CORRELATES OF FUNCTIONAL DISABILITY IN EARLY RHEUMATOID ARTHRITIS: A CROSS-SECTIONAL STUDY OF 706 PATIENTS IN FOUR EUROPEAN COUNTRIES

L. M. SMEDSTAD,*† T. MOUM,* F. GUILLEMIN,‡ T. K. KVIEN,† M. B. FINCH,§ T. P. B. M. SUURMEIJER¶ and W. J. A. VAN DEN HEUVEL¶

*Department of Behavioural Sciences in Medicine, University of Oslo, †Oslo City Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, ‡School of Public Health, University of Nancy, Nancy, France, §Rheumatology Unit, Green Park Health Care Trust, Musgrave Park Hospital, Belfast and ¶Northern Centre for Health Care Research, University of Groningen, The Netherlands

SUMMARY

In this cross-sectional study of 706 European patients with rheumatoid arthritis (RA) of ≤4 yr duration, we examined possible correlates of functional disability assessed by the Health Assessment Questionnaire. First, we examined a subsample of 237 Norwegian patients. The Ritchie index, age, sex, erythrocyte sedimentation rate (ESR) and disease duration correlated significantly with disability, whereas serum rheumatoid factor, hand X-ray changes and educational level did not. Subsequently, we cross-validated these findings in a similar sample of 469 French, Dutch and Northern Irish patients. The results supported the Ritchie index, sex, ESR and disease duration as significant correlates of disability, whereas rheumatoid factor, age and education were not significantly correlated with disability. The correlation between X-ray changes and disability could not be cross-validated. The main findings of this study are that female sex correlates significantly with disability even early in the course of RA, whereas the rheumatoid factor does not.

KEY WORDS: Rheumatoid arthritis, Disability, Prognosis, Age, Sex, Rheumatoid factor.

PROGNOSTICATION of future outcome has proved a difficult concept in the rheumatological literature [1]. The early identification of factors associated with progressive disease in rheumatoid arthritis (RA) remains a major challenge to clinicians and researchers. RA is a potentially disabling disease and runs an unpredictable course. There is evidence that disability develops very early in the course of RA, and that the disease may be more amenable to treatment at an early stage [2]. Strategies for the treatment of RA in the 1990s advocate earlier recognition of progressive disease, accompanied by earlier treatment interventions [3]. Accordingly, the identification of factors indicative of a poor functional outcome early in the course of RA is crucial for tailoring treatment interventions and preventing irreversible joint damage and subsequent functional disability.

In most prognostic studies on RA, two factors are consistently identified as predictors of a poor prognosis, i.e. seropositivity [4-11] and female sex [10, 12-14]. Less consistent associations with a poor outcome are found for the presence of erosions [9, 12, 15, 16], older age [12, 13], persistently elevated erythrocyte sedimentation rate (ESR) [6, 10], high joint activity scores [8, 9], long duration of the disease [13] and low levels of formal education [17].

The aim of this cross-sectional study was to identify variables associated with functional disability early in the course of RA in a cross-cultural European setting. Identical inclusion criteria were applied in four countries, i.e. France, The Netherlands, Northern Ireland and Norway, giving a total sample of 706 patients with RA of 0-4 yr duration (mean 2.0 yr). By examining one of the four study samples, we generated working hypotheses as to which of the study variables could explain a poor functional status. Subsequently, we cross-validated these results in the rest of the sample.

The study aims were: (1) to generate hypotheses as to which variables significantly explain disability as opposed to variables that have no significant correlation to disability in a sample of 237 Norwegian patients with early RA; (2) to cross-validate these findings in a similar sample of 469 patients from France, the Netherlands and Northern Ireland.

PATIENTS AND METHODS

Patients

Patients were sampled from well-defined geographical regions in four European countries. The inclusion criteria were set by the EURIDISS project (European Research on Incapacitating Diseases and Social Support) [18], of which this study is a part. The sampling procedure, as well as the samples, have been described in detail elsewhere [19-21]. The inclusion criteria were as follows: residence in the study area, age 20-70 yr, diagnosis of RA according to the 1987 ARA criteria [22] and disease duration 0-4 yr. Exclusion criteria were the presence of other incapacitating diseases, stage IV according to Steinbrocker's functional class [23] or probable loss to follow-up (e.g. moving foreseen). The non-response rate varied from 12% in The Netherlands to 30% in France.

