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Published in:
Annals of the Rheumatic Diseases

DOI:
[10.1136/ard.2003.019992](https://doi.org/10.1136/ard.2003.019992)

2005

[Link to publication](#)

Citation for published version (APA):

Lindqvist, E., Eberhardt, K., Bendtzen, K., Heinegård, D., & Saxne, T. (2005). Prognostic laboratory markers of joint damage in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, 64(2), 196-201.
<https://doi.org/10.1136/ard.2003.019992>

Total number of authors:
5

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Prognostic Laboratory Markers of Joint Damage in Rheumatoid Arthritis

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HOW TO CITE THIS ARTICLE

Lindqvist E, Eberhardt K, Bendtzen K, *et al.* Prognostic Laboratory Markers of Joint Damage in Rheumatoid Arthritis. *Ann Rheum Dis* Published Online First [date of publication]*. doi: 10.1136/ard.2003.019992

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Prognostic Laboratory Markers of Joint Damage in Rheumatoid Arthritis

Full-length article

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Grants were obtained from the Swedish Medical Research Council, the Österlund and Kock Foundations, the King Gustaf V 80-year Fund, The medical Faculty, Lund University, the Danish Rheumatism Foundation and the Swedish Rheumatism Foundation.

Running title: Prognostic markers in rheumatoid arthritis

Keywords: Rheumatoid arthritis, joint damage, Rheumatoid factors, anti-CCP, Cartilage oligomeric matrix protein (COMP)

Abstract

Objective: To investigate if determination of a set of laboratory markers at baseline provides prognostic information regarding joint damage in hands and feet in rheumatoid arthritis (RA).

Materials and methods: 183 patients with early RA included in a prospective study 1985-1989 were examined. Radiographic changes in hands and feet 5 and 10 years after inclusion were evaluated according to Larsen. The markers analysed were: erythrocyte sedimentation rate (ESR) according to Westergren, HLA-DRB alleles typed by restriction fragment length polymorphism and C-reactive protein (CRP), Cartilage Oligomeric Matrix Protein (COMP), Rheumatoid Factor (RF) of IgG, IgA and IgM type, antibodies against cyclic citrullinated-peptide (anti-CCP) and interleukin-1 α (anti-IL-1 α) analysed by immunoassays. Multiple linear regression with backward elimination was used to evaluate the prognostic value of the variables.

Results: The number of positive patients was for IgG RF 117/176, IgA RF 138/176, IgM RF 139/176, anti-CCP 140/176 and for anti-IL-1 α 40/182. ESR, presence of IgA RF, serum levels of COMP and presence of anti-CCP were significantly associated with more severe joint damage and presence of anti-IL-1 α with less severe joint damage, after 5 years. Baseline CRP and anti-CCP predicted radiographic outcome after 10 years. A stronger prediction was obtained by combining the prognostic factors.

Conclusions: Early determination of anti-CCP, IgA RF, anti-IL-1 α , ESR, CRP and COMP predicted development of joint damage in hands and feet in this cohort. The combination of these measures reflecting different aspects of the disease process should be useful for evaluation of prognosis in individual patients with early RA.

Introduction

Rheumatoid arthritis (RA) has a variable disease course and the lack of reliable prognostic factors that are useful at disease onset is well recognized by practicing rheumatologists. Outcome in RA is complex and relates to several entities such as disease activity, functional status, joint damage and the patients' perception of general health. The synovitis may explain most of the early symptoms experienced by the patients and is also considered to contribute to the development of joint damage and disability. The correlation between inflammation and joint damage has been extensively studied and especially the relation between inflammatory variables, e. g. C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR) and joint damage (1-4). Although there is a link between inflammation and development of joint damage it is well established that joint damage may progress in spite of decreased inflammatory activity, and erosions may develop in RA patients with little clinical signs of inflammation. Therefore, other pathological processes than inflammation have been suggested to be involved in the destructive process (5-7).

We have in this study focused on the destructive process and used joint damage in hands and feet evaluated on radiographs as outcome variable. We selected a number of laboratory variables with suggested prognostic potential and tested their value in a well-defined cohort of RA patients from the 1980s followed from early disease (8). The variables were ESR and CRP reflecting inflammation, Cartilage Oligomeric Matrix Protein (COMP) a marker of cartilage turnover with putative roles in disease chronicity (9), a set of auto antibodies: IgG- IgA- and IgM-RF, anti-cyclic citrullinated peptide antibodies (anti-CCP), interleukin-1 α antibodies (anti-IL-1 α) and shared epitope.

