sex, RF (positive ≥20 IU/ml), anti-CCP antibody (positive >7 IU/ml), and total swollen joint count (SJC) at the baseline visit were selected as potential confounding factors *a priori*, as these fre-

quently affect the diagnostic outcome of inflammatory arthritis.

*Statistical analysis*
Disease and demographic variables were compared between those with and without ankle arthritis. Independent sample *t*-test and chi-square test were used to compare continuous and categorical variables respectively. The Mann-Whitney U-test was used to compare non-normally distributed continuous data. The relative risk (RR), 95% confidence intervals (95% CI) of each diagnostic outcome for the presence of unilateral or bilateral ankle synovitis was calculated with a diagnosis of RA as the referent outcome. RA was selected as referent outcome as this is the most common diagnostic outcome in this cohort. The RR (95%CI) were adjusted for age at hospital visit (tertiles), number of swollen joints (tertiles), sex, and presence of RF or anti-CCP antibodies. The analysis of diagnostic outcomes related to ankle arthritis was stratified according to the number of joints affected at presentation (mono-, oligo-, or polyarthritis) and seropositivity for either RF or anti-CCP antibodies. In order to examine whether diagnostic associations depend on the classification criteria for the referent category, we also analyzed the data using the 2010 ACR/EULAR criteria to classify patients as RA. Statistical significance was set at *p*<0.05. All analyses were performed using STATA version 9.0.

## Results
*Participants and prevalence*
Three hundred and twenty-four patients, 168 (51.9%) women were in-

cluded. Their mean (SD) age was 50.6 (17.8) years. The eventual diagnosis was RA (n=121, 37.3%), SpA (n=50, 15.4%), UA (n=102, 31.5%), acute crystal arthritis (n=21, 6.5%), acute sarcoid arthritis (n=14 (7 definite, 7 possible), 4.3%), connective tissue disease (n=11, 3.4%), and parvovirus arthritis (n=5, 1.5%).

*Descriptive data*
Clinically apparent ankle synovitis was present in 31.8% (n=103) patients at the baseline visit, of whom 58 (17.9%) had unilateral and 45 (13.9%) had bilateral ankle synovitis. Patients with ankle synovitis were younger than those without ankle synovitis with a mean age difference of 4.69 (0.48-8.90) years (Table I).

*Ankle synovitis and diagnostic outcomes*
*– Isolated ankle involvement*
Twenty-five patients presented with isolated ankle synovitis of whom 14 had unilateral and 11 had bilateral ankle synovitis (Fig. 1). Most of these were eventually classified as UA (48%), acute sarcoid arthritis (24%), or SpA (12%). Only 2 (8%) eventually fulfilled the 1987 classification criteria for RA. The arthritis was persistent in 8 patients (3 sarcoid, 2 RA, 1 SLE, 1 SpA, and 1 UA).

*– Ankle involvement with involvement of other joints*
Compared to those without ankle synovitis, patients with any ankle synovitis were significantly more likely to be classified as acute sarcoid arthritis than RA (Table II). This was statistically significant for both unilateral and

bilateral ankle synovitis on univariate analysis. However, after adjusting for possible confounding factors, only bilateral ankle synovitis independently associated with the diagnosis of acute sarcoid arthritis. Patients with unilateral ankle synovitis were significantly more likely to have SpA than RA on univariate analysis, although this was not statistically significant on multivariate analysis (Table II). Substituting 2010 ACR/EULAR criteria for 1987 RA criteria had little impact on the analysis: Both "any ankle synovitis", and "bilateral ankle synovitis" associated with acute sarcoid arthritis (aRR (95%CI) 4.96 (1.41–17.45) and 10.89 (1.30–90.98)). Additionally, unilateral, but not bilateral ankle synovitis associated with a subsequent diagnosis of SpA (aRR (95%CI) 1.56 (1.14–2.14) and 0.94 (0.44-1.99) respectively).

