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ORIGINAL ARTICLE

Ultrasound-detectable grey scale synovitis predicts future fulfilment of the 2010 ACR/EULAR RA classification criteria in patients with new-onset undifferentiated arthritis

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ABSTRACT

Objective: To determine the clinical outcomes for patients with new-onset undifferentiated arthritis (UA), not fulfilling the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) rheumatoid arthritis (RA) classification criteria, and the clinical and imaging predictors of disease progression in these patients.

Methods: A prospective observational study was conducted in treatment-naïve UA patients. Baseline ultrasound involved semiquantitative assessment of grey scale (GS) synovitis and power Doppler activity (PD) at 26 joints. Outcomes were fulfilment of 2010 RA criteria (joint involvement determined clinically) and initiation of methotrexate over 12 months. Cox proportional hazards analysis was used to investigate predictors of outcome.

Results: Of 60 patients, 13(22%) progressed to RA and 32(53%) ever received methotrexate. Analyses of predictors of outcome were conducted in the subgroup (n=41) of patients with complete baseline data. The presence of GS was associated with progression to RA and methotrexate use: HRs (95% CI) were 1.25(1.07 to 1.45) and 1.16(1.02 to 1.32), respectively, for the number of joints with GS≥ grade 2 after adjustment for swollen joints. PD was not predictive in the low levels at which it was observed. Progression to RA was also associated with fulfilment of the 2010 criteria using ultrasound synovitis for enumerating joint involvement, higher baseline disability and radiographic erosion.

Conclusions: This is the first report of ultrasound findings in early UA (defined by presence of clinical synovitis and non-fulfilment of 2010 RA criteria). A significant proportion of patients with UA progressed to RA and/or required methotrexate. GS synovitis was predictive of disease progression.

Key messages

What is already known about this subject?

- Patients with new-onset undifferentiated arthritis (UA) (defined historically by non-fulfilment of the 1987 American College of Rheumatology (ACR) rheumatoid arthritis (RA) criteria) are at risk of progression to RA.
- Ultrasound-detectable synovitis is of prognostic significance in these patients, although precise definitions of imaging synovitis for use in stratifying risk of progression/disease severity in practice are not yet available.

What does this study add?

- This study demonstrates approximately one in five patients with UA, not fulfilling the new ACR/European League Against Rheumatism (EULAR) RA classification criteria, progress to fulfil the criteria, despite contemporary assessment and treatment practices.
- The severity of grey scale (GS) synovitis detected across 26 joints was predictive of progression to RA (defined by 2010 criteria) and methotrexate use, independently of the clinical swollen joint count or disease activity score.

How might this impact on clinical practice?

- Ultrasound of up to 26 joints to determine the presence of GS synovitis is potentially feasible in patients presenting with new-onset UA and is a valid tool for assessment of the need for early disease-modifying anti-rheumatic drug (DMARD) therapy.

INTRODUCTION

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) rheumatoid arthritis (RA) classification criteria provide a means of identifying patients who are likely to benefit from methotrexate early in the course of inflammatory arthritis.[1–3] However,

retrospective analyses of historic early arthritis cohorts demonstrate patients with undifferentiated arthritis (UA), not fulfilling these 2010 ACR/EULAR RA classification criteria, may also be at risk of progression to RA.[4 5] The potential benefits of disease-modifying antirheumatic drug (DMARD) treatment may be lost if treatment is delayed in these patients.[6] Furthermore, there is limited data concerning the natural history/progression of disease in patients with UA in contemporary real-life cohorts. Hence, there is a need to establish modern-day disease outcomes for these patients and methods for predicting which of these patients are likely to have persistent or progressive disease.

Imaging by ultrasound provides a sensitive method for the detection of synovitis in comparison to clinical examination, while MRI is considered as the reference standard.[7 8] Indeed, the 2010 RA criteria allow for joint involvement to be determined by imaging evidence of synovitis when at least one joint is clinically swollen.[1] However, a definition for ultrasound synovitis is not specified. Studies supporting the prognostic value of ultrasound synovitis in patients with suspected early inflammatory arthritis have previously been limited to those defining progression using the 1987 RA criteria.[9 10] These criteria have poor sensitivity in early disease.[11] Other studies have examined its value in predicting the need for methotrexate (the standard for RA used in the development of the 2010 criteria)[12] as well as other measures of disease persistence.[13–15] Participants of these studies have included both patients lacking any clinical joint swelling as well as those already fulfilling 2010 RA criteria.[12–15] Hence, the prognostic value of ultrasound specifically in patients with UA, defined by modern-day criteria, is not fully understood.

