Classification criteria of early rheumatoid arthritis and validation of its performance in a multi-centre cohort

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Abstract

Objective

To develop classification criteria for early rheumatoid arthritis (ERA) based on a large cohort of early inflammatory arthritis patients and to evaluate the performance of these criteria.

Methods

The study population comprised a cohort of early inflammatory arthritis patients with symptom duration less than one year. Classification criteria of ERA were developed by incorporating the most sensitive or specific variables. Performance of the ERA criteria, 1987 ACR and 2010 ACR/EULAR criteria were evaluated.

Results

A total of 803 patients were enrolled in this study. By the end of the one year follow-up, 514 patients were diagnosed with RA, 251 with other rheumatic diseases, and 38 patients with undifferentiated arthritis. The ERA criteria are as follows: 1) morning stiffness ≥30 minutes; 2) arthritis of 3 or more joint areas; 3) arthritis of hand joints; 4) positive RF; 5) positive anti-CCP antibody. Rheumatoid arthritis is defined by the presence of 3 or more of the criteria. The sensitivity (84.4%) of the ERA classification criteria was much higher than the 1987 ACR criteria (58.0%). In a validation cohort of early inflammatory arthritis patients, the area under the ROC curves (AUC) showed a better performance for the ERA criteria (0.906, 95%CI 0.866 to 0.945) than the 1987 ACR criteria (0.786, 95%CI 0.725 to 0.848) and the 2010 ACR/EULAR criteria (0.745, 95%CI 0.677 to 0.814).

Conclusion

A set of ERA classification criteria has been developed with good performance for early RA. It is applicable in clinical practice and research.

Key words

arthritis, rheumatoid, early, classification criteria

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Introduction

Early diagnosis and treat-to-target therapeutic strategy are very important in improving the prognosis of rheumatoid arthritis (RA). During the past 20 years, the 1987 ACR classification criteria for RA has been used worldwide and played an important role in the diagnosis of RA. However, the criteria were developed using patients with longstanding established RA (1) and were not sensitive in diagnosing early disease (2). In order to identify early RA (ERA) patients who would benefit promptly from disease-modifying anti-rheumatic drugs (DMARDs) therapy, the 2010 ACR/EULAR classification criteria for RA were developed (3). However, these criteria were not tested to evaluate its sensitivity and specificity when published (4).

In the last few years, the performance of these criteria and the former 1987 ACR criteria was investigated by several studies. It was suggested that the 2010 ACR/EULAR criteria was only "slight improvement" of performance in overall, compared with the 1987 ACR criteria (5-10). Other studies have shown that lower specificity and over-diagnosis of the 2010ACR/EULAR criteria were noticed when used in newly onset of inflammatory arthritis (5, 10, 12, 13). Moreover, the 2010 ACR/EULAR classification criteria were developed to serve as classifying RA for clinical research but not for diagnosis in daily practice (10-14). Classification criteria is to ensure that homogeneous groups of patients with comparable features are enrolled in scientific research, while diagnostic criteria are used in diagnosis of the deasease. In general, the scoring system of a set of classification criteria is not feasible to use in clinics.

In order to develop criteria which are easily to use in practice for diagnosis of early RA, a prospective multi-centre study was undertaken in a large cohort of patients with early inflammatory arthritis. All data were analysed by experienced rheumatologists and statisticians, and the variables with high sensitivity and specificity in diagnosing RA were identified. The ERA classification criteria were developed and compared with the 1987 ACR criteria and the 2010 ACR/EULAR criteria.

Material and methods

Subject identification

A cohort of patients with early inflammatory arthritis were recruited from twelve large teaching hospitals nationwide in China from June 2009 to Dec 2010. Participants were consecutively enrolled in the study if the following features were present: (1) patients with newly onset of apparent joint swelling at one or more joints without any treatment; (2) more than 16 years old of age; (3) less than 1 year of symptom duration. The patients were diagnosed by experienced rheumatologists based on the clinical and laboratory features. Clinical follow-up was carried out at 3, 6, 9 and 12 months. The data of patients with missing values at baseline and those remaining as undifferentiated arthritis by one year follow-up were excluded from the data analysis. As internationally recognised in other studies, the clinical diagnosis of RA made by experienced rheumatologists regardless to specific criteria was used as gold standard (1, 15).

