Bilateral Evaluation of the Hand and Wrist in Untreated Early Inflammatory Arthritis: A Comparative Study of Ultrasonography and Magnetic Resonance Imaging

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ABSTRACT. ***Objective.*** To compare Doppler ultrasound (US) and 3.0-Tesla magnetic resonance imaging (3.0-T MRI) findings of synovial inflammation in the tendons and joints in an early polyarthritis cohort (patients who presented < 1 year after arthritis onset) using a bilateral hand and wrist evaluation. Also, to evaluate the diagnostic performance of US and MRI findings for rheumatoid arthritis (RA), their ability to predict RA as a diagnostic outcome, and their capacity to improve the accuracy of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria in early arthritis.

Methods. Forty-five patients (40 women, 5 men; mean age 45.6 yrs) with untreated recent-onset polyarthritis participated in this prospective study and were examined using an US and MRI approach including both wrists and hands. After a followup of 12 months, patients were classified as having RA if they fulfilled the criteria for RA. The proportion of synovitis identified by US and MRI for each joint and tendon region was compared by chi-square test. The diagnostic performance of US and MRI for RA identification was evaluated using receiver-operating curve (ROC) analysis. Possible associations between synovitis for each joint and tendon region as identified by US or MRI and RA diagnosis at 12 months were tested by logistic regression analysis. The diagnostic performance of the ACR/EULAR RA classification criteria corrected by US and MRI joint and tendon counts was evaluated using ROC analysis.

Results. Thirty patients fulfilled the ACR/EULAR criteria [early RA (ERA) patients] and the remaining 15 failed to meet these criteria (non-RA). Carpal joint synovitis and tenosynovitis of the flexor tendons was found in 86.7% and 86.7% of patients with ERA on MRI compared with 63.3% and 50% on US, respectively ($p < 0.05$). The global MRI and US counts revealed a good diagnostic performance for RA diagnosis of both techniques, although MRI was statistically significantly better [area under the curve (AUC) = 0.959 and AUC = 0.853, respectively; z statistic = 2.210, $p < 0.05$]. MRI identification of carpal joint synovitis (OR 3.64, 95% CI 1.119–11.841), tenosynovitis of the flexor tendons (OR 5.09, 95% CI 1.620–16.051), and global joint and tendon count (OR 2.77, 95% CI 1.249–6.139) were in the multivariate logistic regression model the most powerful predictors of progression toward RA. In the group of ERA patients with US joint and tendon counts ≤ 10, a statistically significant difference was found between the diagnostic performance for RA of the ACR/EULAR criteria as previously described and the diagnostic performance of the MRI-corrected ACR/EULAR criteria (AUC = 0.898 and AUC = 0.986, respectively; z statistic = 2.181, $p < 0.05$).

Conclusion. 3.0-T MRI identified a higher prevalence of synovitis in comparison to US in an early polyarthritis cohort. Both techniques have good diagnostic performance for RA although MRI reveals a significantly higher diagnostic capability. Synovitis of carpal joints and of flexor tendons as identified by MRI were the most powerful predictors of progression toward RA. In patients with US joint and tendon counts ≤ 10, MRI can significantly improve the diagnostic performance of the 2010 ACR/EULAR classification criteria. (First Release June 1 2013; J Rheumatol 2013;40:1282–92; doi:10.3899/ jrheum.120713)

Key Indexing Terms:
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Early and aggressive use of disease-modifying drugs in rheumatoid arthritis (RA) is a crucial aspect of RA management[1,2,3,4,5]. However, therapeutic decisions are still hindered by nonspecific early clinical and laboratorial features of RA[6,7,8,9]. The 2010 RA classification criteria issued by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)[10] tried to highlight the need for the identification of patients with very early arthritis at high risk for progressing into RA[11] and thus needing early, aggressive treatment, avoiding the conservative approach of the 1987 ACR revised criteria for RA[12], which were very specific for established arthritis but had a low sensitivity for detecting early RA (ERA)[13,14]. In fact, the new criteria may still lead to significant over- and underdiagnosis within the first months after symptom onset[15] and may overlook patients with symmetrical seronegative arthritis and limited joint involvement[16]. Therefore, identification of additional, more sensitive and specific tests for very early detection of RA is needed in the field of rheumatology.

Synovial thickening is the histologic hallmark and the earliest abnormality to appear in RA[17]. The role of ultrasound (US) and of magnetic resonance imaging (MRI) in identifying synovial thickening, optimizing diagnosis, measuring disease activity, and identifying prognostic factors in RA has been studied extensively[17,18].

US is already known to have better reliability in comparison to clinical indices for synovitis evaluation[19] and there is accumulating evidence of its usefulness for the diagnosis and monitoring of several rheumatic disorders[20]. However, US can be time-consuming, has a long learning curve, and is operator-dependent[20,21]. MRI provides a better morphologic characterization than US and is generally recognized as the noninvasive imaging modality of choice for visualization of the inflamed synovium in established RA, and is increasingly being used in the assessment of ERA[17]. Nonetheless, MRI poses financial constraints, requires a longer time for the examination than US, and sometimes requires administration of an intravascular contrast agent[21]. Comparative evaluation of the diagnostic performance and determination of the added value of each technique could have a critical role in patient management.

Studies comparing the diagnostic performance of US with MRI in early arthritis have been focused only on the dominant or clinically most affected hand, with alternative study of joint or tendon disease, and have used a low magnetic field [< 1.5 Tesla (T)][22,23,24]. These limitations may have hindered adequate comparison of the performance of US and MRI in ERA. To our knowledge, there is no reported comparison between Doppler US and 3.0-T MRI findings in ERA.

Our aim was to compare Doppler US and high field-strength 3.0-T MRI findings of synovial inflammation in the tendons and joints in an early polyarthritis cohort (patients who presented < 1 year after polyarthritis onset) using a bilateral hand and wrist evaluation. Additionally, we evaluated the diagnostic performance of US and MRI findings and their ability to predict progression to RA. We also compared US and MRI joint and tendon counts for their ability to improve the accuracy of the 2010 ACR/EULAR RA classification criteria in early arthritis.

