The Value of Magnetic Resonance Imaging and Ultrasound in Undifferentiated Arthritis: A Systematic Review

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ABSTRACT. ***Objective.*** To perform a systematic literature review of the diagnostic and prognostic value of magnetic resonance imaging (MRI) and ultrasound (US) in patients with undifferentiated peripheral inflammatory arthritis (UPIA), and to assess if MRI and US should be done at baseline and repeated, and if so, at what interval.

Methods. Medline, Embase, the Cochrane Library, and abstracts presented at the 2007 and 2008 meetings of the American College of Rheumatology and European League Against Rheumatism meetings were searched for diagnostic and prognostic studies of any duration examining the ability of MRI/US to predict outcome of patients with UPIA. Sensitivity, specificity, predictive values, and positive/negative likelihood ratios (LR+/LR–) were calculated. When available, odds ratios were extracted. Quality was appraised using validated scales.

Results. Regarding MRI, 11 out of 2595 screened references were included: 2 described pure undifferentiated arthritis (UA) populations and 9, mixed populations. Bone edema (LR+ 4.5) and combination of a distinct MRI synovitis and erosion pattern (LR+ 4.8) increased probability of developing rheumatoid arthritis (RA). Absence of MRI synovitis (LR– 0.2) and absence of a distinct synovitis pattern (LR– 0) decreased probability of developing RA. Regarding US, 2 out of 2111 references were included, both mixed populations; no data could be extrapolated for UPIA.

Conclusion. MRI bone edema and combined synovitis and erosion pattern seem useful in predicting development of RA from UPIA. The value of US in UPIA remains to be determined. The absence of MRI synovitis seems useful in excluding development of RA. No data were found about the value of repeating MRI/US. Studies evaluating MRI/US in UPIA are scarce, but current knowledge strongly encourages further testing in UA. (J Rheumatol 2010;38 Suppl 87:31–37; doi:10.3899/jrheum.101072)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS DISEASE ACTIVITY RESPONSE CRITERIA
OUTCOME ASSESSMENT UNDIFFERENTIATED ARTHRITIS

Within the field of imaging in rheumatic diseases, large and exciting advances have been made over the last decade. Although radiographs continue to be the most widely used tool, magnetic resonance imaging (MRI) and ultrasound (US) offer advantages through more sensitive depiction of inflammatory and destructive disease manifestations[1].

In the context of undifferentiated peripheral inflammatory arthritis (UPIA), patients' questions will focus on diagnosis and prognosis: the likelihood of developing a well defined rheumatic disease, what the future holds for disease progression, persistence, functional impairment, and quality of life. The answers to these questions are vital for clinical decision-making, including the choice of treatment[2].

This article is part of the 3e Initiative (Evidence, Expertise, Exchange) in Rheumatology, 2008-2009[3,4,5]. The resulting 10 recommendations on "How to investigate and follow-up UPIA" are described in more detail elsewhere[5]. The objective of this article was to systematically review the available literature about the following question: "What is the diagnostic and predictive value of MRI and US in patients with UPIA? Should they be done at baseline and repeated at what interval?".

MATERIALS AND METHODS

Strategy and criteria for considering studies for this review

The clinical question was structured in the PIO format[6] (Patients, partici-

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pants or problem; Intervention or index test; Outcomes or target conditions), and the eligible types of study were defined.

Patients were defined as "adults with UPIA." The definition of UPIA is controversial and there is no widely accepted classification criterion for this condition. During the 2008-2009 3e Initiative kickoff meeting, experts decided that only patients in whom clinically apparent joint swelling (synovial proliferation or synovial effusion) was observed by the rheumatologist should be included. This is in contrast to some reports that have included patients with inflammatory joint symptoms in the absence of clinically observable joint swelling (a state usually referred as "inflammatory arthralgia"). It was also emphasized that the terms "early arthritis" and "undifferentiated arthritis" should not be considered interchangeable or similar. For the current systematic review, participants were to be patients that, after initial visits and diagnostic investigations, did not fulfill the diagnostic/classification criteria for any rheumatologic disorder. Because we anticipated that very few studies would have included truly undifferentiated populations at baseline, we also kept a record of results from studies in mixed populations (e.g., UPIA + arthralgia, UPIA + early RA), as these could be useful for extrapolating results.