Molecular markers from joint tissue matrix might be used to reflect the destructive process in RA (10). Increased serum levels of COMP have been found to correlate with large joint destruction in patients with RA (11). It has also been shown that COMP is a measure of tissue processes that are distinct from the reactions in inflammation (12-14).

RF and the more recently described anti-CCP (15-17), which is reported to be more specific for RA than RF, have in studies both been shown to be associated with more severe joint damage (18-26). The different subtypes of RF have also been examined in relation to joint damage and some studies have found IgA RF to be more related to joint damage (27-29) but the findings are conflicting (30-31).

IL-1 α is an important proinflammatory cytokine in RA, and naturally occurring anti-IL-1 α were first reported in 1989 (32). These bind with high affinity to IL-1 α , thereby preventing binding of IL-1 α to its receptors and thus neutralizing the biological activity of the cytokine (32-33). Some groups have demonstrated that patients with arthritis that carry the anti-IL-1 α develop a less destructive disease (34-37). The reported frequency of anti-IL-1 α in the population varies from 10-60 % depending on age, sex and assay sensitivity (38).

Genetic predictors for RA, mainly the HLA-DRB1 alleles have been investigated but the results are diverging concerning the prognostic influence on joint damage, disability and disease persistence (24;39-41).

We have in this report examined if combined determination of ESR, CRP, COMP, shared epitope, IgG-, IgA- and IgM-RFs, anti-CCP and anti-IL-1 α provides prognostic information regarding the development of joint damage in hands and feet after 5 and 10 years in a prospective study of early RA patients.

Patients and methods

All new patients with definite RA according to the 1958 ARA criteria were included in a prospective study from 1985 to 1989 at the Department of Rheumatology at Lund University Hospital in southern Sweden. All consecutive patients, 18 years or older with duration of symptoms for less than 2 years, were included. Most patients were referred from primary health care units as a result of a special campaign to recruit cases of recent onset. The study comprises 183 patients (116 women and 67 men). The mean age (SD) was 51.2 years (12.4) and mean duration (SD) of symptoms at inclusion in the study was 11.1 (6.1) months. All patients, irrespective of disease activity, were included and followed prospectively at least annually at a team care unit. Patients with active disease were offered treatment with disease modifying antirheumatic drugs (DMARDs) throughout the study according to general clinical practice, which changed during the study period. Early in the study D-penicillamine and antimalarials were the most commonly used DMARDs, while at the 10-year follow-up 23% of the patients were being treated with methotrexate, which then was the most frequently used drug. During the first 5 years, thirteen patients were treated with methotrexate while from year 5 to 10, forty-six patients were treated with methotrexate. The whole cohort has been followed for at least 10 years and the clinical outcome is presented extensively elsewhere (42).

Radiographic evaluation

In the present study radiographic findings in hands and feet at years 5 and 10 were used as outcome variables. Radiographic outcome over the first 10 years and scoring methodology are described in detail previously (43). In brief, radiographs of hands and feet (standard film in postero-anterior projection) were obtained annually from inclusion to year 5 and at year 10. Joint damage caused by RA was evaluated according to Larsen and Dale (44). Thirty-two joints in hands and feet were assessed. Each joint was compared with a standard reference film and changes were graded from 0-5 where a score of ≥ 2 represents erosive disease. A joint damage score (JDS) was calculated by adding all scores, the wrist multiplied by five, resulting in a range of 0-200 (43). The scoring was made by one of two assessors, years 0-5 were scored in chronological order and the 10-year evaluations were scored separately. Scoring reliability (inter and intraobserver, chronological order versus separately) was evaluated using the intra-class correlation coefficient (ICC) and varied from 0.92-0.99 (43).

Biochemical analyses

Blood samples were collected from all patients at inclusion in the study. ESR was determined according to Westergren and CRP by an electroimmunoassay (45). HLA-DRB alleles were typed by restriction fragment length polymorphism analysis with sequence specific primers as previously described (39). EDTA-plasma and sera were frozen in aliquots and stored at -80°C . Serum COMP was measured with a commercial sandwich-ELISA utilizing two monoclonal antibodies directed against separate antigenic determinants on the human COMP molecule (AnaMar Medical, Lund, Sweden). The detection limit was <0.1 U/L and the intra- and interassay coefficient of variation was $<5\%$. RFs of types IgG, IgA and IgM were analysed with ELISA using commercial kits (Inova Diagnostics, San Diego, CA, USA) according to the manufacturer's instructions. Rabbit IgG was used on the solid phase. The limit for a positive result was set to >6 IU. Anti-CCP was analysed with ELISA using a commercial kit (Inova Diagnostics) in which a synthetic cyclic citrullinated peptide is used as antigen. The lowest value for a positive outcome was set to ≥ 20 U. Anti-IL-1 α were analysed

with radioimmunoassay as previously described (37). The limit for positive results for anti-IL-1 α was defined as binding >10%.