MATERIALS AND METHODS

Patients. From April 2009 until February 2012, 45 consecutive patients were included in the study; they had untreated clinically apparent synovial swelling at 4 or more joints of a 68-joint count[25], including involvement of at least 1 joint of the wrists and hands (excluding the distal interphalangeal joints and the first carpometacarpal joint), and with disease duration < 12 months. Patients were recruited from the rheumatology outpatient clinics of Hospital da Luz and Hospital de Santa Maria in Lisbon; the cohort included 40 women and 5 men, median age 45.6 years (range 18–73 yrs).

After a minimum followup of 12 months, 30 patients fulfilled the 1987 ACR RA criteria[12]. Fifteen patients with polyarthritis did not fulfill the criteria for RA and were classified as non-RA (used as a control group).

Exclusion criteria included pregnancy or breastfeeding; inability to give informed consent; current use of glucocorticoids, methotrexate, or other disease-modifying antirheumatic drugs; active malignancy; cellulites; osteomyelitis; occupation or sports-related overuse; trauma; and contraindications to performing an MRI.

All patients provided written informed consent, and the study conformed to the ethical principles for medical research involving human subjects of the World Medical Association Declaration of Helsinki. The study was approved by the ethics committee of the Faculdade de Medicina da Universidade de Lisboa.

Clinical data. Demographic information such as age and sex was collected in a 5-day range relative to MRI and US examination. The type and distribution of initial joint symptoms, symptom duration, number of tender and swollen joints of a 28-joint count[26], and the patient's overall disease activity on a visual analog scale (VAS; range 0–100 mm) were assessed (CR, with 8 years of experience as a board-certified rheumatologist). The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, presence of immunoglobulin M (IgM) rheumatoid factor (RF), and presence of anticitrullinated protein antibodies (ACPA) were recorded. Disease activity was assessed by calculating the Disease Activity Score with a 28-joint count (DAS28) for each patient[27]. A diagnosis score for the time of initial presentation was calculated according to the 2010 RA classification criteria of the ACR/EULAR[10].

MRI procedure and image evaluation. MRI examination of wrists and hands was performed on the same day as US examination on a 3.0-T device (Magnetom Verio, Siemens Healthcare) using a 6-channel surface phased-array body coil including both hands simultaneously in the field of view (FOV); the patient was placed in the prone position with the hands fixed side by side over the head with the help of several cushions. The

following sequences were acquired before intravenous injection: T1-weighted fast spin-echo sequences in the axial plane [FOV 230 mm; slice thickness (ST) 3.5 mm; repetition time (TR)/echo time (TE) 696/31 ms; matrix 384 × 384; turbo factor (TF) 4; and slice number = 45] and coronal plane (FOV 250 mm; ST 2.0 mm; TR/TE 583/21 ms; matrix 384 × 384; TF 4; and slice number = 24), proton density-weighted fast spin-echo sequence with fat saturation in the coronal plane (FOV 250 mm; ST 2.0 mm; TR/TE 3040/31 ms; matrix 384 × 384; TF 10; and slice number = 24), and spectral adiabatic inversion recovery T2-weighted sequence in the sagittal plane (FOV 250 mm; ST 3.0 mm; TR/TE 4950/79 ms; matrix 384 × 384; TF 14; and slice number = 28). Intravenous injection of gadolinium (Magnevist; Bayer HealthCare) at a standard dose of 0.1 mmol/kg (0.2 ml/kg) was performed using an automatic injector with a flow rate of 2.5 ml/s through a 20-G Abbocath needle into a cubital vein. After injection, a modified T1-weighted fast 3-D gradient-echo volumetric interpolated sequence with fat saturation was acquired (FOV 250 mm; ST 1.1 mm; section gap 0.22 mm; TR/TE 9.29/3.99 ms; matrix 256 × 256; and flip angle 10°) by repeated acquisitions starting at 0:00, 0:28, 0:57, 1:26, 1:54, 2:23, 2:52, and 3:20 min post-contrast administration (scanning time 28 s for each acquisition); the acquisitions were then reconstructed in the coronal plane (slice number = 43) and axial plane (slice number = 48) at 0:00 min, corresponding to the beginning of contrast injection. T1-weighted fast spin-echo sequences with fat saturation in the axial plane (FOV 230 mm; ST 3.5 mm; TR/TE 696/31 ms; matrix 384 × 384; TF 4; and slice number = 45) and coronal plane (FOV 250 mm; ST 2.0 mm; TR/TE 777/21 ms; matrix 384 × 384; TF 4; and slice number = 24) were also acquired after contrast injection.

MRI scoring was performed by MN (4 years' experience fellowship-trained musculoskeletal radiologist, 9 years cross-sectional image interpretation experience) and included the quantification of synovitis in multiple joints of the hands and wrists [distal radioulnar joint; radiocarpal joint; intercarpal and carpometacarpophalangeal (CMC) joints; metacarpophalangeal (MCP) joints; proximal interphalangeal (PIP) joints; excluding the first CMC, the first MCP, and the first PIP]. The reader was blinded to US results. A score of 0 to 3 was assigned for each joint, where 0 was normal with no synovial enhancement and 3 the maximum presumed volume of enhancing tissue in the synovial compartment, according to the RA-MRI score (RAMRIS) defined by Outcome Measures in Rheumatology (OMERACT) imaging studies with validated interobserver intraclass correlation coefficients (ICC)[28]. Tenosynovitis scoring of post-contrast images on a 0 to 3 scale was performed as described by Haavardsholm, *et al* with validated interobserver ICC[29] but including 6 tendon groups on the dorsal side of the wrist (extensor pollicis brevis and abductor pollicis longus, extensor carpi radialis brevis and longus, extensor pollicis longus, extensor digitorum and indicis, extensor digiti minimi, and extensor carpi ulnaris), 1 tendon group on the ventral side of the wrist (flexor digitorium superficialis and profundus), and 5 tendon groups on the ventral side of the hand (first through fifth flexor tendons at the digit level). Both wrists and hands were included in the quantification. MRI indices for each joint or tendon region were obtained by adding the left and right scores (carpal, carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; extensor, all 6 extensor tendon groups on the dorsal side of the wrist; flexor, all 6 tendon groups on the ventral side of the wrist and hand; MCP2–5, second through fifth MCP joints; PIP2–5, second through fifth interphalangeal joints). MRI counts were calculated after converting region grades to binary variables. Images of 15 patients were blindly rescored at least 2 months after initial evaluation for the purpose of intraobserver reliability calculation.