First, the aim of this study was to determine the 1-year outcomes of patients with new-onset UA (defined by the presence of clinical synovitis and non-fulfilment of 2010 RA classification criteria). Second, associations between baseline clinical and ultrasound imaging characteristics and poor prognosis were evaluated. This is the first study to investigate the value of ultrasound in predicting the development of RA, defined by the 2010 RA criteria, in patients with UA.

METHODS

Patients

A prospective observational cohort study was conducted in the Leeds Early Arthritis Clinic. Since June 2010, all DMARD-naïve patients with new-onset inflammatory arthritis were invited to participate. Patients meeting the following criteria were selected: (1) swelling of at least one joint not explicable by a non-RA diagnosis and not fulfilling 2010 ACR/EULAR RA criteria and (2) enrolment up to August 2012. In determining patient eligibility, joint involvement within the 2010 criteria was determined solely by clinical examination. Patients were managed by consultant rheumatologists. Consent was obtained from all participants. The study was approved by the Leeds West Regional Ethics Committee.

Clinical assessments

Data collection at enrolment and every 3 months (or as clinically indicated) thereafter included the disease activity score (DAS-CRP) using swollen joint count (SJC44), the Ritchie Articular Index (RAI), patient visual analogue scale assessment of global disease activity (VASDA) and C reactive protein (CRP).

Imaging

At baseline, ultrasound examination was conducted for 26 joints (elbows, wrists, second-third metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, knees, ankles and first-fifth metatarsophalangeal (MTP) joints). A GE E9 machine was used with 15-6 and 18–8 MHz linear array transducers. The scanning parameters were: B mode frequency (12–18 MHz), B mode gain 44–54 db, power Doppler frequency (7.5–10 MHz), pulse repetition frequency (PRF) 800 Hz (0.8 kHz) and wall filter low–medium. Individual joints were scored for grey scale (GS) synovitis and power Doppler activity (PD) using a semiquantitative grading scale. GS synovitis was graded according to the absence (grade 0) or presence of mild (grade 1), moderate (grade 2) or severe (grade 3) hypoechoic synovial thickening. Power Doppler synovitis was scored according to the following categories: no flow in the synovium/area of GS (grade 0), ≤3 single-vessel signals/≤2 areas of confluent-vessel signals/≤2 single-vessel signals and one area of confluent signal (grade 1), vessel signals in less than half of the area of synovium (grade 2) and vessel signals in more than half of the area of synovium (grade 3). Scoring was performed according to a standard operating procedure showing probe positions and scoring scenarios based on the EULAR/Outcome Measures in Rheumatology Clinical Trials (OMERACT) system, illustrated in figure 1.[16–18]

Global measures of synovitis were total GS and PD scores (sum of the individual scores at each of the 26 joints, ie, maximum 78) and the number of joints with significant GS or PD. In the absence of a standardised definition for the latter,[1] two levels of significance were considered: (1) GS≥ grade 2 for significant GS and PD≥ grade 1 for significant PD, as used by other groups,[12] and (2) more stringent definitions, GS= grade 3 at MTPs (GS≥ grade 2 at other joints) and PD≥ grade 2 at wrists and MTP1 (PD≥ grade 1 at other joints). The latter, more stringent definitions, were considered due to recent findings in healthy controls: GS= grade 2 having been frequently observed at MTPs and PD= grade 1 observed at the wrists and first MTPs.[19] Patients were also reclassified according to fulfilment of the 2010 criteria with joint involvement determined clinically and/or by significant ultrasound synovitis (significant GS and/or PD as per the above definitions).

