The presence of rheumatoid nodules at early rheumatoid arthritis diagnosis is a sign of extra-articular disease and predicts radiographic progression of joint destruction over five years

Britt-Marie Nyhäll-Wåhlin[1], Carl Turesson[2], Lennart TH Jacobsson[2], Jan-Åke Nilsson[2], Kristina Forslind[3], Kristina Albertsson[4], Johan Rönnelid[5], Ingemar F Petersson[6] for the BARFOT study group.

[1]Department of Rheumatology, Falun Hospital, Falun, Sweden

[2]Department Clinical Sciences, Section of Rheumatology, Malmö, Lund University, Sweden

[3]Department of Rheumatology, Helsingborgs lasarett, Helsingborg and Department of Rheumatology, University of Lund, Lund, Sweden

[4]Department of Rheumatology, Karolinska University Hospital, Stockholm, Sweden

[5]Department of Clinical Immunology and Transfusion Medicine, Uppsala University Hospital, Uppsala, Sweden

[6]Departments of Rheumatology and Orthopedics, Lund University Hospital, Lund, Sweden

britt-marie.nyhall-wahlin@ltdalarna.se, Turesson.Carl@mayo.edu, lennart.jacobsson@med.lu.se, jan-ake.nilsson@med.lu.se, kforslind@hotmail.com, kristina.albertsson@karolinska.se, johan.ronnelid@klinimm.uu.se, ingemar.petersson@med.lu.se

Short running title: RA nodules and radiographic progression

Corresponding author:

Britt-Marie Nyhäll-Wåhlin, MD

Department of Rheumatology

Falun Hospital

SE-791 82 Falun, Sweden

britt-marie.nyhall-wahlin@ltdalarna.se

Abstract

Objective: Radiographic damage is an important outcome in rheumatoid arthritis (RA). The disease course varies considerably, and there is a need for simple and reliable prognostic markers. The aim of the study was to determine the utility of early signs of extra-articular disease, manifested as rheumatoid nodules (RN), in predicting radiographic outcome.

Methods: In a cohort (n=1589) of consecutive, newly diagnosed patients with RA, 112 cases with RN at inclusion (7%) were identified. Each case was compared to two age and sex matched controls without nodules from the same cohort. Radiographs of the hands and feet were performed at inclusion, after one, two and five years and scored according to the modified Sharp van der Heijde method (SHS; range 0-448).

Results: Fifty-two cases with RN and 139 controls without RN had available radiographs at baseline and after five years. Cases were more often rheumatoid factor (RF) positive and anti-cyclic citrullinated peptide (anti-CCP) positive, and had higher disease activity and radiographic damage scores at baseline (7.9 vs 2.5). After five years, there was more extensive radiographic damage among the cases (mean SHS progression 21.7 vs 13.5). In bivariate analysis positive RF, positive anti-CCP, SHS, and RN were strong baseline predictors for radiographic progression up to 5 years. In multivariate analysis, positive anti-CCP and SHS at baseline were independently associated with radiographic progression.

Conclusion: The presence of RN at baseline is a marker of extra-articular involvement and severe disease, and a predictor of subsequent joint damage.

Introduction

Rheumatoid arthritis (RA), affecting 0,5–1% of the adult population [1], is characterized by inflammation of the joints, with progressive erosions and cartilage destruction. Damage seen on X-rays is largely irreversible and represents a cumulative process. It has been shown that radiographic progression is associated with loss of physical function [2-5].

Recent studies suggest that overall outcomes in patients with RA have improved considerably over time [6]. However, the disease course varies between patients, and there is a need for reliable predictors of radiographic progression to select patients for early aggressive treatment. In a meta-analysis of the long-term effect of early disease-modifying antirheumatic drug (DMARD) therapy Finckh et al [7] showed the importance of early DMARD initiation for improving disease outcome. At the same time, it is important to avoid overtreatment of patients with a good prognosis [8].

The development of rheumatoid nodules (RN) is the most common inflammatory extra-articular manifestation (ExRA) in RA [9]. Early presence of RN has been suggested to be a predictor of severe ExRA [10]. Different ExRA, including RN, often coexist in patients with severe RA [11]. In long-term follow-up, 30–40% of all patients with RA developed nodules at any time in well-defined samples [12-14]. RN are found predominantly in rheumatoid factor (RF) positive patients [15], but often appear later in the disease. Studies have demonstrated a 2–4-fold increased mortality in patients with ExRA, including RN [10, 13, 16].

