研究成果の刊行に関する一覧表（平成23〜25年度）

研究分担者氏名：松井利浩

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研究成果の刊行に関する一覧表（平成23～25年度）

研究分担者氏名：松下　功

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研究分担者氏名：松下　功

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研究分担者氏名：山中 寿

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研究成果の刊行に関する一覧表（平成23～25年度）

研究分担者氏名：山中　寿

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RHEUMATOLOGY

Original article

Sensitivity and specificity of 2010 rheumatoid arthritis classification criteria

Yuko Kaneko[1], Masataka Kuwana[1], Hideto Kameda[1] and Tsutomu Takeuchi[1]

Abstract

Objective. To validate the sensitivity and specificity of the 2010 RA classification criteria.

Methods. A total of 313 undiagnosed subjects, who first visited Keio University Hospital with joint symptoms, including arthralgia, joint swelling and morning stiffness, without any previous treatment except for NSAIDs, were included in the present study. A clinical diagnosis of RA was made by rheumatologists, and the gold standard diagnosis of RA was defined as an indication for instituting DMARDs for RA.

Results. Seventy-six subjects were diagnosed as gold standard RA. Among these, 8 did not have any swollen joints, 50 were classified as definite RA under the 2010 criteria and the other 18 as not having RA. Eighty-two subjects were eligible for the 2010 criteria, and the sensitivity and specificity under the 2010 criteria were 73.5 and 71.4%, respectively, compared with 47.1 and 92.9% under the 1987 criteria. But the sensitivity of the 2010 criteria decreased to 15.8% when both RF and anti-CCP were negative. According to the result of a receiver-operated characteristic (ROC) curve of the scoring system, if swollen joints and differential diagnosis are not accurately detected, it would be better to use a score of 5 as the cut-off level to detect RA.

Conclusion. The 2010 classification criteria have a high sensitivity and have been verified to be useful for distinguishing RA at an early stage.

Key words: Rheumatoid arthritis, Classification criteria, Scoring system, Sensitivity, Specificity.

CLINICAL SCIENCE

Introduction

RA is a chronic inflammatory disease characterized by progressive destructive arthritis with pain and disability [1]. Recent progress in its treatment, such as MTX and biological DMARDs, has given remarkable benefits to RA patients [2-6]. To manage RA patients appropriately, a diagnosis and a treatment strategy are needed as early as possible [7]. However, at present, an RA diagnosis is usually made under the 1987 ACR classification criteria [8], which are considered to be unsuitable for an early diagnosis [9-10]. Since 2007, the European League against Rheumatism (EULAR) and the ACR have been cooperatively dealing with a revision of the classification criteria, which was finally published in August 2010 [11-13]. The new criteria consist of a classification scoring system, which noticeably puts a great deal of emphasis on small joint involvement and seropositivity of RF or ACPAs. In detail, classification as definite RA is based on the presence of synovitis in at least one joint, the absence of an alternative diagnosis better explaining the synovitis and a total score from individual scores in four domains (the number and site of involved joints, serological abnormality, elevated acute-phase response and symptom duration).

It has been described that the focus of the new classification criteria was not on developing diagnostic criteria or reference tools for primary care physicians, but on facilitating the study of persons with earlier stages of RA. However, since hereafter we are mainly going to use the 2010 classification criteria as an aid in the diagnosis of RA in the clinical field, we should be well acquainted with their strengths and limitations. The aim of this study is to validate the sensitivity and specificity of the 2010 criteria, and to find certain

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characteristics of patients with RA who are not classified as RA and vice versa.

Subjects and methods

This study was a retrospective single centre observational study. In order to optimize the quality and reproducibility of this validation study, the work was designed to comply with the criteria of the Standards for Reporting of Diagnostic Accuracy initiative [14].

Subjects

The subjects, all of whom first visited the out-patient clinic of the Division of Rheumatology, Department of Internal Medicine at the Keio University School of Medicine in January 2009 through March 2010, were reviewed retrospectively. Three hundred and fourteen undiagnosed subjects exhibited joint symptoms, including arthralgia, joint swelling and morning stiffness, without any previous treatment with the exception of NSAIDs. Among these, one patient was excluded from the study because of insufficient laboratory data to comply with the new criteria. Ultimately, 313 subjects were included in the present study. Medical ethics committee approval was waived because the study was a retrospective cohort study using anonymized information.

Diagnoses of RA and other diseases

Diagnoses of RA were made by at least one of six rheumatologists in our institution from a comprehensive standpoint, using clinical histories including when and how symptoms started, physical findings including the site and extent of involved joints and extra-articular lesions, blood tests including RF, ACPA, acute-phase reactants and MMP and X-rays. MRI of symptomatic joints was also used when diagnosis was not able to be settled, and synovitis with bone erosion or osteitis was considered as the presence of RA. Because the absolute gold standard diagnosis of RA does not exist, in the present study, the gold standard for a diagnosis of RA was defined as an indication for instituting DMARDs for RA, including salazosulphapyridine, bucilamine, tacrolimus, MTX, infliximab, etanercept, adalimumab and tocilizumab. The six above-mentioned rheumatologists are all specialists in rheumatology, each with >10 years of clinical experience. Diagnoses of other diseases were also made through a similar process. Subjects regarded as not being affected by particular diseases were termed no appreciable disease (NAD). Subjects observed having modest arthritis but where diagnosis of a particular disease was not sure enough for treatment despite repeated examinations, were termed undifferentiated peripheral inflammatory arthritis (UPIA).

Assessment of clinical manifestations and laboratory findings

Demographics and clinical manifestations, including sex, age, duration of symptoms, the number of tender joints and the number of swollen joints, were evaluated. Blood samples were examined in our hospital laboratory. The upper limits of CRP, measured by dry chemistry (Mitsubishi Chemical Medicine, Tokyo, Japan), the ESR, measured by the Westergren test, IgM-RF, measured by a latex-enhanced immunonephelometric assay (Eiken Chemical, Tochigi, Japan) and anti-CCP, measured by an ELISA (Medical & Biological Laboratories, Nagano, Japan) were 0.35 mg/dl, 10 mm/h for men and 15 mm/h for women, 20 IU/l and 4.5 U/ml, respectively.

