

Prognostic factors for erosive rheumatoid arthritis

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Received on April 13, 2009; accepted in
revised form on June 26, 2009.

Clin Exp Rheumatol 2010; 28: 114-123.

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EXPERIMENTAL RHEUMATOLOGY 2010.

Key words: Erosive rheumatoid,
autoantibodies, acute phase reactants,
smoking, HLA-DRB1, early erosive
imaging.

ABSTRACT

The course of rheumatoid arthritis (RA) varies among patients, ranging from a mild disease with a small impact on patient's functional capacity to a severe, erosive and catastrophic disease accompanied by subluxations, deformities and subsequent poor quality of life. In clinical practice, the prediction of the outcome of RA is substantial in terms of making the right therapeutic decision for each patient. Reliable prognostic factors of long-term outcome are needed, so as to distinguish patients prone to severe disease course from patients with a smaller probability of severe structural damage. For the former group early aggressive treatment is required, whereas in the latter group remission may be achieved with less aggressive and potentially less toxic treatments. In the present review, the predictive role of demographic, clinical, laboratory, imaging, immunological and genetic characteristics of RA patients is discussed.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterised by symmetrical polyarthritis of the small and the large joints, morning stiffness and various extra-articular manifestations (EAM). It affects mainly women (female/ male ratio 3:1), with a prevalence, varying worldwide, between 0.5-1% (1, 2). The disease is characterised by a considerable heterogeneity, in terms of clinical expression and long-term course, thus making it difficult to establish optimal strategies for the treatment of patients with RA, particularly of those with early disease. During the recent years though, it has become clear that RA treatment should aim at suppressing the inflammatory process early and effectively, in order to relieve patient symptoms and achieve better long-term functional and structural outcomes. The goal of early and effective treatment is pursued through

the early use of disease-modifying anti-rheumatic drugs (DMARD) (3, 4), primarily methotrexate (MTX) and through close monitoring of disease activity. Tight disease control by means of timely escalation of drug doses, introduction of DMARD combinations and addition of biological agents have been effective in controlling disease activity and/or achieving remission (5-17). However, more aggressive treatment strategies are often associated with adverse events, as well as higher costs, factors curtailing the unconditional and widespread use of these therapeutic options. Hence, the prospect of distinguishing which patient with early RA is to run a severe disease course and who is not, will be of great value in clinical practice. Such predictors of disease outcome would ideally channel aggressive treatments to patients with adverse prognostic factors, and would reserve less aggressive treatments for patients with a more favourable disease profile, thus preventing undue adverse events and high treatment costs.

Radiological changes

Concerning the various long-term RA outcomes, radiological progression is considered a key variable, because it reflects the cumulative damage in bones and cartilage. The quality of life and functionality of a patient in the long term are influenced, at least in part, by the joint deterioration seen in x-rays (18-20). The x-rays of hands and wrists are commonly used in observational studies, not only because they are easily obtained, but also because the radiological damage in hands and wrists is considered representative of the total structural damage a patient has sustained (21). Figure 1 shows the progression of the radiological damage of a RA patient over a 10-year period. The damage in the small joints of hands and feet predicts the damage in the large joints (22). The small joints of feet are eroded earlier than those of the

Competing interests: none declared.