US procedure and image evaluation. Joints and tendons of the hands and wrists were examined on the day of MRI examination with a GE Logiq 9 scanner equipped with a multifrequency (8–12 MHz) linear array transducer. The trained user (MN) was blinded to the patient's clinical status and to MRI results and the patients were asked not to discuss their symptoms. The scanning method has been described[30] and included evaluation of the distal radioulnar joint, radiocarpal joint, intercarpal and CMC joints, MCP joints, and PIP joints excluding the first CMC, the first MCP, and the first PIP. Tendon evaluation included 6 tendon groups on the dorsal side of the wrist (extensor pollicis brevis and abductor pollicis longus, extensor carpi radialis brevis and longus, extensor pollicis longus, extensor digitorum and indicis, extensor digiti minimi, and extensor carpi ulnaris), 1 tendon group on the ventral side of the wrist (flexor digitorium superficialis and profundus), and 5 tendon groups on the ventral side of the hand (first through fifth flexor tendons at the digit level). Synovial hypertrophy was defined as published[20]. The same probe was used for power Doppler examination, and the pulse repetition frequency was adjusted to provide maximal sensitivity at the lowest possible value but avoiding noise level (between 0.7 and 1.3 kHz).

Greyscale US findings of synovitis and power Doppler positivity were quantified on a 0 to 3 scale for each joint and tendon as described[20]. Greyscale and greyscale plus power Doppler indices for each joint or tendon region (same regions as described in MRI image evaluation section) were obtained by adding the left and right scores. US counts were calculated after converting region grades to binary variables. Images of 15 patients were blindly rescored at least 2 months after initial evaluation for the purpose of intraobserver reliability calculation.

Performance of the 2010 ACR/EULAR criteria in identifying patients with RA. Evaluation of performance of the 2010 ACR/EULAR criteria for identifying patients with RA at baseline was conducted. Diagnostic accuracy was tested again by correcting clinical joint counts with the MRI or US joint and tendon counts. The group of patients with ERA was divided by its median by US joint and tendon count, and the performance of the 2010 ACR/EULAR criteria for identifying patients with RA was further evaluated in each of the subgroups.

Statistical analysis. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc.).

Baseline characteristics were described as proportions for categorical variables and median (interquartile range) for continuous variables. All continuous variables were tested for normality with the Kolmogorov-Smirnov test. The Mann-Whitney test was used for paired comparisons.

The difference between the proportions of synovitis in the different groups was tested by the chi-square test.

The diagnostic performance of US and MRI was evaluated using receiver-operating curve (ROC) analysis. Z statistic was used for pairwise comparison of ROC curves.

Possible associations between synovitis for each group of joints and tendons and RA diagnosis at 12 months were tested by univariate logistic regression analysis. Univariate associations with a p value ≤ 0.05 were included in the multivariate analysis. The final multivariate model was obtained by forward procedure.

The diagnostic performance of the ACR/EULAR RA classification criteria for the diagnosis of RA at baseline evaluation[10] was tested using ROC analysis. The diagnostic accuracy was tested again by correcting clinical joint counts with the MRI or US joint and tendon counts and after dividing the group of patients with ERA by its median by US joint and tendon counts. Z statistic was used for pairwise comparison of ROC curves.

The intrareader reliability was assessed using Cohen's κ statistics. Values of $\kappa < 0.20$ were considered to reflect poor agreement, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good, and > 0.81 excellent.

All tests were 2-sided and p values ≤ 0.05 were considered statistically significant.

RESULTS

Cohort characteristics. The demographic clinical and imaging characteristics of the 45 patients at baseline are shown in Table 1 and are divided into groups according to their diagnoses at the 12-month followup. Thirty patients fulfilled the criteria for RA according to the 1987 ACR

Table 1. Demographic, clinical, laboratory, US, and MR data of patients at baseline. Except where indicated, the values are median (IQR).

Characteristic	ERA, n = 30	Non-RA, n = 15
Number (men/women)	0/30	5/10
Age, yrs	51.0 (21.0)	38.0 (10.0)
Disease duration, mo	5.0 (6.0)	7.0 (5.0)
Tender joint count[a]*	8.0 (11.0)	3.0 (3.0)
Swollen joint count[a]*	4.0 (6.0)	1.0 (1.5)
ESR, mm/h*	28.0 (24.0)	6.0 (8.0)
Overall disease activity (VAS)	60.0 (30.0)	60.0 (29.0)
DAS28*	5.19 (1.61)	3.3 (0.8)
MRI joint and tendon index*	22 (15.0)	3.0 (4.5)
MRI joint and tendon counts*	13.0 (11.0)	3.0 (4.5)
RF (positive/negative)	21/9	3/12
ACPA (positive/negative)	24/6	1/14
US (GS) joint and tendon index*	10.0 (14.0)	2.0 (7.0)
US (GS) joint and tendon counts*	7.0 (9.0)	2.0 (5.0)
US (GS-PD) joint and tendon index*	11.0 (18.0)	2.0 (8.0)
US (GS-PD) joint and tendon counts*	8.0 (11.0)	2.0 (5.5)
ACR/EULAR*	5.0 (2.0)	2.0 (0.5)

Mann-Whitney U test used for paired comparisons. * $p < 0.05$. [a] from 28-joint count. Greyscale, greyscale plus power Doppler, and MRI indices for each joint or tendon region were obtained by adding the left and right scores. US counts were calculated after converting region grades to binary variables. ACPA: anticitrullinated protein antibody; ACR/EULAR: score for RA according to the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria; DAS28: 28-joint Disease Activity Score; ERA: early rheumatoid arthritis; ESR: erythrocyte sedimentation rate; GS: greyscale ultrasound; MRI: magnetic resonance imaging; PD: power Doppler ultrasound; RA: rheumatoid arthritis; RF: rheumatoid factor; US: ultrasound; VAS: visual analog scale.

criteria[12]. Fifteen patients with polyarthritis did not fulfill the criteria for RA and were classified as non-RA.

The non-RA group included 1 patient with systemic lupus erythematosus, 1 with psoriatic arthritis, 2 with fibromyalgia, and 11 with undifferentiated arthritis (5 cases of which were self-limited).