Statistical analysis

Subject characteristics were summarized using medians and ranges, and the values of CRP and ESR, as well as the number of involved joints, were summarized using mean (s.d.). Comparisons of frequency between the two groups were performed using the Pearson chi-squared test. Comparisons of mean value were performed by Student's t-test. Sensitivity vs the false positive frequency (one-specificity) for the scoring system was analysed by a receiver-operated characteristic (ROC) curve. All reported P-values are two-sided. $P < 0.05$ was considered to be statistically significant. Data were analysed with SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

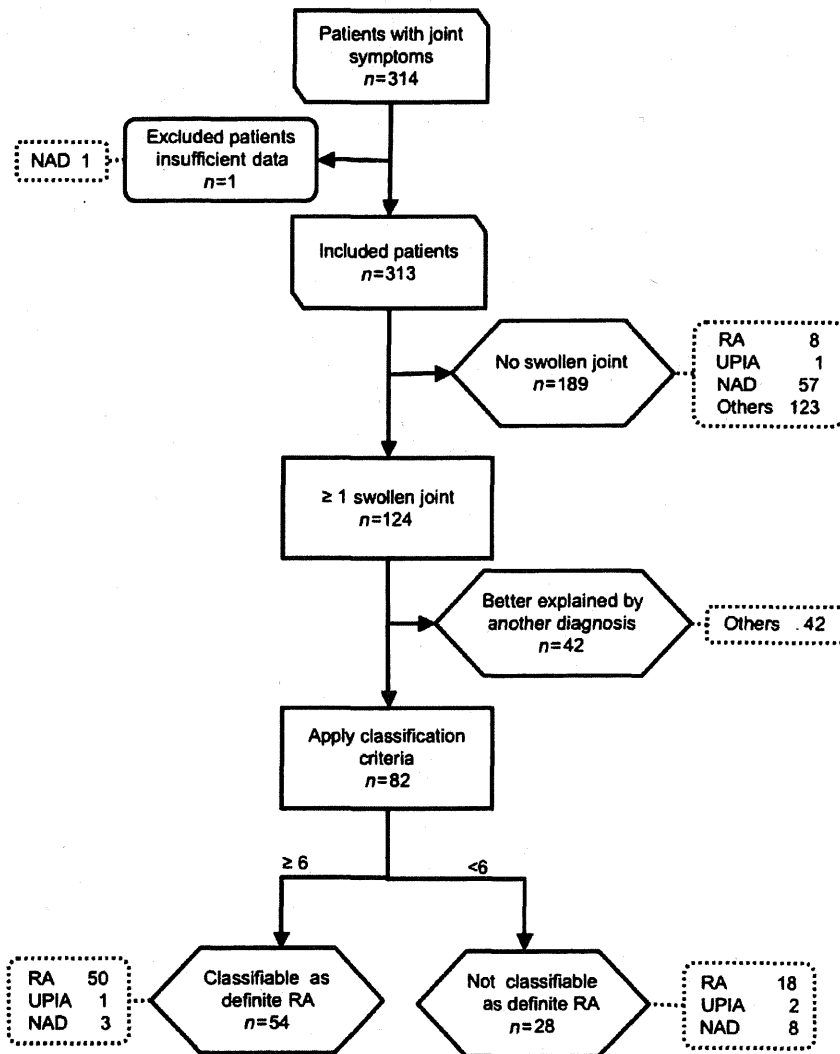### Characteristics and diagnoses of 313 subjects

The subject characteristics were as follows: age, median (range) years, 54 (14–86); sex, n (%), female, 79; duration of symptoms, median (range) weeks, 18 (1–1040); interval between the first visit and the time of diagnosis, median (range) weeks, 2 (1–40). Diagnoses of subjects at the last visit were 76 with RA, 4 UPIA, 68 NAD and 165 other diseases. All subjects were observed until they were diagnosed or for >3 months if they could not be accurately diagnosed (i.e. UPIA).

At the point when the first laboratory and radiographic findings were available, mostly within 3 weeks from the first visit, the patients were assessed and subjected to the 2010 classification criteria. A flow diagram is shown in Fig. 1. Of 313 subjects, 124 had at least one swollen joint and, among these, 82 were eligible to be subjected to the classification scoring system. Fifty-four subjects achieved a total score of ≥6, and their clinical diagnoses were 50 RA, 1 UPIA and 3 NAD. Twenty-eight subjects showed a score of <6, and their diagnoses were 18 RA, 2 UPIA and 8 NAD.

Among 76 RA patients, RF and anti-CCP were positive in 50 (66%) and 46 (61%) patients, respectively. Regarding the length of time between the first visit to our hospital and the time of diagnosis of RA, 71 (93%) subjects were diagnosed within 12 weeks, 3 (4%) within 24 weeks and 2 (3%) after >24 weeks.

Diagnoses of another 165 subjects included OA ($n = 74$), post-menopausal syndrome (PMS; $n = 14$), tendonitis ($n = 13$), SS ($n = 12$), SLE ($n = 6$), PM/DM ($n = 4$), PsA ($n = 4$), viral infection ($n = 4$), PMR ($n = 4$), palindromic rheumatism ($n = 3$), adult onset Still's disease ($n = 3$), post-injury (n = 3), AS ($n = 2$), shoulder periarthritis ($n = 2$),

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Fig. 1 Flow chart of result. Of 314 subjects who visited our institute with joint symptoms without any treatment, 313 subjects were included in this study. One hundred and twenty-four subjects had at least one swollen joint, and among these, 42 were diagnosed with other diseases and 82 were submitted to the scoring system, resulting in 54 subjects with a total score of $\geqslant 6$. The clinical diagnoses of subjects at the last visit are shown in the dotted square.

Patients with joint
symptoms
n=314

NAD 1

Excluded patients
insufficient data
n=1

Included patients
n=313

No swollen joint
n=189

RA   8
UPIA   1
NAD   57
Others 123

$\geq$ 1 swollen joint
n=124

Better explained by
another diagnosis
n=42

Others 42

Apply classification
criteria
n=82

$\geq$ 6   <6

RA   50
UPIA   1
NAD   3

Classifiable as
definite RA
n=54

Not classifiable
as definite RA
n=28

RA   18
UPIA   2
NAD   8

pseudogout ($n = 2$), steroid withdrawal syndrome ($n = 2$), FM ($n = 2$), SSc ($n = 2$), remitting seronegative symmetrical synovitis with pitting oedema ($n = 1$), humeral epicondylitis ($n = 1$), diffuse fasciitis ($n = 1$), sarcoidosis ($n = 1$), infectious endocarditis ($n = 1$), acute respiratory distress syndrome ($n = 1$), amyloid arthropathy ($n = 1$), SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome ($n = 1$) and HScP ($n = 1$).

