Predictors of radiographic progression in the ESPOIR cohort: the season of first symptoms may influence the short-term outcome in early arthritis

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ABSTRACT

Objectives To determine predictors of short-term radiographic progression in an inception cohort of patients with early arthritis.

Methods Patients presenting with synovitis of at least two joints for 6 weeks to 6 months were included in the Etude et Suivi des POlyarthrites Indifferenciées Récentes (ESPOIR) cohort. Univariate analysis was used to determine the relationship between baseline variables and radiographic outcome (assessed by the modified total Sharp score (mTSS)) after 6 and 12 months. Stepwise multiple logistic regression was used to select independent predictive factors. The sensitivity and specificity of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) at baseline in discriminating between erosive and non-erosive disease were determined by receiver operating characteristic (ROC) curves.

Results From data available for 736 patients, radiographic progression at 6 months was independently predicted by baseline ACPA, human leucocyte antigen *(HLA)-DRB1*01 and/or 04* genes, erythrocyte sedimentation rate and mTSS. Interestingly, the season of onset of the first symptoms was associated with the severity of early arthritis (OR 1.66, 95% CI 1.07 to 2.59, in winter and spring vs summer and autumn). Univariate analysis revealed similar results for season at 12 months (OR 1.68, 95% CI 1.20 to 2.37). The peak of the ROC curves for radiographic outcome occurred with ACPA and RF values similar to the cut-offs provided by manufacturers.

Conclusion The authors found the onset of arthritis symptoms during winter or spring associated with greater radiographic progression at 6 months for patients with early arthritis. These data could reinforce the role of environmental factors in the development and outcome of rheumatoid arthritis.

The management of early arthritis is a major issue for rheumatologists. Consensus exists about the need for the early use of disease-modifying anti-rheumatic drugs (DMARD) for patients presenting with arthritis that could evolve into persistent and erosive disease.[1 2] The difficulty is defining which patients will experience joint damage and functional disability or which will show a spontaneously resolving disease. Therefore, short-term predictive factors of outcome would help physicians identify these patients, to propose early intensive therapy and to prevent disease progression.

Radiographic evidence of damage is frequently used as a major assessment criterion for rheumatoid arthritis (RA) outcome. Numerous studies have identified possible initial factors associated with worse radiographic outcome, but the studies contain many discrepancies in terms of the included population, the disease duration and the radiographic score used.[3–6]

Detecting autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) can help physicians to diagnose RA.[7] ACPA are highly specific for RA.[7] Although RF seems less specific, it is an important variable both in the 1987 classification criteria for RA[8] and in the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism criteria.[9] In addition, both autoantibodies are related to a more severe radiographic progression.[3 4 10–15] Currently, the threshold values for RF and ACPA (a quantitative variable), which fit to a qualitative result (positive or negative), are provided by manufacturers and are based on optimal sensitivity and specificity for the diagnoses. Evaluating these thresholds and their predictive values for radiographic progression at 6 and 12 months would be useful.

The main objective of this study was to determine predictive factors of short-term radiographic outcome in an inception cohort of patients with early arthritis, the Etude et Suivi des POlyarthrites Indifferenciées Récentes (ESPOIR) cohort.[16] A secondary objective was to determine thresholds for RF and ACPA that could explain short-term radiographic progression.

METHODS

Study population

The ESPOIR cohort is a nationwide prospective cohort study of adults in France conducted under the auspices of the French Society of Rheumatology. The cohort was constituted by asking general practitioners and rheumatologists to refer patients with early arthritis to one of the 14 university hospitals participating in the ESPOIR cohort. The protocol has been described in detail elsewhere.[16] Briefly, patients were eligible for inclusion if they had a definitive or probable clinical diagnosis of RA or a diagnosis of undifferentiated arthritis with potential for progression to RA. Patients were included if they met the following criteria: age greater than 18 years and less than 70 years, swelling of two or more joints, 6 weeks to 6 months symptom duration and no previous treatment with DMARD or glucocorticoids. Patients with another definite diagnosis of inflammatory rheumatic diseases at the baseline visit were excluded. Patients who were included in the cohort were evaluated every 6 months for 2 years and then once a year. The patients were

routinely treated and followed by private rheumatologists in the geographical area. Between November 2002 and April 2005, 813 patients were consecutively included in the ESPOIR cohort. The study was approved by the Institutional Review Board of Montpellier University Hospital, the coordinating centre. Before inclusion, patients gave their written informed consent.