US and MRI of synovitis in patients with ERA. Carpal, MCP, and PIP joint synovitis was found in 26 (86.7%), 23 (76.7%), and 26 (86.7%) patients on MRI compared with 19 (63.3%), 13 (43.3%), and 16 (53.3%) on US, respectively. Tenosynovitis of the extensor and flexor tendons was found in 20 (66.7%) and 26 patients (86.7%) on MRI compared with 12 (40%) and 15 (50%) on US. All the differences were statistically significant (Table 2; Figure 1).

Diagnostic performance of US and MRI. Evaluation of the performance of US and MRI of the different joint and tendon regions for identifying patients with RA revealed that MRI had the highest area under the curve (AUC) for the different regions, although the difference was not statistically significant for the MCP and PIP joints. MRI and US total counts revealed a good performance of both techniques, although MRI had a statistically significantly better performance than US (AUC = 0.959 and AUC = 0.853, respectively; z statistic = 2.210, p = 0.0271; Table 3).

Table 2. Proportion of ERA patients with synovitis or tenosynovitis as identified by US or MRI in the different joint and tendon regions. Data are n (%).

Characteristic	US, n = 30	MRI, n = 30	p*
Carpal	19 (63.3)	26 (86.7)	0.037
MCP 2–5	13 (43.3)	23 (76.7)	0.000
PIP 2–5	16 (53.3)	26 (86.7)	0.005
Extensor	12 (40)	20 (66.7)	0.038
Flexor	15 (50)	26 (86.7)	0.002

* Chi-squared test. Carpal indicates carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints. MCP 2–5 is the second through fifth metacarpophalangeal joints. PIP 2–5 is second through fifth proximal interphalangeal joints. Extensor is the 6 extensor tendon groups on the dorsal side of the wrist. Flexor is 6 tendon groups on the ventral side of the wrist and hand. ERA: early rheumatoid arthritis; MRI: magnetic resonance imaging. US: ultrasound.

Comparison of median synovitis scores and the association between baseline MRI and US findings and 12-month RA diagnosis. A comparison of the median values of synovitis scores by groups of joints and tendons between ERA patients and non-RA patients is presented in Table 4 for each of the imaging techniques. Associations between baseline synovitis by joint and tendon groups and RA diagnosis at 12 months were tested for MRI and US by univariate and multivariate logistic regression analysis.

With the exception of PIP joints and extensor tendon synovitis, all the variables were associated with progression to RA on univariate analysis.

Carpal joint synovitis (OR 3.64) and tenosynovitis of flexor tendons (OR 5.09) as identified by MRI were the most powerful predictors of progression toward RA on the multivariate logistic regression model.

MRI is a better predictor of RA than US when considering the total joint and tendon counts (OR 2.769; p = 0.012; Figure 2).

Performance of the 2010 ACR/EULAR criteria in identifying patients with RA. Evaluation of the performance of the 2010 ACR/EULAR criteria for identifying patients with RA at baseline revealed that the use of the criteria as described[15] or with US or MRI correction of clinical joint counts resulted in a higher AUC if MRI was taken into consideration (AUC = 0.989), although there was no statistically significant difference in the pairwise comparison of ROC curves (a tendency toward a difference was observed for the comparison ACR/EULAR vs MRI ACR/EULAR, with a p value = 0.048). Patients with ERA were divided into 2 groups by its median in terms of US joint and tendon count; in the group of patients with US joint and tendon counts ≤ 10 a statistically significant difference was found between the AUC of the ACR/EULAR criteria as described and the AUC of the MRI-corrected ACR/EULAR criteria

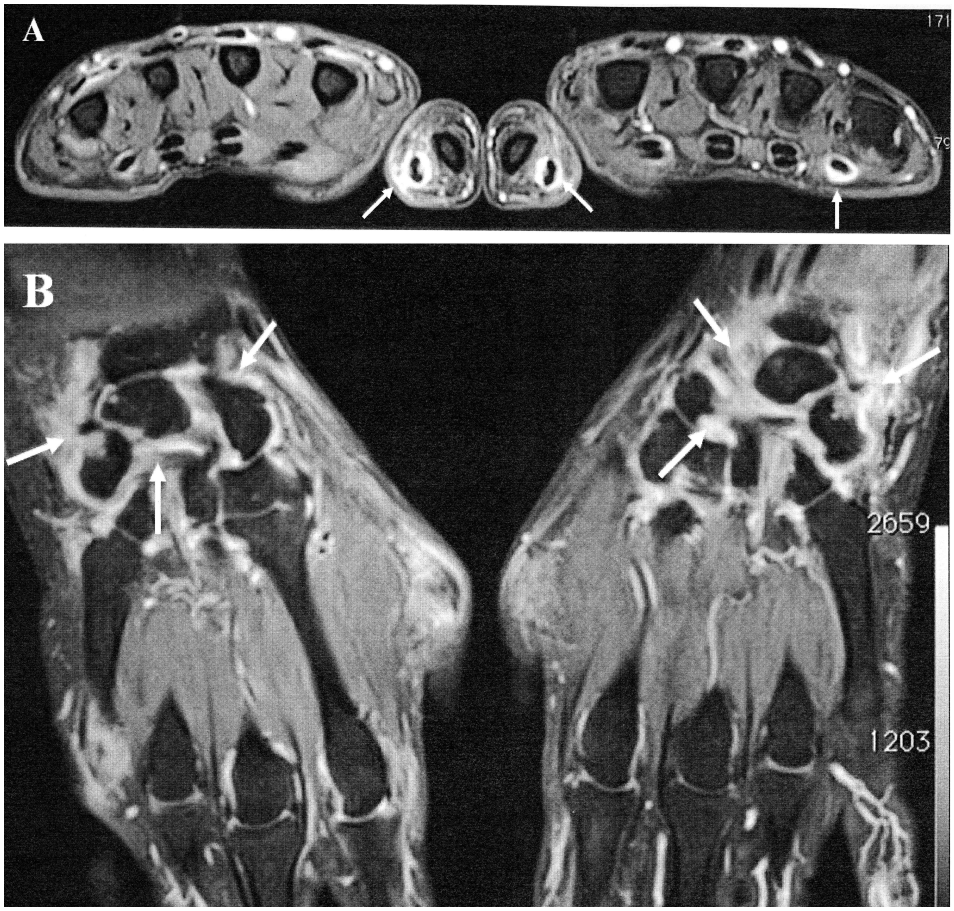

Figure 1A, 1B. Bilateral MRI and ultrasound of the hand and wrist of a 49-year-old woman with early inflammatory arthritis with a disease duration of 9 months; she fulfilled the criteria for RA at presentation. (A) Axial T1 fat-sat sequence after IV contrast administration showing grade 2 (≥ 2 and < 5 mm synovial proliferation with enhancement) tenosynovitis of the flexor tendons of the first digit on the right and the first and fifth digits on the left (arrows). (B) Coronal T1 fat-sat sequence after intravenous contrast administration demonstrating enhancement of bilateral carpal joint synovitis (arrows).

