

Prognostic Factors for Joint Destruction in Rheumatoid Arthritis: A Prospective Longitudinal Study of 318 Patients

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ABSTRACT. Objective. To quantify articular damage and to investigate prognostic factors for joint damage progression in rheumatoid arthritis (RA).

Methods. RA patients satisfying the 1987 American College of Rheumatology criteria and with disease duration under 5 years were sampled from the EURIDISS longitudinal cohort study in Norway, The Netherlands, and France. Hand radiographs were assessed at baseline and at 2 to 3 year followup using Sharp score modified by van der Heijde. Assessment of erosion and joint space narrowing, performed in sequential order by a single reader blinded to patients' characteristics, had high intraobserver reproducibility (intraclass correlation coefficient 0.98–0.99). Baseline prognostic factors were analyzed in a multivariate linear regression model.

Results. A total of 318 patients with RA aged 52.4 years (70.4% were female) and with a mean 2 years' disease duration at baseline were followed over 30 months. Median (quartiles) baseline and followup modified Sharp scores were 3 (0–11) and 9 (1–27), respectively, with 35.8% and then 22.3% of patients with no radiological damage. Controlling for age, sex, and country, the final joint damage was predicted by baseline modified Sharp score, rheumatoid factor positivity, time from disease diagnosis, patient global health assessment, and erythrocyte sedimentation rate, and by followup duration, explaining 76.8% of the outcome variance.

Conclusion. This multinational study confirmed the prognostic role in RA of a set of features previously identified in smaller cohorts. It indicates which disease characteristics should be focused on in the early years of RA to identify patients at higher risk of developing severe disease and who are candidates for aggressive therapy. (J Rheumatol 2003;30:2585–9)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
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Appropriate individual therapy in patients with early rheumatoid arthritis (RA) requires a better understanding of the factors that will predict severe deterioration. While many studies have investigated the prognostic influence of features on final outcome in RA^{1–3}, there is no consensus about the best predictors of outcome during the early stage of the disease. Difficulties arise because many studies are

retrospective, with heterogeneous patient groups, disease durations, and outcome variables. In several longitudinal observational studies, the outcomes of interest have been heterogeneous as well.

There are fewer studies of prognostic features of articular damage in RA^{1,3,4,5}. Many authors agree that a large proportion of eroded joints become damaged in the first years of RA^{6,7}. An erosive disease developing early and progressing rapidly is usually considered to have a bad prognosis⁵. Articular damage following persistent synovitis is irreversible and will lead to functional disability over time. A large-cohort prospective study is required to determine the prognostic value and respective contribution of several factors for future structural damage outcomes. New therapies with potential to control radiographic progression^{8,9} combined with increased knowledge of prognostic factors can improve early management of RA by tailoring individual treatment according to such prognostic markers. Our objective was to quantify articular damage progression over time in a prospective cohort study of patients with RA, using the modified Sharp scoring method on hand radiographs¹⁰, and to investigate prognostic factors for this articular damage.

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MATERIALS AND METHODS

Patients. Patients were sampled from defined regions in 3 European countries as part of the EURIDISS (European Research on Incapacitating Diseases and Social Support) study. The EURIDISS investigation is a multicenter, longitudinal cohort study¹¹ focusing on the relationships between clinical, biological, therapeutic, and social characteristics and the development of impairment in RA. The sampling procedure and sample characteristics are described in detail¹². Briefly, the inclusion criteria were as follows: residency in the study area, age 20–70 years, diagnosis of RA according to the 1987 American College of Rheumatology criteria, and disease duration ≤ 4 years at entry into the cohort study started in 1991. Exclusion criteria were presence of another severe incapacitating disease, stage IV in the Steinbrocker functional classification, or possibility of potential loss to followup by moving residence from the study area.