In a cross-sectional study of patients with established RA, the presence of RN was associated with greater radiographic damage [17], whereas no such association was found in a longitudinal analysis of a smaller sample [18]. Several studies have shown that radiological outcome can be predicted by the presence of RF [19, 20] and antibodies against cyclic citrullinated peptides (anti-CCP) [21-23] at the time of diagnosis of early RA, and the level of anti-CCP seems to be of importance [24]. In an inception cohort of patients with newly presenting inflammatory poly-arthritis [19], inflammatory activity [joint counts and C-reactive protein (CRP)] and immune pathology (RF and RN) predicted the severity of erosions early in the disease. In several studies an association between initial inflammation [erythrocyte sedimentation rate (ESR), CRP, joint counts] and radiological outcome has been reported [25, 26]. In multiple regression analyses anti-CCP and RF have been better predictors for radiological progression than measures of inflammation [27]. In addition, recent studies suggest that early loss of hand bone mineral density is associated with progression of joint damage on conventional radiographs [28].

Smoking is the best established environmental risk factor for the development of RA [29, 30]. Some studies suggest that smoking also influences RA severity [31, 32], but data are conflicting [33]. Previous studies have found that smokers are more likely to develop RN [32, 34].

The aim of this study was to determine the ability for clinically used baseline variables, to predict subsequent radiographic damage, particularly, the predictive role of early signs of ExRA, manifested as early RN.

Methods

Study population

The patients were recruited from the BARFOT (Better Anti-Rheumatic FarmacO Therapy)-register [35], which is a Swedish multicentre observational study of patients with early RA (disease duration ≤ 12 months), satisfying the 1987 American College of Rheumatology classification criteria [36].

The register includes adults (age ≥ 18 years) who are registered by a rheumatologist in the catchment area, which covers a population of approximately 1.5 million. At inclusion a detailed history was obtained using a structured questionnaire including smoking history (smoker, ex-smoker, never smoked). Joints were examined for the presence of soft tissue swelling and/or tenderness and the presence of rheumatoid nodules was recorded. The patients completed the Swedish validated version of the Health Assessment Questionnaire (HAQ) [37] which is scored from 0–3 and the Disease Activity Score (DAS28) [38] was calculated. ESR and RF were measured at the local laboratory.

The patients were examined regularly at each visit; at baseline, after 3, 6, 12, 24 and 60 months. Pharmacologic treatments [glucocorticosteroids (GC) and DMARDs] have been reported at each visit.

During the period September 1992 to October 2001, 1598 patients, the vast majority of European Caucasoid origin, were consecutively included in the BARFOT study. All patients gave their informed consent to participate in the study. The study was

approved by the research ethics committees for the participating centra, and was carried out according to the Helsinki Declaration.

Study design

In this nested case-control investigation all patients with RN at inclusion (as a sign of extra articular disease manifestation) in the register were identified (n=112; 7%). Two controls without RN at inclusion were selected from the same cohort. The controls (n=224) were matched to the cases by gender, age at inclusion, duration of symptoms at inclusion and when possible by geographic region.

Anti-CCP analysis

Sera for analyses of anti-CCP were available in 279 of these patients and 57 missing (Table 1). CCP antibodies were measured with ELISA (Eurodiagnostica, Malmö, Sweden; second generation test). Patients who had an anti-CCP titer ≥ 25 U/mL were considered to be anti-CCP positive.

Radiographic evaluation

Radiographs of both hands and feet (posterior-anterior views) were performed at the first visit (inclusion/baseline) and after one, two and five years. Radiographic damage was scored in chronological order according to the modified Sharp van der Heijde method (SHS) [39-41] by two trained readers (KF and KA) who were blinded to the clinical information. The total SHS score, which includes the hands and the feet, can range from 0 to 448 with the maximum score for erosions (ES) 280 and the maximum score for joint space narrowing (JSN) 168.

A total of 191 patients (52 cases with RN and 139 controls without RN) had available radiographs at both baseline and after five years. Radiographic progression at 5 years was defined as the SHS score at 5 years minus the baseline SHS score.