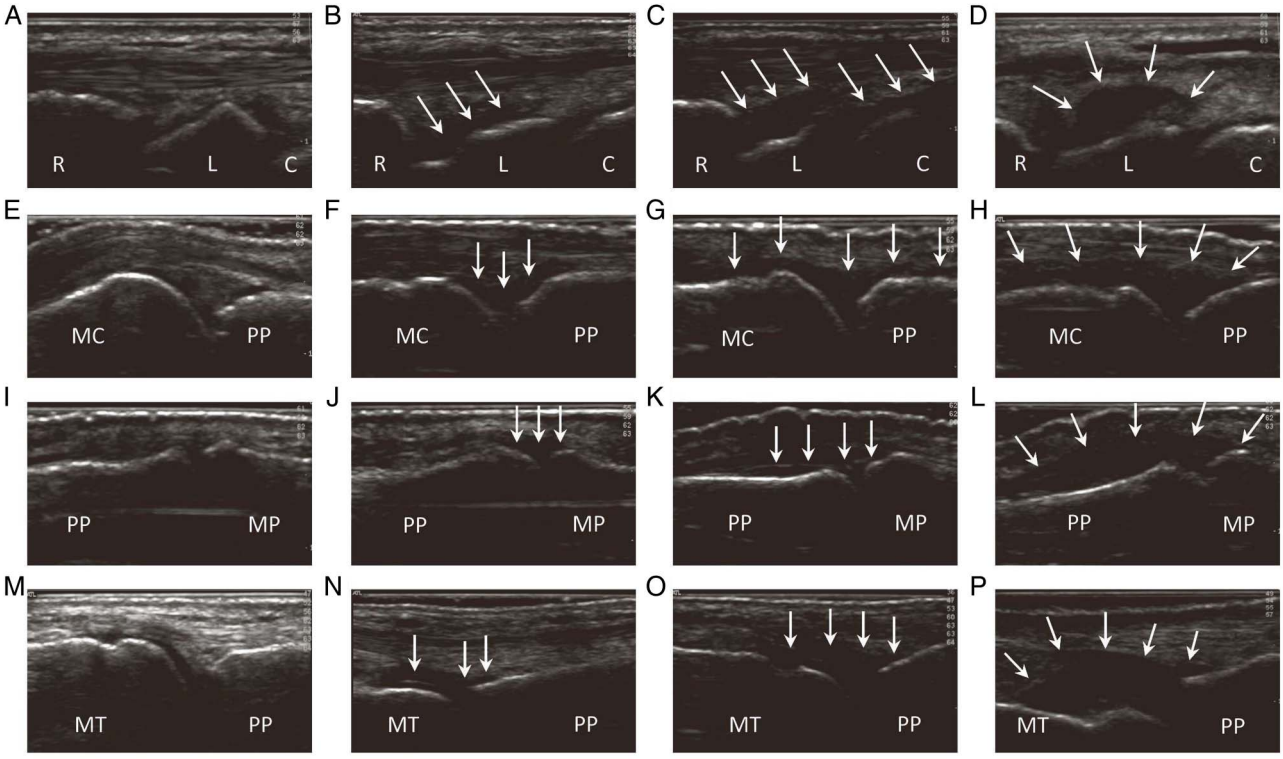

Figure 1 Spectrum of ultrasound grey scale on the dorsal aspects of the wrists ((a) to (d)), MCPs ((e) to (h)), PIPs ((i) to (l)) and MTPs ((m) to (p)): grade 0 ((a), (e), (i) and (m)), grade 1 ((b), (f), (j) and (n)), grade 2 ((c), (g), (k) and (o)) and grade 3 ((d), (h), (l) and (p)). Courtesy of J. L. Nam *et al*, Leeds, reproduced with permission from Annals of the Rheumatic Diseases.[18]
C, capitate; L, lunate; MC, metacarpal; MCPs, metacarpophalangeal joints; MP, middle phalanx; MT, metatarsal; MTP, metatarsophalangeal joints; PIPs, proximal interphalangeal joints; PP, proximal phalanx; R, radius.

Radiologists provided a summary report of plain film radiographs of the hands and feet at baseline.

Outcomes

Primary outcomes over 12 months were: (1) progression to fulfilment of 2010 RA criteria (enumerating joint involvement solely by clinical examination) and (2) initiation of methotrexate.

Statistics

Outcomes were reported in all patients. The last observation was carried forward for patients in whom 12-month data were missing.

Patients with incomplete clinical and imaging examinations at baseline were excluded from further analyses. Differences between included and excluded patients were evaluated using χ^2 or Fisher's exact tests for categorical variables (as appropriate for numbers of expected values), t-tests for continuous variables following a normal distribution and Mann-Whitney U tests for non-parametric data. Predictors of outcome were determined using Cox proportional hazards analysis. To determine whether ultrasound measures were predictive independently of clinical synovitis, adjustment was made for SJC44 and DAS-CRP. The assumption that hazards were proportional was checked.

RESULTS

Patients

Of 441 patients presenting with suspected new-onset inflammatory arthritis, 60 patients with new-onset UA were identified for inclusion (figure 2). Baseline characteristics are shown in table 1.

Outcomes

Observations were carried forward for 10 patients in whom 12-month data were not available. Reasons were non-attendance (n=6), enrolment in a clinical trial (n=1, receiving methotrexate ± adalimumab for UA), assessment not clinically indicated in drug-free remission (n=1) or unknown (n=2).

