The Journal of Rheumatology

The Journal of Rheumatology Volume 37, no. 12

Relative Clinical Influence of Clinical, Laboratory, and Radiological Investigations in Early Arthritis on the Diagnosis of Rheumatoid Arthritis. Data from the French Early Arthritis Cohort ESPOIR

LAURE GOSSEC, CHRISTOPHE COMBESCURE, NATHALIE RINCHEVAL, ALAIN SARAUX, BERNARD COMBE and MAXIME DOUGADOS

J Rheumatol 2010;37;2486-2492
http://www.jrheum.org/content/37/12/2486

Relative Clinical Influence of Clinical, Laboratory, and Radiological Investigations in Early Arthritis on the Diagnosis of Rheumatoid Arthritis. Data from the French Early Arthritis Cohort ESPOIR

LAURE GOSSEC, CHRISTOPHE COMBESCURE, NATHALIE RINCHEVAL, ALAIN SARAUX, BERNARD COMBE, and MAXIME DOUGADOS

ABSTRACT. ***Objective***. To evaluate the relative level of influence of usual investigations in early arthritis on the diagnosis of rheumatoid arthritis (RA).

Methods. Patients: those included in the ESPOIR early arthritis cohort, a national cohort of patients with grade ≥ 2 synovitis for > 6 weeks and < 6 months. The diagnostic properties of variables assessed at baseline were measured against the diagnosis of RA defined by American College of Rheumatology criteria (at any timepoint between inclusion and 12-month followup) and expert opinion. Various models, including (1) clinical data; (2) clinical + radiographic data (plain radiographs); (3) addition of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP); and (4) addition of HLA-DR typing, were assessed by comparing areas under the curves for ROC curves.

Results. Of 731 patients studied, 372 (50.9%) satisfied criteria for RA at 1 year. In univariate analysis, sensitivity was highest for distal articular presentation (94.6%), presence of IgM RF (69.4%), pain on metatarso-phalangeal squeeze test (66.1%), and presence of anti-CCP (65.6%); whereas specificity was highest for nodules (100%), HLA typing: shared-epitope double dose (95.9%), radiographic erosions (86.5%), and anti-CCP antibodies (86.4%). The most efficient model included swollen joint count, morning stiffness, erosions, RF, and anti-CCP. Adding rheumatoid nodules, C-reactive protein, or HLA-DR information was not contributive.

Conclusion. In addition to the clinical variables and radiographs, RF and/or anti-CCP are the single variables of interest that are contributive for the diagnosis of RA. (First Release Oct 15 2010; J Rheumatol 2010;37:2486–92; doi:10.3899/jrheum.100267)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DIAGNOSIS CRITERIA HLA
RECEIVER-OPERATING CHARACTERISTIC CURVE

From the Faculty of Medicine, Paris Descartes University, UPRES-EA 4058, APHP, Department of Rheumatology B, Cochin Hospital, Paris, France.

The ESPOIR cohort was supported by an unrestricted grant from Merck Sharp and Dohme. Two additional grants from INSERM supported the biological database. The French Society of Rheumatology, Abbott, Amgen, and Wyeth supported the ESPOIR cohort study.

L. Gossec, MD, PhD, Faculty of Medicine, Paris Descartes University, UPRES-EA 4058, APHP, Department of Rheumatology B, Cochin Hospital; Institut Universitaire de Recherche Clinique, Montpellier I University, Montpellier, France; C. Combescure, MSc, PhD, Institut Universitaire de Recherche Clinique, Montpellier I University, University of Geneva, Geneva, Switzerland; N. Rincheval, MSc, Institut Universitaire de Recherche Clinique, Montpellier I University; A. Saraux, MD, PhD, Department of Rheumatology, University Hospital Cavale-Blanche, Brest, France; B. Combe, MD, PhD, Montpellier I University, Department of Immuno-rheumatology, Lapeyronie University Hospital, Montpellier, France; M. Dougados, MD, Faculty of Medicine, Paris Descartes University, UPRES-EA 4058, APHP, Department of Rheumatology B, Cochin Hospital.

Address correspondence to Dr. L. Gossec, Service de Rhumatologie B, CHU Cochin, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France. E-mail: laure.gossec@cch.aphp.fr

Accepted for publication July 27, 2010.