Statistical analyses

Bivariate analysis of the association between the outcome variable (radiographic progression at 5 years) and baseline study variables (age, female sex, RA duration, DAS28, HAQ score, ESR, RF, anti-CCP, SHS, RN, history of ever smoking, and current smoking at baseline; Table 4) thought to influence the outcome was performed. Multivariate analysis was carried out and covariates (RF, anti-CCP, SHS, RN) were chosen with respect to results of the bivariate analysis and clinical assumptions. These analyses were performed using a multiple linear regression model. The risk for development of radiological damage is expressed as unstandardised regression coefficient (β est), 95% confidence interval (CI), and a level of significance (p value).

To analyse the differences in radiologic joint damage between RN-cases and controls the changes from baseline (follow up after 5 years minus baseline measurement) were compared by independent t test and presented as mean difference in change between the groups (95% CI). In addition, the medians and interquartile ranges (IORs) are presented for baseline and for progression over 5 years.

Results

A total of 336 patients, 112 cases with RN at inclusion in the BARFOT-register and 224 controls without RN at inclusion were available for evaluation. One hundred and

ninety-one patients, 52 cases and 139 controls, had available radiographs at baseline and also after five years. The demographics and disease characteristics are shown in Table 1. The cases over all had higher disease activity compared with the controls. The cases were more often RF positive and anti-CCP positive and had significantly higher anti-CCP levels (Table 1). Also, they were more often current smokers (47% vs 33%) or former smokers (44% vs 35%). The cases had higher radiographic damage scores (Table 2). The 191 patients with available radiographs at 5 years and the original study cohort of 336 patients were comparable at baseline, except for gender. We found a lower proportion of women among those with available radiographs at 5 years (39% vs 48% in the original cohort). However, this difference did not reach statistical significance.

A majority of the patients started with DMARDs at the first visit (88% of the cases, 81% of the controls) and continued with active treatment during the follow up visits (Table 3). There was no sex difference concerning treatment. The most frequently used DMARD was Methotrexate (MTX) among both cases and controls. About half of the patients started with GC at the first visit (48% of the cases, 42% of the controls), but the use of GC decreased during the follow-up (at five years 21% of the cases and controls were on treatment with GC). The doses of MTX were between 7.5 mg and 20.0 mg weekly. The GC doses varied from 2.5 mg to 10.0 mg daily. Treatment with biologics (almost exclusively tumour necrosis factor inhibitors) was not available until the three final years of the study period and only one patient received biologic treatment at the first visit (Table 3).

In the analyses restricted to patients with available radiographs at baseline and after five years, there was more extensive radiographic damage among the RN cases [mean SHS 7.9 vs 2.5 at baseline and 29.6 vs 16.0 at 5 years (Table 2)]. The pattern was similar for ES and JSN score when analyzed separately (Table 2). Patients with RN had a higher mean SHS compared with the controls at baseline as well as after 1, 2 and 5 years (Figure 1).

In the bivariate analysis, the following parameters were strong baseline predictors for radiographic progression at 5 years: positive RF, positive anti-CCP, SHS and RN (Table 4). As demonstrated in Figure 2 and Table 2, among the 191 patients with available radiographs at baseline and after 5 years, the RN patients had more extensive radiographic progression; mean SHS progression 21.7 (95% CI 14.9 – 28.5) vs 13.5 (95% CI 10.0-17.0). In multivariate analysis, positive anti-CCP at baseline (β est 11.6: 95% CI 4.5-18.6) and SHS at baseline (β est 0.7: 95% CI 0.2-1.2) were independently associated with greater radiographic progression at 5 years (Table 5).

Discussion

In this study we describe an inception cohort of patients with newly diagnosed RA and predictors of increasing radiographic damage focusing on early extra-articular features in the form of RN. The presence of RN at baseline was associated with greater radiographic progression up to 5 years, but its impact was less than that of positive CCP antibodies and baseline SHS, which were the only independent predictors of progressive joint damage in multivariate analysis. Positive RF and anti-

CCP antibodies were more frequent among patients with RN at baseline compared to controls, suggesting that RN is part of a severe RA phenotype.