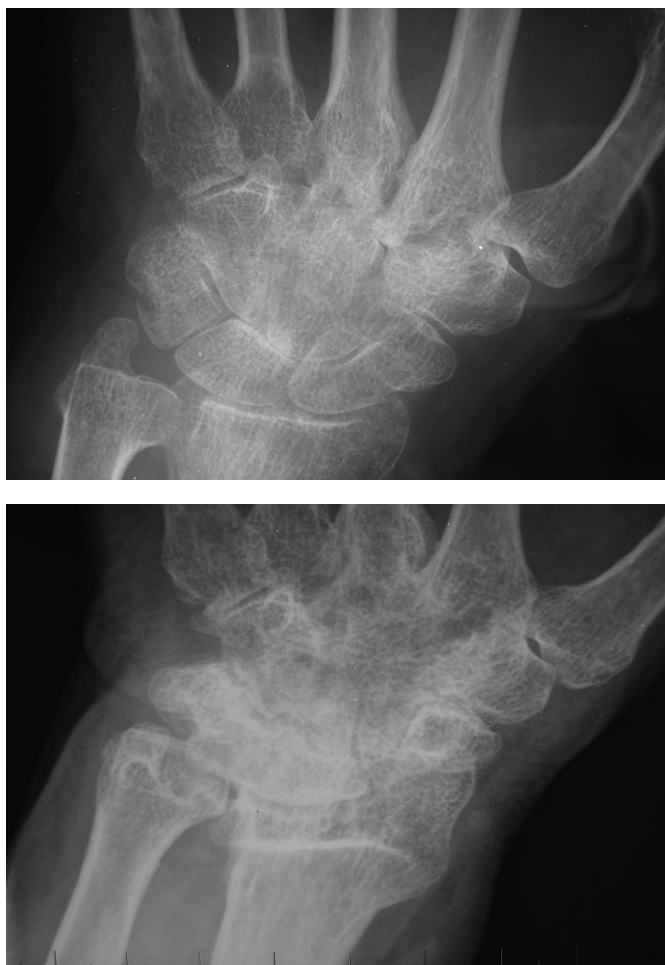


Fig. 1. Rheumatoid arthritis with a two-year disease duration: posteroanterior view of the wrist demonstrating early changes with osteopenia and mild loss of joint spaces and some erosions in a pancarpal distribution (A). Same patient, 8 years later: posteroanterior view of the wrist showing advanced changes with osteopenia severe joint space narrowing and extensive erosions in a pancarpal distribution (B).

hands according to Hulsmans *et al.* (23), however, x-rays of feet are not always evaluated in the studies.

Plenty of scoring systems of x-rays of hands, wrists and feet have been developed so far, in order to quantify joint damage. Each one focuses on different features of structural damage such as erosions, joint space narrowing, osteoporosis, soft tissue swelling, subluxation, ankylosis, cyst formation etc. The most common systems are Sharp score, Larsen score and their modifications (24-27). Genant score (28, 29), Rattigen score (30), and other scoring methods have also been proposed and are minor variations of the previous two. No matter which scoring system is used in observational studies, the finding that the radiological damage increases in the disease course is common among the studies. However, the rate of the radiological progression differs between patients. Thus, a small proportion of RA patients present more than 50% of the

maximum possible damage at first 5 years from the disease onset, whereas others have no damage even after 20 years (31). Graudal *et al.* described the patterns of radiological progression (32). Five main types of progression were suggested: 1) a rare type (<1%), with no radiographic progression at all; 2) a type with a slow or moderate onset, but an accelerating progression (39%); 3) a type with a moderate-to-fast onset and a later stable progression rate (11%); 4) a type with a fast onset, but a later decreasing progression rate (30%); and 5) a type characterised by slow onset, then acceleration and later deceleration (20%). Scott suggested that these patterns can be reduced to 4 similar patterns: 1) Linear progression; 2) Rapid onset with a later plateau; 3) Slow onset with acceleration and 4) Non progression (31). In the study by Machold *et al.* (33), erosive disease developed in 63.6% of the patients over 3 years, with the majority (74.3%) already appearing

in the first year and 97.2% by the end of the second year, whereas in another study 95% of the RA patients had at least 1 eroded joint over 6 years (23).

Numerous multivariate analyses have been conducted in order to identify possible prognostic factors of radiological progression in RA. There are differences between their results, possibly due to different study design and to different length of follow-up. Differences in treatment may also be responsible for these conflicting results, since biologic agents (with a more potent anti-erosive efficacy than traditional DMARDs) are used in the more recent studies. Several long-term observational studies have been published so far. Table I summarises potential prognostic factors of radiological progression in RA.

The aim of this article is to review the prognostic role of demographic, genetic, clinical, laboratory, immunological and imaging characteristics of RA patients, in order to provide potential prognostic clues for structural damage, when evaluating these patients.

Demographic factors

Age

There are conflicting results in the literature with regard to the role of age at the time of RA diagnosis in predicting the radiological outcome. Peltomaa *et al.* (34) showed that patients with late onset RA (>55 years) had higher Larsen score for hands at baseline in comparison with patients with early onset RA (<55 years), but during the follow up the radiological progression was the same in both groups. Similarly, in the study by Papadopoulos *et al.*, elderly RA patients (>60 years) presented with more severe joint involvement at disease onset than younger patients, but age at disease onset did not influence the outcome in terms of radiological progression (35). On the contrary, in the long-term study by Kaarela *et al.* (36), old age at disease onset correlated with radiological progression. However other long-term studies have not confirmed the relationship between age at disease onset and radiological progression (37, 38).