(0.898 vs 0.986; z statistic = 2.181, p = 0.029; Table 5; Figure 3).

Reliability. The intrareader agreement was good for US (κ = 0.792) and excellent for MRI (κ = 0.870).

DISCUSSION

Our study identified a significantly higher prevalence of joint and tendon synovitis by MRI in comparison to US in an ERA cohort. We also demonstrated significantly better diagnostic performance of 3.0-T MRI in comparison to US for RA diagnosis. In this 1-year followup study we additionally found that synovitis of the radiocarpal joint and tenosynovitis of the flexor tendons as identified by MRI were independent predictors of progression to RA.

Because of evidence that identification of tenosynovitis may be of critical value for the diagnosis of ERA[23,31,32,33], our study included joint but also tendon evaluation at multiple hand and wrist regions. Indeed, the reported prevalence of tenosynovitis in established RA was based mainly on clinical examination varying from 5% to 55%[34]. The published data on patients with established RA comparing US with MRI reported tendon sheath widening in 34% of flexor tendons and 10% of extensor tendons by MRI compared with 21% and 5%, respectively, using US[35]. In untreated ERA, the work by Wakefield, *et al*[23] comparing both techniques demonstrated a high frequency of flexor tenosynovitis occurring in 57 (28.5%) of 200 joints in 24 (48%) of 50 patients on US compared with 128 (64%) of 200 joints in 41 (82%) of 50 patients on MRI. Extensor tenosynovitis was found in 14 joints (7%) of 9 patients (18%) on US compared with 80 joints (40%) of 36 patients (72%) on MRI. MRI revealed an increased sensitivity in comparison to US. These results are in accord with our work that also demonstrated a significantly higher percentage of patients with tenosynovitis identified by MRI in comparison to US. However, our work suggested a slightly higher preva-

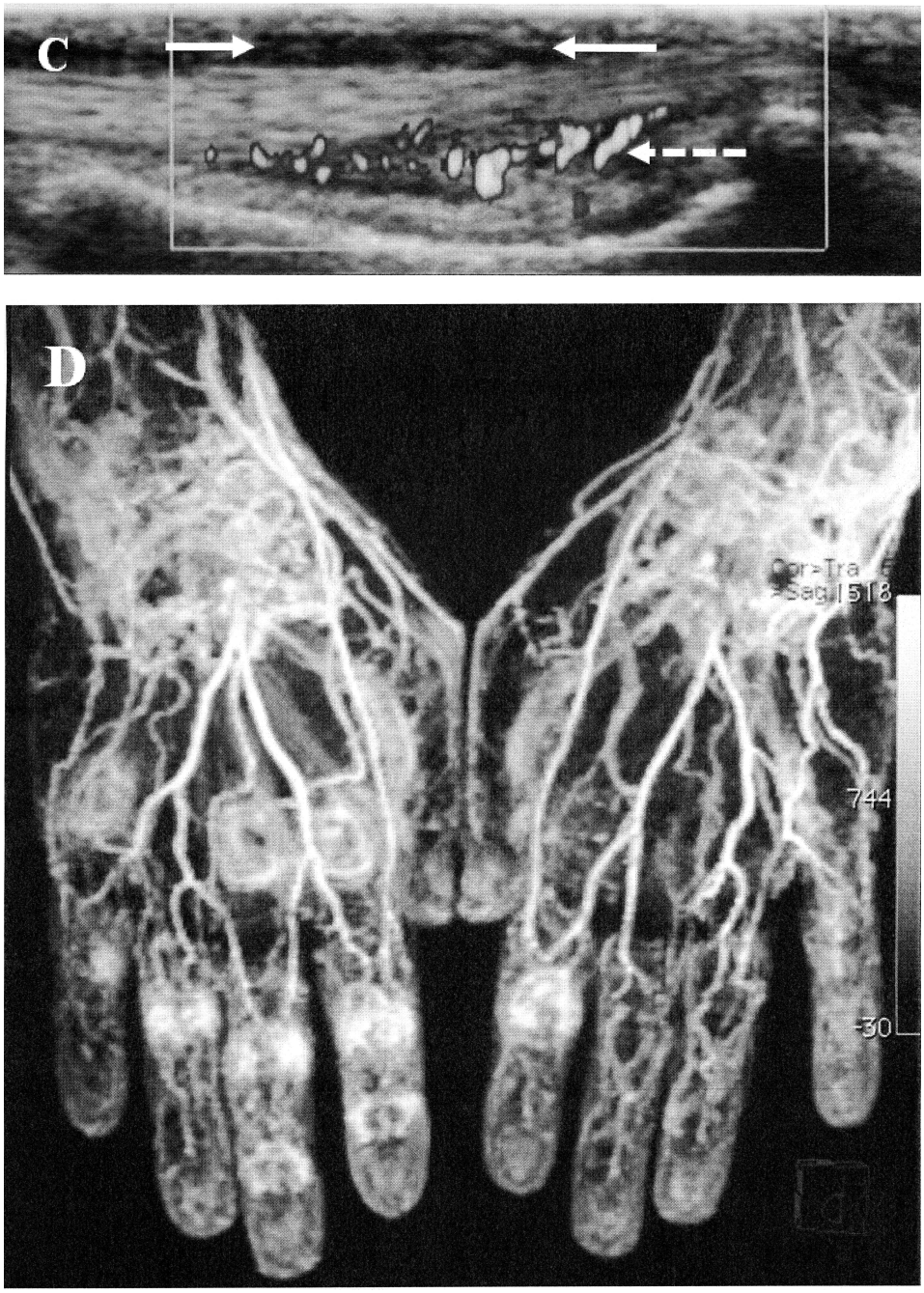

Figure 1C, 1D. (C) Ultrasound examination of the fifth digit on the left hand demonstrating tenosynovitis (arrows) and active power Doppler signal (dashed arrows). (D) Magnetic resonance maximum intensity projection of a 3-D digitally subtracted dataset of the volumetric interpolated breath-hold examination acquisition after contrast administration. The image demonstrates increased vascularity of synovitis of carpal, metacarpophalangeal, and interphalangeal joints. The tubelike appearance of digit tenosynovitis is also clearly depicted.

