Prediction of 20-year outcome at onset of seropositive rheumatoid arthritis

J.K. Jäntti, K. Kaarela, R.K. Luukkanen, H.J. Kautiainen

Rheumatism Foundation Hospital, Heinola and 1Satalinna Hospital, Harjavalta, Finland.

Juha K. Jäntti, MD; Kalevi Kaarela, MD, PhD; Reijo K. Luukkainen, MD, PhD; Hannu J. Kautiainen, BA.

Please address correspondence and reprint requests to: Juha K. Jäntti, MD, Rheumatism Foundation Hospital, FIN-18120 Heinola, Finland.

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ABSTRACT

Objective
With the advent of new and expensive antirheumatic treatments with potentially serious side effects, it would be essential to identify as early as possible those rheumatoid arthritis (RA) patients who have a poor prognosis. Here study was made of the prognostic value of different markers recorded at the onset of RA.

Methods
At the 20-year follow-up of our prospective study, 66 patients had rheumatoid factor-positive (RF+) RA. At commencement of follow-up (disease duration < 6 months), the prognostic value of 19 demographic, laboratory, clinical and radiographic variables was tested to explain the 20-year Larsen score for peripheral joints and the Health Assessment Questionnaire (HAQ) index using Somers’ d for asymmetrical associations.

Results
An association was observed between onset blood platelets (0.17), serum IgG (0.18), the onset Larsen score (0.53) and the 20-year Larsen score. Old age (0.30), serum orosomucoid (0.17), the function score (0.28), morning stiffness (0.28), and grip strength (0.24) were associated with the 20-year HAQ.

Conclusion
The correlation between the investigated entry variables and end-point outcome was poor. In our discussion we conclude that the most important prognostic factor in RF+ RA is the treatment.

Introduction
Rheumatoid factor-positive rheumatoid arthritis (RF+RA) is a chronic autoimmune disease, which predisposes the patient to subsequent destruction of joints and leads to permanent disability and even to premature death in 20% of subjects (1). Some patients may have a good prognosis. Early and aggressive therapy seems to improve the long-term outcome (2). Recognition of factors indicative of poor outcome would make it possible to identify cases in need of aggressive therapy.

In 1983 we published a paper on the prediction of radiological destruction in RA using the three-year results of a prospective study entitled the Heinola Follow-up Survey of Arthritis (3). Follow-up of RA patients in this inception cohort has now continued for 20 years. In the present study we investigated the prognostic value of early markers in the prediction of the long-term outcome of RA.

Patients and methods
During the years 1973-1975 a total of 121 patients with recent (< 6 months) RA were studied at the Rheumatism Foundation Hospital in Heinola. The selection criteria, data collection strategy and details of the patients are described elsewhere (4). Out of the 103 RF+RA patients seen at their eight-year check-up, 66 attended the 20-year follow-up, while 30 others had died and 7 were unable to attend (5). The disease had been erosive in 65 of the 66 patients (6). Disease-modifying antirheumatic drugs (DMARDs) used during the first 8 years were in most cases aurothiomalate and/or chloroquine (5).

In reading the radiographs, destruction was graded by the Larsen method (7). Radiographs of the hands and feet were taken in the dorsovolar projection. Larsen grades for the I-V metacarpophalangeal joints and wrists and the II-V metatarsophalangeal joints (20 joints) were added up to form a Larsen score of 0-100 (6). Disability was assessed by the Health Assessment Questionary (HAQ) index (8). A continuous scale (0-3) of functional disability indices was applied. The following entry variables were compared with the Larsen score and HAQ: sex, age, grip strength, function score (5), number of swollen joints (PIP, MCP, wrist, elbow, shoulder, sternoclavicular, jaw, MTP, subtaloid, ankle, knee; maximum 46), ACR 1987 criteria for RA (1st to 7th) (9, 10), sum of the ACR criteria, erosiveness (erosion in any joint), Larsen score of 0-100, HLA B27, ESR, blood haemoglobin, blood platelets, serum IgA, IgG and IgM, serum C1 esterase inhibitor, and serum orosomucoid.

Somers’ d coefficient for asymmetrical associations was used to measure the relationships between the individual variables at the start of the follow-up and the 20-year Larsen score and HAQ (11); Somers’ d is a measure of association for asymmetric cases in which one variable is considered the response and one ex-
planatory. In addition we used stepwise logistic regression analysis to explain the end-point Larsen score. Larsen scores were formed dichotomically using the median as the intersection. Spearman’s rank correlation was used to study the correlation between the 20-year Larsen score and HAQ.