Clinical assessment

A standard diagnostic evaluation was performed on the first visit. The following data were collected: demographic data (age, sex, place of birth, place of residence, ethnic group, profession), socioeconomic data, comorbidities, tobacco exposure, alcohol consumption and family history of RA, duration of symptoms at first visit, presence of a release mechanism, clinical features (morning stiffness, disease activity score in 28 joints (DAS28),[17] functional disability evaluated by the Stanford health assessment questionnaire (HAQ),[18] extra-articular manifestations, psoriasis, squeeze test in metacarpophalangeal and/or metatarsophalangeal joints, and each item of 1987 ACR criteria for RA).[8] Patients were asked when they had experienced their first fixed swollen joint, and this date was used to define the duration of symptoms at the first visit and the season of the first symptoms.

Biological assessment

Erythrocyte sedimentation rate (ESR; mm/h) was measured at baseline in each centre by standard methods. Measurements of the following variables were performed at baseline in a central laboratory (Immunology Department, Bichat Hospital, Paris, France): C-reactive protein (CRP; mg/l), IgM RF tested by ELISA (Ménarini, Rungis, France; positive if ≥9 IU/ml), anti-cyclic citrullinated peptide 2 antibodies (anti-CCP) tested by ELISA (DiaSorin, Antony, France; positive if ≥50 units/ml). human leucocyte antigen *(HLA)-DRB1* genotyping was performed at baseline.

Radiographic evaluation

Radiographs of the hands, wrists and feet in the posteroanterior view were taken for each patient at baseline, 6 and 12 months. Images were centralised and scored according to modified total Sharp score (mTSS)[19] by an experienced rheumatologist (CL) who was blinded to the patient's other data, in known chronological order. For each patient, an erosion score, a joint-narrowing score and a total radiographic score were assessed. In order to evaluate the reproducibility of the radiographic scoring, a set of 30 patients representing the entire range of status—and change scores that was observed during the first read was selected and scored again by the same reader. Intraclass correlation coefficients were greater than 0.99 for both status (baseline and 1 year)—and change scores. The smallest detectable change was calculated at a 1.0 mTSS unit. Radiographic progression was defined by an increase of at least 1 point in the mTSS or the erosion score assessed at baseline and after 6 and 12 months.

Statistical analysis

Univariate analysis of the relationship between all baseline values and outcome measures involved the Pearson's χ^2 test or Fisher's exact test. Continuous variables were transformed into categorical variables with the median value used as the cut-off (or the cut-off provided by the manufacturer for biological data). Logistic regression analyses were used to determine relevant independent baseline variables to predict the 6 and 12-month radiographic outcomes. The explanatory variables included in the model were selected from results of the univariate analysis. A forward stepwise procedure was used to select variables to be included in the model, based on significance levels of 0.15 for inclusion and 0.1 for exclusion. Significance was defined as $p<0.05$ for variables in the multivariate model.

The sensitivity and specificity of RF, anti-CCP and both RF and anti-CCP tests at baseline in discriminating between erosive and non-erosive disease (defined by a status mTSS >0) at 6 months and 12 months were determined. Optimal cut-offs for these tests were derived from receiver operating characteristic (ROC) curves with a cost function. Areas under the ROC curves (AUC) were compared as previously described.[20] The AUC represents the likelihood that the value of the test for 'progressor' is higher than the value of the test for 'non-progressor'. Statistical analysis involved use of SAS version 8.1 for Windows.

RESULTS

Patient characteristics

For the 813 patients included in the cohort, baseline radiographic data were available for 736. The baseline characteristics of the patients are shown in table 1.