Of 60 patients with UA at baseline, 13 (22%) progressed to fulfil 2010 RA criteria over 12 months. The proportion of patients progressing according to their 2010 RA classification criteria score at baseline (score of at least six out of 10 required for classification as definite RA)[1] was: 0/2 with a score of one, 0/3 score two, 2/12 (17%) score three, 3/24 (13%) score four and 8/19 (42%) score five. Persistent UA was observed in a further 32 (53%) patients (DMARD or corticosteroid exposure within the preceding 3 months in 31 patients and joint swelling without treatment in one patient). Among the remaining 15 patients, outcomes were resolution of synovitis (n=13) and alternative

diagnoses (inflammatory osteoarthritis n=1, psoriatic arthritis n=1).

Of the total 60 patients, 32 (53%) patients ever received methotrexate. Eight of these patients had disease progressing to RA (included in the total of 13 patients progressing to RA, with alternative DMARDs/corticosteroids being administered in five). Methotrexate was started prior to progression in six and after progression in two.

Predictors of outcome

Forty-one patients had complete baseline data for analysis (figure 2). No statistically significant differences were observed between included and excluded patients (table 1).

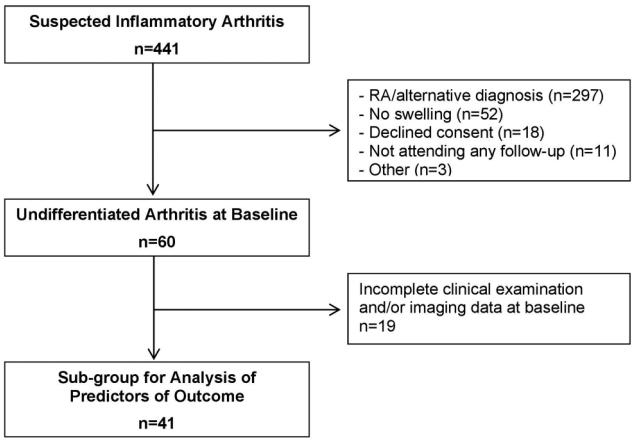

Figure 2 Patient disposition.

Progression to RA and the requirement for methotrexate were significantly associated with greater baseline GS synovitis (table 2). These associations remained significant after adjustment for SJC44 and DAS-CRP. Progression to RA was also associated with fulfilment of 2010 criteria including US synovitis in the determination of joint involvement, presence of radiographic erosions and Health Assessment Questionnaire (HAQ) score.

To further explore the significant relationships between baseline GS synovitis and clinical outcomes, Kaplan-Meier survival plots were constructed (figure 3). At least half of all patients with >4 joints with GS≥ grade 2 (or ≥2 joints meeting the higher threshold definition for significant GS, GS= grade 3 at MTPs 1-5 or ≥ grade 2 at other joints), continuing under follow-up at 12 months, had progressed to RA (figures 3A, B). In comparison, among patients without any GS≥ grade 2 at baseline no progression was observed. By 12 months, methotrexate was required in up to one-third of patients with at <2 joints with GS≥ grade 2 versus up to two-thirds of patients with ≥2 joints with GS≥ grade 2 (figure 3C).

DISCUSSION

This is the first study to demonstrate that ultrasound synovitis predicts progression to fulfilment of the 2010 RA classification criteria. On ultrasound examination of

Table 1 Baseline characteristics of patients included in the analysis of predictors of outcomes and those excluded due to incomplete data. Values are median (IQR) or n (%), unless otherwise stated

		Subgroup for Analysis of predictors of outcome		
	All n=60	Included n=41	Excluded n=19	p Value
Age, mean (SD)	46 (14)	45 (15)	48 (11)	0.4
Female	39 (65%)	27 (66%)	12 (63%)	0.8
Symptom duration, months	9 (4–17)	9 (4–18)	8 (4–17)	0.8
ACPA positive	4 (7%)	3 (7%)	1 (5%)	1.0
Early Morning Stiffness ≥60 min	31 (52%)	19 (46%)	12 (63%)	0.3
RAI	3 (2–6)[a]	3 (2–6)	2 (1–3)[a]	0.1
SJC44	2 (1–4)[a]	2 (1–5)	2 (1–3)[a]	0.7
CRP, mg/L	7 (0–23)	6 (0–22)	10 (0–27)	0.4
Patient VASDA, mm	43 (25–66)[a+b]	45 (25–68)[b]	34 (17–63)[a]	0.7
DAS-CRP	2.3 (1.6–2.9)[b+c]	2.3 (1.8–2.9)[b]	1.8 (1.3–2.5)[c]	0.2
HAQ	0.3 (0.1–0.9)[a+d]	0.3 (0.1–0.9)[d]	0.6 (0.1–1.1)[a]	0.9
US of 26 joints at baseline: total GS score	9 (5–16)[e]	9 (5–17)	NA[e]	NA
Total PD score	1 (0–2)[e]	1 (0–2)	NA[e]	NA
Number of joints with GS≥ grade 2	2 (1–5)[e]	2 (1–5)	NA[e]	NA
Number of joints with PD≥ grade 1	1 (0–1)[e]	1 (0–1)		
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined clinically or by GS≥ grade 2 and/or PD≥ grade 1	4/42 (10%)	4 (10%)	NA[e]	NA
Radiographic erosion in the hands and/or feet	4/55 (7%)	3 (7%)	1 (7%)[f]	1.0