The study was approved by the Ethics committee of Lund University.

Statistical analysis

Comparisons between groups were analysed by Mann-Whitney's test, Wilcoxon's test or χ^2 test where appropriate. Pearson correlation coefficients expressed the relationships between assessed variables. Multiple linear regression with backward elimination was performed to decide the degree of explanation of the different variables to Larsen score years 5 and 10. The following independent variables were entered as continuous variables: ESR, CRP, COMP and age at inclusion. IgG-, IgA- and IgM-RF, anti-CCP, anti-IL-1 α , shared epitope and sex were entered as dichotomised independent variables. The variance inflation factor (VIF) was used to check for collinearity between the independent variables. All tests were two tailed and limit value for significance and elimination in the regression analysis was set at $p < 0.05$.

Results

The baseline characteristics of the patients are given in Table 1.

Table 1

Baseline characteristics of the 183 early RA patients. Continuous variables are expressed as means (SD).

Age at onset	Years	51 (12.4)
Females/males	No	116/66
Presence of "Shared Epitope"	%	85
CRP	mg/L	27 (33)
ESR	mm/1h	36 (28)
COMP	U/L	11.9 (3.7)
Larsen at baseline	U	8 (9)
IgG RF positivity	%	67
IgA RF positivity	%	78
IgM RF positivity	%	79
Anti CCP positivity	%	80
Anti-IL1 α positivity	%	22

U - units

After 10 years 157 patients were still followed. Of the 26 patients missing the 10-year radiographic evaluation, 17 had died, 5 had moved from the area, 3 were excluded due to old age or other diseases and 1 refused to undergo the examination. The median (interquartile range (IQ)) Larsen score year 5 was 42 (17-60) with a range from 0 to 152. At year 10 the median (IQ) Larsen score was 54 (28-80) with a range from 0 to 162. At inclusion, the number of patients positive for IgG RF was 117/176 (66%), for IgA RF 138/176 (78%), for IgM RF 139/176 (79%), for anti-CCP 140/176 (80%) and for anti-IL-1 α 40/182 (22%). The concordance between the various rheumatoid factors and anti-CCP-antibodies was high. Over half, 101/176 (57%) of the patients had all 3 RFs and anti-CCP. One hundred and seventy of the patients were genotyped and of these 145 (85%) carried the shared epitope. Fifty-four (32%) carried the epitope on both alleles.

Correlation:

Table 2 shows the correlation coefficients for the assessed variables.

Table 2

Correlation coefficients, significance and number of observations of the variables analysed.

		Larsen score Year 5	Larsen score Year 10	ESR Year 0	CRP Year 0	COMP Year 0	IgG Year 0	IgA Year 0	IgM Year 0	Anti- CCP Year 0	Anti- IL1 α Year 0	Epitope Single dose
Larsen score Year 10	P C N	0.848*** 129										
ESR Year 0	P C N	0.436*** 139	0.397*** 155									
CRP Year 0	P C N	0.403*** 116	0.391*** 128	0.737*** 147								
COMP Year 0	P C N	0.198* 133	0.133 150	0.228** 169	0.221** 142							
IgG RF Year 0	P C N	0.233** 136	0.205* 152	0.124 174	0.036 143	-0.105 166						
IgA RF Year 0	P C N	0.392*** 136	0.363*** 152	0.137 174	0.047 143	-0.106 166	0.593*** 176					
IgM RF Year 0	P C N	0.233** 136	0.248** 152	0.129 174	0.164 143	-0.133 166	0.579*** 176	0.610*** 176				
Anti-CCP Year 0	P C N	0.344*** 136	0.420*** 152	0.128 174	0.131 143	-0.117 166	0.296*** 176	0.556*** 176	0.464*** 176			
Anti-IL-1 α Year 0	P C N	-0.111 141	-0.092 157	0.004 181	-0.016 148	0.055 171	0-.103 176	0.021 176	-0.086 176			
Single dose Shared Epitope	PC N	0.108 137	0.114 154	0.074 169	0.095 139	-0.093 162	0.018 165	0.145 165	0.186* 165	0.263** 165	-0.080 171	
Double dose Shared Epitope	PC N	0.145 138	0.115 155	0.040 171	0.171* 141	0.033 164	0.066 167	0.126 167	0.095 167	0.191* 167	-0.103 173	0.288** 171

*** Correlation is significant at the 0.001 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). P C= Pearson Correlation, N= Number of patients

ESR and CRP were strongly correlated. The various subtypes of RFs showed relatively strong correlation. Anti-CCP showed highest relation to IgA RF and in descending order to IgM and IgG RF. ESR, CRP and IgA RF were correlated significantly but rather weak to the Larsen score while COMP only showed a weak correlation to Larsen score at year 5, ESR and CRP.