The index test was defined as a certain MRI feature (e.g., synovial fluid, synovitis, erosion, bone edema, and tenosynovitis) or US feature [e.g., US power-Doppler (PD) and US greyscale (GS) scores], as defined in the study.

The outcomes were defined as the development of well defined rheumatic diseases (e.g., RA, psoriatic arthritis) or relevant disease outcomes (e.g., remission, radiographic progression). The use of internationally validated diagnostic/classification criteria [e.g., 1987 American College of Rheumatology (ACR) criteria for RA[7]] and validated outcome measures was given more value when appraising the definition of outcome.

Three types of studies were considered for inclusion: (1) cohort studies in which patients from a given UPIA population had MRI or US at baseline and in whom the outcome after a period of followup was recorded; (2) retrospective case-control studies in which patients had MRI or US at baseline and in whom it is known that they had UPIA when the baseline investigation was performed; and (3) randomized controlled trials of patients with UPIA that implicitly addressed the question of diagnostic or prognostic value, as each arm of a trial can be seen as a cohort study.

Methodology

Details of search methods for identification of studies, selection of articles, data extraction and analysis, and quality assessment used in the selection and appraisal of the articles can be found in Appendix 1, 2, and 3 of the online version (www.3eupia.com).

RESULTS

Magnetic resonance imaging

A total of 1734 articles and 861 meeting abstracts were found. After title and abstract screening, 15 articles[8,9,10,11,12,13,14,15,16,17,18,19,20,21,22], 3 meeting abstracts (already published or later published in article format[10,11,23], and one additional paper from hand searching[24] remained for review. The inclusion criteria were fulfilled by 11 articles[8,9,10,11,12,13,14,15,16,17,23], which were included in the systematic review. Two articles included truly undifferentiated populations[8,23] while the other 9 included mixed populations[9,10,11,12,13,14,15,16,17] at baseline. A detailed flowchart can be found in Appendix 4 and reasons for exclusion after full article review can be found in Appendix 6 of the online version (www.3eupia.com).

UPIA populations. Study characteristics and results for UPIA populations are summarized in Tables 1 and 2.

Tamai, *et al*[23] evaluated 129 patients with UPIA; all the patients expressed rheumatic manifestations of the wrists and finger joints at study entry. At prospective followup after 1 year, 75 patients (58.1%) had disease progression that fulfilled 1987 ACR criteria for RA[7]. Contrast enhanced MRI images were evaluated for bone edema, bone erosion, and synovitis at 15 sites in each finger and wrist. Patients who were positive for at least 2 of 3 objective measures [anti-cyclic citrullinated peptide antibodies (anti-CCP) and/or IgM rheumatoid factor, MRI-proven symmetric synovitis, and MRI-proven bone edema and/or bone erosion] progressed to RA at 1 year with a positive likelihood ratio (LR+) of 2.8 and a negative likelihood ratio (LR–) of 0.4 [sensitivity (SE) 68%, specificity (SP) 76%]. Further, in 22 UPIA patients positive for both anti-CCP and MRI-proven bone edema who were considered to have progressed to RA at 1 year, the SP and positive predictive value (PPV) was increased to 100% (however, SE was 29%). Anti-CCP alone and bone edema alone had SP of 93% and 91%, respectively (SE 57% and 41%, respectively). MRI synovitis had a LR– = 0.2 regarding progression to RA (SE 91%, SP 44%).