A total of 516 patients in France (n = 51), Norway (n = 205), and The Netherlands (n=260) included in the EURIDISS study had hand radiographs at the time of inclusion. Patients underwent annual standard clinical examination. Hand radiographs were obtained at the 2-year followup visit in Norway and at 3-year followup in France and The Netherlands in a total of 318 patients. Among the 516 patients, those without a radiograph at followup (n = 198) did not show any statistically significant difference from the 318 patients regarding age, sex, or clinical and baseline radiographic characteristics, except for a lower proportion of extraarticular manifestations and slightly worse overall evaluation of health (Table 1). Among the 318 patients there were no baseline differences by followup duration or country.

Assessment measures. At onset and at the yearly followup visits, clinical, biological, and therapeutic data were recorded by a rheumatologist or a rheumatology research nurse. These data included age, sex, disease dura-

tion since diagnosis and since first symptoms, Ritchie index¹³, presence of subcutaneous nodules, and any other extraarticular manifestations (mucocutaneous, hematological, neurological, renal, other), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF; IgM-RF was measured at one center for all samples with an ELISA technique and World Health Organization international standard reference RF preparations¹²), Steinbrocker functional class, Health Assessment Questionnaire (HAQ), patient's overall estimation of health on 100 mm visual analog scale, and investigator's overall estimation of health by the Karnofsky performance status index.

Outcome measures. All patients had posteroanterior radiographs for both hands on the same film at onset and at followup. Patients were excluded when radiographs were not technically correct due, for example, to inaccurate joint positioning or incorrect film exposure.

The Sharp method modified by van der Heijde (modified Sharp) was used to score hand radiographs. This scoring method is sensitive to detect radiologic changes in RA^{10,14}, and our collaborative group has a member with broad experience of its use^{6,15}. The validity of its use for hand radiographs has only recently been documented; it was found to have high intra/interobserver reliability^{16,17}.

Erosion was scored for articular areas in both hands: 5 metacarpophalangeal (MCP) joints, 5 proximal interphalangeal (PIP) joints, first metacarpal base, multangular, lunate, ulna, radius, and navicular. Erosions were given a score of 1 if there was a discrete interruption of the cortical surface. If there was a greater defect, a score was assigned according to the amount of surface area involved. The maximum erosion score in a joint of the hand was 5.

Joint space narrowing (JSN) was scored for 15 articular joints in both hands (5 MCP joints; the 2nd, 3rd, 4th and 5th PIP joints, 3rd, 4th and 5th

Table 1. Patients' characteristics at baseline and followup (n = 318).