Radiographic outcome

Radiographic data were available for 719 and 673 patients at 6 and 12 months, respectively. Baseline characteristics of patients were similar to those of the whole cohort. Mean progression (SD) of the mTSS, erosion score and joint space narrowing score were, respectively, 0.78 (2.56), 0.62 (2.07) and 0.17 (0.86) at 6 months. At 12 months, respective values were 1.48 (4.27), 1.22 (3.53) and 0.27 (1.20).

In total, 150 patients (20.9%) showed a mean progression of at least 1 point on the mTSS at 6 months and 189 (28.1%) at 12 months; 140 patients (19.5%) had a mean progression of at least 1 point of the erosion score at 6 months and 181 (26.9%) at 12 months.

Predictive factors of radiographic outcome at 6 months

On univariate analysis, the progression of the mTSS at 6 months was significantly associated with the following baseline parameters (table 2): age (median 50.2 years old), female sex, ESR and CRP level, positivity for IgM RF or anti-CCP, *HLA-DRB1*01and/or *04* genes, baseline radiographic scores (erosion score, joint space narrowing score and mTSS) and fulfilment of 1987 ACR criteria for RA.

Table 1 Baseline characteristics of the study population (n=736)

Female (n (%))	564 (76.63)
Age (years, mean (SD))	48.34 (12.32)
Caucasian (n (%))	683 (92.80)
Symptom duration at first visit (months, mean (SD))	3.36 (1.73)
IgM RF positive (n (%))	341 (46.33)
Anti-CCP positive (n (%))	290 (39.40)
ESR (mm/h, mean (SD))	29.45 (24.67)
CRP (mg/l, mean (SD))	21.90 (31.99)
DAS28 (mean (SD))	5.11 (1.31)
HAQ (mean (SD))	0.97 (0.68)
mTSS (mean (SD))	5.76 (7.70)
Modified Sharp erosion score (mean (SD))	2.76 (4.68)
Modified Sharp joint space narrowing score (mean (SD))	3.00 (4.42)
*HLA-DRB1*01 or 04* gene (n (%))	401 (57.53)
RA 1987 ACR criteria (n (%))	531 (72.15)

ACR, American College of Rheumatology; anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HLA, human leucocyte antigen; mTSS, modified total Sharp score; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 2 Baseline predictive factors of radiographic outcome at 6 and 12 months (univariate analysis)

	Progression of mTSS at 6 months		Progression of mTSS at 12 months	
Baseline variables	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
mTSS (median 3)	3.44 (2.33 to 5.09)	<0.001	2.93 (2.06 to 4.17)	<0.001
Anti-CCP positivity	3.84 (2.63 to 5.61)	<0.001	3.95 (2.77 to 5.63)	<0.001
IgM-RF positivity	2.53 (1.74 to 3.67)	<0.001	2.61 (1.84 to 3.69)	<0.001
ESR (>28 mm)	2.30 (1.60 to 3.33)	<0.001	2.13 (1.51 to 3.00)	<0.001
CRP (median 10 mg/l)	1.96 (1.36 to 2.83)	<0.001	1.86 (1.33 to 2.62)	<0.001
*HLA-DRB1*01 or *04* 'single copy'	2.54 (1.65 to 3.92)	<0.001	2.30 (1.55 to 3.41)	<0.001
*HLA-DRB1*01 or *04* 'double copy'	3.88 (2.07 to 7.26)	<0.001	3.28 (1.80 to 5.98)	<0.001
DAS28 (median 5.07)	1.44 (0.99 to 2.08)	0.050	1.14 (0.81 to 1.59)	0.460
Swollen joint count (median 6)	1.23 (0.86 to 1.77)	0.256	0.85 (0.60 to 1.19)	0.333
Tender joint count (median 6)	0.77 (0.54 to 1.11)	0.161	0.61 (0.44 to 0.86)	0.005
Age (median 50.2 years)	1.80 (1.24 to 2.56)	0.002	1.57 (1.12 to 2.21)	0.009
Sex (female)	1.63 (1.09 to 2.43)	0.016	1.81 (1.23 to 2.65)	0.002
HAQ score (median 0.88)	1.02 (0.71 to 1.46)	0.910	0.99 (0.71 to 1.38)	0.944
Season winter vs summer	2.17 (1.26 to 3.73)	0.005	2.01 (1.22 to 3.32)	0.006
Season spring vs summer	2.00 (1.16 to 3.47)	0.013	1.68 (1.01 to 2.80)	0.046
Season winter vs autumn	1.90 (1.15 to 3.14)	0.012	1.71 (1.08 to 2.71)	0.022
Season spring vs autumn	1.76 (1.06 to 2.93)	0.029	1.43 (0.89 to 2.29)	0.136
Season (winter and spring) vs (summer and autumn)	1.94 (1.34 to 2.81)	<0.001	1.68 (1.20 to 2.37)	0.003
Smoking	1.39 (0.96 to 1.99)	0.079	1.32 (0.94 to 1.86)	0.105
Alcohol consumption	0.73 (0.47 to 1.15)	0.174	0.59 (0.39 to 0.89)	0.012
ACR criteria for RA ≥4	1.88 (1.20 to 2.95)	0.005	1.36 (0.917 to 2.01)	0.126