Regression analyses:

ESR, COMP, IgA RF, anti-CCP and anti-IL-1 α were found to explain 44% of the variance in Larsen score year 5. The last step of the regression analysis is given in Table 3.

Table 3

Final step in multilinear regression analysis with backward elimination. Larsen score year 5 is dependent variable and the laboratory analyses are used as independent variables.

Model	Unstandardized Coefficients		Sig.	95% Confidence Interval for B		Collinearity Statistics
	B	Std. Error		Lower Bound	Upper Bound	
(Constant)	-10.579	9.216	0.254	-28.862	7.704	
ESR	0.333	0.077	0.000	0.180	0.487	1.118
COMP	1.637	0.662	0.015	0.323	2.950	1.086
IgA RF	19.132	6.803	0.006	5.638	32.627	1.558
ANTI-CCP	14.465	6.313	0.024	1.942	26.988	1.551
Anti-IL-1 α	-13.341	4.977	0.009	-23.215	-3.467	1.023

a Dependent Variable: LARSEN Score year 5

VIF=Variance inflation factor

Increased ESR and COMP levels, presence of IgA RF and anti-CCP antibodies were significantly associated with more severe joint damage and presence of anti-IL-1 α with less severe joint damage. The variance inflation factor (VIF) being close to 1 demonstrates that the measurements represent different entities, except IgA RF and anti-CCP where a VIF of 1.6 indicates a certain degree of multicollinearity.

Presence of shared epitope, age at inclusion in the study and sex did neither influence the results after 5 nor after 10 years.

Thirty two percent of the variance in Larsen score year 10 could be explained by CRP and anti-CCP. Anti-IL-1 α , IgA RF and COMP were not significantly associated with Larsen scores at year 10 (p-values of 0.06, 0.12 and 0.16 respectively). The last step of the regression analyses is given in Table 4.

Table 4

Last step in multilinear regression analysis with backward elimination. Larsen score year 10 is dependent variable and the laboratory analyses are used as independent variables

Model	Unstandardized Coefficients		Sig.	95% Confidence Interval for B		Collinearity Statistics
	B	Std. Error		Lower Bound	Upper Bound	VIF
(Constant)	18.180	6.442	0.005	5.460	30.901	
CRP Year 0	0.4175	0.097	0.000	0.233	0.617	1.042
Anti-CCP	36.609	7.201	0.000	22.346	50.872	1.042

a Dependent Variable: Larsen score Year 10

VIF = variance inflation factor

To be able to use these findings to predict development of joint damage in individual patients an interpretation of the results from the analysis with the Larsen score year 5 as dependent variable is given in Table 5A and the Larsen score year 10 in Table 5B. Importantly, if more than one risk factor is present in the same patient, the effect is additive.

Table 5 A

Interpretation of the results from regression analysis useful for the prediction of joint damage in individual patients. The Larsen score year 5 was used as dependent variable

Variable assessed at baseline	Interpretation
ESR	An increase of 1 mm/1h in ESR corresponds to an average increase in Larsen score of 0.3
IgA RF	With positive IgA RF the Larsen score is on average 19,1 units higher
Anti-IL-1 α	With positive anti-IL-1 α the Larsen score is on average 13.3 units lower
COMP	An increase of 1 unit corresponds to an average increase in Larsen score of 1.6
Anti-CCP	With positive anti-CCP the Larsen score is on average 14.4 units higher

Table 5B

Interpretation of the results from regression analysis useful for prediction of joint damage in individual patients. Larsen score year 10 was used as dependent variable

Variable assessed at baseline	Interpretation
CRP	An increase of 1 mg/L corresponds to an average increase in Larsen score of 0.42
Anti-CCP	With positive anti-CCP the Larsen score is on average 37 units higher

Due to missing data in one or more variables only 107/177 patients year 5 and 119/157 year 10 could be included in the regression analyses. At year 5, patients not included in the analyses had higher CRP values ($p < 0.05$) and tended to be IgA RF positive less frequently

($p=0.09$). At year 10 patients not included in the analyses were older ($p<0.01$) and more often men ($p<0.05$). An increased mortality among older men contributed to this (46). No other significant differences between assessed variables were found at any time point.