*– Stratified analysis by number of swollen joints, and presence of RF or anti-CCP antibody*
Ankle synovitis did not associate with any diagnostic outcome in monoarthritis, polyarthritis, or oligoarthritis in the presence of RF or anti-CCP antibodies. Among patients presenting with oligoarthritis and seronegative for rheumatoid factor and anti-CCP antibodies, ankle synovitis was associated with a diagnosis of SpA (RR (95%CI) 6.15 (1.58–23.88)) and UA (RR (95%CI) 4.07 (1.05–15.81)). Also, in this subset of patients, ankle synovitis associated with a diagnosis of acute sarcoid arthritis (RR (95%CI) 8.14 (2.12–31.27)). On using the 2010 ACR/EULAR criteria to classify patients as RA, ankle synovitis was associated with acute

**Table I.** Baseline characteristics of patients.

| | Clinical ankle involvement | | | | $p^1$ | $p^2$ |
|---|---|---|---|---|---|---|
| | no (n=221) | any (n=103) | unilateral (n=58) | bilateral (n=45) | | |
| Age, mean (SD)[3] | 52.16 (17.48) | 47.47 (18.08) | 44.31 (19.19) | 51.46 (15.90) | 0.03 | 0.05 |
| Gender, n (%)female | 117 (52.9%) | 51 (49.5%) | 30 (51.7%) | 21 (46.7%) | 0.58 | 0.61 |
| Rheumatoid factor positive, n (%) | 63 (28.8%) | 25 (25.0%) | 13 (23.2%) | 12 (27.3%) | 0.48 | 0.63 |
| Anti-CCP antibody positive, n (%) | 54/214 (25.2%) | 21/100 (21.0%) | 9/56 (16.1%) | 9/44 (20.5%) | 0.41 | 0.57 |
| Swollen joint count, median (IQR)[4] | 3 (1-6) | 3 (2-7) | 2 (2-4) | 6 (3-12) | <0.01 | <0.01 |
| Tender joint count, median (IQR)[4] | 3 (1-8) | 4 (2-12) | 3 (1-7) | 7 (3-15) | 0.08 | <0.01 |

[1]No *vs*. any ankle involvement; [2]Unilateral *vs*. bilateral ankle involvement; [3]Independent sample *t*-test; [4]Mann-Whitney test.
Missing data: rheumatoid factor 5 patients (2 without, 3 with ankle arthritis); anti-CCP antibody 10 patients (7 without, 3 with ankle arthritis).
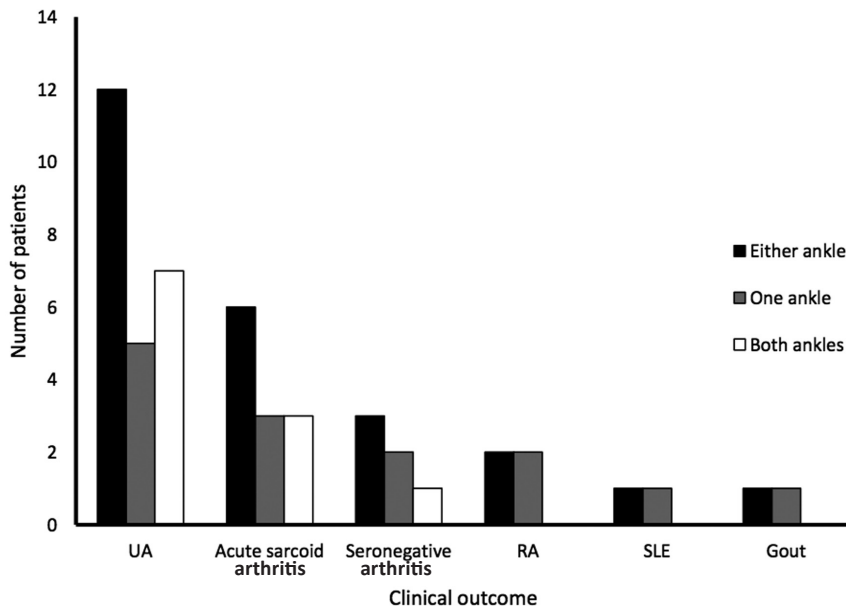
**Fig. 1.** Outcomes of patients presenting with isolated ankle synovitis.
UA: unclassified arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus.

sarcoid arthritis (RR (95%CI) 8.33 (1.25–55.35)). Similarly there was a trend towards an association between ankle synovitis at presentation and a diagnosis of SpA (RR (95%CI) 6.48 (0.97–42.93)), and UA (RR (95%CI) 4.61 (0.70–30.55)) rather than RA.