All patients gave their informed consent before inclusion in the study. The study protocol was approved by the People's Hospital Medical Ethics Committee, Beijing University.

Data collection

The clinical features of arthritis at baseline were collected, including duration of arthritis at first visit, involved joint areas, symmetric arthritis, arthritis of large joints, arthritis of hand joints, morning stiffness, and rheumatoid nodules. Rheumatoid factor (RF), anticyclic citrullinated peptide (CCP) antibody, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured at baseline. Radiographs of hands were performed and interpreted by two radiologists. Characteristic radiographic changes of RA included radiographic joint erosions or unequivocal bony decalcification localised in or most marked adjacent to the involved joints (1).

Statistical analysis

Two different statistical methods were used to develop classification criteria. In the first method, all the clinical and

laboratory variables were analysed by calculating the sensitivity, specificity and accuracy to identify the potential contributions to the new criteria. Those variables most sensitive and specific to the classification of RA were selected and enrolled into sets of classification criteria. Several sets of classification criteria were developed. The sensitivities and specificities of different sets of classification criteria were evaluated. The criteria with best performance were proposed as the final classification criteria. In this model, all individual criteria had the same weights. The resulting rule of the classification was in the form "for a given subject, if X out of Y items are present, the subject can be classified as RA" (1, 15). In the second method, the variables most sensitive and specific for diagnosing RA recorded at baseline were entered into a logistic regression model in which the dependent variable was the final diagnosis by rheumatologists. Multicollinearity of the variables was detected before entering into the logistic regression. In the analysis, a backward variable selection procedure was performed, with a significance level of 0.10 to remove the non-significant variables. A version of diagnostic model was constructed for clinical use by substituting the ORs with weighted scores. Score 1 was for ORs between 0.5 and 1.5, score 2 for ORs between 1.5 and 2.5, and score 3 for ORs between 2.5 and 3.5, score 4 for ORs more than 3.5.

Data analysis was performed with the standard software packages, SPSS17.0. For normally distributed data, the results were expressed as means ± SD; differences in means were assessed using Student's *t*-test. Proportions were compared using a χ^2 test. The sensitivities and specificities of the sets of criteria for the classification of RA were calculated using the clinical diagnosis by experienced rheumatologists as the gold standard. Diagnostic value of criteria was analysed by Receiver Operating Characteristic (ROC) curve. The area under the ROC curve (AUC) provides a measure of the overall discriminative ability of the criteria. The ROC area and its 95% confidence intervals were estimated using the non-parametric approach. *P*-values less than 0.05 were considered statistically significant.