Rheumatoid arthritis (RA) is a frequent chronic inflammatory disease that can lead to severe morbidity[1]. It has been shown that early initiation of disease-modifying therapy is an important prognostic factor[2,3]. To this end, early diagnosis is important[4]. To date, the most widely validated[5] and most frequently used criteria for the diagnosis of RA are the 1987 American College of Rheumatology (ACR) classification criteria[6], pending further appraisal of the recently presented ACR/EULAR criteria[7].

Many elements can contribute to the diagnosis of RA. These include (1) history and clinical examination, which have no specific cost but are time-consuming; (2) imaging to detect structural damage, such as through widely used standard radiographs; (3) biologic signs of autoimmunity: rheumatoid factor (RF) and anti-cyclic citrullinated protein (anti-CCP); and (4) genetics, such as human leukocyte antigen (HLA) typing. Although studies have confirmed the individual value of each of these elements[8,9,10,11,12,13,14,15], to our knowledge there are few data in early arthritis regard-

ing "diagnostic strategies," i.e., assessing the relative influence on diagnosis of the different diagnostic elements. The only published studies in this regard are the Leiden strategies[16,17,18]. The relative results of different diagnostic elements is an important issue for several reasons; the first is expense: although clinical examination has no specific cost beyond the salary of the rheumatologist but takes time, biological tests such as autoimmunity tests and especially genetic typing, are costly. Radiographs, also costly, are justified not only for diagnosis but also as a predictive factor and for an ulterior comparison during followup[19]. The second reason to assess diagnostic tests is the need for rapid diagnosis in early arthritis[2,3,4]. Performing unnecessary diagnostic tests may lead to delay in diagnosis. Therefore determination of the most efficacious, but also most effective diagnostic strategy in early arthritis is important.

The objective of our study was to determine the relative diagnostic value of clinical, laboratory, and genetic elements for the diagnosis of RA, in early arthritis, using data from the French ESPOIR early arthritis cohort.

MATERIALS AND METHODS

Study design. The ESPOIR cohort (in French, the study and followup of early undifferentiated arthritis) is an ongoing, 10-year followup, multicenter early arthritis cohort[20]. With approval of the Montpellier University ethical committee, 16 university hospital rheumatology departments provided patients, covering a large part of the country. Clinical, laboratory, and imaging data were collected at baseline, then every 6 months for the first 2 years, then once a year. Data analyzed in the present study pertain to baseline and the first year of followup.

Participants. The inclusion criteria were the following: patient provided signed informed consent, was age 18–70 years, had 2 or more swollen joints, with a duration > 6 weeks and < 6 months, used no previous disease-modifying drugs and no steroids, and had no definite diagnosis of a disease other than RA or undifferentiated arthritis[20]. Thus, the ESPOIR cohort consists of both early undifferentiated inflammatory arthritis and recently developed RA.

Definition of outcome. The "gold standard" for the diagnosis of RA was the following: cumulative fulfillment of ACR classification criteria for RA[6], i.e., ≥ 4 elements present out of a possible 7; AND investigator's visual analog scale score (≥ 75/100) supporting a diagnosis of RA. The presence of each element of the ACR criteria was assessed cumulatively at baseline and at the 2 subsequent visits at 6 and 12 months of followup[21,22].

Data collection. At baseline, an exhaustive data collection was performed according to recommendations in early arthritis[23], including the following elements: (1) Demographic variables: age, sex, ethnicity, symptom duration. (2) Clinical history: mode of onset (constant vs intermittent), duration of morning stiffness, extraarticular symptoms. (3) Clinical examination: number and localization of painful and swollen joints (out of 28), with joints of the hands, wrists, and feet classified as distal articular presentation, induced pain by metatarso-phalangeal squeeze test, presence of nodules. (4) Radiographs: hand and wrist anteroposterior radiographs and feet anteroposterior and oblique views were taken at baseline and analyzed in each center by the investigator, in accord with usual practice. Patients' radiographs were analyzed as: specific erosions (on hands and/or feet radiographs), yes/no. (5) Biology: acute-phase reactants, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP: positive cutoff 10 mg/l); IgM and IgA RF (ELISA, Marini, Paris, France; positive cutoff 9 IU/ml); anti-CCP2 antibodies (ELISA, DiaSorin, Antony, France; positive cutoff 50 U/ml). (6) HLA-DR typing: HLA-DRB1* genotypes were determined in each center, and analyzed as HLA-DRB1*01, and/or *04: presence of single dose or double dose of these alleles[15].