Comparison of the 2010 and 1987 criteria

Table 1 presents a comparison of the 2010 and 1987 criteria. For 82 subjects who had at least one swollen joint not better explained by other diseases, the sensitivity of the 2010 criteria was much better than that of the 1987

criteria, but the specificity was worse (73.5 *vs* 47.1% and 71.4 *vs* 92.9%, respectively). The positive predictive values (PPVs) were comparable, and the negative predictive values (NPVs) and the positive likelihood ratios were better in the 1987 criteria (92.5 *vs* 97.0%, 35.7 *vs* 26.5% and 2.6 *vs* 6.6%, respectively).

Features of RA patients with or without classification as RA under the new criteria

Features of 68 RA patients with or without classification as RA are shown in Table 2. The positivity of RF and/or anti-CCP and the swollen/tender small joint counts were significantly higher in patients who were classifiable as definite RA under the 2010 criteria than in those who

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TABLE 1 Comparison of sensitivity, specificity and accuracy between the 1987 and 2010 criteria

	1987 criteria	2010 criteria				
		Subjects with swollen joints not better explained by other diseases			All subjects with swollen joints	All subjects
Outcome measure	(n = 82)	(n = 82)	Seropositive[a] (n = 54)	Seronegative[b] (n = 28)	(n = 124)	(n = 313)
Sensitivity, %	47.1	73.5	95.9	15.8	73.5	72.4
Specificity, %	92.9	71.4	20.0	100	80.4	89.9
PPV, %	97.0	92.5	90.4	100	82.0	69.6
Negative prediction value, %	26.5	35.7	33.3	36.0	71.4	91.0
Positive likelihood ratio	6.6	2.6	1.2	NA	3.8	7.2

[a]RF and/or anti-CCP was positive. [b]Both RF and anti-CCP were negative. NA: not available.

TABLE 2 Comparison of RA patients who were classifiable as RA with those who were not

Characteristic	Classifiable (n = 50)	Not classifiable (n = 18)	P-value
RF positivity	43 (86)	1 (6)	<0.001
Low titre[a]	17	0	
High titre[a]	26	1	
Anti-CCP positivity	40 (80)	0 (0)	<0.001
Low titre[a]	3	0	
High titre[a]	37	0	
CRP positivity	32 (64)	14 (78)	0.38
CRP level, mean (s.d.), mg/dl	2.2 (3.1)	2.4 (3.4)	0.83
ESR positivity	45 (90)	15 (83)	0.43
ESR level, mean (s.d.), mm/h	55 (39)	54 (44)	0.44
Swollen small joint count[b], mean (s.d.)	5.1 (4.9)	2.5 (2.2)	0.01
Swollen large joint count[b], mean (s.d.)	1.6 (1.8)	0.6 (0.9)	0.09
Tender small joint count[b], mean (s.d.)	3.7 (3.3)	1.9 (1.9)	0.006
Tender large joint count[b], mean (s.d.)	1.6 (2.2)	0.8 (1.3)	0.76

Values are n (%) unless otherwise indicated. P values <0.05, given in italics, were considered to be statistically significant. [a]High titre was defined as a value that was more than three times the upper limit in our own institute, following the new criteria. [b]Small/large joint was determined in accordance with the 2010 criteria.

were not. We divided 82 subjects into two groups according to the presence or absence of RF and/or anti-CCP, and the sensitivity and specificity were re-evaluated, as shown in Table 1. In the group of patients in whom RF and anti-CCP were both negative, sensitivity decreased remarkably to 15.8%. If we could include all subjects who had at least one swollen joint (n = 124), or all subjects who were recruited in the present study (n = 313), in the 2010 criteria, the specificity would increase (Table 1).

RA patients who were not classifiable as RA under the new criteria

Eighteen RA patients were not classifiable as RA under the new criteria at the point when the first laboratory and radiographic findings became available. Six patients exhibited small erosions on X-rays, but these were not significant and it was not obvious whether their histories were compatible with the 2010 criteria. Five patients were diagnosed with RA by reference to MRI findings. In

addition, eight patients who had not had any swollen joints on the first visit and had not been subjected to the scoring system were later found to have swollen joints and were diagnosed with RA. Seven of a total of 26 patients had come to satisfy the 2010 criteria as definite RA during the period of 3–33 weeks from the first visit, whereas the others were treated with DMARDs before being able to fulfil the new criteria.

Cases of patients with other diagnoses who achieved a total score of ⩾6 under the 2010 criteria

If the 2010 criteria were applied to all subjects who were recruited in the present study, 11 subjects given other diagnoses achieved a total score of ⩾6. The features of these patients are shown in Table 3. Their diagnoses included three NAD, one UPIA, one PsA, two OA, one PMS, one SS, one SLE and one DM. Except for cases with an arthritis similar to RA, NAD and OA subjects with a minor count of swollen joints, high-titre RF positivity and

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TABLE 3 Features of non-RA patients who achieved total score of ⩾6

Physical and experimental findings on the first visit										
Sex	Age	TJC	SJC	ESR	CRP	RF	Anti-CCP	Duration, weeks	Diagnosis	Treatment
F	31	1	3	28	0.9	41	0	21	UPIA	–
F	34	1	1	8	0.01	76	0	265	NAD	–
F	59	0	2	10	0.03	72	0	18	NAD	–
F	41	1	1	16	0.11	0	31	28	NAD	
M	46	3	2	58	10.22	153	100	12	PsA	MTX
M	43	10	11	26	0.06	0	0	9	DM	PSL
F	50	4	5	14	0.06	28	9.8	14	SLE	NSAIDs
F	55	2	1	18	0.02	64	0	104	PMS	–
F	53	1	1	18	0.1	79	0	52	OA	–
F	62	3	2	13	0.1	0	23	520	OA	–
F	57	14	6	4	0.01	0	0	11	SS	–

TJC: tender joint count (both small and large); SJC: swollen joint count (both small and large); PSL: prednisolone.

mildly elevated ESR were apt to be misclassified as having RA under the 2010 criteria.