Sex

Female sex is considered a predictive

factor of poor outcome in RA. Indeed, in several studies it has been identified as an independent predictor of radiological progression. Female sex was the strongest prognostic factor of Larsen progression at 2 years in the stepwise logistic regression analysis of Sanmarti's study (39) and the second [after anti-cyclic citrullinated peptide antibodies (anti-CCP)] strongest contributor to the overall prediction model in the 10-year study by Syversen *et al.* (38). On the other hand, in another observational study, male sex was a major prognostic factor of remission [Disease activity score-28 joints (DAS-28 <2.6)] at 5 years and at other time points (40). In the same study women showed less favourable disease course, while these results could not be explained by differences in disease duration, age and treatment with DMARDs or steroids. However female sex was not a prognostic factor of radiological deterioration in another study (41).

Disease duration

Disease duration constitutes an important predictive factor for radiological damage. It has been shown that the radiological damage at presentation correlates with the duration of disease symptoms or patient's complaints prior to the first visit to the doctor (42). Long-lasting untreated disease may result in catastrophic joint damage (43,44).

Body mass index

In the study by Kaufmann *et al.* (45), body mass index (BMI) at baseline was found to correlate with the radiographic damage in terms of the annual increase of the Larsen score. In a stepwise logistic regression analysis, low body weight was proved to be a significant predictor of rapid joint damage. The authors proposed BMI as a sensitive and inflammation-independent predictor of radiological outcome of RA. However, the hypothesis that BMI is independent of inflammation is debated in the literature. Abnormal body composition (abnormal proportion and body distribution of fat and lean mass) has been described in patients with RA, even in those in normal weight BMI range (46). The combination of muscle loss and fat

Table I. Potential prognostic factors of radiological damage in rheumatoid arthritis.

Demographic	Genetic
- Age	- Shared epitope
- Sex	- PTPN22 gene
- Disease duration	Autoantibodies
- Smoking	- Rheumatoid factor
- Body mass index	- Anti-cyclic citrullinated peptide antibodies
Clinical	- Anti-peptidyl-arginine deiminase-4 antibodies
- Symmetrical polyarthritis	Bone markers
- Disease activity score	- Matrix metalloproteinase-3
- Health assessment questionnaire score	- RANKL/OPG ratio
- Extra-articular manifestations	- Human cartilage glycoprotein-39
Inflammatory markers	- Cartilage oligomeric matrix protein
- Erythrocyte sedimentation rate	- Collagen cross-linked C-telopeptide
- C-reactive protein	Early imaging damage

mass gain, referred to as "sarcopenic obesity", is seen in those patients. An association of reduced body cell mass with inflammatory cytokine levels in patients with RA has been described years ago (47). Additionally, adipose tissue itself is a potent source of inflammatory adipokines, such as tumor necrosis factor α , interleukin-6, adiponectin and others, that may contribute to systemic inflammation through induction of hepatic C-reactive protein (CRP) production (48).

Cigarette smoking

Among the life style factors that have been implicated in the prognosis of RA (2), cigarette smoking is the most studied. Smokers show higher radiological damage than never smokers, while this association seems to be time- and dose-dependent (49-53). Manfredsdotir *et al.* (54) suggested that smoking-associated joint damage in RA patients may be mediated by smoking-induced immunological changes, including rheumatoid factor (RF) production. In contrast, cigarette smoking did not correlate with radiological damage in other studies (55-57). In the study by Finckh *et al.* (55), radiographic joint damage progressed at an equivalent rate in smokers and non-smokers, although heavy smokers demonstrated significant less radiographic disease progression than mild smokers and generally more favourable functional outcomes, suggesting that cigarette smoking may be important in the initiation of RA, but may not accelerate RA disease progression. In the study by Westhoff *et al.* (56), it was shown that RA pa-

tients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers with the same RF status. In addition, cigarette smoking has also been associated with EAM and particularly with rheumatoid nodules, which are factors associated with progressive joint damage (2).