Statistical analysis. Descriptive analysis: percentages were given for qualitative variables and mean and standard deviation for quantitative variables. Comparisons between patients with and without diagnosis of RA (as defined above) were performed using chi-square, Fisher's exact test, or Student t test as appropriate.

Univariate analysis of diagnostic elements: all the diagnostic elements were put in binary form (using common clinical cutoffs or median value). For each element, the sensitivity, specificity, and accuracy were assessed with an exact 95% confidence interval (Clopper-Pearson method[24]).

Combination of diagnostic elements: 7 predetermined models were considered, combining different elements. Each model corresponded to a strategy. The first model included only clinical elements. In the second model, the radiographs were added. The third, fourth, and fifth models included not only the clinical signs and radiographs but also various biological variables (respectively, ESR and CRP, then adding RF or anti-CCP). The sixth model included all items from the fourth and fifth models, i.e., CRP, RF, and anti-CCP. The seventh and last model was the most complete, including HLA typing. For each model, the corresponding elements were introduced in a logistic regression model to predict the diagnosis of RA only if the p value in univariate analysis was < 0.20. A descending stepwise process was applied to keep only the relevant variables. The goodness-of-fit was checked using the Hosmer-Lemeshow statistic.

Evaluation of the diagnostic abilities of the 7 models: For each model and for each patient, a diagnostic score equal to the sum of the regression coefficients present in the patient at baseline was assessed. The global diagnostic ability of these scores was assessed by nonparametric receiver-operating characteristic (ROC) curves. The areas under the curve (AUC) and 95% confidence intervals were calculated[25]. AUC were compared using the nonparametric method of Delong, *et al*[26] for paired data. The optimal cutoff was determined minimizing the number of misclassified patients[27]. For indicative purposes, sensitivity and specificity were assessed at these cutoffs.

For the model considered as optimal, points for a simplified prediction rule were derived from the regression coefficient and the validity of the simplified rule was assessed by comparing AUC of ROC curves.

In all the analyses, results were considered significant if $p < 0.05$. Analysis was performed using SAS version 9.1 and S-Plus version 8.

RESULTS

Patients' characteristics. In all, 813 patients were included in the ESPOIR cohort. For the purpose of this study, the 731 patients who had complete data regarding the ACR diagnostic criteria for RA[6] after 1 year were analyzed.

Patients' characteristics are shown in Table 1. Mean (± SD) age at inclusion was 48 ± 12 years, 77% were female, 92% were Caucasian; mean synovitis duration at baseline was 149 ± 183 days. Symptom onset was rapid in 51%, insidious in 41%, and by flares in 8%. The mean swollen joint count was 7.2 ± 5.3 at inclusion.

Univariate analysis of the diagnostic elements. After 1 year, 372 patients (50.9%) fulfilled the definition of RA. Patients' baseline characteristics and the sensitivity and specificity of variables of interest to predict the diagnosis of RA are summarized in Tables 1 and 2. In univariate analysis, sensitivity was highest for distal articular presentation (94.6%), presence of IgM RF (69.4%), pain on metatarso-phalangeal squeeze test (66.1%), presence of anti-CCP (65.6%), and morning stiffness > 30 minutes (65.6%); whereas specifici-

Table 1. Characteristics of 731 patients with early arthritis according to final diagnosis. For HLA-DR typing and radiographs, percentages were calculated on available data. Unless otherwise noted, results are presented as N (%).