Duer, *et al*[8] investigated 41 patients with arthritis and subjective symptoms in the hands, who remained unclassified despite conventional clinical, biochemical, and radiographic examinations. Patients who fulfilled the 1987 ACR criteria for RA[7] or had radiographic bone erosions were excluded. Contrast enhanced MRI of the wrist and 2nd–5th metacarpophalangeal joints of the most symptomatic hand was performed and the MRI pattern was compared with final diagnosis after a 2-year followup period (RA vs non-RA, according to 1987 ACR criteria). The combination of a distinct MRI synovitis and erosion pattern of RA (for definitions see Table 2) had a LR+ = 4.8 and a LR– = 0.4 (SE 64%, SP 87%) for development of RA. When the synovitis and erosion pattern of RA was combined with a scintigraphy pattern of RA, SP and PPV increased to 100%, but at the cost of a low SE (45%). MRI bone edema was not assessed in this study. That same MRI synovitis pattern alone had a LR– = 0 for progression to RA (SE 100%, SP 60%).

Mixed populations. Study characteristics and results for mixed populations are summarized in Tables 3 and 4. These populations included patients with UPIA, as well as patients with arthralgia or those with an established diagnosis at baseline[9,10,11,12,13,14,15,16,17].

Ultrasound

A total of 1250 articles and 861 meeting abstracts were found. After title and abstract screening, 3 articles[19,20,25] and 3 meeting abstracts (already or later published in article format[26,27]) were retained for full article review. Inclusion criteria were fulfilled by 2 articles (mixed populations only). A detailed flowchart can be found in Appendix 5 (www.3eupia.com) and reasons for exclusion

Table 1. Baseline patient characteristics in included studies (UPIA populations).

Study	Followup, mo (range)	Female, n (%)	Age, median, yrs (range)	Disease Duration, median, mo (range)	SJC, median (range)	CRP, median, mg/dl (range)	ESR, median, mm/h (range)	RF+, n (%)	Anti-CCP+, n (%)	X-ray Erosions, n (%)
Duer[8] 41 patients (UPIA)	24 (NA)	35 (85.4)	55 (17–78)	18 (6–180)	4 (2–18)	1 (< 0.8–12)	8 (1–54)	14 (34.1)	NR	0 (0)
Tamai[23] 129 patients (UPIA)	12 (NA)	100 (77.5)	NR (16–80)	3 (0.5–24)	NR (0–26)	NR (0–18.4)	NR	55 (42.6)	47 (36.4)	NR

UPIA: undifferentiated peripheral inflammatory arthritis; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; NA: not applicable; NR: not reported.

Table 2. Performance of each variable at baseline (UPIA populations) for prediction of progression to rheumatoid arthritis (RA).