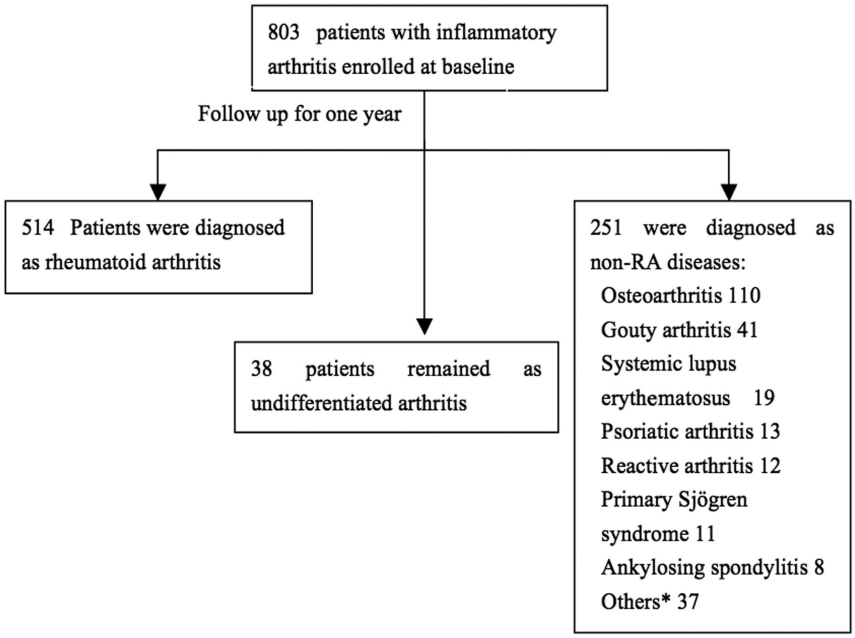

Fig. 1. 803 subjects were included in this study. The clinical diagnoses of subjects at the last visit are shown in the square. *others included mixed connective tissue diseases, adult-onset Still's disease, undifferentiated spondylitis, systemic sclerosis, crystal-induced arthritis, polymyositis, dermatomyositis, and enteropathic arthritis.

Comparison of the performance of the ERA criteria, 1987 ACR criteria and 2010ACR/ EULAR criteria

To compare the performance of the ERA criteria, 1987 ACR criteria, and 2010 ACR/EULAR criteria, we obtained detailed data from a validating cohort of 197 consecutive subjects with early inflammatory arthritis at Peking University Third Hospital. The sensitivities and specificities of the ERA criteria, 1987 ACR and 2010 ACR/ EULAR criteria were determined, and the areas under the curve (AUC) were assessed.

Results

Characteristics and diagnoses of the recruited patients

Eight hundred and three patients with inflammatory arthritis enrolled at baseline were followed up until a definite diagnosis was made by experienced rheumatologists. By the end of the one-year follow-up, 514 RA, 251 other

Table I. Demographic characteristics of rheumatoid arthritis (RA) and control subjects with non-RA rheumatic diseases.

Groups	Diseases	Cases	Male/Female	Age (year, $\bar{x}$ ± SD)	Symptom duration (weeks, $\bar{x}$ ± SD)
RA	Rheumatoid arthritis	514	147/367	47.9 ± 14.2	22.7 ± 15.7
Non-RA	Total	251	109/142	49.1 ± 16.2	20.5 ± 17.6
	Osteoarthritis	110	30/80	54.4 ± 11.7	25.0 ± 18.3
	Gout	41	39/2	48.9 ± 15.4	11.4 ± 11.1
	Systemic lupus erythematosus	19	4/15	32.0 ± 14.1	20.5 ± 18.5
	Psriatic arthritis	13	9/4	44.5 ± 8.8	21.7 ± 15.6
	Reactive arthritis	12	5/7	39.9 ± 19.8	9.7 ± 13.4
	Sjögrens' syndrome	11	0/11	55.0 ± 15.8	29.3 ± 22.5
	Ankylosing spondylitis	8	7/1	32.4 ± 14.6	27.9 ± 17.9
	Others*	37	15/22	48.4 ± 20.6	15.8 ± 15.3

*Others included mixed connective tissue diseases, adult-onset Still's disease, serum negative spondylitis, systemic sclerosis, crystal-induced arthritis, polymyositis, dermatomyositis, and enteropathic arthritis.

rheumatic diseases were diagnosed and 38 patients remained as undifferentiated arthritis. The 251 non-RA patients turned out to be osteoarthritis, gouty arthritis, systemic lupus erythematosus, psoriatic arthritis, reactive arthritis, primary sjogren's syndrome, ankylosing spondylitis, and some other rheumatic diseases (Fig. 1). The Table I presented the demographic characteristics of the RA patients and controls.