Clinical features

There are conflicting results from the literature concerning the predictive value of various clinical parameters for radiographic damage in RA. In the long-term study by Kaarela *et al.* (36), symmetrical polyarthritis in peripheral joints at disease onset and morning stiffness strongly correlated with destructive joint disease. The number of swollen joints was an independent predictive factor of radiological progression. None of these factors were shown to be independent prognostic factors of radiological progression at 10 years in the study by Courvoisier *et al.* (37). In the recent report by Machold *et al.* (33), none of the clinical variables at onset was useful to distinguish patients with erosive and non-erosive disease, but, in the final regression model, cumulative clinical activity substantially contributed to explaining radiological progression. Thus, cumulative measures of disease activity including joint counts, pain estimation on visual analogue scale, acute phase reactants and DAS 28 predicted radiological progression. Similar results were obtained not only for DAS-28 but also for simplified disease activity index (SDAI) and clinical disease activity index (CDAI) in an-

other study (58), where the time-averaged composite disease activity measures were associated with radiological progression. With regard to large joints only and particularly the elbows (59), the mean DAS-28-CRP (3) both at 2 and at 10 years were higher in patients of the group with more deteriorated elbows (defined as a Larsen grade ≥ 3 at 10 years) than those of the group with less deteriorated elbows (defined as Larsen grade ≤ 2 at 10 years).

Health Assessment

Questionnaire score

According to published studies, the functional capacity in RA based on Health Assessment Questionnaire (HAQ) score is influenced by disease activity in early RA and by joint damage in established RA (18-20). However HAQ score at baseline did not predict radiological progression in several studies (37, 38, 60, 61), indicating that the presumed association between HAQ and radiographic score possibly appears later in the disease course.

Extra-articular manifestations

In the past, EAM have been correlated with male sex, cigarette smoking, worse joint damage, elevated inflammatory markers and the presence of RF and the shared epitope (SE) (62). Among the EAM those considered to be predictive of radiological progression in RA are rheumatoid nodules and anemia of chronic disease (low serum iron and normal ferritin levels) (63). Indeed, when erosions were considered as the outcome variable in RA course, nodules and anemia predicted erosions with a high odds ratio similar to that of RF and the SE (64). After stratification of RA patients to nodular and non-nodular, in the study by Saraux *et al.* (65), it was shown that nodular patients presented with an accelerated rate of radiological progression than non-nodular patients. Although the relationship between erosive disease and extra-articular manifestations remains uncertain, de Rycke *et al.* (66) suggested that RF is implicated in the pathogenesis of both of them in RA patients.

Inflammatory markers

Erythrocyte sedimentation rate (ESR) is a recognized predictive factor of radiographic deterioration in most studies. Both short-term (64, 67-69) and long-term (36-38, 70) studies are in agreement with this. On the contrary, the predictive role of CRP is doubted in the literature. The results of the short-term studies show that CRP at baseline either correlates with radiological progression (67, 71) or is not prognostic (72). In the study by Plant *et al.* (73), the radiological progression was 5-fold higher in patients with high levels of CRP than in patients with low CRP levels. In long-term studies, CRP is either not studied (70, 74), or is found not prognostic (36, 37) or, if found prognostic, it was not an independent factor for radiological damage (38). However, as mentioned above, the mean concentration of CRP over the years correlates statistically significantly with joint damage progression (75). These controversial results merit further investigation.

Genetic factors

The presence of the SE-containing DRB1 alleles and especially of HLA-DRB1*0401 has been found to play a role in RA progression, leading to more severe forms of disease in many short-term studies (67, 76-81). According to the results by Rojas-Villarraga *et al.* (82), the median time until the appearance of substantial radiographic joint damage (defined as a Sharp/van der Heijde erosive score equal to 5) decreased as the number of the SE alleles increased, reflecting a more rapid damage in patients with two SE alleles in comparison with patients with one or no SE alleles. In two long-terms studies (37, 74), this predictive value was confirmed at 3 and 5 years, but it was lost after 5-10 years indicating that SE influences short- but not long-term radiological outcome in RA.

The SE allele carriership and the presence of anti-CCP antibodies were the strongest prognostic markers for radiographic progression in the study by Kaltenhäuser *et al.* (83). The simultaneous presence in a patient of both markers was associated with higher Larsen scores compared with patients

positive for either marker alone, indicating a possible additive effect of these markers. It has been shown that SE alleles predispose for both RF and anti-CCP production (84). It remains controversial if the presence of the SE constitutes an independent or an anti-CCP-dependent prognostic factor for radiological deterioration.