ACR, American College of Rheumatology; anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HLA, human leucocyte antigen; mTSS, modified total Sharp score; RA, rheumatoid arthritis; RF, rheumatoid factor.

Interestingly, the season of onset of the first symptoms affected the severity of early arthritis: the mTSS after 6 months was worse if symptoms had started in winter or spring rather than summer or autumn (table 2). The cumulative probability of 6 months mTSS change score in patients having their first fixed swollen joint occurring in winter/spring versus summer/autumn is presented in figure 1. The radiographic outcome was not significantly associated with any clinical variable (including joint counts). The baseline parameters associated with the progression of the erosion score were similar (data not shown).

Stepwise logistic regression analysis of predictive factors of the progression of mTSS at 6 months showed that baseline anti-CCP, *HLA-DRB1*01 and/or 04* genes, ESR and mTSS were associated with radiographic outcome at 6 months (table 3). The season of onset of the first symptoms being winter and spring (vs summer and autumn) was again an independent predictive factor of the progression of mTSS (OR 1.66, 95% CI 1.07 to 2.59, p=0.025). Similarly, season was a predictive factor when the erosion score was used as an outcome measure (OR 1.67, 95% CI 1.07 to 2.61, p=0.026).

We searched for potential confounders of these results. The number of patients included in the cohort and the percentage of patients with the onset of a first swollen joint were fairly distributed in all four seasons (25.1% of the patients with onset of a fixed first swollen joint in winter, 24.3% in spring, 22.7% in summer and 27.8% in autumn, p=0.25). Results were not influenced when we stratified the centres into a southern area (Montpellier, Toulouse and Bordeaux University Hospitals, p=0.33) and a northern area (other university hospitals, p=0.22), or when we considered smoking habit (p=0.54) or alcohol consumption (p=0.80). Disease activity and positivity or level of IgM-RF and anti-CCP were also equivalent in all four seasons (data not shown).

Other baseline variables associated with the progression of the erosion score by logistic regression were anti-CCP (OR 4.03, 95% CI 2.57 to 6.31, p<0.001), ESR (OR 1.93, 95% CI 1.24 to 2.99, p=0.003) and median mTSS (OR 2.51, 95% CI 1.61 to 3.93, p<0.001).