The sensitivities and specificities of the criteria items

Table II listed the variables at baseline. The variables with high sensitivities in diagnosing RA included symmetric arthritis and arthritis of hand joints (swelling of wrist, MCP or PIP) , which were all higher than 90%, and followed by arthritis of 3 or more joint areas, positive RF, and positive anti-CCP antibody. Typical radiological changes of joint, positive anti-CCP antibody, and morning stiffness lasting at least 30 minutes had high specificities (Table III). Shoulder, elbow or MTP swelling, and the subcutaneous nodules were specific, but not sensitive.

Performance of the classification criteria in early RA patients

To select a better classification criteria set, several putative criteria were proposed using sensitive and/or specific variables (Table IV), and named as RA-4, RA-5, RA-6, and RA-7 criteria according to the number of enrolled variables. The performance value of these criteria and the 1987 ACR criteria were analysed. The sensitivities of the RA-4, 5, 6 and RA-7 criteria were 69.1%, 84.4%, 95.3% and 85.0%, respectively. The specificities of them were 92.4%, 87.4%, 63.3% and 84.9%, respectively. The sensitivity and specificity of the 1987 ACR criteria were 58.0% and 93.6%. It was shown that the sensitivity of the 1987 ACR criteria was relatively low, while the RA-5, RA-6 and RA-7 criteria improved the sensitivity significantly in the early RA patients. In the patients with symptom duration less than 6 weeks, the sensitivities of the RA-4, 5, 6 and RA-7 criteria were 60.0%, 80.0%, 95.7% and 80.0%, respectively. The specificities of them were 90.0%, 87.1%, 71.4% and 87.1%, respectively. The set of RA-5 criteria had the best overall performance with fewer criteria items. It was recommended as new classification criteria of ERA (Table IV).

Table II. Comparison of the sensitivity, specificity, and accuracy of potential criteria for RA.

Criterion	Sensitivity(%)	Specificity(%)	Accuracy (%)
Historical information			
Duration of symptoms ≥6 weeks	73.9	37.5	55.7
Morning stiffness ≥60 minutes	51.2	89.2	70.2
Morning stiffness ≥30 minutes	65.8	81.7	73.8
Swelling joints			
Temporomandibular joint	1.60	100	50.8
Sternoclavicular joint	0.4	100	50.2
Shoulders	8.6	98.4	53.5
Elbows	16.9	97.6	57.3
Wrists	66.0	80.5	73.3
Metacarpophalangeal joints (MCP)	59.3	74.5	66.9
Proximal interphalangeal joints (PIP)	73.5	64.5	69.0
Distal interphalangeal joints (DIP)	2.5	96.4	49.5
Hips	1.0	100	50.5
Knees	35.8	83.7	59.8
Ankles	27.6	88.8	58.2
Metatarsophalangeal joints (MTP)	16	90	53.0
Arthritis of 2 or more joint areas (total of 14 areas)*	94.4	46.2	49.3
Arthritis of 3 or more joint areas (total of 14 areas)*	74.9	76.5	75.7
At least 1 area swollen in a wrist, MCP or PIP joint	94.0	44.6	69.3
At least 1 area swollen in a wrist or PIP joint	90.3	43.4	66.9
Large joint involvement	53.1	74.9	64.0
Symmetric arthritis	96.3	30.7	63.5
Subcutaneous nodules	1.9	100	51.0
Radiologic and laboratory findings			
Typical radiographic changes	28.4	88.8	58.6
Bone erosions	7.20	98.4	52.8
Positive RF**	67.7	78.1	72.9
High-positive RF†	49.8	93.2	71.5
Positive anti-CCP antibody**	66.1	98.0	82.1
High-positive anti-CCP antibody†	48.4	98.4	73.4
ESR increased	73.5	54.0	63.8
CRP increased	60.7	68.5	64.6

*The 14 joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
**Positive refers to IU values that are more than the upper limit of normal for the laboratory and assay.
†High-positive refers to IU values that are 3 times the upper limit of normal for the laboratory and assay.