	Netherlands, Baseline, n = 132	Norway, Baseline, n = 170	France, Baseline, n = 16	All Countries, Baseline, n = 318	Baseline Characteristics of Patients Lost to Followup, n = 198	All Countries at Followup, n = 318
Age, yrs	53.4 (12.2)	51.2 (12.6)	57.8 (10.3)	52.4 (12.4)	53.8 (12.4)	—
Female, %	65.9	74.7	62.5	70.4	67.1	—
Time from first symptoms, yrs						
Mean (SD)	4.6 (4.7)	2.8 (1.5)	5.0 (2.6)	3.6 (3.4)	4.2 (4.1)	—
Median [quartiles]	3.3 [1.9–4.8]	2.7 [1.6–3.9]	4.5 [3.4–5.0]	3.0 [1.8–4.3]	3.3 [1.9–4.7]	—
Time from disease diagnosis, yrs						
Mean (SD)	2.1 (1.2)	1.8 (1.2)	3.6 (1.1)	2.0 (1.2)	2.1 (1.3)	—
Median [quartiles]	2.1 [1.0–3.2]	1.6 [0.8–2.8]	4.0 [2.5–4.4]	2.0 [0.9–3.1]	2.2 [1.0–3.1]	—
Subcutaneous nodes, %	13.6	12.9	18.8	13.5	14.3	24.2
Extraarticular manifestations, %	12.1	19.4	37.5	17.3	8.6*	27.8
Steinbrocker classification						
I, %	8.4	8.3	6.3	8.2	10.1	8.8
II, %	77.1	75.7	68.7	75.9	69.0	76.5
III, %	14.5	16	25	15.8	20.8	14.7
HAQ, 0–3						
Mean (SD)	1.10 (0.78)	0.88 (0.61)	1.28 (0.58)	0.99 (0.69)	1.09 (0.77)	0.97 (0.69)
Median [quartiles]	1.12 [0.50–1.62]	0.87 [0.37–1.25]	1.37 [0.87–1.62]	1.00 [0.37–1.50]	1.00 [0.50–1.62]	1.00 [0.37–1.50]
Karnofsky index, 0–100	74.2 (12.5)	77.2 (10.0)	74.0 (12.5)	75.8 (11.3)	74.3 (12.5)	77.3 (11.1)
Ritchie index, 0–72	11.2 (10.3)	9.2 (5.8)	13.8 (8.5)	10.3 (8.2)	11.0 (9.7)	9.3 (8.3)
OEH, 0–100	60.6 (21.3)	42.8 (24.6)	43.3 (18.6)	50.8 (24.5)	55.8* (21.1)	57.2 (21.5)
ESR, mm/h	27.9 (22.8)	25.1 (19.1)	16.7 (13.3)	25.9 (20.6)	29.5 (23.4)	21.9 (17.7)
Rheumatoid factor positive, %	79.4	75.5	75.0	77.2	23.9	—
Modified Sharp score						
Mean (SD)	8.9 (18.5)	9.8 (17.4)	12.7 (15.1)	9.6 (17.7)	8.3 (14.2)	20.0 (30.7)
Median [quartiles]	3 [0–10]	2 [0–11]	6.5 [3.5–17.5]	3 [0–11]	2.5 [0–11]	9 [1–27]
Erosive RA**, %	66.7	60.0	87.5	64.2	59.1	77.7

* p < 0.05 vs baseline characteristics of patients followed up. ** Modified Sharp erosion score over 0. OEH: Patient's overall evaluation of health.

carpometacarpal joints; the multangular-navicular joint, the capitate-navicular-lunate joint; and the radiocarpal joint). Four grades of JSN were recognized: 1 = focal or doubtful; 2 = general, \leq 50% of the original joint space; 3 = general, $>$ 50% of the original joint space, or subluxation; 4 = ankylosis. The maximum combined score is 280.

After a training period in the rheumatology department in Groningen, reading of all hand radiographs was performed by a single reader (NG). The investigator performed hand radiographs in each center (Groningen, Nancy, Oslo), blinded to clinical characteristics, but aware of the baseline radiograph when reading followup radiographs, as recommended¹⁸.

Intrareader reproducibility was assessed by twice reading 10 radiographs, 3 weeks apart. In each center, interreader reproducibility was assessed with a second local reader on 10 radiographs. Reading of both erosions and JSN showed high intrareader [intraclass correlation coefficients (ICC) 0.98 and 0.96, respectively] and interreader reproducibility (ICC ranging from 0.94 to 0.86). A second training session was performed in the training center, during the study, to maintain quality of reading.

Data analysis. Patients' characteristics and outcomes are described using mean and standard error or percentages where appropriate. Group comparisons of continuous variables and categorical variables were conducted by nonparametric Kruskal-Wallis and Fisher exact tests, respectively, and association of baseline quantitative measures with modified Sharp score at followup was assessed by Spearman correlation coefficient. The distribution of the modified Sharp score at each measurement time was skewed. A boxcox transformation prevented departure from normality. The transformed outcome variable was then analyzed using a linear regression model. Candidate variables for multivariate analysis were age, sex, country, duration of followup, and baseline variables reaching the 0.10 alpha level of significance in univariate analysis. The final model was checked for stability using stepwise forward and backward procedures. All analyses were performed using SAS software with alpha level = 0.05 for significance.