Discussion

In this study we could demonstrate that laboratory variables explained about half of the variance in the Larsen score after 5 years. Serum COMP levels, anti-CCP and anti-IL-1 α added prognostic information to ESR and IgA-RF, which were the strongest predictors of joint damage in hands and feet after 5 years. After 10 years anti-CCP was the only significant predictor together with CRP. We found inflammatory parameters to demonstrate relationship to joint destruction, which is in concordance with many earlier reports (3-4;43). The various RF subtypes factors correlated to each other. However, as in many previous studies IgA-RF turned out to have the best prognostic power after 5 years. The lack of significant association for IgA-RF at year 10 could be caused by the existing collinearity between anti-CCP and IgA-RF. We have earlier reported that IgG-RF showed the strongest relation to joint damage after 2 years follow up of this cohort (47). The discrepant findings might be explained by the shorter follow up period, different assessment methods, and fewer patients. Furthermore presence of anti-CCP predicted a more destructive RA both after 5 and 10 years. The 5 year findings are in concordance with other studies (19-21). The current study extends these results by showing that this holds out also in a longer perspective. Anti-CCP appears early in the disease course and has a high specificity for RA (48). Anti-CCP might therefore be a valuable additional predictive tool in the management of RA patients. The strong concordance between RFs and anti-CCP resulting in that very few patients lacking RF will be positive for anti-CCP restricts the clinical importance of using both antibodies. We also found COMP, a marker reflecting another aspect of the disease process, to yield additive predictive value. COMP shows very weak associations to both inflammatory parameters and autoantibodies. This protein was originally isolated and characterized as a cartilage matrix component but has subsequently also been found in other tissues e.g. synovium, tendon and meniscus (for references see (14)). However, numerous studies in human and experimental arthritis clearly indicate that changes in serum levels of COMP relate to processes in cartilage (10;12;14). Thus, serum COMP is a potential marker of changes in the cartilage turnover and increased serum levels may occur early in the course of RA as a sign of cartilage involvement. The present study lends further support to this interpretation by showing that the serum concentration of COMP at inclusion was prognostic for future small joint damage. The original COMP assay and the one used in the present study measures both intact and fragmented COMP, which limits the possibility to discriminate between matrix synthesis and degradation (9). Refinement of the technology enabling specific measurement of select fragments will most likely increase the prognostic utility of COMP. The observations regarding COMP in this study is at variance with findings in a previous study of ours, where COMP was not found to be prognostic for small joint damage in a subset of patients from the early RA cohort (49). A possible explanation for this discrepancy is that a different COMP assay with a polyclonal antibody was used (9).

The naturally occurring anti-IL-1 α were found to predict less severe radiographic outcome in this cohort. This finding is in concordance with some previous studies (34-37), but it may be apparent only with prolonged disease, because a 2-year follow-up in an early RA cohort failed to show this relation (50). This latter study did not correct for presence of RF and anti-CCP, which may have contributed to the diverging results.

Presence of shared epitope in single or double dose did not provide any predictive information on development of joint damage in this study. We have earlier found that presence of shared

epitope was not related to functional outcome (42). These findings are in agreement with several other reports indicating that genetic screening should not be performed routinely in early arthritis clinics (40).

The variance of radiographic damage that could be explained in our multivariate models were 44% after 5 years and 32% after 10 years by baseline laboratory assessments. Even if the degree of explanation is fairly moderate our findings can be used as guidance when trying to predict risk of joint damage in individual patients as shown in Tables 5A and B. So far no other better predictors have been recognized. The prognostic value of our laboratory assessments was somewhat less apparent for the 10-year outcome. One explanation for this might be that about 75% of the joint damage had already occurred after 5 years (43).

Furthermore, the therapeutic strategy used in this cohort changed over time. During the first 5 years only 7% (n=13) of the patients were treated with Methotrexate compared with 27% (n=46) during the following 5 years. Although this figure is low compared with current strategy it could still influence the results as Methotrexate has been shown to modify progression of joint damage (51). Modification of the disease course by effective treatment strategies will increasingly hamper the evaluation of new potential prognostic markers in the future (52). Therefore our cohort of conservatively treated patients, as compared to current standards, will be valuable for such studies.

In conclusion, in this prospective early RA cohort ESR/CRP, COMP, and presence of IgA RF, anti-CCP and anti-IL-1 α assessed at presentation provided prognostic information regarding future joint destruction. The laboratory measures used were selected to reflect different aspects of the disease process. The combination of markers was found to yield additive prognostic information.

Disclosure: Tore Saxne and Dick Heinegård are co-founders and share-holders in AnaMar Medical.

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