Availability of scoring system and difficulties in detection of swollen joints and differential diagnoses

In the present study, 82 patients were subjected to the scoring system. A ROC curve depicted to decide the best cut-off score showed that the best was 6, as was the same with the definition of 2010 criteria (data not shown). However, it is not always easy to detect swollen joints and accurately make diagnoses of other diseases. Supposing a doctor had difficulty in assessing swollen joints and differential diagnoses, we tried to assign all 313 subjects to the scoring system. The results are shown in Fig. 2A. The median score was 7 in RA and 2 in non-RA subjects. A ROC curve in this setting was depicted (Fig. 2B) and the ROC plot that was the closest to the upper left corner was a score of 5 in this setting.

Discussion

Over the past decade, the clinical setting of RA has changed considerably. Destructive joint damage was shown to begin at an early stage [15, 16], and an early diagnosis with aggressive therapy may alter or modify the natural history of this destructive and dreadful disease [17]. The 1987 ACR classification criteria used widely to diagnose RA have been criticized for their low discriminative ability in recent onset arthritis [9, 10]. The main cause of this was that the 1987 criteria were created using data from established RA patients with a mean disease duration of 7.7 years [8]. Harrison *et al.* [9] reported that the Norfolk Arthritis Register data showed that only 38% of new cases of inflammatory polyarthritis could be classified as RA using the 1987 criteria when first seen. Moreover, only 50% of RA patients satisfied the 1987 criteria at 6 months and only 80% even at 2 years after enrolment [9]. Thus, the 2010 classification criteria were developed in order to

distinguish RA earlier and start effective treatment as soon as possible to prevent or minimize joint destruction [7, 11–13].

At the time the 1987 criteria were declared, sensitivity and specificity were reported to be 91–94 and 89%, respectively [8]. In our study, sensitivity and specificity were 47.1 and 92.9%, respectively, using the 1987 criteria, while those using the 2010 criteria were 73.5 and 71.4%. van der Linden *et al.* [18] reported that both the sensitivity and specificity of the 2010 criteria were 74% when using DMARD-initiation within the first year as RA outcome in the Leiden Early Arthritis clinic. Our data were quite similar to their results. The sensitivity was better under the 2010 criteria, although the specificity, NPV and the likelihood ratio were better under the 1987 criteria. These results demonstrate that the 2010 criteria are superior to the 1987 criteria for the detection of RA in early stages, rather than for diagnoses. However, sensitivity under the new criteria decreased to 15.8% when both RF and anti-CCP were negative, which is considered to be a limitation of the new criteria. For example, a seronegative patient with 10 swollen/tender joints and elevated CRP and ESR for >6 weeks, who was strongly suspected to have a persistent and destructive disease (i.e. RA), could not achieve a total score of 6.

Eighteen RA patients and an additional eight patients without any swollen joints when first seen, were not classifiable as RA under the 2010 criteria at the point when the first laboratory and radiographic findings became available. Among these, while 19 patients had been treated with DMARDs before being subjected to the new criteria and could not be considered assessable because of improvement, the other seven patients who were just observed with or without NSAIDs came to be classifiable as having RA within 33 weeks (six within 12 weeks and one at 33 weeks). When we subjected the patients to the new criteria cumulatively over 12 weeks, the sensitivity increases up to at least 81.6%. It can be said that these criteria are useful to diagnose RA within 12 weeks, even

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Fig. 2 (A) Scores of 313 subjects under the scoring system. The distribution of the scores at the point when first laboratory and radiographic findings were available is shown. The median scores were 7 and 2 in RA patients and non-RA subjects, respectively. (B) A ROC curve. A ROC curve was depicted to decide the best cut-off score. The ROC plot that was the closest to the upper left corner was a score of 5.
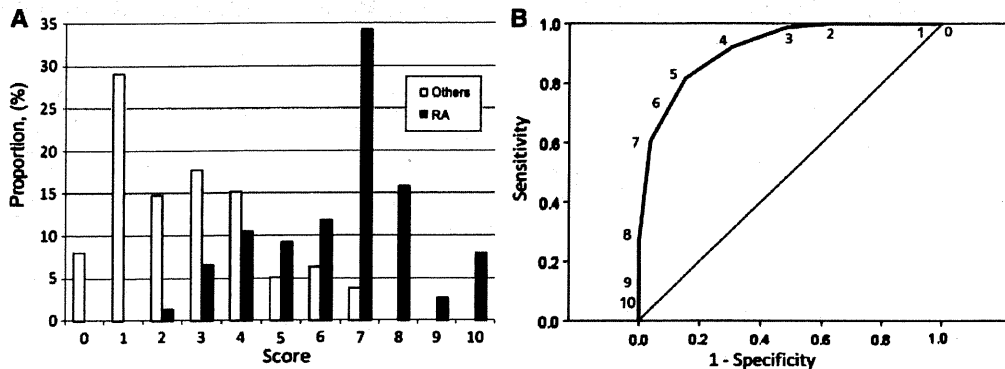
if we could not classify patients as having RA when first seen.

Meanwhile, except for cases with an arthritis similar to RA, NAD and OA subjects with one or two small swollen joints, non-specific high-titre RF positivity and mildly elevated ESR tended to be misclassified as having RA. If we were to classify such subjects as RA and start treatment with DMARDs, we might overtreat them. So we should be careful with this point when using the 2010 criteria.

The utility of the scoring system in various situations was also verified. Even if swollen joints and other diseases could not be accurately assessed, that is, if all patients with joint symptoms were to be submitted to the 2010 criteria, the sensitivity would be comparable and the specificity would be raised to 89.9%. Considering the result from the ROC curve, we could make presumptions about whether subjects with joint symptoms might be affected with RA if they were to attain a cut-off score of 5. Young *et al.* [19] reported that there has been little change in referral time from onset of symptoms to a rheumatologist over 25 years in a large RA inception register in the UK. It is important to avoid delay in consultation to rheumatologists as well as to make an early diagnosis of RA. If primary care physicians were to use the 2010 criteria, they might better refer patients to a rheumatologist or at least monitor them carefully under the UPIA recommendation [20] with a score of 5, so as not to miss RA patients.

There are some limitations to this study. One of these was the definition of the gold standard for RA. This definition contained risk of misdiagnosis. And the data used by rheumatologists in our institution to diagnose RA were partly corresponding to items of the new criteria, so the sensitivity might be highly overestimated. However, since the six rheumatologists who diagnosed the subjects in this study were all specialists in rheumatology, each with >10 years of clinical experience, almost all of the

diagnoses were believed to be correct. Moreover, we determined the institution of not only MTX but also other DMARDs to be the gold standard. Since in our country, MTX is permitted for use by the Health, Labour and Welfare Ministry only after other DMARDs fail, only 44 (57%) of 76 patients had MTX initiated as their first treatment. Another limitation was that this study was a hospital-based study. Since our hospital is a major academic medical institute, there is a possibility that many of our subjects were more likely to have RA, and the PPV might be estimated as higher than it really is.