Construction of classification criteria by logistic regression analysis model

Potential diagnostic determinants were entered in a logistic regression analysis. These included morning stiffness ≥30 minutes, arthritis of 3 or more joint areas, arthritis of hand joints, symmetric arthritis, symptom duration ≥6 weeks, rheumatoid nodules, typical radiological changes, positive RF, and positive anti-CCP antibody obtained at baseline. In all analyses, a backward variable selection procedure was performed, resulting non-significant variable as 0.10. A classification criteria model was constructed for clinical use by substituting the regression coefficient with approximate value (Table V). Total scores ranged from 0 to 10 for each RA patient by calculating values of the variables based on the clinical and immunological features. Sensitivity and specificity of each diagnostic score were evaluated. When the cut point was set at 5, the sensitivity and specificity were 86.4% and 88.4% respectively. In the patients with symptom duration less than 6 weeks, the sensitivity and specificity were 82.9% and 90.0%, respectively.

Comparison of discriminative ability of different criteria in the multi-centre cohort

The discriminative ability of different criteria was evaluated by ROC curves.

Table III. Criteria sets investigated for classification of RA and their performance characteristics.

Criterion	RA-4 criteria	RA-5 criteria	RA-6 Criteria	RA-7 criteria	1987ACR criteria
1 Morning stiffness ≥60 minutes	—	—	—	—	√
2 Morning stiffness ≥30 minutes	—	√	√	√	—
3 Arthritis of 3 or more joint areas (total of 14 areas)*	√	√	√	√	√
4 Arthritis of hand joints: At least 1 area swollen in a wrist, MCP or PIP joint	√	√	√	√	√
5 Symmetric arthritis	—	—	√	√	√
6 Subcutaneous nodules	—	—	—	—	√
7 Positive RF	√	√	√	√	√
8 Typical radiographic changes	—	—	—	√	√
9 Positive anti-CCP antibody	√	√	√	√	—
Criteria required	≥3 of 4	≥3 of 5	≥3 of 6	≥4 of 7	≥4 of 7
Sensitivity (%)	69.1	84.4	95.3	85.0	58.0
Specificity (%)	92.4	87.4	63.3	84.9	93.6
Positive predictive value (%)	94.9	93.1	84.2	92.0	94.9
Negative predictive value (%)	58.6	73.2	86.9	73.5	52.1

*The 14 joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

Table IV. Classification criteria for early rheumatoid arthritis (ERA)*.

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least 30 minutes
2. Polyarthritis	At least 3 joints areas have had swelling. The 14 areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.
3. Arthritis of hand joints	At least 1 area swollen in a wrist, MCP or PIP joint.
4. Positive RF	Positive refers to IU values that are more than the upper limit of normal for the laboratory and assay.
5. Positive anti-CCP antibodies	Positive refers to IU values that are more than the upper limit of normal for the laboratory and assay.

*A patient can be classified as rheumatoid arthritis if he/she has satisfied at least 3 out of these 5 criteria.

Table V. Classification criteria based on logistic regression analysis model.

Variables	Regression coefficient	Approximate score
Positive anti-CCP antibody	4.17	4
Arthritis of ≥3 joint areas (total of 14 areas)*	1.58	2
Morning stiffness ≥30 minutes	1.38	1
Symmetric arthritis	1.28	1
Arthritis of hand joints: At least 1 area swollen in a wrist, MCP or PIP joint	0.97	1
Positive RF	0.68	1

Application of these criteria provides a score of 0–10, with a score of 5 or greater being indicative of the presence of definite RA. The sensitivity of it is 86.4%, and the specificity is 88.4%.
*The 14 joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints.

The AUC of ROC curves of the ERA criteria and the logistic regression model criteria showed good discrimination with values of 0.925 (95%CI 0.907 to 0.944) and 0.944 (95% CI 0.928 to 0.959), respectively. The discriminative ability of the 1987 ACR criteria was significantly lower (ROC AUC 0.834, 95% CI 0.608 to 0.862) than that of the ERA criteria and the logistic regression model criteria.