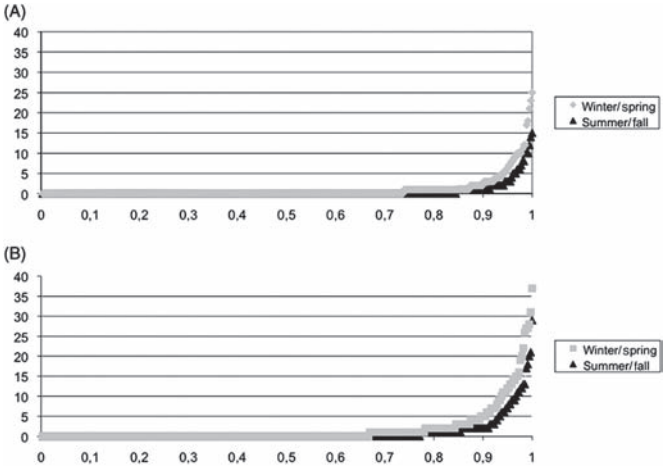

Figure 1 (A) Cumulative probability plots of 6 months modified total Sharp score (mTSS) change score in patients having their first fixed swollen joint occurring in winter/spring versus summer/autumn. (B) Cumulative probability plots of 12 months mTSS change score in patients having their first fixed swollen joint occurring in winter/spring versus summer/autumn.

Predictive factors of radiographic outcome at 12 months

On univariate analysis, the radiographic progression assessed by mTSS at 12 months was significantly associated with age, female sex, alcohol consumption, tender joint count, ESR and CRP level, positivity for IgM RF and anti-CCP, *HLA-DRB1*01and/or *04* genes and radiographic scores (table 2). The progression of mTSS after 12 months was worse if symptoms had occurred in winter or spring rather than summer or autumn (OR 1.68, 95% CI 1.20 to 2.37, p=0.003) (table 2). Similar data

Table 3 Final model of stepwise logistic regression analysis of predictive factors of the progression of mTSS at 6 and 12 months

	6 Months (AUC 0.771)		12 Months (AUC 0.780)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Anti-CCP positivity	2.94 (1.88 to 4.59)	<0.001	4.14 (2.64 to 6.47)	<0.001
Baseline mTSS > median	2.56 (1.64 to 3.99)	<0.001	2.40 (1.56 to 3.68)	<0.001
*HLA-DRB1*01 or 04* 'double dose'	2.67 (1.30 to 5.50)	0.008	2.73 (1.34 to 5.57)	0.008
*HLA-DRB1*01 or 04* 'single dose'	1.86 (1.13 to 3.05)	0.014	1.67 (1.04 to 2.67)	0.014
ESR > median	2.04 (1.32 to 3.14)	0.001	2.13 (1.38 to 3.29)	0.001
Season (winter and spring) vs (summer and autumn)	1.66 (1.07 to 2.59)	0.025		

anti-CCP, anti-cyclic citrullinated peptide; AUC, area under the curve; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; mTSS, modified total Sharp score.

were obtained when the outcome variable was progression of the erosion score (OR 1.66, 95% CI 1.18 to 2.35, p=0.004) for winter or spring versus summer or autumn. Other baseline variables associated with progression of the erosion score were, for the most part, similar as compared with at 6 months.

On multivariate analysis, progression of the mTSS at 12 months was associated with baseline anti-CCP, HLA-DRB1*01 or 04 'double copy' and 'single copy', ESR and median mTSS (table 3).

Stepwise logistic regression analysis did not select season as an independent predictive factor of the radiographic evidence of disease progression at 12 months, with the mTSS or the erosion score.

Sensitivity and specificity of RF and anti-CCP: ROC curve analysis

ROC curve analysis was used to determine a cut-off of RF and anti-CCP at which radiographic progression at 6 and 12 months could be accurately predicted.

ROC curves for RF, anti-CCP and the combination of RF and anti-CCP for progression of mTSS at 12 months are presented in figure 2. At 12 months, curves did not differ for RF and anti-CCP (AUC 0.65, 95% CI 0.60 to 0.70 and AUC 0.68, 95% CI 0.64 to 0.72, respectively, p=0.099) or for anti-CCP and the combination (AUC 0.68, 95% CI 0.63 to 0.73, p=0.899 vs ROC curve for anti-CCP). Nevertheless, ROC curves for RF plus anti-CCP were more informative than ROC curves for RF alone to explain the progression of the mTSS (p=0.023). Differences between ROC at 6 months were not significant (data not shown).