In conclusion, the present study showed that the 2010 classification criteria have high sensitivity and are useful for distinguishing early RA. However, it should be cautioned that the sensitivity decreased remarkably when both RF and anti-CCP were negative and that subjects with a small number of swollen joints, non-specific high-titre RF positivity and mildly elevated ESR were apt to be misclassified as having RA. If general physicians use the 2010 criteria to distinguish RA, a cut-off score of 5 would be better in order not to miss RA patients. Further studies with a larger cohort may be needed to optimize these criteria in the practical field.

Rheumatology key messages

- The 2010 classification criteria have high sensitivity and are useful for distinguishing early RA.
- The sensitivity of the 2010 classification criteria decreased remarkably when both RF and anti-CCP were negative.
- A cut-off score of 5 might be better in the practical field.

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American College of Rheumatology/European League Against Rheumatism Remission Criteria for Rheumatoid Arthritis Maintain Reliable Performance When Evaluated in 44 Joints

Yuko Kaneko, Harumi Kondo and Tsutomu Takeuchi

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American College of Rheumatology/European League Against Rheumatism Remission Criteria for Rheumatoid Arthritis Maintain Reliable Performance When Evaluated in 44 Joints

Yuko Kaneko, Harumi Kondo, and Tsutomu Takeuchi

ABSTRACT. Objective. To investigate the performance of the new remission criteria for rheumatoid arthritis (RA) in daily clinical practice and the effect of possible misclassification of remission when 44 joints are assessed.

Methods. Disease activity and remission rate were calculated according to the Disease Activity Score (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and a Boolean-based definition for 1402 patients with RA in Keio University Hospital. Characteristics of patients in remission were investigated, and the number of misclassified patients was determined — those classified as being in remission based on 28-joint count but as nonremission based on a 44-joint count for each definition criterion.

Results. Of all patients analyzed, 46.6%, 45.9%, 41.0%, and 31.5% were classified as in remission in the DAS28, SDAI, CDAI, and Boolean definitions, respectively. Patients classified into remission based only on the DAS28 showed relatively low erythrocyte sedimentation rates but greater swollen joint counts than those classified into remission based on the other definitions. In patients classified into remission based only on the Boolean criteria, the mean physician global assessment was greater than the mean patient global assessment. Although 119 patients had ≤ 1 involved joint in the 28-joint count but > 1 in the 44-joint count, only 34 of these 119 (2.4% of all subjects) were found to have been misclassified into remission.

Conclusion. In practice, about half of patients with RA can achieve clinical remission within the DAS28, SDAI, and CDAI; and one-third according to the Boolean-based definition. Patients classified in remission based on a 28-joint count may have pain and swelling in the feet, but misclassification of remission was relatively rare and was seen in only 2.4% of patients under a Boolean definition. The 28-joint count can be sufficient for assessing clinical remission based on the new remission criteria. (J Rheumatol First Release June 15 2013; doi:10.3899/jrheum.130166)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   REMISSION CRITERIA   44 JOINTS   VERIFICATION

Therapeutic developments over the past several decades in the treatment of rheumatoid arthritis (RA) have made remission an achievable goal. While different remission criteria had been used, new criteria have recently been presented by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)[1]: the index-based criteria defined as a Simplified Disease Activity Index (SDAI) of ≤ 3.3 and a Boolean-based definition requiring 4 criteria to be ≤ 1 [patient global assessment (PGA; in cm), swollen and tender joint counts

(SJC, TJC), and C-reactive protein (CRP; in mg/dl)]. Definitions for clinical practice were also proposed: a Clinical Disease Activity Index (CDAI) level of ≤ 2.8 and a Boolean-based definition requiring 3 criteria to be ≤ 1, eliminating the CRP. In the past, the most widely used criteria were the Disease Activity Score (DAS) and DAS28, with 44 and 28 joints assessed, respectively. While the 44-joint count is more comprehensive, the 28-joint count correlates well with the full joint count[2,3,4] and is easier to assess and more convenient in daily practice; the newly suggested criteria are also based on a 28-joint count. However, the 28-joint count excludes evaluation of ankle and foot joints, potentially leading to misclassification of patients to remission status, particularly if the patient has disease activity only in the ankles and feet.

While van Tuyl, *et al*[5] did report that residual disease activity in the forefeet had a limited effect on outcome using a 38-joint count, it remains unclear whether using only a

28-joint count is sufficiently accurate in evaluating remission, because the van Tuyl team did not assess activity in the ankles. We assessed the performance of the new remission criteria in daily clinical practice and evaluated the effects of possible misclassification of remission on their performance when 44 joints are assessed instead of 28.

MATERIALS AND METHODS

All patients with RA in Keio University Hospital were evaluated cross-sectionally in the period December 2011 to February 2012. Joint counts were assessed by 6 rheumatologists, all of whom had at least 10 years' experience. The 44-joint count includes ankle (n = 2), metatarsophalangeal (n = 10), sternoclavicular (n = 2), and acromioclavicular (n = 2) joints, as well as the usual 28-joint count.

Findings for laboratory data included CRP, erythrocyte sedimentation rate (ESR), and matrix metalloproteinase-3 (MMP-3). Patient pain, patient global assessment (PGA), and physician global assessment (PhGA) were measured on a visual analog scale ranging from 0 to 100 mm. A Health Assessment Questionnaire (HAQ) was filled out by each patient.

We first classified patient disease activity into states of remission and low, moderate, and high activity, based on DAS28, SDAI, and CDAI values, and then examined the number of criteria that were satisfied under a Boolean-based definition. We also assessed the characteristics of patients in remission according to each definition and then evaluated the number of misclassified patients — those classified into remission based on a 28-joint count but as nonremission based on a 44-joint count for each definition criterion. In addition, for patients with an involved joint count ≤ 1 in the 28-joint count but > 1 in the 44-joint count (meaning they could have been misclassified into remission under the Boolean definition) who were not classified into remission, variables that prevented them from being misclassified were also investigated.

Comparisons of mean values were performed using Student's t test with IBM SPSS version 20.0 (IBM Corp.).