Consistent with the literature, radiographic damage occurs early in the disease course [42-44]. In the present study 69% of the RN-patients and 53% of the controls had radiological destructions (SHS) already within 12 months after their first symptoms (baseline X-ray). The radiological damage progressed over time, which is in accordance with others [45, 46], and after five years 83% of the RN-patients and 80% of the controls had developed radiographic damage.

It would be likely that those patients with a more severe disease and also extra-articular manifestations had received more potent anti-rheumatic pharmacological treatment. In this cohort the majority of the patients received conventional RA treatment at the first visit and continued with active treatment with no significant differences between RN-cases and controls. Most patients were included before biologic anti rheumatic treatment was in routine use.

Surprisingly, we found no association with radiographic joint damage and smoking, neither current smoking nor ever smoking (Table 4), despite the fact RN-cases were more often ever smokers compared to the controls, 91% vs 68%. Smoking increases the risk for developing RN [47] and other severe extra-articular manifestation [48], but might not be directly involved in the joint destruction. In agreement with us neither Westhof et al [49] nor Finckh et al [33] found smoking to have an effect on joint damage.

We also did not find any association for markers of inflammation (DAS28 and ESR) or functional disability (HAQ) with radiographic progression. This is in accordance with Machold et al [42], who found that clinical and laboratory criteria (DAS28, ESR, CRP, HAQ) could not predict radiographic outcome in very early RA (symptoms ≤ 3 months) followed for 3 years. On the other hand, some other studies have found an association between disease activity, measured using ESR or the number of swollen joints, and subsequent development of erosions [45].

In the present study we only modelled the influence of baseline variables, which is a limitation. Thus we cannot exclude the possibility that a continuing high level of ESR, DAS28 or HAQ contributed to increasing damage. Anti-CCP status, the only laboratory variable showing an association with SHS at five year in our multiple regression analysis, has however earlier proven to be very stable over time in follow-up during up to five years [50]. Other limitations of the study are the small sample size and that only 57% of the patients had available radiographs both at baseline and after five years.

One strength of this study was the long observational period of 5 years. The BARFOT-cohort is followed continuously according to a structured protocol, which offers the opportunity to study the course of RA radiographically from the early disease onset. If the patients are included late in the disease, they can have developed radiographic damage and are already selected for severe disease. Therefore it is important to identify the study population as close as possible to disease onset, as in the present sample.

The main aim of this study thus was to determine the usefulness of baseline RN as a manifestation of extra-articular disease together with other baseline variables in predicting later radiographic outcome at five years. We showed that RN at early RA diagnosis was associated with radiographic progression of joint destruction over five years, but that this association did not reach significance in multivariate analysis. Furthermore, we confirmed that the presence of erosive disease and CCP antibodies at baseline predicted radiographic progression.

Conclusion

This study showed that the presence of extra-articular manifestation as seen as RN at baseline is a marker of severe disease and a predictor of subsequent joint damage, but anti-CCP antibodies and the initial radiographic score were the only independent predictors of radiographic progression.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Figure 1: Radiographic damage at baseline, after one, two and five years of follow up in RA patients without and with rheumatoid nodules (RN) at baseline

Figure 2: *Progression of radiographic damage at five years in RA patients without and with rheumatoid nodules (RN) at baseline

Table 1
Baseline characteristics for patients with rheumatoid nodules (RN) versus controls without rheumatoid nodules (non-RN)

	All patients at baseline		Patients with available radiographs at baseline and after five years	
	n=336		n=191	
	Cases (RN)	Controls (non-RN)	Cases (RN)	Controls (non-RN)
	n=112	n=224	n=52	n=139
Female (%)	48	48	39	50
Age (years) mean (SD)	56.3 (14.0)	56.5 (14.0)	54.8 (11.9)	54.8 (13.4)
RA duration (months) mean (SD)	6.7 (4.1)	6.1 (3.0)	6.2 (3.3)	6.3 (3.0)
DAS28 mean (SD)	5.45 (1.82)	5.05 (1.28)	5.33 (1.26)	5.03 (1.38)
HAQ score mean (SD)	1.04 (0.67)	0.94 (0.62)	0.95 (0.60)	0.90 (0.62)
ESR mean (SD)	39.4 (22.9)	35.8 (25.5)	37.8 (23.3)	34.0 (24.3)
RF+ (%)	77	60	81	61
Anti-CCP analyses	n= 71	n= 208	n= 36	n= 131
Anti-CCP+ (≥25 U/ml) (%)	78	59	75	57
Anti-CCP level median U/ml IQR	331 36 – 1109	113 0 – 646	270 27 – 977	85 0 – 615
Smoking history	n=100	n=191	n=47	n=124
Current smokers n (%)	51 (51)	66 (35)	22 (47)	41 (33)
Former smokers n (%)	40 (40)	65 (34)	21 (44)	43 (35)
Never smoked n (%)	9 (9)	60 (31)	4 (9)	40 (32)