RESULTS

Patient characteristics at baseline and at followup are presented in Table 1. A total of 318 patients (70.4% were women) aged 52.4 years, with a mean (SD) of 2 (1.2) years' disease duration at baseline, were followed over an average 30 months. Baseline and followup median (quartiles) modified Sharp scores were 3 (0–11) and 9 (1–27), respectively, with 35.9% and then 22.3% of patients, respectively, with no radiological damage.

Table 2 describes the prognosis univariate analysis. There was a significant univariate relationship of a higher modified Sharp followup score with a longer duration of followup ($r = 0.18$), a higher modified Sharp score at baseline (0.82), a

Table 2. Association of baseline variables with radiographic damage (modified Sharp score) at followup (univariate nonparametric analysis).

Baseline Variables	Spearman r	CI 95%
Age	0.14	0.03; 0.25
Time from first symptoms	0.15	0.05; 0.26*
Time from disease diagnosis	0.22	0.12; 0.32
ESR	0.32	0.23; 0.42*
Karnofsky index	-0.27	-0.37; -0.17*
Patient overall evaluation of health (OEH)	0.05	-0.06; 0.16
Ritchie index	0.05	-0.05; 0.16
Modified Sharp score	0.84	0.80; 0.88*

* $p < 0.0001$.

higher ESR (0.30), a higher HAQ score (0.21), and a poor physician global assessment by Karnofsky index (0.24). RF seropositivity was not related with modified Sharp score at followup in univariate nonparametric analysis.

In multivariate analysis, forward and backward stepwise selection from the candidate independent variables yielded a similar stable final model (Table 3). A higher modified Sharp score at followup was predicted by a higher baseline modified Sharp score, shorter time from disease diagnosis, RF positivity, higher ESR, worse patient overall estimation of health, and longer duration of followup. According to the final model R^2 , these variables explained 76.8% of the variance of the outcome variable.

DISCUSSION

This investigation, following 318 patients, is one of the largest cohort studies of prognostic factors for radiographic damage in RA. Our results reveal good performance of a combination of characteristics in the first years of disease, i.e., baseline radiographic score, time from disease diagnosis, RF positivity, ESR, patient's overall estimation of health, and duration of followup, to predict future radiographic score at an average 30 months, including variables in accord with previous investigations in early RA^{19,20}.

The quality of the outcome measurement was ensured by the validity of the modified Sharp method documented to be sensitive to detect changes over time¹⁰. This was restricted to hand radiographs in this study. Foot radiographs were not considered in our study, since the modified Sharp method was published after our study design was established. However, members of our collaborative research group were trained to use this method^{6,15,19}, and the reader in charge was found to have a high intraobserver reproducibility, which provides optimal ability to detect changes¹⁷. Moreover, the high interobserver reproducibility in each center supports the reliability of the scoring method and generalizability of the results. These properties reinforce the prognosis accuracy of the identified variables.

Hand radiograph readings were conducted according to OMERACT recommendations¹⁸: all patients had both hands on one radiograph film, in posteroanterior views; both erosions and joint space narrowing, accepted as the most specific features in RA, were scored; radiographs were read in sequential order; and reproducibility was assessed using adequate statistics and served as a quality control. Although it has been proposed that 2 readers would be optimal to reduce random error without introducing extra expense, our strategy involved a single trained reader. But particular attention was focused on training by (1) using trained professional readers, (2) a pre-session of training in common, and (3) per-study quality control against deviance. Increasingly, comparative studies of different scoring methods emphasize that training of readers is essential to provide reliable results¹⁶.

Table 3. Factors associated with higher radiographic damage at followup (by modified Sharp score). Candidate variables not included in the final model: age, symptom duration, sex, extraarticular manifestation, treatment, Karnofsky index, RF, country, HAQ.