**Results**

Figure 1 shows the distribution of the Larsen scores and HAQ indices and their mutual correlations at the 20-year follow-up. The age-adjusted correlation coefficient between the HAQ index and the Larsen score was 0.46. Table I shows the association between the investigated prognostic indicators at the first hospitalization and the 20-year Larsen scores and HAQ indices. Blood platelets, serum IgG and moderately Larsen score correlated with end-stage destruction of peripheral joints. As expected, old age, the function score, morning stiffness, grip strength and, additionally, serum orosomucoid correlated with the HAQ index. In the stepwise logistic regression analysis only the baseline Larsen score entered and explained the later joint destruction (OR = 1.4 [95% CI 1.1 to 1.8]). In this analysis RF was discarded.

**Discussion**

The course of RA varies widely from mild to malignant and destructive. Early cases may in rare instances remit spontaneously, but RF+ RA is in most cases a progressive disease leading to continuously increasing joint damage during 20 years after onset (6, 12). Nowadays there is substantial evidence to show that treatment may improve the prognosis, and in planning therapy it would thus be of prime importance to know as early as possible whether the disease will be mild or severe. The prognostic factors associated with RA have been evaluated in many studies; numerous clinical, laboratory, radiological, genetic and socio-demographic variables have been used as markers. Radiologically detected joint damage and functional outcome have been used as outcome measures in most studies. The predictive value of these prognostic markers has, however, been low and inconsistent, for a number of

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**Table I.** Somers’ *d* asymmetrical associations between the entry explanatory baseline variables and the 20-year response Larsen score and HAQ in 66 seropositive rheumatoid arthritis patients.

<table>
<thead>
<tr>
<th>Explanatory variables at onset</th>
<th>Larsen score</th>
<th>HAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Somer’s <em>d</em></td>
<td>95% CI</td>
</tr>
<tr>
<td>Demographic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>0.18</td>
<td>-0.13 to 0.48</td>
</tr>
<tr>
<td>Age at entry</td>
<td>-0.02</td>
<td>-0.21 to 0.17</td>
</tr>
<tr>
<td>HLA B27</td>
<td>0.27</td>
<td>-0.01 to 0.55</td>
</tr>
<tr>
<td>Laboratory tests:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>0.08</td>
<td>-0.07 to 0.23</td>
</tr>
<tr>
<td>Serum rheumatoid factor</td>
<td>&lt; 0.00</td>
<td>-</td>
</tr>
<tr>
<td>Blood platelets</td>
<td>0.17</td>
<td>0.02 to 0.33</td>
</tr>
<tr>
<td>Serum C1 esterase inhibitor</td>
<td>0.02</td>
<td>-0.16 to 0.20</td>
</tr>
<tr>
<td>Serum orosomucoid</td>
<td>-0.01</td>
<td>-0.17 to 0.16</td>
</tr>
<tr>
<td>Serum IgG</td>
<td>0.18</td>
<td>0.01 to 0.36</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>0.02</td>
<td>-0.16 to 0.20</td>
</tr>
<tr>
<td>Serum IgM</td>
<td>0.12</td>
<td>-0.06 to 0.29</td>
</tr>
<tr>
<td>Clinical measures:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function score</td>
<td>-0.06</td>
<td>-0.24 to 0.11</td>
</tr>
<tr>
<td>Morning stiffness (ACR criterion 1)</td>
<td>0.21</td>
<td>0.13 to 0.55</td>
</tr>
<tr>
<td>Sum of ACR criteria</td>
<td>0.10</td>
<td>-0.11 to 0.32</td>
</tr>
<tr>
<td>Number of swollen joints</td>
<td>-0.03</td>
<td>-0.22 to 0.15</td>
</tr>
<tr>
<td>Grip strength of hands</td>
<td>&lt; 0.00</td>
<td>—</td>
</tr>
<tr>
<td>Radiographic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsen score</td>
<td>0.33</td>
<td>0.17 to 0.50</td>
</tr>
<tr>
<td>Radiographic changes (ACR criterion 7)</td>
<td>0.15</td>
<td>-0.23 to 0.53</td>
</tr>
<tr>
<td>Erosions</td>
<td>0.02</td>
<td>-0.26 to 0.30</td>
</tr>
</tbody>
</table>
possible reasons. The patient selection criteria, follow-up times and outcome measures have varied in the studies. Also, the more active treatment of RA in recent years may have modified the predictive value of prognostic markers. Our 3-year prognostic study in 1983 relied upon the ACR 1958 criteria (3, 13). In 107 RA patients radiological changes, grip strength and ESR were the best predictors of the Larsen score of 0 - 200. At the 8-year follow-up 200 patients were studied, of whom 106 had RA and 94 non-specific arthritis. (5). Ninety-four clinical, laboratory and radiological variables were compared with seven facets of outcome. The best predictors were polyarthritis, RF, radiological changes, morning stiffness, ESR and old age. These results still constitute valid clinical prognostic factors for an arthritic patient.