Characteristic	All Patients, n = 731	Diagnosis of RA, n = 372	No Diagnosis of RA, n = 359	p*
Sex, n (%) female	562 (76.9)	281 (75.5)	281 (78.2)	0.38
Age, yrs, mean (SD)	48.4 (12.2)	49.2 (11.7)	47.6 (12.7)	0.072
Symptom duration, days, mean (SD)	218 (258)	224 (266)	213 (250)	0.25
Synovitis duration, days, mean (SD)	149 (183)	157 (197)	141 (168)	0.23
Synovitis duration > median (112 days)	364 (49.8)	195 (52.4)	169 (47.0)	0.14
Clinical features				
Morning stiffness ≥ 30 mn	424 (58)	244 (65.6)	180 (50.1)	< 0.0001
Pain on MTP squeeze test	428 (58.6)	246 (66.1)	182 (50.7)	< 0.0001
Painful joint count (of 28), mean (SD)	8.5 (7.0)	9.4 (7.3)	7.4 (6.5)	< 0.0001
Painful joint count ≥ 6 (median)	358 (49)	208 (55.9)	150 (41.8)	0.0001
Swollen joint count (of 28), mean (SD)	7.2 (5.3)	8.6 (5.5)	5.8 (4.8)	< 0.0001
Swollen joint count ≥ 6 (median)	325 (44.5)	207 (55.6)	118 (32.9)	< 0.0001
Rheumatoid nodules	9 (1.2)	9 (2.4)	0	0.003
Distal articular presentation	656 (89.7)	352 (94.6)	304 (84.7)	< 0.0001
Constant (not intermittent) presentation	509 (69.6)	245 (65.9)	264 (73.5)	0.024
Symmetric presentation	431 (59.0)	236 (63.4)	195 (54.3)	< 0.0001
Biology				
ESR, mm/h, mean (SD)	29.3 (24.8)	32.4 (25.4)	26.2 (23.7)	0.0008
ESR > 28 mm/h	276 (38.1)	164 (44.3)	112 (31.6)	0.0004
CRP, mg/l, mean (SD)	20.5 (33.3)	24.6 (34.8)	16.3 (31.1)	0.0007
CRP > 10 mg/l	334 (45.6)	196 (52.7)	138 (38.4)	< 0.0001
Presence of IgM RF	342 (46.8)	258 (69.4)	84 (23.4)	< 0.0001
Presence of anti-CCP	293 (40.0)	244 (65.6)	49 (13.6)	< 0.0001
HLA-DR 1, 4 double-dose†	61 (8.9)	47 (13.7)	14 (4.1)	< 0.0001
Radiographs				
Radiographic erosions (yes)	149 (22.8)	106 (31.8)	43 (13.5)	< 0.0001

* p Value comparing patients with versus those without diagnosis of RA in univariate analysis by t test or Fisher's exact test, as appropriate. † HLA-DR 1, 4 double-dose: DR 1/1 or 1/4 or 4/4. MTP: metatarso-phalangeal; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; CCP: cyclic citrullinated protein.

Table 2. Diagnostic ability for the diagnosis of RA of some variables collected at baseline, presented by decreasing sensitivity.

Variable	Sensitivity Estimate (95% CI)	Specificity Estimate (95% CI)
Distal articular presentation	94.6 (91.8–96.7)	15.3 (11.8–19.5)
Presence of IgM RF	69.4 (64.4–74.0)	76.6 (71.9–80.9)
Pain on MTP squeeze test	66.1 (61.1–70.9)	49.3 (44.0–54.6)
Morning stiffness ≥ 30 min	65.6 (60.5–70.4)	49.9 (44.6–55.2)
Presence of anti-CCP	65.6 (60.5–70.4)	86.4 (82.4–89.7)
Symmetric presentation	63.4 (58.3–68.3)	45.7 (40.4–51.0)
Painful joint count ≥ 6	55.9 (50.7–61.0)	58.2 (52.9–63.4)
Swollen joint count ≥ 6	55.6 (50.4–60.8)	67.1 (62.0–72.0)
CRP > 10 mg/l	52.7 (47.5–57.9)	61.6 (56.3–66.6)
ESR > 28 mm	44.3 (39.2–49.5)	68.4 (63.2–73.2)
Radiographic erosions	31.8 (26.9–37.1)	86.5 (82.3–90.1)
HLA-DR 1, 4 double-dose	13.7 (10.2–17.8)	95.9 (93.1–97.7)
Nodules	2.4 (1.1–4.6)	100.0 (99.0–100.0)

For abbreviations see Table 1.

ty was highest for nodules (100%), HLA typing: shared-epitope double dose (95.9%), radiographic erosions (86.5%), and anti-CCP antibodies (86.4%).