Independent Variable	Regression Coefficient*	p	Partial R ²
Baseline			
Modified Sharp score	1.0	< 0.0001	0.698
Time from disease diagnosis	-0.14	0.034	0.004
ESR	0.02	< 0.0001	0.034
RF positive	4.92	0.048	0.003
Patient's OEH	0.01	0.002	0.02
Followup duration	0.57	0.001	0.007
Total R ²			0.768

* Linear regression model with boxcox transformation of modified Sharp scores. OEH: patient's overall evaluation of health

The representativeness of this European sample has been reported¹². Briefly, sampling representativeness was ensured on a geographical basis, conforming to local public and/or private practices and referral systems in each county and country in order to comprehensively cover each health care system. Among the incident and prevalent cases identified in each catchment area in each country, the characteristics of patients included in the cohort did not differ from those not included. In this cohort, we studied a subsample of 318 patients with RA with 2 years' mean disease duration at entry among 516 patients with baseline radiographs available. Those without followup hand radiographs did not differ by age, sex, clinical characteristics, or baseline radiograph scores, thus ruling out a selection bias based on clinical severity of disease during followup.

For this population, the multivariate linear regression model revealed that time from disease diagnosis, RF positivity, ESR, patient's overall evaluation of health at baseline, radiographic articular damage at baseline, and duration of followup were prognostic factors, i.e., were associated with the level of joint destruction after an average 2.5 years of disease progression. The negative adjusted regression coefficient of the time from disease diagnosis in the multivariate model can be interpreted as follows: the longer the time from onset at a given radiographic damage at baseline, the less the radiographic damage after a given duration of followup. This illustrates a decrease in the progression of radiographic damage over time, which differs from recent findings²¹. The baseline radiographic score is strongly associated with score at followup, which is responsible for a high part of the variance explained in the multivariate model. Thus, additional variables add lower contribution to the model. At onset, disease activity expressed by ESR has already proved to be a poor prognostic factor^{15,19,22-26}, as is CRP^{15,16,25,27,28}. Many studies show that RF positivity is commonly a poor prognostic factor^{17,24,27-30}. Other prognostic factors were inconsistent in some studies, such as older age^{23,25}, tender joint count²⁶, grip strength^{22,26}, cumulative joint inflammation³⁰, HLA-Dw4¹⁹, early radiological damage^{22,23,30}, nodes, disease duration²⁷, and low hemo-

globin²⁹. The heterogeneity of samples and the different methodologies explained discrepant results across previous studies. Several studies involved early RA, with disease development for less than 2 years²⁸. Since our study covers RA of less than 5 years at inclusion, it allows extension of the predictive value of these factors, i.e., disease activity, RF positivity, and baseline joint damage, to a longer time frame after disease diagnosis. The treatment regimen in this observational cohort has been documented³¹. They did not enter the final multivariate models for predicting final joint damage, possibly because their effect might be too heterogeneous or too weak compared to other determinants. This might change in the future with new therapies.

Among identified determinants, disease activity assessed by ESR adds moderate contribution to the model, while baseline joint damage contributes for the major part to the outcome. The new therapies might be active modifiers over these 2 prognostic factors, thus changing the disease profile in the future.

Other studies have proposed consideration of genetic markers as prognostic factors³². However there is a debate about the added value of genetic predictors over and above that for RF, since RF likely has a higher or similar level of prediction, with a lower cost³³.

Our study confirms the prognostic role of a set of features (RF positivity, ESR, patient's overall evaluation of health at baseline, radiographic articular damage at baseline, shorter time from disease diagnosis, and duration of followup) identified in smaller cohorts. It indicates which disease characteristics should be focused on in the early years of disease to determine which patients are at higher risk of developing a severe disease. These results are also of practical interest for identifying patients with RA who may be candidates for new aggressive therapies, thus needing early referral and early treatment. The multinational structure of the study and the control of the method indicate that the results can be generalized to other settings and patient cohorts.

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