lence of tenosynovitis in ERA [flexor tenosynovitis in 15 of 30 patients (50%) on US compared with 26 of 30 (86.7%) on MRI, and extensor tenosynovitis in 12 of 30 patients (40%) on US compared with 20 of 30 (66.7%) on MRI]. The relevance of tenosynovitis identification by MRI is highlighted by our finding of better diagnostic performance of flexor and extensor tenosynovitis as identified by MRI for the diagnosis of RA in comparison to US identification. The multivariate logistic regression model identified flexor tenosynovitis recognized by MRI as one of the most powerful predictors of RA (OR 5.099). US evaluation of minor degrees of tenosynovitis is challenging[36]. 3.0-T MRI

Table 3. Performance of ultrasound (US) and magnetic resonance imaging (MRI) in identifying patients with rheumatoid arthritis (RA). Data refer to MRI and US (GS-PD) counts.

Synovitis	AUC (95% CI)	p	Z statistic (p)
MRI carpal	0.890 (0.793, 0.987)	**0.000**	2.473
US carpal	0.757 (0.616, 0.897)	**0.005**	**(0.0134)**
MRI MCP 2–5	0.817 (0.692, 0.941)	**0.001**	1.860
US MCP 2–5	0.702 (0.548, 0.856)	**0.028**	**(0.0628)**
MRI PIP 2–5	0.714 (0.548, 0.881)	**0.020**	1.407
US PIP 2–5	0.567 (0.396, 0.737)	0.470	(0.1596)
MRI extensor	0.813 (0.684, 0.942)	**0.001**	2.606
US extensor	0.706 (0.556, 0.855)	**0.026**	**(0.0092)**
MRI flexor	0.926 (0.846, 1.000)	**0.000**	3.817
US flexor	0.731 (0.586, 0.876)	**0.012**	**(0.0001)**
Total MRI	0.959 (0.857, 1.000)	**0.000**	2.210
Total US	0.853 (0.740, 0.966)	**0.000**	**(0.0271)**

P values given in bold type are significant. Z statistic results from pairwise comparison of receiver-operating characteristic curve (ROC; US vs MRI). AUC: area under the ROC; carpal: carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; extensor: 6 extensor tendon groups on the dorsal side of the wrist; flexor: 6 flexor tendon groups on the ventral side of the wrist and hand; GS: greyscale ultrasound; PD: power Doppler US; MCP 2–5: second through fifth metacarpophalangeal joints; PIP 2–5, second through fifth proximal interphalangeal joints.

has high field strength, high signal-to-noise ratio, and good image quality[37,38,39,40,41,42] and is known to provide precise and complete morphological analysis of the hands and wrists[43], justifying its better performance as compared to US.

The comparative study by Terslev, *et al*[44] involving joint synovitis concludes that estimates of synovial inflammatory activity by Doppler US and postcontrast MRI were comparable. However, the main focus of the study was the comparison of synovial inflammatory activity measures and not the presence versus absence of synovitis. In addition, that study was conducted in patients with established RA, restricting the comparison with our results. Even so, the finding of a 75% agreement between the 2 imaging modalities and a moderate κ value of 0.45 in that study leaves space for questioning which imaging modality is best for identifying synovitis on the basis of an individual joint or tendon. In a study of 46 patients with recently diagnosed RA (onset within 2 years) by Hoving, *et al*[22], the percentage of participants with joint synovitis at baseline was higher by MRI in comparison to US evaluation (71.7% vs 54.3%). These findings are in line with our results, which document a higher proportion of synovitis detection by MRI. Our results revealed carpal synovitis to be present in 19 out of 30 patients (63.3%) on US compared with 26 out of 30 patients (86.7%) on MRI. There is a better diagnostic performance of carpal synovitis as identified by MRI for the diagnosis of RA in comparison to US identification (MRI AUC = 0.890 vs US AUC = 0.757; p = 0.0134); the multivariate logistic regression model identified carpal synovitis recognized by MRI as one of the most powerful predictors of RA (OR 3.641; p = 0.032). Synovitis of PIP joints and of extensor tendons was not predictive of progression toward RA on univariate regression, suggesting that those are nonspecific regions of synovial inflammation probably more affected by mechanical causes.

Consideration of the total joint and tendon count revealed good diagnostic performance by both MRI (AUC = 0.959; p = 0.000) and US (AUC = 0.853; p = 0.000), although with a statistically significant better performance of MRI (p = 0.0271).

We tried to identify a strategy by which MRI and US joint and tendon counts could contribute to improvement of the diagnostic performance of the 2010 ACR/EULAR RA classification criteria[10]. The mean initial ACR/EULAR score in our ERA cohort was < 6, confirming that some patients were not being identified by the new criteria as having RA at the time of presentation. Our results are in agreement with studies indicating that despite improved performance of the 2010 criteria, overdiagnosis and underdiagnosis may remain important issues in ERA, and that the new criteria may fail to identify RA patients with symmetrical seronegative arthritis and limited joint involvement[12,16,45]. Indeed, in our ERA cohort, taking into consideration the group of patients with US joint and tendon count ≤ 10, the diagnostic performance of the ACR/EULAR criteria in terms of AUC was significantly improved by correcting clinical joint counts with MRI joint and tendon counts (AUC = 0.898 and AUC = 0.986, respectively; p < 0.05). The relevance of MRI correction in this subset of patients is highlighted by the low performance of the original 2010 ACR/EULAR criteria in this group (AUC =

Table 4. Comparison of median (interquartile range) value of synovitis scores for early rheumatoid arthritis (RA) and non-RA patients and the association between baseline MRI and US findings and 12-month RA diagnosis (univariate and final multivariate logistic regression models): joint and tendon analysis by region. Data refer to MRI and US (GS-PD) counts.