Validation of the ERA criteria, 1987 ACR criteria and 2010 ACR/EULAR criteria

In a cohort of 197 patients with early inflammatory arthritis, in which 102 patients were RA and 95 were other rheumatic diseases, including osteoarthritis, systemic lupus erythematosus, gouty arthritis, psoriatic arthritis, reactive arthritis, ankylosing spondylitis, and some other rheumatic diseases. Sensitivities of the ERA criteria, 1987 ACR criteria and 2010 ACR/EULAR criteria were 78.4%, 38.2% and 83.3%, respectively. The specificities were 86.3%, 98.9% and 54.7%, respectively. The AUC value of ROC curves of the ERA criteria (0.906, 95% CI 0.866 to 0.945) was better than the 1987 ACR criteria (0.786, 95% CI 0.725 to 0.848) and the 2010 ACR/EULAR criteria (0.745, 95% CI 0.677 to 0.814) (Fig. 2).

Discussion

The American Rheumatism Association (ARA) first began to propose diagnostic criteria for RA in 1956. Since then, the criteria were revised for several times. In 1987, the American College of Rheumatology (ACR) published a revised set of seven classification criteria (1), which has been used in clinical practice and research for more than 20 years. Until 2010, new classification criteria for RA were derived by ACR and EULAR and were applied to individuals with undifferentiated inflammatory arthritis (3). The sensitivity and specificity of these criteria were not evaluated when published (4). Recently, several studies have shown that the 2010 ACR/EULAR criteria classify more RA patients at an earlier phase of the disease, compared with the 1987 ACR criteria, but its specificity is much lower than the 1987 ACR criteria (5-13), and not feasible clinically due to the scoring system. Moreover, over diagnosis by the 2010 ACR/EULAR criteria is becoming an issue that needs to be considered (5, 10, 12, 13). Using the criteria as diagnostic criteria carries risk of overtreatment (16).