Optimal cut-offs for these tests were derived from ROC curves by the use of a cost function. The best ratio of sensitivity to specificity was obtained with a 4 or 5 weighting in each model. The peak of the ROC curves for each gold standard (progression of the mTSS and erosion score at 6 and 12 months) occurred at anti-CCP and RF values similar to the cut-offs provided by the manufacturer. Nevertheless, calculated cut-offs to explain radiographic outcome at 12 months were lower than those obtained at 6 months, which indicates that, even at low titres, the presence of antibodies was associated with erosive change (table 4).

DISCUSSION

Evaluating the short-term prognosis of RA is of great importance because patients at risk of developing erosive arthritis should start receiving DMARD as early as possible, even if they do not yet fulfil established classification criteria for inflammatory rheumatological diseases.[1] Therefore, we used a primary care-based cohort of patients with inflammatory polyarthritis, reflecting the spectrum of patients attending early arthritis clinics.

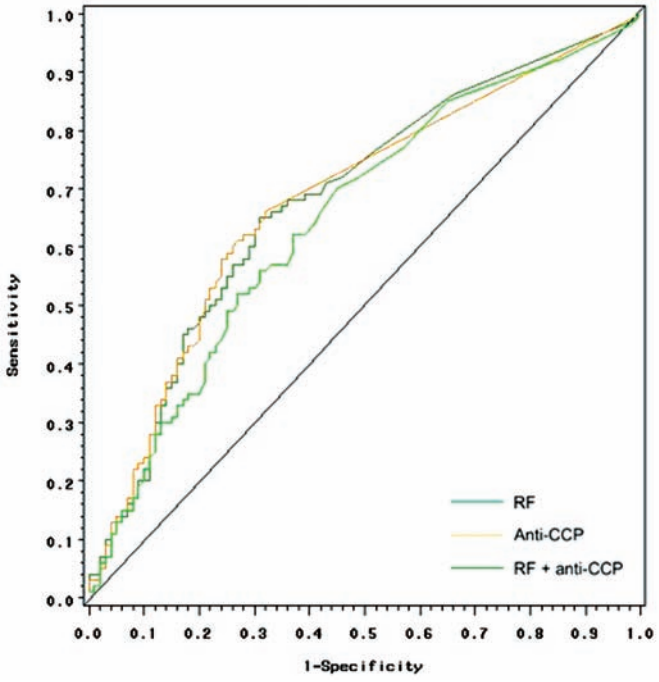

Figure 2 Receiver operating characteristic curves for rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies and both RF and anti-CCP for progression of modified total Sharp score at 12 months.

The primary objective of our study was to determine predictors of short-term radiographic progression in an inception cohort of patients with early arthritis. We found that the best independent predictive factors were baseline mTSS, anti-CCP, shared epitope and ESR. These results are in agreement with other previous studies, which showed baseline radiographic score,[3–6 21] acute phase reactants,[4–6 21–23] ACPA,[4 22] presence of the shared epitope[3 21 23] as the best predictors of structural damage in the short term. It is interesting to note that these factors were confirmed in the ESPOIR cohort, which included many patients with very early arthritis. The important AUC at 6 and 12 months suggest that these predictive factors are consistent to identify in the short-term patients with a poor radiographic outcome in clinical practice. Besides these usual initial variables, multivariate analysis revealed the season of symptom onset (winter or spring) as an independent predictive factor of structural progression at 6 months. The onset of arthritis symptoms during winter or spring was also associated with greater radiographic evidence of disease progression at 12 months, although only by univariate analysis. These results could not be explained by the percentage of patients developing a first swollen joint, gender,

Table 4 Sensitivity, specificity, positive likelihood ratios and calculated cut-offs for each test by use of a cost function (weighting of 5)