Evaluation of diagnostic strategies. The variables composing the 7 models of increasing complexity (from clinical data only to clinical + radiographic + immunology + HLA typing data) are shown in Table 3, with the corresponding AUC of ROC curves, and the sensitivity, specificity and accuracy at the optimal cutoffs. Figure 1 shows the AUC increased slightly (but significantly, p = 0.01) from model 1 to model 2, but not from model 2 to model 3 (p = 0.51). Thus, radiographs appeared to be of diagnostic value whereas acute-phase reactants were not. An important gap was observed between models 3 and 4 (where RF was added): the AUC increased from 0.70 to 0.81 (p < 0.01), and acute-phase reactants disappeared from the model since they did not bring additional information in the multivariate model. Diagnostic properties of models including RF, anti-CCP, or RF + anti-CCP were globally similar (Table 3). The information brought by the HLA-DR typing was not contributive to the diagnosis, on top of the other tests, since the AUC of model 7 was not different from that of model 6 (p = 0.53).

Sensitivity was low for the clinical model, model 1 (51.3%, Table 3). It increased when radiographs were added (model 2: 60.4%), and by adding RF (from model 3 to model 4, 63.1% to 81.4%, respectively). Sensitivity was highest for model 4 comprising RF, and decreased when

Table 3. Diagnostic properties of different models to predict RA according to baseline variables entered in the model.

Model	Variables Retained in the Model	Sensitivity at Cutoff* (95% CI)	Specificity at Cutoff* (95% CI)	Accuracy, %	AUC of ROC curve (95% CI)
1: clinical variables	SJC, distal articular presentation, morning stiffness, MTP pain	51.3 (46.1–56.5)	74.1 (69.2–78.6)	62.5	0.67 (0.63–0.71)
2: clinical + radiographs	SJC, distal articular presentation, morning stiffness, MTP pain, and erosions	60.4 (54.9–65.7)	71.8 (66.5–76.7)	66.0	0.70 (0.66–0.74)
3: model 2 + ESR and CRP	SJC, distal articular presentation, morning stiffness, erosions, and CRP	63.1 (57.6–68.3)	67.7 (62.3–72.8)	65.3	0.70 (0.66–0.74)
4: model 3 + IgM RF	SJC, morning stiffness, erosions, CRP, and RF	81.4 (76.8–85.4)	67.4 (62.0–72.5)	74.5	0.81 (0.78–0.84)
5: model 3 + anti-CCP	SJC, morning stiffness, erosions, and anti-CCP	68.5 (63.2–73.4)	84.0 (79.5–87.9)	76.1	0.83 (0.80–0.86)
6: model 3 + RF and anti-CPP	SJC, morning stiffness, erosions, RF, and anti-CCP	73.6 (68.5–78.2)	81.5 (76.8–85.6)	77.5	0.84 (0.81–0.87)
7: model 6 + HLA-DR typing	SJC, morning stiffness, erosions, RF, anti-CCP, and HLA typing	70.2 (64.8–75.2)	87.5 (83.2–91.0)	78.6	0.84 (0.81–0.87)

SJC: swollen joint count. For abbreviations see Table 1. * Assessed at the cutoff minimizing the number of misclassified patients (number of false-positive + number of false-negative).

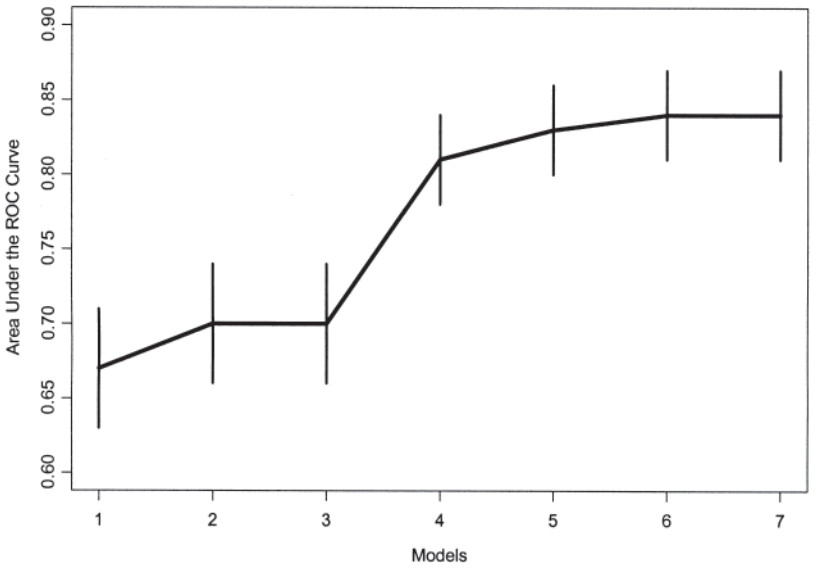

Figure 1. Areas under the ROC curves representing the diagnostic properties of the various models, with confidence intervals (see Table 3 for details on the models).