Missing data in [a]12, [b]8, [c]13, [d]6, [e]18 and [f]5 cases.
ACPA, anti-cyclic citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C reactive protein; DAS-CRP, disease activity score; EULAR, European League Against Rheumatism; GS, grey scale; HAQ, Health Assessment Questionnaire; NA, not applicable (summary statistics not performed due to insufficient data); PD, power Doppler activity; RA, rheumatoid arthritis;RAI, Ritchie articular index; SJC44, swollen joint count of 44 joints; US, ultrasound; VASDA, visual analogue scale disease activity assessment.

Table 2 Subgroup analyses of patients with complete clinical examination and imaging data: association between baseline characteristics and progression to fulfilment of 2010 ACR/EULAR RA criteria and the requirement for methotrexate over 12 months (n=41). Values are median (IQR) or n (%) unless otherwise stated

	Progression to RA				**Ever required methotrexate**			
	Yes n=9	**No n=32**	**HR (95 % CI)**	**p Value**	**Yes n=18**	**No n=23**	**HR (95 % CI)**	**p Value**
Age, mean (SD)	48 (15)	44 (15)	1.01 (0.97 to 1.06)	0.5	46 (14)	43 (16)	1.01 (0.98 to 1.04)	0.7
Female	7 (78%)	20 (63%)	1.67 (0.35 to 8.04)	0.5	12 (67%)	15 (65%)	0.82 (0.31 to 2.18)	0.7
Symptom duration, months	12 (5-29)	9 (4-18)	1.00 (0.98 to 1.03)	0.8	**15 (5-26)**	**6 (3-14)**	**1.01 (1.00 to 1.03)**	**0.04**
ACPA positive	0	3 (9%)	NA	NA	1 (6%)	2 (9%)	0.72 (0.10 to 5.41)	0.7
Early Morning Stiffness ≥60 min	5 (56%)	14 (44%)	1.53 (0.41 to 5.69)	0.5	7 (39%)	12 (52%)	0.75 (0.29 to 1.95)	0.6
RAI	6 (3-8)	3 (2-6)	1.33 (0.99 to 1.79)	0.06	4 (3-6)	3 (1-6)	1.06 (0.88 to 1.28)	0.5
SJC44	4 (1-6)	2 (1-4)	1.12 (0.87 to 1.45)	0.4	3 (1-4)	2 (1-5)	0.98 (0.80 to 1.18)	0.8
CRP, mg/L	0 (0-10)	6 (0-22)	1.01 (1.00 to 1.03)	0.07	9 (0-28)	6 (0-17)	1.01 (0.99 to 1.02)	0.4
Patient VASDA, mm	59 (33-75)[a]	45 (23-64)[b]	1.03 (0.99 to 1.06)	0.1	**64 (38-74)[c]**	**30 (17-60)[d]**	**1.03 (1.01 to 1.06)**	**0.02**
DAS-CRP	2.8 (2.1-3.1)[a]	2.2 (1.9-2.6)[b]	3.15 (0.81 to 12.2)	0.1	2.2 (2.0-2.6)[c]	2.1 (1.5-2.7)[d]	1.75 (0.77 to 3.98)	0.2
HAQ	**0.9 (0.1–1.3)**	**0.3 (0.1-0.8)[e]**	**3.73 (1.40 to 9.94)**	**0.009**	0.5 (0.1-0.9)[c]	0.3 (0.1-0.8)[c]	1.04 (0.43 to 2.55)	0.9
Total GS score (unadjusted)	**16 (12-19)**	**8 (4-12)**	**1.11 (1.03 to 1.20)**	**0.008**	**12 (9-18)**	**7 (2-12)**	**1.09 (1.02 to 1.15)**	**0.01**
Adjusted for SJC44			***1.11 (1.03** to **1.20)***	***0.008***			***1.09 (1.02** to **1.15)***	***0.01***
Adjusted for DAS-CRP			***1.10 (1.01** to **1.19)***	***0.03***			***1.09 (1.03** to **1.17)***	***0.02***
Number of joints with significant GS synovitis:								
-Any joint ≥ grade 2 (unadjusted)	**5 (4–8)**	**1 (0–3)**	**1.25 (1.07 to 1.45)**	**0.004**	**3 (1–6)**	**1 (0–3)**	**1.16 (1.02 to 1.32)**	**0.03**
Adjusted for SJC44			***1.25 (1.07** to **1.45)***	***0.004***			**1.16 (1.02 to 1.32)**	**0.02**
Adjusted for DAS-CRP			***1.21 (1.03** to **1.43)***	***0.02***			**1.18 (1.01 to 1.38)**	**0.04**
-MTPs= grade 3, other joints ≥ grade 2 (unadjusted)	**2 (1–3)**	**0 (0–1)**	**1.43 (1.10 to 1.87)**	**0.008**	**1 (0–3)**	**0 (0–2)**	1.24 (0.99 to 1.54)	0.06
Adjusted for SJC44			***1.44 (1.09** to **1.91)***	***0.01***			1.24 (0.99 to 1.53)	0.06
Adjusted for DAS-CRP			***1.43 (1.05** to **1.95)***	***0.02***			1.26 (0.96 to 1.94)	0.09
Total PD score (unadjusted)	0 (0-1)	1 (0-2)	1.07 (0.70 to 1.63)	0.8	0 (0-2)	1 (0-2)	1.00 (0.76 to 1.31)	1.0
Adjusted for SJC44			*1.06 (0.69 to 1.63)*	*0.8*			*1.00 (0.76 to 1.32)*	*1.0*
Adjusted for DAS-CRP			*1.05 (0.71 to 1.56)*	*0.8*			*0.96 (0.71 to 1.28)*	*0.8*
Number of joints with significant PD synovitis:								
-Any joint ≥ grade 1 (unadjusted)	0 (0–1)	1 (0–1)	0.94 (0.43 to 2.05)	0.9	0 (0–1)	1 (0–1)	0.85 (0.50 to 1.47)	0.6
Adjusted for SJC44			*0.91 (0.41 to 2.02)*	*0.8*			0.85 (0.50 to 1.47)	0.6
Adjusted for DAS-CRP			*0.97 (0.46 to 2.02)*	*0.9*			0.85 (0.50 to 1.47)	0.7
-Wrists and MTP1 ≥ grade 2, other joints ≥ grade 1 (unadjusted)	0 (0–0)	0 (0–1)	1.12 (0.54 to 2.34)	0.8	0 (0–1)	0 (0–1)	1.13 (0.71 to 1.81)	0.6