Synovitis	ERA	Non-RA	Univariate Logistic Regression Analysis OR (95% CI) (R^2)	p (c stat)	Multivariate Logistic Regression Analysis OR (95% CI) (R^2)	p (c stat)
MR Carpal	3 (4)*	0 (0.5)*	3.320 (1.555, 7.087) (0.40)	**0.002** (0.890)	3.641 (1.119, 11.841) (0.487; 0.596)	**0.032** (0.979)
US Carpal	2 (2)*	0 (1*)	2.288 (1.159, 4.517) (0.21)	**0.017** (0.757)		
MR MCP 2–5	2 (3)*	0 (0)*	3.136 (1.353, 7.268) (0.29)	**0.008** (0.817)		
US MCP 2–5	0 (3)*	0 (0)*	1.648 (1.026, 2.647) (0.15)	**0.039** (0.702)		
MR PIP 2–5	3 (3)*	1 (3.5)*	1.650 (1.108, 2.455) (0.16)	**0.014** (0.714)		
US PIP 2–5	1 (3)*	2 (3)*	1.192 (0.861, 1.651) (0.03)	0.289 (0.567)		
MR Extensor	1 (2)*	0 (0)*	6.330 (1.602, 25.012) (0.30)	**0.008** (0.813)		
US Extensor	0 (2)	0 (0)	2.764 (0.953, 8.017) (0.18)	0.061 (0.706)		
MR Flexor	4 (3)*	0 (0)*	4.373 (1.802, 10.609) (0.49)	**0.001** (0.926)	5.099 (1.620, 16.051) (0.487; 0.596)	**0.005** (0.979)
US Flexor	1 (3)*	0 (0)*	1.984 (1.102, 3.571) (0.19)	**0.022** (0.731)		
Total MR	13 (11)*	3.0 (4.5)*	1.996 (1.237, 3.221) (0.54)	**0.005** (0.959)	2.769 (1.249, 6.139) (0.544)	**0.012** (0.959)
Total US	7 (9)*	2.0 (5.0)*	1.356 (1.108, 1.659) (0.33)	**0.003** (0.853)	0.727 (0.445, 1.186) (0.544)	0.201 (0.959)

Mann-Whitney U test used for paired comparisons. * $p < 0.05$. P values given in bold type are significant. R^2: Cox & Snell R square; carpal: carpal synovitis, including radioulnar, radiocarpal, and intercarpal-carpometacarpal joints; ERA: early rheumatoid arthritis; extensor: 6 extensor tendon groups on the dorsal side of the wrist; flexor: 6 flexor tendon groups on the ventral side of the wrist and hand; GS: greyscale ultrasound; PD: power Doppler ultrasound; MCP 2–5: second through fifth metacarpophalangeal joints; MR: magnetic resonance; PIP 2–5: second through fifth interphalangeal joints; RA: rheumatoid athritis.

0.898, p = 0.052). Despite the better performance of US-corrected ACR/EULAR criteria in the same group in comparison with the criteria as described, the difference was not statistically significant (AUC = 0.930 and AUC = 0.898, respectively). On the other hand, if we take into consideration the complete cohort of patients or the patients with US joint and tendon count > 10, there was no statistically significant improvement of the 2010 ACR/EULAR performance. Our findings suggest that there is a specific subset of patients that can benefit from MRI joint and tendon counts, and this should be explored in a larger cohort.

One of the strengths of our study was the bilateral evaluation by both US and MRI. This was critical for a precise evaluation of the inflammatory burden and for determination of the diagnostic potential of each technique. Indeed, previous clinical and MRI descriptions of ERA depicted asymmetric joint involvement in 30%–94% of patients and symmetricization occurring only after significant progression of the RA[15,46,47,48,49,50,51].

There are also some limitations in our study. We have not studied bone erosions or bone edema. Bone edema was shown to strongly predict the progression to RA in a cohort of patients with undifferentiated arthritis[52]. However, bone edema is a strict MRI finding and US has low sensitivity for bone erosions, hindering comparison between techniques. In addition, proliferation of the synovium is one of the earliest changes in RA and bone erosions represent a late stage in the disease process. Thus, we focused our comparative study on synovitis evaluation. As well, the sample size of our study was modest at only 45 patients. The inclusion criteria were strict: disease duration, polyarthritis involvement, no

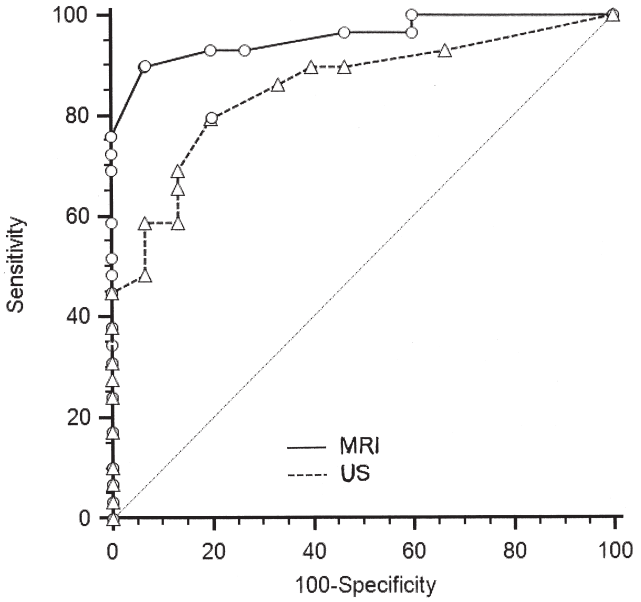

Figure 2. Receiver-operating curve of the diagnostic performance of total ultrasound (US) and magnetic resonance imaging (MRI) joint and tendon count for identifying RA. Area under the curve (AUC) for US 0.853 (95% CI 0.740-0.966). AUC for MRI 0.959 (95% CI 0.857-1.000).

previous treatments, and the prospective design of the study. However, we believe that the homogeneity of the groups in the study mitigated this. The lack of double-reading is also a limitation. However, the use of strictly validated quantification measures might compensate for this.

Our data confirm that MRI identified a higher prevalence of synovitis in comparison to US in an early arthritis cohort. In addition, our study identified both techniques as good diagnostic performers in respect to RA diagnosis, although MRI revealed a significantly higher diagnostic capability. Synovitis of the carpal joints and of the flexor tendons as identified by MRI was the most powerful predictor of progression toward RA. In patients with US joint and tendon counts ≤ 10, MRI can improve the diagnostic performance of the 2010 ACR/EULAR classification criteria.