substituting anti-CCP for RF (model 5: 68.5%); the more complete models 6 and 7 did not reach the level of sensitivity of model 4 (73.6% and 70.2%, respectively). Specificity varied in the opposite way: it decreased slightly between the clinical model and the model with RF (models 1 to 4: 74.1% to 67.4%, respectively). It was higher for models 5, 6, and 7, which include anti-CCP (84.0%, 81.5%, and 87.5%).

Optimal model to predict RA. The model that may be considered optimal to predict RA was model 6, which includes clinical and radiographic data, as well as a combination of RF and anti-CCP (Table 4). A simplified score was derived from the regression coefficients, and Table 5 shows the observed percentage of patients who experienced progression in relation to the calculated prediction score. The simplified prediction model had good diagnostic properties: the AUC of the ROC curve was 0.84 (95% CI 0.81–0.87), therefore there was no loss of discriminative ability compared to model 6.

DISCUSSION

The comparative diagnostic values of clinical, biological, and radiological elements in early arthritis have been compared. Results indicate that the most effective combination for the diagnosis of early RA is the association of certain elements of anamnesis and clinical examination, with radiographs, RF, and/or anti-CCP. The added diagnostic value of assessing acute-phase reactants and HLA-DR typing was not evident in this study. RF and anti-CCP showed similar diagnostic properties; the addition of the 2 tests added

Table 4. Characteristics of model 6 to predict RA.

	Regression Coefficient	OR	(95% CI)	p	Point*
Swollen joint count ≥ 6	0.98	2.66	(1.80–3.95)	< 0.0001	2
Morning stiffness ≥ 30 min	0.48	1.61	(1.09–2.39)	0.016	1
Radiographic erosions	0.75	2.11	(1.31–3.40)	0.002	2
Presence of IgM RF	0.98	2.66	(1.65–4.30)	< 0.0001	2
Presence of anti-CCP	1.82	6.17	(3.70–10.28)	< 0.0001	4

* Point for the simplified prediction rule derived from the regression coefficient.

Table 5. Total scores and predictive values for the diagnosis of RA at 1 year, by application of the simplified model described in Table 4. Values are the number (% of each line) of patients with a given score.

Total Score	No Progression to RA, n = 359	Progression to RA, n = 372
0	73 (91)	7 (9)
1	67 (84)	13 (16)
2	54 (72)	21 (28)
3	56 (58)	41 (42)
4	14 (54)	12 (46)
5	18 (44)	23 (56)
6	8 (24)	26 (76)
7	7 (12)	51 (88)
8	6 (15)	35 (85)
9	13 (16)	69 (84)
10	1 (7)	13 (93)
11	2 (8)	22 (92)

slightly to the diagnostic properties and may be proposed where possible.

In clinical practice, patients presenting with early arthritis frequently have an undifferentiated disease that may progress to RA, or they may have a more benign disease course. The ACR criteria have been criticized for their low discriminative ability in patients presenting with recent-onset arthritis[5]. The recently presented ACR/EULAR criteria will hopefully have better discrimination in early disease. However, assessment of the value of each diagnostic element in early arthritis to identify patients who will progress to RA is needed, since recommendations strongly suggest that treatment is effective in the early phase of arthritis, before the disease is established[23].

The small number of patients with erosive disease and of patients with nodules in our study influences the diagnostic capacities of these elements; however, our results are in keeping with those from other early RA cohorts[28].

Erosions were searched for only with plain radiographs. Magnetic resonance imaging is a promising tool in this field[29] and has been integrated into a prediction rule[30]. However, erosions seen on plain radiographs remain the gold standard and plain radiographs are the tool usually available in clinical practice. Further, the radiographic analyses could be discussed as the radiographs were analyzed globally (erosions yes/no) for the purposes of this study; thus, no complex scores were used[31]. This is also in keeping with daily practice situations. However, it is subject to potential bias, as the clinician may in fact score "typical erosion" when the diagnosis is evident[11]. Other predictive models have shown the importance of radiographic erosions in diagnosis[16].