Continued

Table 2 Continued

	Progression to RA				Ever required methotrexate			
	Yes n=9	No n=32	HR (95 % CI)	p Value	Yes n=18	No n=23	HR (95 % CI)	p Value
Adjusted for SJC44			*1.15 (0.55 to 2.41)*	*0.7*			1.13 (0.71 to 1.81)	0.6
Adjusted for DAS-CRP			*1.11 (0.55 to 2.25)*	*0.8*			1.13 (0.71 to 1.81)	0.7
Fulfilment of 2010 ACR/EULAR RA criteria with joint involvement determined by US:								
-GS≥ grade 2 and/or PD≥ grade 1	3 (33%)	1 (3%)	**8.73 (1.99 to 38.3)**	**0.004**	3 (17%)	0	1.98 (0.57 to 6.86)	0.3
-GS≥ grade 2 (3 at MTPs) and/or PD≥ grade 1 (2 at wrists)	2 (22%)	0	**16.3 (2.67 to 99.1)**	**0.002**	2 (11%)	0	2.42 (0.56 to 10.6)	0.2
Radiographic erosion in the hands/feet	2 (22%)	1 (3%)	**25.3 (2.30 to 279)**	**0.008**	3 (17%)	0	3.23 (0.93 to 11.2)	0.07

Missing data in [a]1, [b]7, [c]3, [d]5 and [e]6 cases.
ACPA, anti-cyclic citrullinated protein antibody; ACR, American College of Rheumatology; CRP, C reactive protein; DAS-CRP: disease activity score; EULAR, European League Against Rheumatism; GS, grey scale; HAQ, Health Assessment Questionnaire; MTP, metatarsophalangeal; NA, not performed; assumptions for testing not met; PD, power Doppler activity; RA, rheumatoid arthritis; RAI, Ritchie articular index; SJC44, swollen joint count of 44 joints; US, ultrasound; VASDA, visual analogue scale disease activity assessment.