Carriage of a missense polymorphism (1858C→T; rs2476601) in the protein tyrosine phosphatase N22 (PTPN22) gene has been shown in many studies to confer an increased risk for developing RA (85-89) and to influence the risk for other autoimmune diseases, that are classically characterised by circulating autoantibodies, such as systemic lupus erythematosus, Graves' disease, myasthenia gravis, and type 1 diabetes mellitus (90, 91). PTPN22 encodes a tyrosine phosphatase, which modulates the activation of kinases such as Lck, involved in early events of T cell-receptor signalling. The predisposing 1858T allele encodes a protein with higher catalytic activity, which is a more potent negative regulator of T cell activation (92). It is less clear whether this autoimmune risk-conferring variant (the T allele) may influence the disease phenotype and the clinical outcome, as well as if there is an association between the SE and the PTPN22 risk variant.

In a recent 10-year study (93), the reported association between RA susceptibility and carriage of the T allele was confirmed, and additionally, an association between the annual progression rate of the Sharp-van der Heijde score and T-allele carriership ($p = 0.01$), was also found. This association was also present when only patients carrying the SE were analysed. On the contrary, in another recent study (94), no association was detected between any of the single nucleotide polymorphisms (SNPs) spanning the PTPN22 gene tested, including the PTPN22*1858C→T polymorphism, and either erosion status or Larsen score by the fifth year. Further investigation is needed to clarify whether the PTPN22 1858T risk-conferring variant is associated not only with disease susceptibility, but also with the rate of radiographic progression in RA.

Autoantibodies

Rheumatoid factor

RF is a known predictive factor of radiological short-term and long-term outcome in RA (37,38,60,61,70,95-101). Its predictive value has been confirmed in many studies and it involves mainly the two RF isotypes, IgA and IgM. However Kaarela (36) did not recognise RF as an independent prognostic factor and Lindqvist in his observational study (102) showed that RF independently of isotype did not predict radiological progression. Studies comparing the predictive value of the two isotypes conclude that IgA is better than IgM RF (54,103,104).

Anti-cyclic citrullinated peptide antibodies

The presence of anti-CCP antibodies constitutes a strong and independent prognostic factor according to many studies (33, 38, 40, 42, 82, 102, 103, 105, 106). To our knowledge, only two studies do not fully support this association (107, 108). Reasons for this discrepancy in one of the studies may be the use of anti-CCP 1 test (which is less sensitive than the newer anti-CCP 2 and anti-CCP 3 tests) or a different study design. In the study by Syversen *et al.*, the presence of anti-CCP antibodies was the strongest independent predictor and 1 of the 4 variables in a model predicting the 10-year radiological progression in RA patients (38). This study is unique in the literature for having examined not only the predictive role of the presence of anti-CCP antibodies, but also of their levels in radiological progression. Levels of anti-CCP antibodies seem to be an independent predictor factor of radiological progression. Patients with high anti-CCP titers (>200 IU/ml) were ten times more likely than anti-CCP negative patients to progress in the van der Heijde modified Sharp score over a decade, and about five times more likely than patients with low-moderate levels (25-200 IU/ml). In the study by Courvoisier *et al.* (37), it was shown that not only the presence of anti-CCP antibodies at baseline, but also of ACPA (anti-citrullinated protein/peptide autoantibodies) in total, with the inclusion of data on

anti-perinuclear and anti-keratin antibodies, were independent predictive factors of the total Sharp/van der Heijde score after 10 years.

Reports comparing the performance of both anti-CCP antibodies and RF in predicting radiological progression, agree that anti-CCP antibodies are strongest predictive factor than RF. The predictive role of RF for radiological progression is independent of the presence of anti-CCP according to some studies (33, 102, 103, 107), but in others it is anti-CCP-dependent (40, 106, 108). On the other hand, the use of a higher cut-off point to determine the positivity of RF (40 IU/L instead of 20 IU/L) eliminated the additional prognostic value of anti-CCP in Nell's study (109) but not in Syversen's (38).