Study; no. at Baseline; no. (%) of final RA Diagnoses; Quality	Index Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+ (95% CI)	LR– (95% CI)
Duer[8]; baseline UPIA = 41; final RA = 11 (26.8); NOS = 8 stars, LE = 2b	1. MRI synovitis and erosion pattern of RA*	64	87	64	87	4.8 (1.7–13.2)	0.4 (0.2–0.9)
	2. MRI synovitis pattern of RA*	100	60	48	100	2.5 (1.6–3.9)	0 (NA)
	3. MRI erosion pattern of RA*	64	77	50	85	2.7 (1.2–6.0)	0.5 (0.2–1.1)
	4. MRI synovitis or erosion pattern of RA*	100	50	42	100	2.0 (1.4–2.9)	0 (NA)
	5. MRI synovitis and erosion* and scintigraphy patterns of RA‡	45	100	100	83	Inf	0.5 (0.3–0.9)
	6. RF+	36	67	29	74	1.1 (0.4–2.8)	1.0 (0.6–1.6)
	7. CRP > 1 mg/dl	64	63	39	83	1.7 (0.9–3.3)	0.6 (0.3–1.3)
	8. Larsen grade 1†	36	97	80	81	10.9 (1.4–87)	0.7 (0.4–1.0)
	9. Scintigraphy pattern of RA‡	64	74	50	83	2.5 (1.1–5.3)	0.5 (0.2–1.1)
Tamai[23]; baseline UPIA = 129; final RA = 75 (58.1); NOS = 8 stars; LE = 2b	1. MRI synovitis	91	44	69	77	1.6 (1.3–2.1)	0.2 (0.1–0.5)
	2. MRI symmetric synovitis	75	59	72	63	1.8 (1.3–2.6)	0.4 (0.3–0.7)
	3. MRI bone edema	41	91	86	53	4.5 (1.9–10.7)	0.6 (0.5–0.8)
	4. MRI bone erosion	29	91	81	48	3.2 (1.3–7.8)	0.8 (0.7–0.9)
	5. MRI bone edema and/or erosion	48	83	80	54	2.9 (1.5–5.5)	0.6 (0.5–0.8)
	6. IgM RF	52	70	71	51	1.8 (1.1–2.8)	0.7 (0.5–0.9)
	7. Anti-CCP	57	93	91	61	7.7 (3.0–20.3)	0.5 (0.4–0.6)
	8. IgM RF and/or anti-CCP	67	67	74	59	2.0 (1.3–3.0)	0.5 (0.4–0.6)
	9. MMP-3	36	85	77	49	2.4 (1.2–4.9)	0.8 (0.6–0.9)
	10. CRP positivity	68	70	76	61	2.3 (1.5–3.6)	0.5 (0.3–0.7)
	11. Two out of 3 of: anti-CCP+ and/or IgM RF+, MRI symmetric synovitis, and MRI bone edema and/or bone erosion	68	76	80	63	2.8 (1.7–4.7)	0.4 (0.3–0.6)
	12. Anti-CCP and MRI bone edema	29	100	100	50	Inf	0.7 (0.6–0.8)

* MRI synovitis/erosion pattern of RA: several joints, not 1st carpometacarpal (CMC1) joints; † Larsen grade 1 denotes the presence of joint space narrowing, soft tissue swelling and/or juxtaarticular halisteresis; ‡ Scintigraphic pattern of RA: several joints, but not distal interphalangeal joints and CMC1. UPIA: undifferentiated peripheral inflammatory arthritis; PPV/NPV: positive/negative predictive value. LR+/LR–: positive/negative liklihood ratio. Inf: denominator is zero. NOS: Newcastle-Ottawa Scale; LE: level of evidence; MRI: magnetic resonance imaging; RF: rheumatoid factor; CRP: C-reactive protein; anti-CCP: anti-cyclic citrullinated peptide antibodies; MMP-3: matrix metalloproteinase 3; NA: not applicable.

after full article review can be found in Appendix 6 of the online version (www.3eupia.com). Study characteristics and results for the 2 mixed populations[26,27] are summarized in Tables 5 and 6.

DISCUSSION

This systematic review summarizes and evaluates available evidence on the value of MRI and US in UPIA.

Our results show that MRI bone edema (LR+ 4.5) is more likely to be seen in patients with UPIA who develop RA than in those who do not, and that the combination of MRI bone edema and anti-CCP positivity is highly specific for development of RA (LR+ infinite, i.e., SP = 100%)[23]. However, the absence of both these features does not allow excluding development of RA[23]. On the other hand, results also showed that patients without MRI synovitis have decreased probability of developing RA (LR– 0.2)[23].

In another study, the combination of a distinct MRI synovitis and erosion pattern with involvement of several hand joints, but not the first carpometacarpal joint, was more like-

Table 3. Patient characteristics at baseline in included studies (mixed populations).