## Discussion

This study reports on the diagnostic outcomes associated with ankle synovitis in an early inflammatory arthritis cohort. Importantly, patients were recruited very early in the course of their disease *i.e.* within 3 month of the onset of symptoms of inflammatory arthritis, a period in which the prediction of outcome can be particularly challenging given that disease persistence is an important variable in several predictive algorithms (8). This study suggests that bilateral ankle synovitis associates with a diagnosis of acute sarcoid arthritis, and in those presenting with oligoarthritis without RF or anti-CCP antibody, it associates with a diagnosis of SpA and UA, but not RA. Moreover, our data suggest that only a third of patients with isolated ankle arthritis develop persistent disease - UA or sarcoid arthritis being the most common diagnostic outcomes.

This is the first prospective study to examine the diagnostic outcomes of ankle synovitis in an early arthritis sample. There are several strengths of this study. Firstly, all consenting patients with ≥1 swollen joint, presenting with early inflammatory arthritis to an early arthritis clinic were included. This limits the possibility of selection bias. Secondly, all patients had standardised baseline and follow-up assessments. Validated, established, and widely used international classification criteria were

**Table II.** Clinical outcomes in patients with ankle synovitis.

| Outcome | | Clinical ankle involvement | | | Any *vs.* no ankle involvement | | Unilateral *vs.* no ankle involvement | | Bilateral *vs.* no ankle involvement | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | n= | − 221 | + 103 | unilat. 58 | bilat. 45 | RR (95%CI) | aRR[1] (95%CI) | RR (95%CI) | aRR[1] (95%CI) | RR (95%CI) | aRR[1] (95%CI) |
| RA | | 91 | 30 | 16 | 14 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| SpA | | 31 | 19 | 13 | 6 | 1.53 (0.96-2.43) | 1.44 (0.89 - 1.33) | 1.76 (1.06-2.92) | 1.51 (0.94-2.42) | 1.18 (0.57-2.46) | 1.32 (0.64-2.74) |
| UA | | 71 | 31 | 19 | 12 | 1.16 (0.86-1.57) | 1.15 (0.91 -1.46) | 1.23 (0.87-1.76) | 1.14 (0.87-1.48) | 1.05 (0.67-1.65) | 1.11 (0.78-1.59) |
| Acute sarcoid arthritis[2] | | 3 | 11 | 3 | 8 | 8.41 (2.48-28.55) | 5.68 (1.22-26.44) | 4.95 (1.08-22.68) | 2.14 (0.36-12.63) | 11.39 (3.29-39.49) | 10.15 (1.13-90.89) |
| Crystal arthritis | | 15 | 6 | 3 | 3 | 1.18 (0.49-2.81) | 0.73 (0.27-1.97) | 1.12 (0.36-3.49) | 0.55 (0.17-1.84) | 1.25 (0.40-3.86) | 1.04 (0.14-7.96) |
| CTD | | 6 | 5 | 3 | 2 | 2.31 (0.75-7.09) | 1.07 (0.31-3.66) | 2.55 (0.70-9.33) | 1.49 (0.38-5.91) | 2.02 (0.45-9.15) | 0.47 (0.04-6.08) |
| Parvovirus | | 4 | 1 | 1 | 0 | 0.77 (0.09-6.60) | -/- | -/- | -/- | -/- | -/- |

[1]Multivariate relative risk adjusted for age at hospital visit (tertiles), number of swollen joints (tertiles), gender, rheumatoid factor or anti-CCP antibody (absent 0, present 1). [2]Definite or possible.
RR relative risk, 95%CI 95% confidence interval, aRR adjusted relative risk, RA rheumatoid arthritis, SpA seronegative spondyloarthritis, UA unclassified arthritis, CTD connective tissue disease.