Anti-peptidyl-arginine deiminase-4 antibodies (anti-PAD4)

Peptidyl-arginine deiminase-4 (PAD4) is an enzyme responsible for the citrullination of proteins and thus may play a role in the development of RA (110). The presence of serum IgG antibodies against human PAD4 is estimated at approximately 23% of Caucasian RA patients. In the study by Halvorsen *et al.* (111), the presence of anti-human PAD4 autoantibodies correlated longitudinally with greater radiological damage, in a weaker, though, fashion than RF and anti-CCP antibodies. Even in the presence of anti-CCP antibodies, anti-hPAD4-positive patients had a trend towards higher Sharp/van der Heijde scores over time than anti-hPAD4-negative patients.

Serological biomarkers

The predictive role of other serological markers is of great interest. Baseline serum level of matrix metalloproteinase-3 (MPP-3), the enzyme involved in the degradation of cartilage proteoglycans, was strongly associated with final Sharp/van der Heijde score in the 10-year longitudinal study by Courvoisier *et al.* (37). This study confirmed the results of other short-term studies previously published (112, 113). Eklund *et al.* showed that serum interleukin-1 beta (IL-1 β) levels were associated with the presence of erosions in recent

onset RA (114). Although IL-1 levels correlated with the baseline number of eroded joints, they did not predict radiographic joint damage at 2 years. Other serological biomarkers reflecting bone and cartilage destruction such as receptor activator of nuclear factor- κ B ligand (RANKL), osteoprotegerin (OPG), human cartilage glycoprotein-39, cartilage oligomeric matrix protein (COMP) and collagen cross-linked C-telopeptide (CTX-I) have been studied in a recent observational study (115). No association between the baseline serum levels of these biomarkers and the 10-year increase in the Sharp/van der Heijde score was found, except for the CTX-I. The CTX-I levels correlated with subsequent joint destruction, although this association was weak. Another study, however, showed that the ratio of circulating OPG to RANKL predicted subsequent bone destruction (116). More studies are needed in this field to identify stronger predictive factors of radiological progression.

Early imaging findings

Early radiographic damage has significantly been associated with the likelihood of subsequent structural deterioration, in both short- (40, 42, 67, 68) and long-term (36, 37, 74) studies. However, the predictive value of early radiographic damage has not been studied in all long-term studies. In the report by Courvoisier *et al.*, baseline erosion score, according to the van der Heijde modified Sharp scoring system, was the best independent predictor of the 10-year radiographic damage (37). Baseline radiographic score was also an independent predictive factor of radiological progression in Kaarela's study (36), while Larsen score at the beginning was a predictive factor for radiographic progression during years 0-5 and 5-10 in Lindqvist's study (74). Apart from x-ray scores, magnetic resonance imaging (MRI) score at baseline can predict radiological outcome in RA. McQueen showed that initial MRI score of the wrist could predict x-ray erosions at 2 years (117). Few years later, the same author suggested that baseline MRI bone oedema predicts 6-year radiographic scores, whereas base-

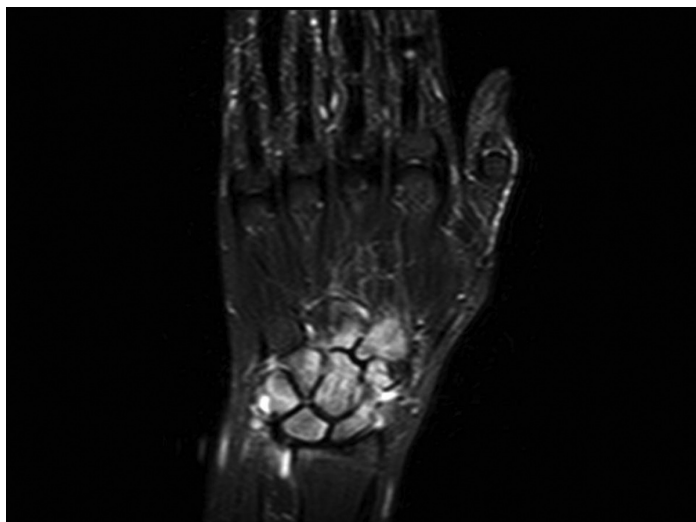


Fig. 2. A 62-year-old female with rheumatoid arthritis: coronal, short time inversion recovery (STIR) scan [TR/2500ms, TE/60ms, TI/160ms] shows high signal intensity of all carpal bones suggestive of bone oedema.