CCP=cyclic citrullinated peptide; DAS=Disease Activity Score; ESR=erythrocyte sedimentation rate; HAQ=Health Assessment Questionnaire; IQR=interquartile range; RA=rheumatoid arthritis; RF=rheumatoid factor; SD=standard deviation

Table 2
Radiographic scores and progression for RN cases and controls

Radiographic progression defined as mean/median score value at 5-years follow-up minus baseline score value

Patients with available radiographs at baseline and after five years n=191				
	Mean (95% CI)		Median (IQR)	
	Cases (RN) n=52	Controls (non-RN) n=139	Cases (RN) n=52	Controls (non-RN) n=139
SHS baseline	7.9 (3.4 – 12.4)	2.5 (1.8 – 3.2)	3.0 (0-8.1)	1.0 (0-3.0)
SHS 5 years	29.6 (20.4 – 38.7)	16.0 (12.4 – 19.6)	16.5 (3.3-45.3)	9.0 (2.0-21.0)
SHS progression	21.7 (14.9 – 28.5)	13.5 (10.0 – 17.0)	13.0 (2.3-34.8)	7.0 (1.0-15.0)
ES baseline	3.7 (1.8 – 5.7)	1.3 (0.9 – 1.7)	1.0 (0-4.8)	0 (0-1.0)
ES 5 years	12.0 (7.7 – 16.3)	6.7 (4.7 – 8.6)	6.5 (1.0-21.8)	3.0 (0-7.0)
ES progression	8.3 (4.3 – 12.4)	5.4 (3.5 – 7.3)	2.3 (0-10.0)	1.5 (0-6.0)
JSN baseline	4.2 (1.5 – 6.8)	1.2 (0.8 – 1.7)	0 (0-3.8)	0 (0-2.0)
JSN 5 years	17.5 (11.3 – 23.8)	9.3 (7.3 – 11.3)	9.5 (0-26.8)	5.0 (0-14.0)
JSN progression	13.4 (9.0 – 17.8)	8.1 (6.1 – 10.0)	7.5 (0-22.0)	4.0 (0-10.0)

CI=confidence interval; ES=erosion score; IQR=interquartile range; JSN=joint space narrowing; SHS=Sharp van der Heijde score; RN=rheumatoid nodules

Table 3
Anti rheumatic pharmacologic treatment for cases (n=52) and controls (n=139) with available radiographs at baseline and after five years

	Cases (RN)	Controls (non-RN)
First visit/inclusion n=191	**n=52**	**n=139**
No DMARDs (%)	n=6 (12)	n=26 (19)
Biologics (%)	n=1	n=0
Methotrexate (%)	n=28 (54)	n=57 (41)
Glucocorticosteroids (%)	n=25 (48)	n=59 (42)
Visit 12 months n=191	**n=52**	**n=139**
No DMARDs (%)	n=8 (15)	n=30 (22)
Biologics (%)	n=3 (6)	n=2 (2)
Methotrexate (%)	n=30 (58)	n=64 (46)
Glucocorticosteroids (%)	n=22 (42)	n=54 (39)
Visit 24 months n=189	**n=52**	**n=137**
No DMARDs (%)	n=12 (23)	n=33 (24)
Biologics (%)	n=4 (8)	n=4 (3)
Methotrexate (%)	n=26 (50)	n=63 (46)
Glucocorticosteroids (%)	n=15 (29)	n=48 (35)
Visit 60 months n=178	**n=47**	**n=131**
No DMARDs (%)	n=9 (19)	n=38 (28)
Biologics (%)	n=5 (10)	n=11 (8)
Methotrexate (%)	n=25 (53)	n=60 (46)
Glucocorticosteroids (%)	n=10 (21)	n=27 (21)