used to allocate outcomes. This, therefore, limits the possibility of attribution bias. However, there are some limitations to this study. Firstly, patients with inflammatory arthritis symptom of >3 months duration were excluded. This limits the generalisability of the study findings. Similarly, patients with mild symptoms not requiring hospital referral were not captured. This highlights the need to perform equivalent studies in primary care settings. Moreover, 50% patients classified as acute sarcoid arthritis had no-intra-thoracic involvement on chest x-ray. However, the prevalence of acute sarcoid arthritis in this study (4.3%) is comparable to that reported in other early arthritis cohorts, providing external validity to these findings (14). Additionally, the sample size is relatively small, and the results from this study should be validated in larger datasets.

The low risk of progression to RA in those with isolated ankle arthritis reported in this study is in agreement with previous reports which suggest that <10% patients with early monoarthritis are eventually classified as RA (9-11). Other studies which include patients with symptoms of <12 months suggest that those with monoarthritis do not developed RA (12, 13). However, this may reflect a decreasing chance of developing RA with increasing duration of monoarthritis. Ankle synovitis is a common manifestation of acute gout. However, only one patient with isolated ankle synovitis had gout in this study. The low prevalence of gout may be attributed to the fact that patients with acute crystal arthritis are most commonly managed by their general practitioners in the UK, and are not always referred to hospital specialists.

In this study, bilateral ankle synovitis was associated with a diagnosis of acute sarcoid arthritis. This extends findings in previous reports to the first 12 weeks of disease covered by our cohort (14). Similarly, among those presenting with oligoarthritis and seronegative for RF or anti-CCP antibodies, ankle synovitis associated with diagnosis of SpA. This again is in keeping with observations from hospital based case series (2, 4, 15).

However, all of these studies lacked a comparison group. The current study validates the specificity of these findings in a population of patients closer to the onset of their inflammatory joint symptoms. The analysis also suggests that the association between ankle synovitis and non-RA diagnoses does not depend on the classification criteria used, and provides internal validity to the findings. In summary, clinical examination is critical to establishing and narrowing down the differential diagnosis of inflammatory arthritis just like it is integral to the assessment of disease activity (16). Just as questionnaires administered over the telephone help in discriminating patients with inflammatory and non-inflammatory arthritis (17), novel questionnaires with targeted questions enquiring about specific joint involvement may help in the differential diagnosis of inflammatory arthritis, and further improve the effectiveness of early arthritis clinics (18).

Few studies have examined the full range of diagnostic outcomes in a cohort of inflammatory arthritis patients (19). Most examine disease persistence, development of RA *versus* unclassified arthritis, or the occurrence of erosions. Patients with other diagnoses (*e.g.* psoriatic arthritis) are either excluded (20, 21) or the studies are restricted to patients with oligo- or polyarthritis (22). Thus, while they assist in the prediction of RA at an academic level, they do not guide clinicians in predicting other diagnostic outcomes in a real world population which is equally important.

In conclusion, the pattern of ankle joint involvement at baseline predicts diagnostic outcomes. Moreover, our findings about a range of non-RA diagnostic outcomes associated with ankle involvement in early inflammatory arthritis raises the question as to whether ankle arthritis should feature as a negative scoring variable in the predictive models of RA (23). Finally, at a time when there is a race for identifying predictive biomarkers, a systematic study of all potential diagnostic outcomes associated with specific patterns of joint involvement at baseline is still warranted.