26 joints, the baseline total GS score and the number of joints with significant GS synovitis were associated with progression and methotrexate use.

HRs for the risk of progression to 2010 RA with increasing total GS score and number of joints with significant GS (GS≥ grade 2 or a more stringent definition for significant GS: GS=grade 3 at MTPs/grade 2 at other joints) were of the order of 1.1, 1.2 and 1.4, respectively. This suggests a 10%, 20% and 40% increase in the risk of progression for each unit increase in total GS score or each additional joint affected. CIs indicate some uncertainty in these estimates (with the true increase in risk likely lying between 3–20%, 7–45% and 10–87%, respectively); however, the associations remained statistically significant after statistical adjustment for the number of swollen joints/disease activity, without significant change in HRs or CIs. This demonstrates the added value of ultrasound over clinical examination in the initial assessment of patients who clinically do not fulfil the 2010 RA criteria.

Results suggest the presence of at least two joints with GS≥ grade 2 (of the 26 joints examined), was clinically relevant to determining the future use of methotrexate. For the purposes of predicting progression to RA, the presence of at least five joints with GS≥ grade 2 (or at least two joints with significant GS defined as grade 3 at MTPs and ≥ grade 2 at other joints) appeared to discriminate patients with low or high risk of progression. It must be borne in mind that methotrexate initiation in patients with UA in this observational study could feasibly have prevented progression to RA in a proportion of patients. Ultrasound examination of up to 26 joints, to determine the presence of significant GS synovitis defined by these thresholds, is potentially feasible within time constraints in a clinical setting in patients presenting with UA.

If ultrasound-detected subclinical synovitis was used, in addition to clinical examination, in defining joint involvement in the application of the 2010 RA criteria at baseline, this was also predictive of clinical progression. Although potentially specific in the prediction of progression, the sensitivity of this measure (on the basis of the 26-joint ultrasound examination) was relatively low; only four patients fulfilled the criteria including the less stringent definition for significant GS and/or PD synovitis (GS≥ grade 2 and/or PD≥ grade 1) in the definition of joint involvement, at baseline.

PD was infrequently observed in the 26-joint examination in this early UA cohort. When detected, it was not associated with outcome; the statistical power to detect a relationship being limited by the low levels of PD observed. GS in untreated patients has previously been shown to be predictive of persistent arthritis,[13 15] the need for methotrexate[12] and progression to fulfilment of the 1987 ACR RA criteria.[9] In untreated patients it probably has the same implications for prognosis as PD which has also been associated with these outcomes and the need for early DMARD therapy.[9 10 12–14] In contrast,