Study, Population, no. (type)	Followup, mo (range)	Female, n (%)	Age, median, yrs (range)	Disease Duration, median, mo (range)	SJC, median (range)	CRP, median, mg/dl (range)	ESR, median, mm/h (range)	RF+, n (%)	Anti-CCP+, n (%)	X-ray Erosions, n (%)
Mori[9], 17 (UPIA + arthralgia)	27.4 (13–40)	14 (82.4)	57.7 (43–77)	NR	2.6 (0–12)	0.25 (0–1.5)	NR	10* (58.8)	4 (23.5)	0 (0)
Narváez[10], 40 (UPIA + early RA)	20 (12–42)	28 (70.0)	54 (31–65)	4 (1.5–12)	8 (4)†	1.8 (0.7)†	33 (20)†	0 (0)	7 (17.5)	0 (0)
Zampogna[11], 39 (UPIA + early RA)	38.4‡ (4–84)	29 (74.4)	51.3‡ (25–79)	NR (< 9)	NR	N	NR	NR	NR	NR
Tamai[12], 113 (UPIA + early RA + non-RA)	12 (NA)	NR	NR	4.8‡ (NR)	NR	1.6§ (2.5)†	NR	54§ (67.5)	54§ (67.5)	NR
Solau-Gervais[13], 30 (UPIA + arthralgia + early RA)	30.6 (12–NR)	NR	46.8 (11.2)†	7.8 (6.2)†	2 (0–7)	2.2 (4.2)†	18 (14.8)†	10 (33.3)	0 (0)	0 (0)
Boutry[14], 56 (UPIA? + arthralgia + early RA, SLE, Sjögren?)	29 (4–72)	38 (67.9)	46 (17–69)	NR	NR	NR	NR	NR	NR	0 (0)
Klarlund[15], 13 (UPIA + arthralgia)	12 (NA)	12 (92.3)	NR (13–68)	NR (1–13)	NR (0–11)	1 (1–1)	NR (3–24)	4 (30.8)	NR	NR
Sugimoto[16], 50 (UPIA? + arthralgia + RA)	26 (4–71)	41 (82.0)	44 (19–74)	NR	NR	NR	NR	19** (39.6)	NR	0 (0)
Sugimoto 96[17], 27 (UPIA? + RA? + non-RA?)	9.7 (NR)	24 (88.9)	46.6 (19–75)	NR	NR	NR	NR	10 (37.0)	NR	0 (0)

* Anti-agalactosyl IgG antibodies were measured and not RF; † standard deviation; ‡ mean; § data available for only 80 patients with final diagnosis of RA; ** Only 48 patients with known RF status. UPIA: undifferentiated peripheral inflammatory arthritis; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; NA: not applicable; NR: not reported.

ly to be seen in UPIA patients who developed RA (LR+ 4.8) than in patients who did not[8]. The combination of MRI pattern plus scintigraphy pattern with involvement of several joints (but not distal interphalangeal joints or first carpometacarpal joint) was even more specific for development of RA (LR+ infinite, i.e., SP = 100%)[8]. However, again, none of these features ruled out development of RA[8]. On the other hand, results also showed that patients without the above MRI synovitis pattern had decreased probability of developing RA (LR– 0, i.e., SE for RA = 100%)[8].

Results based on MRI studies in mixed populations[9,10,12,13,14,15,16,17] must be viewed with caution due to the heterogeneity of the study populations and the different measurements and outcomes that were used and that made the pooling of data impossible. Overall, they provide some evidence for the usefulness of MRI (bone edema, synovitis, and erosions) in predicting RA, but direct extrapolation of results to UPIA cannot be done.

Regarding US, no studies were found in UPIA. We describe one study in a cohort of patients with very early inflammatory hand symptoms[26] and another in a population with mainly (very) early RA[27]. Again, extrapolation of results to UPIA cannot be done, although they suggest that US-PD signal and US-GS synovitis can be regarded as potential candidates for future studies in UPIA. However, their usefulness in this population remains undetermined.