RESULTS

Characteristics of all study patients and those in remission for each definition. Of the 1449 patients with RA in our hospital, 47 were excluded because of insufficient data, resulting in a total of 1402 patients (83% female) included in study analysis. Mean patient age was 60.1 years, mean disease duration 10.9 years, and mean DAS28 was 2.8. About half the patients were treated with a biologic agent (Table 1).

Characteristics of patients in remission according to DAS28, SDAI, and CDAI values as well as Boolean-based criteria are shown in Table 1. The remission rates were 46.6% in DAS28, 45.9% in SDAI, 41.0% in CDAI, and 31.5% under a Boolean definition. The mean value of HAQ score was significantly better in patients in remission under the Boolean definition than in those deemed to be in remission based on the other definitions.

Comparison of characteristics of patients in various remission states by definition. We compared the characteristics of patients whose remission status varied among the 4 sets of remission criteria (Table 2). Patients classified into remission based only on the DAS28 showed relatively low ESR but higher PGA values and SJC than those classified into remission based on the other definitions, while those

classified into nonremission using only DAS28 showed relatively high ESR. Although few patients were classified into remission only by the Boolean definition, their mean PhGA was greater than their mean PGA score.

Possible misclassification with assessment of 44 joints instead of 28 joints. We then investigated the effect of possible misclassification into remission on the performance of each remission definition when 44 joints were assessed instead of the 28-joint count. The numbers of patients classified into remission using the 28-joint count but as nonremission with the 44-joint count were 38, 40, 36, and 34 under the DAS28, SDAI, CDAI, and Boolean definitions, respectively, which means the possible remission rate would be 43.9%, 43.1%, 38.4%, and 29.0% according to the 44-joint count. Although the effect of possible misclassifications on performance was smallest using the Boolean definition, the difference was modest (Figure 1A).

A total of 119 patients (8.5% of all subjects) had ≤ 1 involved joint in the 28-joint count but > 1 in the 44-joint count, indicating the potential for misclassification into remission using the Boolean definition. However, only 34 of these 119 patients (2.4% of all subjects) were actually misclassified into remission, which was averted largely due to the presence of high PGA (45%), high SJC (1%), high TJC (1%), high CRP (1%), or a combination of several findings (24%) (Figure 1B). Given these findings, the remission rate could have potentially decreased from 31.5% to 29.0% using a Boolean definition when 44 joints were assessed.

DISCUSSION

Our study investigated effects of possible misclassification of remission on the performance of new ACR/EULAR remission criteria when 44 joints are assessed instead of 28, and we found that misclassification was relatively rare and was seen only in 2.4% of patients under a Boolean definition.

Although assessment of all joints is clearly required in a patient assessment, a 28-joint count has frequently been used because it has been recognized to provide as much information as a full joint count with considerably greater feasibility. However, there should be a compromise between comprehensiveness and feasibility[6], and several groups have studied the residual disease activity in feet and ankles of patients in remission using a reduced joint count. Landewé, *et al* showed that remission defined by DAS28, which excludes ankles and feet, is inferior to the original DAS definition because of residual swelling and tenderness in the ankles and feet[7]. Kapral, *et al* compared the extended joint count with the limited joint count in DAS28 and SDAI, noting a negligible difference in findings, because other components of remission criteria would be higher in patients with foot joint involvement, helping to avoid misclassification[8]. In our study, we noted only a modest effect of

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Table 1. Characteristics of all patients studied and patients in remission according to SDAI, CDAI, and Boolean-based definition. Data are expressed as mean (SD), unless otherwise indicated.

Characteristic	All Patients	Remission			
		DAS28	SDAI	CDAI	Boolean
No. cases (%)	1402 (100)	654 (46.6)	644 (45.9)	575 (41.0)	441 (31.5)
Age, yrs	60.1 (14.5)	56.8 (14.9)	58.1 (14.6)	58.2 (14.8)	57.3 (14.9)
Disease duration, yrs	10.9 (9.9)	8.9 (8.3)	9.3 (8.8)	9.2 (8.8)	8.4 (8.1)
TJC28 (n, %)					
0	931 (66.4)*	608 (93.0)	606 (94.1)	548 (95.3)	400 (90.7)
1	204 (14.6)*	34 (5.2)	34 (5.3)	24 (4.2)	41 (9.3)
≥ 2	267 (19.0)*	12 (1.8)	4 (0.6)	3 (0.5)	0
SJC28, n (%)					
0	762 (54.4)*	522 (79.8)	567 (88.0)	521 (90.6)	364 (82.5)
1	228 (16.2)*	74 (11.3)	68 (10.6)	52 (9.0)	77 (17.5)
≥ 2	412 (29.4)*	58 (8.9)	9 (1.4)	2 (0.4)	0
TJC44, n (%)					
0	884 (63.1)*	579 (88.5)	581 (90.2)	526 (91.5)	381 (86.4)
1	194 (13.8)*	44 (6.7)	48 (7.5)	36 (6.3)	50 (11.3)
≥ 2	324 (23.1)*	31 (4.7)	15 (2.3)	13 (2.3)	10 (2.3)
SJC44, n (%)					
0	692 (49.4)*	478 (73.1)	523 (81.2)	480 (83.5)	333 (75.5)
1	218 (15.5)*	84 (12.8)	87 (13.5)	69 (12.0)	79 (17.9)
≥ 2	492 (35.1)*	92 (14.1)	34 (5.3)	26 (4.5)	29 (6.6)
CRP, mg/dl	0.4 (1.0)*	0.1 (0.2)	0.1 (0.3)	0.2 (0.4)	0.1 (0.2)
ESR, mm/h	28.2 (27.3)*	13.3 (8.2)	21.5 (23.7)	22.1 (25.0)	20.1 (25.3)
MMP-3, mg/dl	106 (184)*	83 (54)*	77 (47)	78 (55)	73 (38)
PGA, mm	22.5 (22.7)*	12.7 (15.5)*	8.2 (8.0)*	7.3 (7.1)*	3.6 (3.0)
Pain VAS, mm	21.9 (22.8)*	12.4 (15.9)*	8.2 (8.0)*	7.5 (8.6)*	4.4 (6.0)
PhGA, mm	9.9 (14.2)*	3.3 (7.1)	1.7 (3.0)	1.5 (2.9)*	2.3 (6.2)
HAQ	0.63 (0.75)*	0.34 (0.55)*	0.29 (0.50)*	0.29 (0.50)*	0.18 (0.66)
DAS28	2.8 (1.1)*	1.9 (0.5)	2.1 (0.6)	2.1 (0.6)	2.0 (0.7)
SDAI	6.0 (7.2)*	2.2 (2.3)*	1.3 (1.0)*	1.2 (0.9)*	1.0 (1.1)
CDAI	5.6 (6.7)*	2.1 (2.3)*	1.2 (1.0)*	1.0 (0.8)*	0.9 (1.0)
Biologic agent use, %	48.0	52.6	50.5	49.5	50.2
Methotrexate use, %	72.4	74.3	74.4	73.8	74.3
Corticosteroid use, %	26.5*	20.7*	17.6	17.8	14.6
Comorbidity[†], %	18.5	14.4	14.3	13.9	13.9