In the present study the diagnosis was sharpened to RF+ cases fulfilling the ACR 1987 criteria. We therefore believe that these 66 patients truly represent what is meant by RA. One might argue that patients with the poorest prognosis would have died during the 20 years of follow-up. To our surprise, however, the mean radiological progression of the disease in these patients did not differ at the 8-year or the 15-year follow-up from that in the whole group (6).

Fifty-five (83%) patients in the present study fulfilled at least four ACR 1987 criteria at the commencement of follow-up. (10). This may explain why neither the number of ACR criteria nor any individual ACR criterion correlated significantly with the Larsen score within these RF+ patients.

The frequency of the HLA B27 antigen in Finland is 14.5%, which is higher than in most central or south European countries (14). At the 15-year follow-up we analysed the rate of radiological constancy of hips within Larsen scores 0 to 2. For HLA B27 antigen-positive RA patients it was 62% and for negative cases it was 87% (p = 0.02) (15). In the present study the mean Larsen score in 18 HLA B27-positives was 54.3 and in the remaining 48 negatives 41.3 (NS). The number of swollen joints did not correlate with the Larsen score or HAQ. This is evidently due to the nature of our material, which was collected in the very early stage of the disease when only 4 patients had 20 or more swollen joints. Twenty-nine patients (44%) had radiological erosions at onset and 50 (76%) fulfilled the seventh ACR 1987 criterion; these findings did not predict the future destruction of joints, but a baseline Larsen score of 0-100 did, as in other papers.

None of the entry laboratory parameters indicating disease activity correlated highly significantly with the Larsen score or the HAQ. This may be attributed to the fact that only a cross-section of them could be considered. If the longitudinal levels could be taken into account, their predictive value might be better. For instance, the prognostic value of a single measurement of ESR and CRP for the progress of radiological destruction is low, while constantly high levels in repeated investigation over two years are significantly correlated with the development of new erosions in RA patients (16).

In 1996 van Zeben and Breedveld reviewed 36 publications on factors prognostic of RA (17). Poorer outcome was associated with RF, HLA DR4, high disease activity, rheumatoid nodules, radiological abnormalities, poor functional status and grip strength. The accuracy of prediction of these individual factors was low, but together they predicted erosions with an accuracy of 70-80%.

In 1997 Kirwan and Quilty analysed 112 publications to elucidate prognostic criteria in RA (18). In addition to methodological flaws in some studies, the prognostic indicators were only moderately successful. In many of the reviewed studies the outcome was diagnosis of RA at one or two years of persistent disease. Such studies resemble our 8-year study with several positive correlations (5). HLA DR4 was not available in our study. In 1997 Wagner et al. concluded that HLA DR genotyping and DR4 subtype determination with RF were early risk markers for severe RA (19). In contrast, in 1998 Möttönen et al. found no prognostic significance with HLA DR4 or RA associated alleles with regard to the functional or radiological outcome of early RA patients followed for 6 years (20). High clinical activity at baseline and RF were the best predictors of a poor prognosis.

The recent Finnish 2-year therapy study of 195 patients with early RA emphasized the prognostic significance of treatment (21). Starting treatment with a combination of DMARDs resulted in remission 2.5 times more often compared with single-drug therapy.

The aim of the present prospective study was to ascertain whether the variables at onset correlate with the end-point outcome in RA. The results were mostly negative. The Larsen score and functional status are of some use. We conclude that baseline data is not strongly prognostic for the patient status 20 years later and that treatment is the most important prognostic factor for RF+ RA.

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