Definite answers about the diagnostic and prognostic value of MRI and US in UPIA can be achieved only through well conducted longitudinal studies of patients with UPIA. Studies of this kind are scarce, particularly in truly undifferentiated populations. The value of MRI and US should be compared with other potentially useful variables; this should be done not only by assessing the performance of the single variables alone, but also using multivariate logistic regression analysis with the aim of developing the best possible predictive model, which has never been done taking into account MRI and US[28]. The definition of a positive index test is also of great importance; ideally this should be done using validated and reproducible scoring systems. For the clinician, US may have some advantages due to low operating costs and easy accessibility; however, extremity MRI has potential to address the question of high costs of MRI. Lastly, no data were found about the value of repeating MRI or US in UPIA, and this should also be a matter of future study. Recent new ACR/EULAR criteria for RA[29] should also be taken into account in the future, as several of the patients we describe as having UPIA will likely be labelled as RA.

In conclusion, a distinct MRI pattern of erosion and synovitis and presence of MRI bone edema increased the probability of developing RA from UPIA; however, some patients with UPIA presenting these MRI features may remain undifferentiated, or develop other diseases, or have a self-limited course. The absence of MRI synovitis decreased the probability of developing RA; however, some patients without MRI synovitis may still develop RA. Regarding US assessment, US-PD signal and US-GS synovitis are potential candidates for future studies in UPIA. Current knowledge already provides evidence for the usefulness of MRI in

Table 4. Performance of each variable at baseline (mixed populations) for the prediction of progression to rheumatoid arthritis (RA).

Study; year; no. at baseline; no. (%) of final RA Diagnoses; Quality	Index Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+ (95% CI)	LR– (95% CI)
Mori[9]; baseline mixed = 17*; final RA = 5 (29.4); NOS = 7 stars, LE = 2b	1. MRI criterion (MIP)† plus CARF+ and/or anti-CCP+	100	75	63	100	4.0 (1.5–11)	0 (NA)
	2. Symmetrical hand synovitis with MRI (MIP)†	100	50	45	100	2.0 (1.1–3.5)	0 (NA)
	3. CARF+	100	58	50	100	2.4 (1.2–4.7)	0 (NA)
	4. Anti-CCP+	60	92	75	85	7.2 (1.0–53)	0.4 (0.1–1.3)
	5. CARF+ and/or anti-CCP+	100	58	50	100	2.4 (1.2–4.7)	0 (NA)
Narváez[10]; baseline mixed = 40; final RA = 31 (77.5); NOS = 6 stars, LE = 2b	1. MRI synovitis with BME or erosions	100	78	94	100	4.5 (1.3–15)	0 (NA)
	2. Anti-CCP+	23	100	100	27	Inf	0.8 (0.6–0.9)
Tamai[12]; baseline mixed = 113; final RA = 80 (70.8); NOS = 7 stars, LE = 2b	Respectively ≥: 1, 2, or 3 of: anti-CCP+, MRI symmetric synovitis, MRI BME and/or bone erosion	96	30	77	77	1.4 (1.1–1.7)	0.1 (0.04–0.4)
		83	85	93	67	5.4 (2.4–12)	0.2 (0.1–0.3)
		50	97	98	44	17 (2.4–115)	0.5 (0.4–0.6)
Solau-Gervais[13]; baseline mixed = 30; final RA = 16 (53.3); NOS = 6 stars, LE = 2b	MRI OMERACT MCP erosion score > 15	63	71	71	63	2.2 (0.9–5.4)	0.5 (0.3–1.1)
Boutry[14]; baseline mixed = 47‡; final RA = 28 (59.6)‡; NOS = 6 stars, LE = 2b	1. MRI MCP BME	71	95	95	69	14 (2–93)	0.3 (0.2–0.5)
	2. MRI MCP synovitis	100	0	60	Inf	1.0 (1.0–1.0)	Inf
	3. MRI MCP bone erosions	61	53	65	48	1.3 (0.7–2.2)	0.7 (0.4–1.4)
	4. MRI MCP bone defects	39	79	73	47	1.9 (0.7–5.0)	0.8 (0.5–1.1)
	5. MRI MCP tenosynovitis	68	53	90	38	1.4 (0.8–2.5)	0.6 (0.3–1.2)
	6. MRI wrist BME	39	84	79	70	3.9 (1.3–11)	0.5 (0.3–0.9)
	7. MRI wrist synovitis	100	0	60	Inf	1.0 (1.0–1.0)	Inf
	8. MRI wrist bone erosions	100	16	64	100	1.2 (1.0–1.4)	0 (NA)
	9. MRI wrist bone defects	64	37	60	41	1.0 (0.7–1.6)	1.0 (0.4–2.1)
	10. MRI wrist tenosynovitis	96	21	64	80	1.2 (1–1.6)	0.2 (0–1.4)
Klarlund[15]; baseline mixed = 13; final RA = 5 (38.5); NOS = 7 stars, LE = 2b	1. MRI erosions	20	100	100	67	Inf	0.8 (0.5–1.2)
	2. MRI tenosynovitis	60	63	50	71	1.6 (0.5–5)	0.6 (0.2–2.1)
Sugimoto[16]; baseline mixed = 29§; final RA = 8 (27.6); NOS = 6 stars, LE = 2b	Bilateral MRI synovitis of the same joint area (wrist, MCP, or PIP)	88	90	78	95	9.2 (2.4–35)	0.1 (0–0.9)
Sugimoto[17]; baseline mixed = 27; final RA = 16 (59.3); NOS = 6 stars, LE = 2b	Bilateral MRI synovitis of the same joint area (wrist, MCP, or PIP)	100	73	84	100	3.7 (1.4–9.6)	0 (NA)
Zampogna[11]; baseline mixed = 39; final RA = 12 (30.8); NOS = 7 stars, LE = 2b	MRI rate of early enhancement ratio (REE)**, MRI relative enhancement (RE)**, morning stiffness, SJC, TJC, patient global, Ritchie index, DAS, HAQ, ESR, IgM RF, anti-CCP	1. Need for immunosuppressive treatment at the end of followup: predicted by higher REE and lower RE (MvA); 2. RA ACR criteria during followup: predicted by higher RE (MvA); 3. RA ACR criteria at the end of followup: MRI not predictive (MvA); 4. Complete remission††: predicted by lower RE (UvA)					