DMARD= disease modifying antirheumatic drug; RN=rheumatoid nodules

Table 4
Bivariate linear regression analyses with radiographic progression at 5 years as the dependent variable

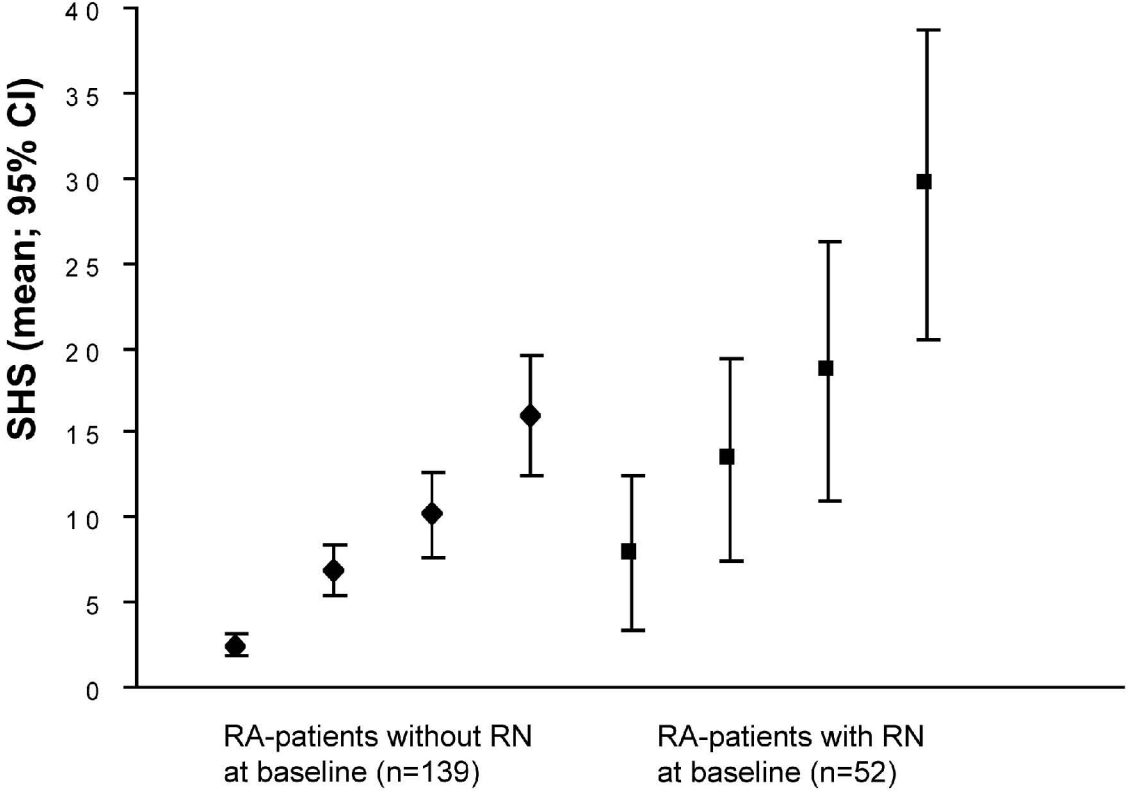
Variables at baseline	Bivariate regression		
	β est	95% CI	p
Age (years)	0.069	-0.175 to 0.312	0.579
Female sex	-0.128	-6.441 to 6.186	0.968
RA duration (months)	0.222	-0.796 to 1.240	0.667
DAS28	0.091	-2.274 to 2.456	0.940
HAQ score	-0.245	-5.656 to 5.165	0.929
ESR	0.111	-0.020 to 0.241	0.095
RF+	13.020	6.615 to 19.425	<0.001
Anti-CCP+ (>25 U/ml)	14.742	8.319 to 21.164	<0.001
Sharp van der Heijde score	0.505	0.174 to 0.836	0.003
Rheumatoid nodules	8.207	1.230 to 15.183	0.021
Ever smoked	-0.856	-8.741 to 7.028	0.830
Current smoker	1.918	-5.222 to 9.058	0.597