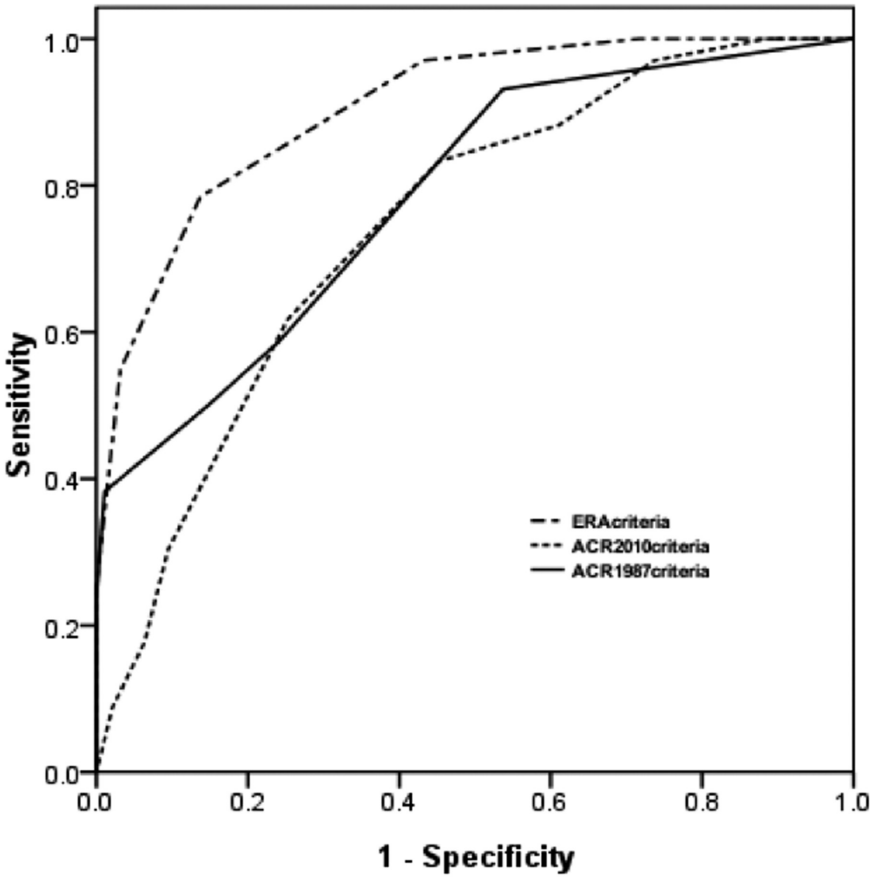

Fig. 2. Receiver operating characteristic (ROC) curves of the ERA criteria, 2010 ACR/EULAR criteria, and 1987 ACR criteria. The curves plot the relationship between the true-positive rate (sensitivity) and the false-positive rate (1-specificity) for different cutoff levels of test positivity. The areas under the curve (AUC) for the ERA criteria, 2010 ACR/EULAR criteria, and 1987 ACR criteria are 0.906 (0.866 to 0.945), 0.745 (0.677 to 0.814), and 0.786 (0.725 to 0.848).

To establish classification criteria which fit the clinical characteristic of early RA patients, this study proposed a series of new criteria by analysing the clinical and laboratory features and radiological changes in a large cohort of early inflammatory arthritis in multicentre. Compared with the 1987 ACR criteria, the main changes of the ERA criteria were as follows: morning stiffness less than 30 minutes instead of 60 minutes, removing rheumatoid nodules and the limitation of symptom duration lasting more than 6 weeks, adding anti-CCP antibody as a new criterion. Unlike the 2010 ACR/EULAR criteria, the inflammatory markers such as ESR or CRP were not included in the ERA criteria based on the results of statistical analysis. This is consistent with clinical findings, since they are also often elevated in many other rheumatic diseases. In addition, symmetric arthritis is not a specific feature of early RA, and typical radiological changes are uncommon in early RA, therefore, these two variables are not introduced into the new ERA criteria.

By comprehensive analysis, ERA criteria were proposed. The sensitivity of the ERA criteria was 84.4%, higher than the 1987 ACR criteria (58.0%), while the specificity was 87.4%, slightly decreased compared with the 1987 ACR criteria (93.6%). The AUC of the ROC curves showed a better performance for the ERA criteria (0.925) than the 1987 ACR criteria (0.834) in the discrimination of patients with and without RA. In addition to the 5 items criteria of the ERA criteria proposed in this study, a set of RA criteria with scoring system was developed using logistic regression analysis method. The diagnosis of definite RA is made by a total score ≥5 (maximum score = 10). Both the logistic regression model criteria and the ERA criteria had similar performance values with ROC AUC values of 0.944 and 0.925, which were both higher than the 1987 classification criteria (0.834). However, like the 2010ACR/EUALR criteria, the scoring system of logistic model criteria is more complicated than the ERA criteria.

The performance value of the ERA criteria was compared with the 1987 ACR criteria and the 2010 ACR/EULAR criteria in this study. The AUC of ROC curves of the ERA criteria was higher than the 1987 ACR criteria and the 2010 ACR/EULAR criteria. These results indicated that the ERA criteria had better performance than the other two criteria. In addition, the performances of the 2010 ACR/EULAR criteria and the 1987 ACR criteria have been evaluated in several studies. Most of the researches showed that the sensitivity of the 2010 ACR/EULAR criteria was higher than the 1987 ACR criteria, yet the specificity decreased dramatically (5-12). The data highlighted that over diagnosis of the 2010ACR/EULAR classification criteria may be an important issue in very early disease. More reliable classification criteria for early RA should be established (17). The proposed ERA criteria in this study showed better performance than the 2010 ACR/EULAR criteria, and more applicable in clinical practice.

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