	Sensitivity (%)	Specificity (%)	Positive likelihood ratio	Calculated cut-off
6 months Δ mTSS >0				
RF	70	55	1.56	8.06
Anti-CCP	65	68	2.03	36.86
	65	67	1.97	50.84
12 months Δ mTSS >0				
RF	85	35	1.31	4.95
Anti-CCP	66	68	2.06	25.10
6 months Δ erosion score >0				
RF	73	55	1.62	7.99
Anti-CCP	66	69	2.13	90.03
12 months Δ erosion score >0				
RF	87	35	1.34	4.95
Anti-CCP	68	68	2.12	25.01

anti-CCP, anti-cyclic citrullinated peptide; mTSS, modified total Sharp score; RF, rheumatoid factor.

the proportion of smokers or alcohol consumers, place of residence, positivity or level of RF and anti-CCP. Another potential confounding factor may have been due to summer holiday, generating patients' or doctors' delays and consequently patients being seen after the summer vacation. However, we can assume that the influence of this phenomenon was minor, as the number of patients included in the cohort was fairly distributed in all four seasons. The fact that the same results were found with two adjoining seasons (winter and spring, summer and autumn) and both at 6 and 12 months in univariate analysis reinforces these findings. However, as it is the first study demonstrating a seasonal influence on the severity of arthritis, we cannot exclude the possibility that our results could be a spurious finding as a result of testing multiple predictors. The literature contains conflicting and inconsistent data concerning the influence of the seasons on disease outcome.[27–29] These data reinforce the probable role of environmental factors in the pathogenesis of RA.[24–30]

Several mechanisms can be suggested to explain our results. First, an environmental factor such as an unknown virus or bacterial agent with increased prevalence in winter could influence protein citrullination. Interestingly, the role of *Porphyromonas gingivalis* in the susceptibility of RA and in the production of ACPA has recently been suggested.[25 26] Infections are well known possibly to promote or exacerbate other autoimmune diseases.[31 32]

Second, vitamin D is synthesised more in the summer and could have immunoregulatory properties in RA.[33] Vitamin D receptors are present in macrophages and synovial cells of patients with RA. The vitamin was shown to inhibit T-cell proliferation and decrease pro-inflammatory cytokine synthesis in vitro.[34 35] Vitamin D intake was shown potentially to prevent the development of RA in a prospective cohort of 29 368 women.[36] Nielen *et al*[37] did not find any difference in vitamin D levels in RA patients and healthy subjects. However, vitamin D levels were higher in RA patients in Italy than in those in Estonia, especially in winter,[38] and were inversely correlated with disease activity as assessed by the DAS28 in both populations.[39] Data from the Norfolk Arthritis Register revealed an inverse relation between 25-hydroxyvitamin D levels and tender joint count, DAS28 score and HAQ score at baseline in patients with early inflammatory polyarthritis.[40]

The weaker influence of seasons at 12 months compared with 6 months could be explained by a lower power of initial environmental factors on disease progression in the medium term.

A secondary objective of our study was to determine a threshold for RF and anti-CCP antibodies that could explain radiographic progression at 6 and 12 months. We used a cost function to obtain the best ratio of sensitivity to specificity for each ROC curve. At 6 months, cut-offs were similar to those provided for the diagnosis of RA, which suggests that these cut-offs are clinical decision-making cut-offs. They were lower at 12 months, which suggests that RF and anti-CCP may be associated with the development of erosions even at titres that would have been considered negative according to the manufacturer. Bukhari *et al*[41] searched for a cut-off for anti-CCP to predict erosions at 5 years in an early arthritis cohort and found similar results, indicating that the absence of anti-CCP antibodies could not be used to identify individuals who do not require treatment, because even low titres could be associated with the development of erosions.

In summary, we found the onset of arthritis symptoms during the winter or spring to be associated with greater radiographic evidence of disease progression at 6 and, to a lesser extent, at 12 months besides other more usual initial clinical variables. Multivariate analysis revealed the season of symptom onset as an independent predictive factor of radiographic outcome only at 6 months. The influence of seasons on disease outcome should be evaluated in other early arthritis cohorts, especially short-term studies of northern populations.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Institutional Review Board of Montpellier University Hospital, the coordinating centre.

Provenance and peer review Not commissioned; externally peer reviewed.

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