The gold standard used here for the diagnosis of RA should be discussed. The association of the ACR criteria assessed cumulatively[22] with expert opinion aims at enhancing the diagnostic properties of the ACR criteria, as these properties are low in the context of early RA[5]. Using the ACR criteria as part of the definition may lead to incorporation bias, which results when the index test (prediction model) forms part of the reference standard, as is the case here since several significant variables are part of the ACR criteria. This may cause overestimation of the discriminative ability of the model[32]. To partly solve this problem, it was decided to associate expert opinion to the ACR criteria, although incorporation bias still exists in this case. Anti-CCP antibodies in our study have a rather low specificity (86%); however, this is in keeping with other studies where, for example, specificities of 88%[30], 89%[17], and 92%[33] have been reported. Longer followup of the ESPOIR cohort is under way and will allow confirmation of the diagnoses.

This study has major strengths. The ESPOIR cohort is a national cohort of early arthritis[20]. Because of its entry criteria (more than 2 swollen joints for 6 weeks to 6 months), which are close to clinical practice, because of its large number of participants, and because of the extensive data collection at each visit, this cohort is well adapted to the objective of our study, with a good representation of patients with early arthritis. An early arthritis cohort such as ESPOIR may be better adapted to assess diagnostic values than an undifferentiated arthritis cohort excluding patients with RA[32] since it corresponds to real-life situations. Further, the statistical analysis based on AUC of ROC curves is an interesting technique to compare the diagnostic properties of different strategies and may be used even when correlation between the items exists, as is the case here[34]. However, patients were treated during followup as deemed appropriate by their physicians, since ESPOIR is an observational cohort, and this could potentially modify the natural history of the disease, which should be taken into account. On the

other hand, ESPOIR mimics natural conditions closely because of its observational design, which leads to better generalizability of the results.

To our knowledge, 2 other studies have assessed diagnostic capacities of various items in early RA[16,17]. In our study, the importance of the swollen joint count and of morning stiffness for diagnosis has been confirmed, as have radiographs and RF, whereas HLA typing, once again, was not of high diagnostic value[16]. HLA typing may, however, be of interest in individual cases, for example in certain patients with anti-CCP-negative early arthritis. The first Leiden study also found radiographs to be important[16], but this was not evidenced in the second Leiden study[17]. In both of these models, RF and anti-CCP antibodies were both independent predictors, as in the present study.

We have assessed the sequential diagnostic value of various items for the diagnosis of RA using ROC curves. Results indicate the best diagnostic strategy involves clinical variables, radiographs, and RF/anti-CCP. Further followup of the ESPOIR cohort and of other early arthritis cohorts will allow longer-term determination of outcome and prognostic studies in this early arthritis population.

ACKNOWLEDGMENT

We thank S. Martin for the centralized immunology testing, and the ESPOIR steering committee and all the ESPOIR investigators for active patient recruitment.

APPENDIX

List of study collaborators. Investigators of the French Early Arthritis Cohort ESPOIR: F. Berenbaum, Paris-Saint Antoine; M.C. Boissier, Paris-Bobigny; A. Cantagrel, Toulouse; B. Combe, Montpellier; M. Dougados, Paris-Cochin; P. Fardelonne, Amiens; B. Fautrel, P. Bourgeois, Paris-La Pitié; R.M. Flipo, Lille; P. Goupille, Tours; F. Liote, Paris-Lariboisière; X. Le Loet, Rouen; X. Mariette, Paris Bicetre; O. Meyer, Paris Bichat; A. Saraux, Brest; T. Schaeverbeke, Bordeaux; and J. Sibilia, Strasbourg.