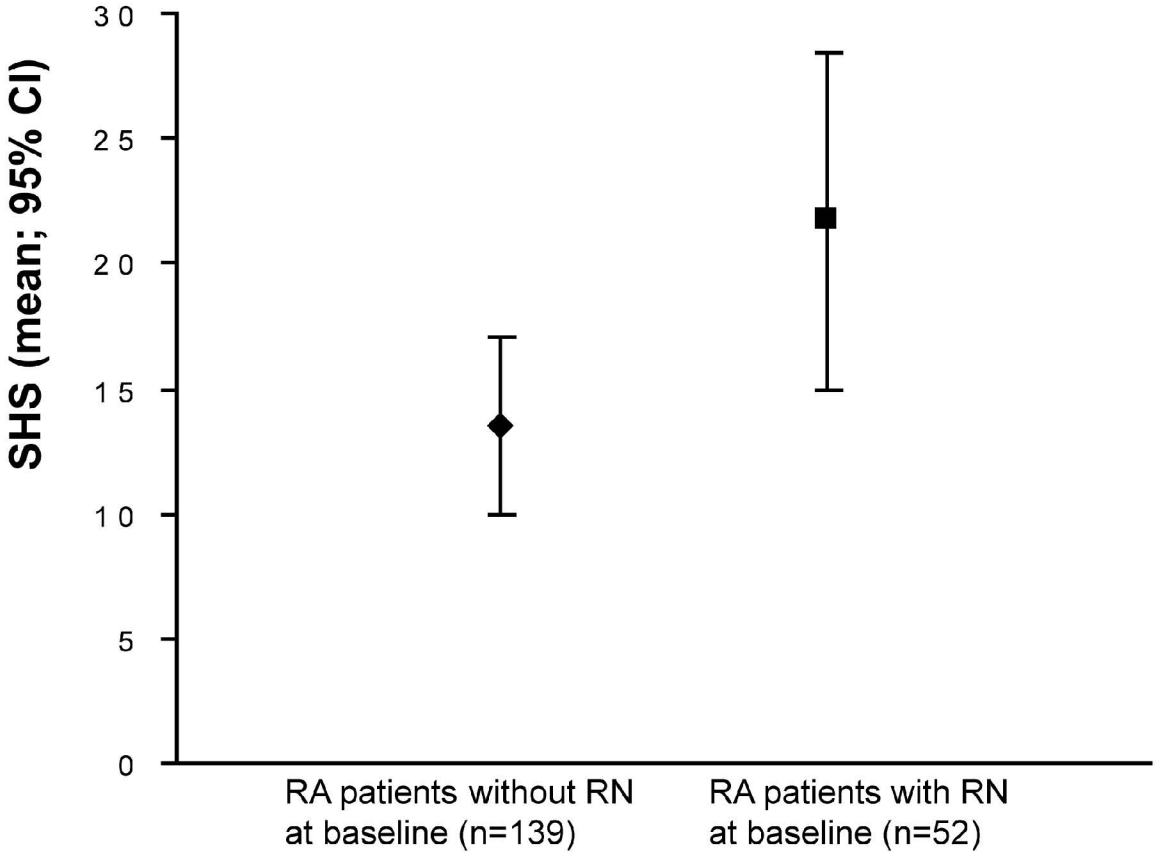
CCP=cyclic citrullinated peptide; DAS=Disease Activity Score; ESR=erythrocyte sedimentation rate; HAQ=Health Assessment Questionnaire; IQR=interquartile range; RA=rheumatoid arthritis; RF=rheumatoid factor; SD=standard deviation

Table 5
Multiple regression analyses with radiographic progression at 5 years as the dependent variable

Variables at baseline	Multiple regression		
	β est	95%CI	p
RF+	5.727	-1.585 to 13.040	0.124
Anti-CCP+ (>25 U/ml)	11.571	4.505 to 18.637	0.001
Sharp van der Heijde score	0.695	0.219 to 1.171	0.004
Rheumatoid nodules	0.503	-7.204 to 8.210	0.898

CCP=cyclic citrullinated peptide; CI=confidence interval; RF=rheumatoid factor


SHS (mean; 95% CI)
40
35
30
25
20
15
10
5
0
RA-patients without RN at baseline (n=139)
RA-patients with RN at baseline (n=52)



*Radiographic progression: SHS score at 5 years minus SHS score at baseline