* p < 0.05 compared with Boolean definition. [†] Comorbidity included chronic infection, interstitial lung disease, current or previous malignancy, viral hepatitis, and chronic renal failure. DAS28: 28-joint count Disease Activity Score; SDAI: Simplified Disease Activity score; CDAI: Clinical Disease Activity score; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP-3: matrix metal-loprotease-3; PGA: patient global assessment; VAS: visual analog scale; PhGA: physician global assessment; HAQ: Health Assessment Questionnaire.

possible misclassification into a remission category on the performance of the provisional ACR/EULAR remission criteria. While 8.5% of patients had ≤ 1 involved joint in a 28-joint count, but > 1 in a 44-joint count, only 2.4% were misclassified into remission under the Boolean-based definitions, mainly due to PGA values. Reinforcing the findings of the ACR/EULAR remission task force in their development of these new criteria that the effect of missing residual disease activity in the ankles and feet appeared to be limited because patients with activity in those joints showed increased levels in other measures in the definition, we demonstrated here that the 28-joint count can be sufficiently accurate in assessing remission status based on Boolean definition criteria. However, whereas the disease

duration of our study patients varied considerably, Wechalekar, et al examined 123 patients with RA who had synovitis symptoms for less than 24 months and reported that remission criteria using 28-joint counts did not adequately identify the resolution of foot synovitis[9]. This should be confirmed in a large population in a future study.

We also observed that 46.6%, 45.9%, and 41.0% of patients with RA could be deemed to be in remission using DAS28, SDAI, and CDAI values, respectively, with 31.5% remaining valid even using a Boolean-based definition. The remission rates with SDAI and CDAI were quite similar to that under DAS28 and were higher than values in other reports[5,10,11]. We believe this discrepancy exists because about half of our patients were treated with biologic agents,

Table 2. Comparison of characteristics of patients in various remission states stratified by definition.

DAS28 remission	Yes	Yes	No	Yes	No	No
SDAI remission	Yes	Yes	Yes	No	No	No
CDAI remission	Yes	Yes	Yes	No	No	No
Boolean remission	Yes	No	Yes	No	Yes	No
Number	351	125	60	136	16	594
Age, yrs	54.2 (15.2)	57.9 (14.2)	60.1 (13.9)	56.2 (15.4)	65.5 (11.7)	62.8 (13.8)
Disease duration, yrs	7.9 (7.6)	9.3 (8.2)	10.6 (10.1)	10.9 (9.5)	6.8 (7.1)	12.6 (10.8)
TJC28, n (%)						
0	342 (97.4)	122 (97.6)	48 (80)	106 (77.9)	4 (25)	206 (34.7)
1	9 (2.6)	2 (1.6)	12 (20)	19 (14.0)	12 (75)	136 (22.9)
≥ 2	0	1 (0.8)	0	11 (8.1)	0	252 (42.4)
SJC28, n (%)						
0	316 (90.0)	124 (99.2)	44 (73.3)	58 (42.6)	2 (12.5)	128 (21.5)
1	35 (10.0)	0	16 (26.7)	27 (19.9)	14 (87.5)	115 (19.4)
≥ 2	0	1 (0.8)	0	51 (37.5)	0	351 (59.1)
TJC44, n (%)						
0	342 (97.4)	118 (94.4)	48 (80)	99 (72.8)	4 (25)	192 (32.3)
1	8 (2.3)	3 (2.4)	12 (20)	19 (14.0)	12 (75)	114 (19.2)
≥ 2	1 (0.3)	4 (3.2)	0	18 (13.2)	0	288 (48.5)
SJC44, n (%)						
0	316 (90.0)	116 (92.8)	48 (73.3)	52 (38.3)	2 (12.5)	110 (18.5)
1	27 (7.7)	6 (4.8)	11 (18.3)	24 (17.6)	10 (62.5)	96 (16.2)
≥ 2	8 (2.3)	3 (2.4)	1 (1.7)	60 (44.1)	4 (25.0)	388 (65.3)
CRP, mg/dl	0.1 (0.1)	0.1 (0.2)	0.2 (0.3)	0.1 (0.4)	0.2 (0.3)	0.8 (1.4)
ESR, mm/h	14.9 (9.0)	14.5 (7.3)	53.4 (54.0)	8.9 (5.1)	31.1 (12.2)	39.7 (29.1)
MMP-3, mg/dl	75 (39)	86 (68)	66 (35)	102 (67)	72 (38)	138 (273)
PGA, mm	3.4 (3.0)	16.9 (4.5)	3.8 (3.1)	31.4 (21.9)	5.3 (3.3)	36.7 (24.1)
Pain VAS, mm	4.1 (6.1)	15.2 (8.8)	5.0 (5.4)	29.9 (22.5)	6.9 (5.3)	35.7 (24.5)
PhGA, mm	1.5 (3.1)	0.8 (1.8)	2.9 (3.4)	9.6 (12.3)	17.3 (22.3)	18.6 (16.3)
HAQ	0.16 (3.4)	0.45 (0.57)	0.30 (0.43)	0.69 (0.72)	0.17 (0.26)	0.99 (0.82)
DAS28	1.8 (0.5)	2.0 (0.5)	2.9 (0.4)	2.2 (0.4)	3.1 (0.2)	3.8 (0.92)

DAS28: 28-joint count Disease Activity Score; SDAI: Simplified Disease Activity score; CDAI: Clinical Disease Activity score; TJC: tender joint count; SJC: swollen joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloprotease-3; PGA: patient global assessment; PhGA: physician global assessment.