† MRI criterion: MRI synovitis was diagnosed if there was significant intraarticular enhancement, or periarticular synovial tendinitis after gadolinium-enhanced 3D transverse images were processed by means of the maximum intensity projection (MIP) method. ‡ Data available for 47/56 patients (final diagnosis: 28 RA, 14 SLE, 5 Sjögren; not analyzed: 2 reactive arthritis, 3 ACR criteria at baseline. ** The MRI synovial enhancement ratio was calculated both as rate of early enhancement (REE) per second during the first 55 seconds and as relative enhancement (RE) at t seconds; the REE shows the slope of the curve of contrast uptake and is steeper if inflammation is higher; the RE indicates the steady state of enhancement. †† Remission was defined as the absence of morning stiffness, absence of tender and swollen joint count, and normal acute-phase reactants. * Initial cohort was 21 patients but 4 (19%) did not complete followup. PPV/NPV: positive/negative predictive value; LR+/LR–: positive/negative liklihood ratio; Inf: denominator is zero; NOS: Newcastle-Ottawa Scale; LE: level of evidence; MRI: magnetic resonance imaging; BME: bone marrow edema; anti-CCP: anti-cyclic citrullinated peptides antibodies; CARF: anti-agalactosyl IgG antibodies; MCP: metacarpophalangeal joints; PIP: proximal interphalangeal joints; SJC: swollen joint count; TJC: tender joint count; DAS: disease activity score; HAQ: health assessment questionnaire; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; NA: not applicable; MvA: mutivariate analysis. UvA: univariate analysis.

Table 5. Patient characteristics at baseline in included studies (mixed population).