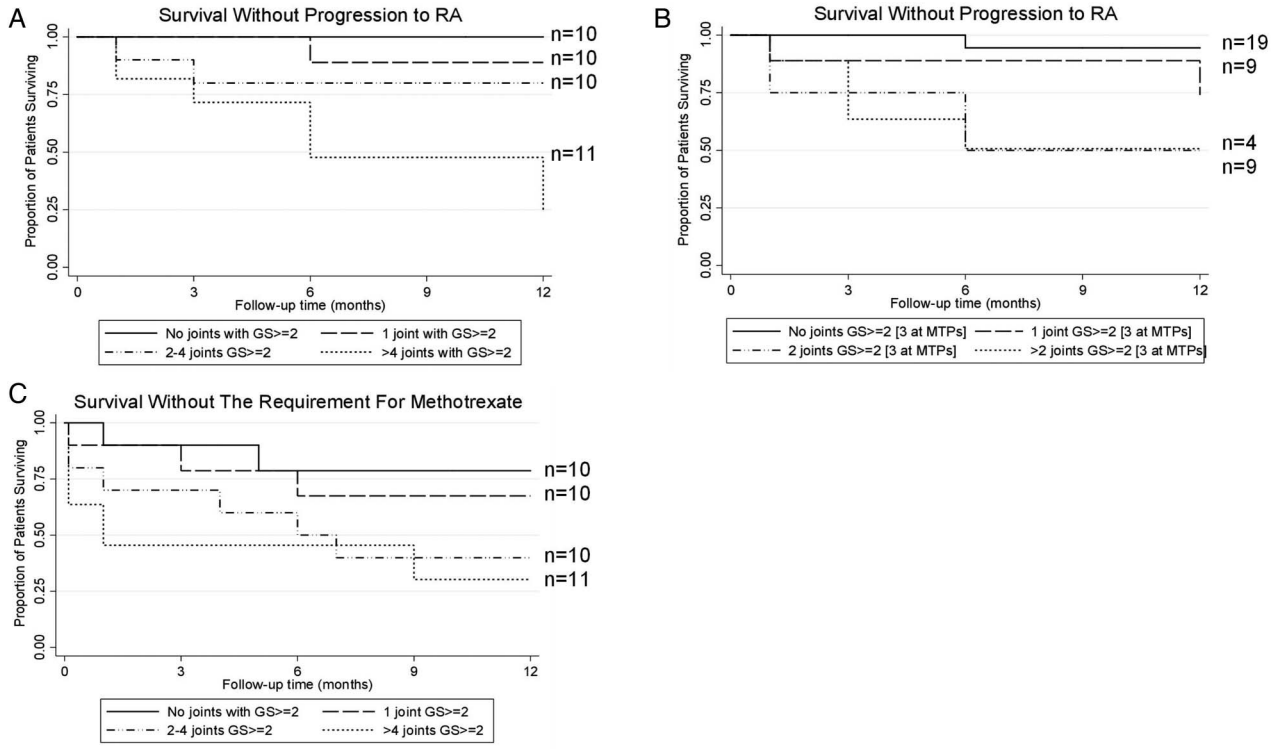

Figure 3 Kaplan-Meier survival plots for survival without: (A) progression to RA according to the number of joints with significant synovitis defined by GS≥ grade 2 at any of 26 joints, or (B) GS= grade 3 at MTPs 1–5 or ≥ grade 2 at any other joint, (C) the need for methotrexate according to the number of joints with significant synovitis defined by GS≥ grade 2 at any of 26 joints. The number of patients per group at baseline is denoted by n. GS, grey scale; MTP, metatarsophalangeal; RA, rheumatoid arthritis.

in late disease, after therapy, GS reflects previous inflammation and correlates with disease duration,[20] whereas PD reflects inflammation at whatever stage of disease.

A high rate of DMARD use was observed in comparison to that reported in previous UA cohorts.[4] This may reflect increasing awareness of the benefits of early therapy. A significant rate of progression to 2010 RA was also observed, higher than that reported in a previous study in the United Kingdom (10%), although patients with >3 months of symptoms were excluded in this very recent-onset UA cohort.[5]

Other studies investigating the predictive validity of ultrasound in patients with at least one swollen joint demonstrate rates of progression to fulfilment of 1987 RA over 12–18 months of 42–50%.[9 10] Filer *et al* studied 58 patients with early inflammatory arthritis (26 of whom already fulfilled the 2010 RA criteria at baseline). Global GS and PD measures across 38 joints significantly increased the area under the curve when modelled with the Leiden prediction score.[21] Implications for clinical practice are not immediately clear, particularly given then number of joints to be examined in calculating a global score and as use of the Leiden score is not routinely undertaken in clinical practice.[9] Salaffi *et al*[10] demonstrated the number of joints with PD≥ grade 2 in the hands and wrists was predictive of progression, independently of serological status, inflammatory markers and presence of early morning stiffness >30 min. Of note, no adjustment was made for clinical evidence of synovitis. Ozgul *et al*[22] studied patients with suspected RA not fulfilling 1987 ACR RA criteria, but only examined one US parameter which not precisely defined (symmetric polyarticular synovitis, with 'synovitis' defined as any sign of pathology including erosion, any synovial hypertrophy or effusion or tendon abnormalities). Importantly, all three of these studies included patients fulfilling 2010 RA criteria at baseline. Arguably, these patients are already considered to be at high risk for persistent and/or aggressive disease, and may not all be considered for US assessment in daily clinical practice.

The observational study design suggests results are generalisable to clinical practice. However, associations with initiation of methotrexate may be affected by bias. When baseline ultrasound was missing, patients were excluded from subsequent analyses. However, comparing baseline characteristics with included patients did not identify any significant differences from those with the US data. Other limitations include the small sample size (although similar to the aforementioned single-centre early arthritis cohort studies).[9 13 22] This precluded the use of several variable multivariate analyses or stratification, for example, by baseline 2010 RA classification criteria score. Of particular note, only a small number of patients were anti-cyclic citrullinated protein antibody

(ACPA) positive; although patient numbers are too small to draw any clinically meaningful conclusion it is interesting that none of the ACPA positive patients progressed to RA. Owing to the known prognostic significance of ACPA, it would also be useful to stratify for ACPA in order to determine the value of US in ACPA positive and ACPA negative patients in larger studies.

These results confirm the prognostic value of ultrasound in the management of patients with early UA. In particular, the degree of GS appears to be a sensitive indicator of disease progression in DMARD-naïve patients. The balance between the added value of limited joint ultrasound and the clinical resources required to perform it appears to be favourable.

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Notes