REFERENCES

1. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
2. Wiles NJ, Lunt M, Barrett EM, Bukhari M, Silman AJ, Symmons DP, et al. Reduced disability at five years with early treatment of inflammatory polyarthritis: results from a large observational cohort, using propensity models to adjust for disease severity. Arthritis Rheum 2001;44:1033-42.
3. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-51.
4. Finckh A, Liang MH, van Herckenrode CM, de Pablo P. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: A meta-analysis. Arthritis Rheum 2006;55:864-72.
5. Banal F, Dougados M, Combescure C, Gossec L. Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis. Ann Rheum Dis 2009;68:1184-91.
6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
7. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580-8.
8. Symmons DP. Classification criteria for rheumatoid arthritis — time to abandon rheumatoid factor? Rheumatology 2007;46:725-6.
9. Avouac J, Gossec L, Dougados M. Diagnostic and predictive value of anti-CCP (cyclic citrullinated protein) antibodies in rheumatoid arthritis: a systematic literature review. Ann Rheum Dis 2006;65:845-51.
10. Bohndorf K, Schalm J. Diagnostic radiography in rheumatoid arthritis: benefits and limitations. Baillieres Clin Rheumatol 1996;10:399-407.
11. Devauchelle-Pensec V, Saraux A, Alapetite S, Colin D, Le Goff P. Diagnostic value of radiographs of the hands and feet in early rheumatoid arthritis. Joint Bone Spine 2002;69:434-41.
12. Rantapää-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48:2741-9.
13. Gossec L, Dougados M, Goupille P, Cantagrel A, Sibilia J, Meyer O, et al. Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. Ann Rheum Dis 2004;63:675-80.
14. Gossec L, Baro-Riba J, Bozonnat MC, Daurès JP, Sany J, Eliaou JF, et al. Influence of sex on disease severity in patients with rheumatoid arthritis. J Rheumatol 2005;32:1448-51.
15. Taneja V, Behrens M, Basal E, Sparks J, Griffiths MM, Luthra H, et al. Delineating the role of the HLA-DR4 "shared epitope" in susceptibility versus resistance to develop arthritis. J Immunol 2008;181:2869-77.
16. Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002;46:357-65.
17. van der Helm-van Mil AH, le Cesie S, van Dongen H, Breedveld FC, Toes RE, Huizinga TW. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum 2007;56:433-40.
18. van der Helm-van Mil AH, Detert J, le Cessie S, Filer A, Bastian H, Burmester GR, et al. Validation of a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: moving toward individualized treatment decision-making. Arthritis Rheum 2008;58:2241-7.
19. Gossec L, Fautrel B, Pham T, Combe B, Flipo RM, Goupille P, et al. Structural evaluation in the management of patients with rheumatoid arthritis: development of recommendations for clinical practice based on published evidence and expert opinion. Joint Bone Spine 2005;72:229-34.
20. Combe B, Benessiano J, Berenbaum F, Cantagrel A, Daurès JP, Dougados M, et al. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007;74:440-5.
21. Saraux A, Berthelot JM, Chalès G, Le Henaff C, Thorel JB, Hoang S, et al. Ability of the American College of Rheumatology 1987 criteria to predict rheumatoid arthritis in patients with early arthritis and classification of these patients two years later. Arthritis Rheum 2001;44:2485-91.
22. Wiles N, Symmons DP, Harrison B, Barrett E, Barrett JH, Scott DG, et al. Estimating the incidence of rheumatoid arthritis: trying

to hit a moving target? Arthritis Rheum 1999;42:1339-46.
23. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2007;66:34-45.
24. Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26:404-13.
25. Hanley JA, MacNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
26. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 1988;44:837-45.
27. Zhou X-H, Obuchowski NA, McClish DK. Statistical methods in diagnostic medicine. New York: John Wiley & Sons, Inc.; 2002.
28. Aletaha D, Huizinga TW. The use of data from early arthritis clinics for clinical research. Best Pract Res Clin Rheumatol 2009; 23:117-23.
29. Døhn UM, Ejbjerg BJ, Hasselquist M, Narvestad E, Møller J, Thomsen HS, et al. Detection of bone erosions in rheumatoid arthritis wrist joints with magnetic resonance imaging, computed tomography and radiography. Arthritis Res Ther 2008;10:R25.
30. Tamai M, Kawakami A, Uetani M, Takao S, Arima K, Iwamoto N, et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. Arthritis Rheum 2009;61:772-8.
31. van der Heijde DM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol 1996;10:435-53.
32. Visser H, Hazes JM. The diagnosis and prognosis of early arthritis: comment on the editorial by Scott. Arthritis Rheum 2003;48:856-7.
33. Kuriya B, Cheng CK, Chen HM, Bykerk VP. Validation of a prediction rule for development of rheumatoid arthritis in patients with early undifferentiated arthritis. Ann Rheum Dis 2009; 68:1482-5.
34. Charpin C, Balandraud N, Guis S, Roudier C, Toussirot E, Rak J, et al. HLA-DRB1*0404 is strongly associated with high titers of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis. Clin Exp Rheumatol 2008;26:627-31.