A

B

□ PGA (62%)

□ SJC (1%)

⊟ TJC (1%)

▨ CRP (1%)

⊟ PGA, CRP (14%)

◩ PGA, SJC (12%)

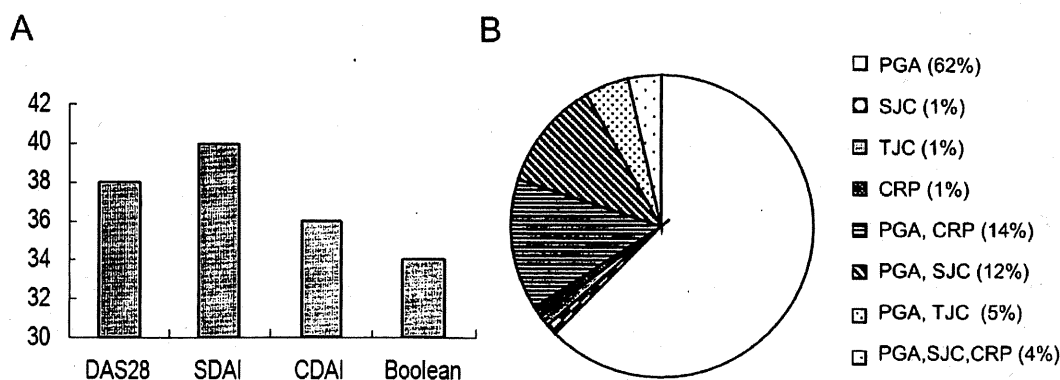⊡ PGA, TJC (5%)

□ PGA,SJC,CRP (4%)

Figure 1. A. Number of patients classified as "in remission" in the 28-joint count but as "nonremission" when 44 joints were assessed. This number was smallest under a Boolean definition, but the difference was modest. B. Variables preventing patients with ≤ 1 involved joint in the 28-joint count but > 1 in the 44-joint count from being misclassified as "in remission." Almost all reasons (97%) included patient global assessment (PGA). DAS28: 28-joint Disease Activity Score; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; SJC: swollen joint counts; TJC: tender joint counts; CRP: C-reactive protein.

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which can lead patients not only into remission but into a deep remission. While the prevalence of clinical remission in patients with RA after 6 months of treatment with anti-tumor necrosis factor (TNF) agents was previously reported to be 27% in DAS28 and 6% under Boolean definitions[12], we noted that patients received various biologic agents in our study, i.e., 65% were receiving anti-TNF, 26% tocilizumab, and 9% abatacept.

Some patients were classified into the remission category based on only DAS28 or Boolean criteria. Reflecting the marked difference in the formulas between the DAS28 and SDAI, CDAI, and Boolean definitions, patients who were classified into remission based only on DAS28 showed relatively low ESR but higher values for PGA and SJC than those classified into remission based on the other definitions, while those classified as being in nonremission based only on DAS28 showed relatively high ESR. Moreover, while Studenic, et al reported that pain is the most important determinant in the PGA whereas it is mostly joint swelling in the PhGA[13], in our study the mean PhGA of patients classified into remission based only on Boolean definitions was found to be greater than the mean PGA, and interestingly, this phenomenon was noted only in that particular group. The relatively low number of patients in this group, however, hampered our investigation, and future studies should therefore assess this matter in greater detail.

Several limitations to our study warrant mention. First, we assessed remission status cross-sectionally at 1 timepoint. It is known that there are patients with predominant foot involvement who could be underestimated in the 28-joint count, as reported by Bakker, et al[14], and because the aim of sustained remission is to achieve little or no radiographic and functional deterioration, we need to also examine structural and functional outcomes under 44-joint counts longitudinally. Second, all data used in this study were obtained from a single hospital in Japan. While we are confident that our patients are representative of those in other clinics nationally, because our hospital is one of the biggest rheumatology centers in Japan, the high rate of use of biologic agents might hinder generalizations about the results.

In daily clinical practice, roughly half of patients with RA can be deemed to be in a state of clinical remission based on DAS28, SDAI, and CDAI values, while one-third can be so classified under a Boolean-based definition. Patients deemed to be in remission based on a 28-joint count may show pain and swelling in the feet, but misclassification was relatively rare in our study and was observed in only 2.4% of patients under a Boolean definition. The 28-joint count seems to be sufficient for assessing remission using the ACR/EULAR remission criteria.

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RHEUMATOLOGY

Concise report

The power Doppler ultrasonography score from 24 synovial sites or 6 simplified synovial sites, including the metacarpophalangeal joints, reflects the clinical disease activity and level of serum biomarkers in patients with rheumatoid arthritis

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Abstract

Objective. We evaluated the significance of the power Doppler ultrasonography (PDUS) score by comparing it with serum biomarkers and clinical disease activity.

Methods. We measured the PDUS scores of 24 synovial sites in 12 joints in 22 RA patients. For convenience, the PDUS scores of six synovial sites in six joints were also examined. Each joint was scored for a power Doppler (PD) signal on a scale from 0 to 3. The PDUS scores are the sums of the PD signal scores for the 24 synovial sites or the 6 synovial sites. On the same day, serum variables as well as clinical disease activity were evaluated.

Results. The PDUS scores from the 24 joint sites were significantly positively correlated with DAS of 28 joints (DAS-28), simplified disease activity index (SDAI), clinical disease activity index (CDAI) and serum biomarkers including MMP-3, VEGF and tissue inhibitor of metalloproteinases-1 (TIMP-1). Accordingly, the PDUS scores from the six synovial sites greatly correlated with those from the 24 joint sites. Clinical disease activities as well as serum variables were also clearly correlated with the PDUS scores from the six synovial sites.

Conclusion. The standard as well as the simplified PDUS scores well reflected clinical disease activity and serum variables, including angiogenic factors. Our data reaffirm the utility of ultrasonography for monitoring disease activity in patients with RA.

Key words: Ultrasonography, Power Doppler, Rheumatoid arthritis, Vascular endothelial growth factor.

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Introduction

The greater resolution of superficial musculoskeletal structures offered with the use of high-frequency transducers, along with the high sensitivity of current colour Doppler and power Doppler (PD) US, have led to increasing use of US in rheumatic diseases [1]. Naredo *et al.* [2] reported 12-joint simplified PD ultrasonographic assessment as the original US scoring system. Recently, Kurosaka *et al.* [3] examined a relatively large number of patients and found a correlation of PD signal intensity with

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