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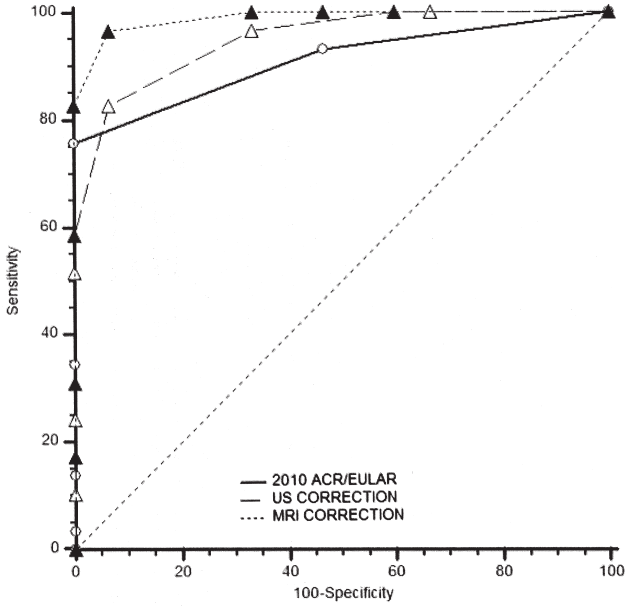
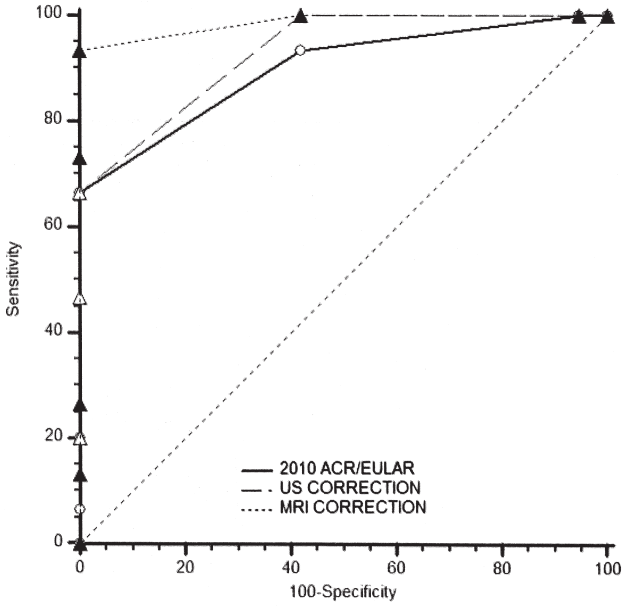
Table 5. Performance of the ACR/EULAR criteria for identifying rheumatoid arthritis (RA) patients. ACR/EULAR values presented as median (interquartile range).

Criteria	Value	AUC	(95% CI)	p*	Z statistic (p)
All patients, n = 30					
ACR/EULAR	5.0 (2.0)	0.909	(0.783–0.975)	**0.040**	1.974 (0.048)[#]
US ACR/EULAR	7.0 (2.0)	0.948	(0.836–0.992)	**0.028**	—
MRI ACR/EULAR	7.0 (2.0)	0.989	(0.898–1.000)	**0.009**	1.974 (0.048)[#]
US ≤ 10, n = 15					
ACR/EULAR	5.0 (1.0)	0.898	(0.746–0.975)	0.052	2.181 (**0.029**)[†]
US ACR/EULAR	5.0 (2.0)	0.930	(0.787–0.989)	**0.032**	—
MRI ACR/EULAR	6.0 (1.0)	0.986	(0.872–1.000)	**0.014**	2.181 (**0.029**)[†]
US > 10, n = 15					
ACR/EULAR	5.0 (1.0)	0.940	(0.802–0.993)	**0.047**	—
US ACR/EULAR	7.0 (1.0)	1.000	(0.897–1.000)	**0.000**	—
MRI ACR/EULAR	7.0 (1.0)	1.000	(0.897–1.000)	**0.000**	—

* Receiver-operating characteristic curve (ROC) analysis. Z statistic results from pairwise comparison of ROC curves (ACR/EULAR versus US ACR/EULAR versus MRI ACR/EULAR). [†]: Pairwise comparison with statistically significant association. [#] Represents a tendency. ACR/EULAR: performance of ACR/EULAR score for identifying RA patients; US ACR/EULAR: performance of ACR/EULAR score for identifying RA patients, with correction of the clinical joint counts by the US joint and tendon counts; MRI ACR/EULAR: performance of ACR/EULAR score for identifying RA patients, with correction of the clinical joint counts by the MRI joint and tendon counts; US ≤ 10: patients with US joint and tendon counts ≤ 10; US > 10: patients with US joint and tendon counts > 10; AUC: area under the ROC; MRI: magnetic resonance imaging; US: ultrasound.





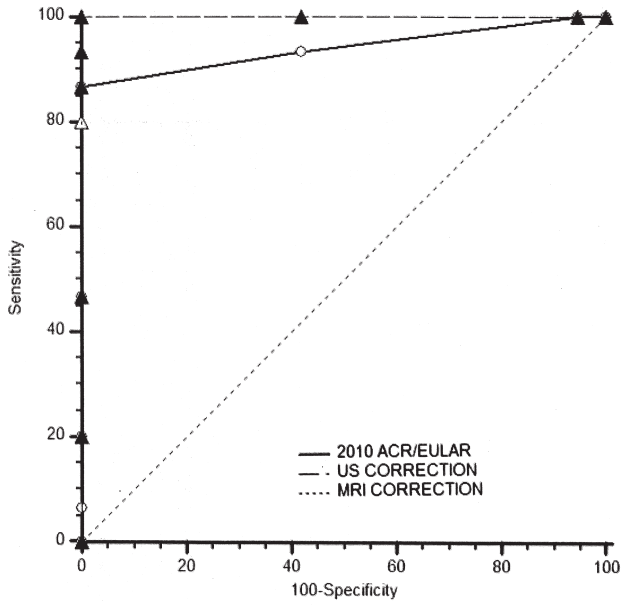


Figure 3. Receiver-operating curves using ACR/EULAR criteria as described[15] for identifying patients with RA, ultrasound (US)-corrected ACR/EULAR, and magnetic resonance imaging (MRI)-corrected ACR/EULAR. Curves are presented for the complete group of early RA patients (A) and for early RA patients with US joint and tendon counts ≤ 10 (B) and > 10 (C).

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