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**Measures**

Data on disease duration and current medication were collected from the medical files of the patients, whenever available, and/or from medical history taking. Joint tenderness, assessed by the Ritchie articular index [24], number of s.c. nodules and Steinbrocker's functional class [23] were recorded by a rheumatologist or a rheumatology research nurse. Blood samples were drawn for the analysis of ESR and rheumatoid factor (RF). The analyses of IgM-RF were performed at one centre for all samples, applying an ELISA technique and WHO international standard reference RF preparations [25]. In the Norwegian sample, radiographic changes were assessed by one experienced radiologist on anteroposterior hand radiographs according to the Larsen score [26]. The dependent variable, i.e. self-reported functional disability, was assessed by the Health Assessment Questionnaire (HAQ) [27], which has been validated in Dutch [28], French [29] and Swedish [30], which is very similar to the Norwegian language. This disability questionnaire examines eight dimensions of activities of daily living. The item with the highest score within each dimension is selected. A sum score representing the average value of the eight dimensions is computed. This sum score may have any value from zero (able to do without any difficulty) to three (unable to do). The Cronbach's α of the HAQ sum score, reflecting its internal consistency, was 0.89 in the pooled sample.

The level of formal education was recorded and coded according to the International Standard Classification of Education [31], and subsequently recoded into levels of education ranging from 1 (<7 yr of education) to 7 (≥16 yr of education).

**Data analyses**

National differences with respect to categorical and continuous variables were examined by χ² tests and one-way analyses of variance (ANOVAs), respectively. To counteract the possibility of a type I error, the latter were corrected for the multiple comparisons performed by means of the modified least significant difference tests; a procedure available in the software program SPSS.

To explore the multivariate effects of possible correlates of disability represented by the HAQ score, linear multiple regression analyses were applied. A forward stepwise selection of independent variables was chosen to identify variables that contributed significantly to the explained variance in HAQ score. This procedure was first conducted in the Norwegian sample, and subsequently repeated in the rest of the sample in order to examine the cross-cultural validity of the variables selected in the first regression procedure.

Possible interaction effects between pairs of independent variables were explored by entering multiplicative terms in the regression equation. For all analyses, two-sided t-tests and 5% levels of significance were chosen.

**RESULTS**

Patient characteristics of the four samples are presented in Table I. There were no significant differences between the four countries with respect to sex ratio or age at inclusion. Disease duration was significantly longer in Norway than in The Netherlands (2.3 and 1.8 yr, respectively). The level of education was significantly lower in France compared to the three other countries, and significantly higher in Norway than in The Netherlands.

Table II presents clinical variables in the four national samples. The percentage of seropositive patients ranged from 62% in France to 81% in The Netherlands. However, the differences in seropositivity between the countries were not significant at the 5% level. The Ritchie index and ESR did not differ significantly between the four samples. The percentage of patients currently using disease-modifying anti-rheumatic drugs (DMARDs) differed significantly between Norway (52% on DMARDs) and the other three countries (68% in France, 69% in The Netherlands and 78% in Northern Ireland, respectively). Hand X-ray changes were present in 55% of the Norwegian sample. The mean HAQ score ranged from 0.93 in Norway and France to 1.20 in Northern Ireland. These differences in HAQ scores were not, however, statistically significant when correcting for the multiple comparisons performed.

Table III presents the results from the forward stepwise regression analyses in the Norwegian sample (n = 237) with the HAQ score as the dependent variable. The Ritchie index, sex, ESR, age at inclusion and disease duration were all selected as significant

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>Patient characteristics by country,* mean values and (s.d.)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Norway</td>
</tr>
<tr>
<td>% Females</td>
<td>73.8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51.9 (13.6)</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>Level of education</td>
<td>3.6 (1.5)</td>
</tr>
<tr>
<td>1 = &lt;7 yr</td>
<td>7 = ≥16 yr</td>
</tr>
</tbody>
</table>

*NS, non-significant difference at the 5% level.