Study	Followup, mo (range)	Female, n (%)	Age, mean, yrs (SD)	Disease Duration, median, mo (SD)	SJC, median (SD)	CRP, median, mg/dl (SD)	ESR, median, mm/h (SD)	RF+, n (%)	Anti-CCP+, n (%)	X-ray Erosions, n (%)
Freeston[26] 50 (UPIA? + Arthralgia)	12 (NA)	38 (76)	NR (21–80)†	< 3 (NR)	NR	NR	NR	12* (24)	17* (35)	NR
Sciree[27] 106 (33 UPIA + 73 early RA)	24 (NA)	75 (70.8)	59.5 (14.4)	3.8 (2.8)	12.5 (7.6)	1.9 (2.4)	31.8 (22.4)	41 (39)	30 (29)	NR

* Data available for only 49 patients; † Range. SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated antibodies; UPIA: undifferentiated peripheral inflammatory arthritis; NA: not applicable; NR: not reported.

Table 6. Performance of each variable at baseline (mixed population) for the prediction of progression to persistent inflammatory arthritis (Freeston, *et al*[26]) or for the prediction of relapse (Sciré, *et al*[27]).

Study; Population, no.; Final Diagnosis, no. (%); Quality	Index Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+ (95% CI)	LR– (95% CI)
Feeston[26]; baseline mixed = 49* (UPIA? + arthralgia); final pIA = 38 (77.6); NOS = 7 stars, LE = 2b	1. US GS ≥ 1†	92	18	80	40	1.1 (0.8–1.5)	0.4 (0.1–2.3)
	2. US GS ≥ 2†	76	64	88	44	2.1 (0.9–4.7)	0.4 (0.2–0.8)
	3. US GS = 3†	47	91	95	33	5.2 (0.8–35)	0.6 (0.4–0.8)
	4. US PD ≥ 2†	71	82	93	45	3.9 (1.1–14)	0.4 (0.2–0.6)
	5. US PD ≥ 2†	50	100	100	35	Inf	0.5 (0.4–0.7)
	6. US FT in any finger	47	64	82	26	1.3 (0.6–3.0)	0.8 (0.5–1.4)
	7. Erosive on US‡	53	73	87	31	1.9 (0.7–5.3)	0.7 (0.4–1.1)
	8. RF+	32	100	100	30	Inf	0.7 (0.6–0.8)
	9. Anti-CCP+	45	100	100	34	Inf	0.6 (0.4–0.7)
Sciré[27]; baseline mixed = 106 (33 UPIA + 73 Early RA); final RA = 106 (100); NOS = 7 stars, LE 2b	1. Ultrasound (44 joints): US-JC, US PD, US GS 2. SJC, RAI, DAS 3. CRP, ESR 4. Steroid use	DAS relapse after achieving a DAS ≤ 1.6 at 2 consecutive visits 3 mo apart, after ≥ 12 mo followup; US-PD was the only significant predictor of disease flare (OR 12.8; 95% CI 1.6–103.5; multivariate logistic regression)					

* 1/50 patients lost to followup; † bilateral MCP joints, flexor tendons, and wrists were scanned and each joint was scored for GS and PD on a 0–3 semi-quantitative scale; dichotomized values on the table are for any joint, i.e., minimum of 1 joint; ‡ at least 1 erosion in any joint. UPIA: undifferentiated peripheral inflammatory arthritis; pIA: persistent inflammatory arthritis; RA: rheumatoid arthritis; PPV/NPV: positive/negative predictive value. LR+/LR–: positive/negative liklihood ratio. Inf: denominator is zero. NOS: Newcastle-Ottawa Scale; LE: level of evidence; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; US PD: power doppler ultrasound; US GS: greyscale ultrasound; US FT: ultrasound finger tenosynovitis; US JC: joint count ultrasound; SJC: swollen joint count; RAI: Ritchie Articular Index; DAS: Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

UPIA and strongly encourages further testing of both MRI and US in undifferentiated arthritis.

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