## References

1. MJAAVATTEN MD, HAUGEN AJ, HELGETVEIT K *et al*.: Pattern of joint involvement and other disease characteristics in 634 patients with arthritis of less than 16 weeks' duration. *J Rheumatol* 2009; 36: 1401-6.
2. KVIEN TK, GLENNAS A, MELBY K: Prediction of diagnosis in acute and subacute oligoarthritis of unknown origin. B*r J Rheumatol* 1996; 35: 359-63.
3. 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.
4. GLADMAN DD, SHUCKETT R, RUSSELL ML, THORNE JC, SCHACHTER RK: Psoriatic arthritis (PSA)--an analysis of 220 patients. *Q J Med* 1987; 62: 127-41.
5. KINGSLEY G, SIEPER J: Third International Workshop on Reactive Arthritis. 23-26 September 1995, Berlin, Germany. Report and abstracts. *Ann Rheum Dis* 1996; 55: 564-84.
6. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
7. NASH P, MEASE PJ, BRAUN J, VAN DER HEIJDE D: Seronegative spondyloarthropathies: to lump or split? *Ann Rheum Dis* 2005; 64 (Suppl. 2): ii9-13.
8. GREEN M, MARZO-ORTEGA H, McGONAGLE D *et al*.: Persistence of mild, early inflammatory arthritis: the importance of disease duration, rheumatoid factor, and the shared epitope. *Arthritis Rheum* 1999; 42: 2184-8.
9. FLETCHER MR, SCOTT JT: Chronic monarticular synovitis. Diagnostic and prognostic features. *Ann Rheum Dis* 1975; 34: 171-6.
10. INAOUI R, BERTIN P, PREUX PM, TREVES R: Outcome of patients with undifferentiated chronic monoarthritis: retrospective study of 46 cases. *Joint Bone Spine*. 2004; 71: 209-13.
11. KAARELA K, TIITINEN S, LUUKKAINEN R: Long-term prognosis of monoarthritis. A follow-up study. *Scand J Rheumatol* 1983; 12: 374-6.
12. BINARD A, ALASSANE S, DEVAUCHELLE-PENSEC V *et al*.: Outcome of early monoarthritis: a followup study. *J Rheumatol* 2007; 34: 2351-7.
13. DEVLIN J, GOUGH A, HUISSOON A, PERKINS P, JUBB R, EMERY P: The outcome of knee synovitis in early arthritis provides guidelines for management. *Clin Rheumatol* 2000; 19: 82-5.
14. VISSER H, VOS K, ZANELLI E *et al*.: Sarcoid arthritis: clinical characteristics, diagnostic aspects, and risk factors. *Ann Rheum Dis* 2002; 61: 499-504.
15. HELLIWELL P, MARCHESONI A, PETERS M, BARKER M, WRIGHT V: A re-evaluation of the osteoarticular manifestations of psoriasis. *Br J Rheumatol*. 1991; 30: 339-45.
16. NEMOTO T, OGASAWARA M, MATSUKI Y *et al*.: Can routine clinical measures predict ultrasound-determined synovitis and remission in rheumatoid arthritis patients? *Clin Exp Rheumatol* 2014; 32: 54-60.
17. BRUSCHI E, CASU C, FILIPPINI D *et al*.: Improving diagnosis of early inflammatory

arthritis : results of a novel triage system. *Clin Exp Rheumatol* 2013; 31: 606-9.

18. GOVONI M, SCIRÉ CA, MANARA M *et al*.: Does early arthritis clinic organisation improve outcomes? What evidence is there? A systematic review. *Clin Exp Rheumatol* 2013; 31: 443-51.

19. KURIYA B, VILLENEUVE E, BOMBARDIER C: Diagnostic and prognostic value of history-taking and physical examination in undifferentiated peripheral inflammatory arthritis: a systematic review. *J Rheumatol* 2011; 87 (Suppl.): 10-4.

20. BUKHARI M, LUNT M, BARTON A, BUNN D, SILMAN A, SYMMONS D: Increasing age at symptom onset is associated with worse radiological damage at presentation in patients with early inflammatory polyarthritis. *Ann Rheum Dis* 2007; 66: 389-93.

21. QUINN MA, GREEN MJ, MARZO-ORTEGA H *et al*.: Prognostic factors in a large cohort of patients with early undifferentiated inflammatory arthritis after application of a structured management protocol. *Arthritis Rheum* 2003; 48: 3039-45.

22. HARRISON B, SYMMONS D: Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcome at three years. *Rheumatology* (Oxford) 2000; 39: 939-49.

23. VAN DER HELM-VAN MIL AH, DETERT J, LE CESSIE S *et al*.: Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making. *Arthritis Rheum* 2008; 58: 2241-7.