line MRI synovitis does not, implying a significant role of bone oedema as a pre-erosive lesion (118). A magnetic resonance image of bone oedema in a RA patient's hand is shown in Figure 2. In the study by Tamai *et al.*, bone oedema determined by hand MRI was considered to reflect the presence of severe disease in patients with early RA, since the number of bones scored as positive for bone oedema correlated with the number of other types of MRI lesions (synovitis, erosions) and the levels of CRP, MMP-3 and IL-6 (119). Also patients with bone oedema were more likely anti-CCP positive, had higher anti-CCP antibody titers and DAS-28-CRP score and were more often carriers of the SE-containing HLA-DRB1*0405 allele, compared to patients without bone oedema. In a recent report, MRI bone oedema proved to be the strongest predictor of subsequent radiographic progression in early RA and the only independent predictor of delta-TSS (total Sharp/van der Heijde score) (120). Additionally, in the last years, a new predictive factor has been recognized, when hand bone mineral density (BMD) was measured by digital x-ray radiogrammetry (DXR) in RA patients (121,122). In the study by Hoff *et al.*, hand bone loss after 1 year in early RA was an independent predictor of the Sharp/van der Heijde score at 5 and 10 years in all patient subgroups studied (patients stratified according to anti-CCP positivity and baseline x-ray damage) (121). Finally, musculoskeletal

ultrasonography (US) enables rheumatologist sonographers to recognise premature changes in joints affected by RA (such as synovitis and erosions) (123, 124) that plain radiographs cannot, especially in early stage of the disease (125). In the short-term study by Brown *et al.* (126), baseline scores on musculoskeletal US synovial hypertrophy and power Doppler in individual joints were significantly associated with the progress in the Genant-modified Sharp score. A significant association between the power Doppler score and the radiological progression was found even in totally asymptomatic joints. The quantification of the sonographic findings in valid scoring system form is necessary and challenging, since this will help the research to identify their exact role in predicting patients' outcome in long term and thus, may have an impact in therapeutic decisions.

In summary, various demographic, clinical, laboratory, imaging, immunological and genetic predictors have been recognised so far as regards the future course of RA. Nevertheless, their use is limited by certain drawbacks: first of all, their predictive value is not absolute, which means that a patient having a certain adverse prognostic factor may run an unexpectedly mild disease course or respond well to treatment, whereas another patient lacking such a predictor may still have a severe and relentless disease. Furthermore, the multiplicity of predictors and the variety of their combinations on every patient makes it often

puzzling to preclude all from the beginning how a patient will do in the short and long term. Second, plenty of these predictors have not been integrated into disease prediction models and have not been tested in prospective observational trials. To our knowledge, only two prediction models for erosive arthritis have been described (38, 127). Therefore, for the time being there are no strong data, so as to establish suggestions concerning treatment strategies based on predictive factors. Third, although some prognostic factors are evident (*e.g.* gender, age at disease onset, etc.) or routinely assessed (ESR, RF, anti-CCP antibodies), others are much more troublesome and costly to assess (*e.g.* HLA-DRB1 genotype) or even assessed solely at certain research centers (*e.g.* PTPN-22 polymorphisms). Consequently, evaluating as many predictive factors as possible is not feasible, is time- and money-consuming and may still yield inconclusive results with regard to the prediction of the disease outcome of any individual patient a rheumatologist is called to treat. However, in early patients with inflammatory synovitis, it is mandatory to measure the number of tender and swollen joints, the CRP and ESR, as well as RF and anti-CCP antibodies and to perform hand and wrist x-rays (128).

In conclusion, one should keep in mind that structural damage is a result of the inflammatory process (129) and that it may still progress despite apparent clinical remission, because inflammation may still smolder subclinically. Pursuing remission early means close monitoring of the patient and prompt treatment modifications according to disease status. After all, early response to treatment is itself a predictive factor of disease status at later time points (130), while disease activity averaged through time is in turn a predictor of structural damage (33, 58). Furthermore, early treatment of RA with DMARDs has been associated with lower radiographic progression rates in the long-term (44, 131). Therefore, it is on the rheumatologist to tailor his/her treatment taking into account both the prognostic factors that are routinely available in daily practice, as well as the mode each individual patient responds to treatment.

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