*Differences with respect to continuous variables were examined with correction for multiple comparisons with modified least significant difference tests.
correlates of disability, explaining a total of 44% of the adjusted variance in HAQ score. Sex was scored as 1 for males and 2 for females, implying that female sex was associated with higher disability. With a level of significance at \( P < 0.05 \), the remaining eligible independent variables were not entered into the equation, indicating that they would not reach this level if entered. These variables, i.e. level of education, X-ray changes and RF, and the corresponding \( P \) values at the last step of the forward procedure, are also listed in Table III.

We repeated the above analyses omitting the X-ray changes from the model, as this variable was not available for the rest of the European sample. This resulted in the same variables being selected as significant correlates of disability, i.e. the Ritchie score, sex, ESR, age at inclusion and disease duration, whereas education and RF again failed to contribute significantly to the explained variance in disability.

To cross-validate the above findings, forward stepwise regression analyses were performed in one pooled sample \( (n = 469) \) containing the French \( (n = 135) \), Dutch \( (n = 283) \) and Northern Irish \( (n = 51) \) patients (Table IV). Disability measured by the HAQ score was still the dependent variable, and the set of eligible independent variables was the same as in the analyses of the Norwegian sample with the exception of X-ray changes, which were not available. Repeatedly, the Ritchie index, ESR, disease duration and sex were selected as significant correlates of disability, explaining totally 40% of the variance in HAQ score, whereas age at inclusion was not entered into the model. Consistent with the results in the Norwegian sample, neither level of education nor RF was significantly correlated with disability.

In both of the above regression models, the RF was coded as a dichotomous variable in terms of presence or absence. We then repeated the analyses including the RF as a continuous variable in the set of eligible independent variables. The results were similar to those presented in Tables III and IV, i.e. the RF was still not entered into any of the two models, whereas the same variables as above were selected as significant correlates of disability.
Using multiplicative terms in a regression equation including all variables selected in our two stepwise procedures, we explored, in the pooled sample of 706 patients, the possibility that the Ritchie index shows differential effects on the HAQ depending on the sex and age of the patient. No significant second-order interactions were identified by the multiplicative terms involving the Ritchie index and sex, and the Ritchie index and age, respectively.

Although ANOVAs revealed no significant differences in HAQ scores between the four countries when correcting for the multiple comparisons performed (Table II), we also wanted to explore possible national differences in disability with a multivariate approach. Forward linear regression analyses with the HAQ score as the dependent variable were performed in the pooled sample of 706 patients. Independent variables were country (entered as a set of dummies) as well as the correlates of disability identified above. Controlling for the Ritchie index, ESR, sex, disease duration and age, the dummy variables indicating country of residence contributed as a set significantly to the variance in HAQ score (F = 4.85, P = 0.002). Using Norway as the reference sample, patients in the Netherlands and Northern Ireland had significantly higher mean HAQ scores, whereas the mean HAQ score in France was slightly, but not significantly, lower than in the Norwegian reference sample.

**DISCUSSION**

We consider the four national samples to be sufficiently similar to permit comparisons between one sample and the other three. Furthermore, we regard our samples as representative of early RA with respect to demographic and clinical variables (Tables I and II). The percentage of seropositive individuals is characteristic of samples identified in hospital settings [32].

The most striking finding of this study is the consistent lack of a correlation between the RF and functional disability. This goes contrary to a substantial body of follow-up studies of RA. In a prospective study by Sherrer *et al.* [12] with an average follow-up time of 11.9 yr, the presence of RF was one of the best predictors of disability. Wolff and colleagues [5] found that a positive RF at presentation of RA indicated a poor outcome in terms of disability 5 yr later. In a cohort study of 128 patients with RA, Suarez-Almazor and co-workers [7] found that the presence of RF was related to more severe outcomes in terms of joint counts and radiological scores assessed after 6-7 yr disease duration. van Zeben and colleagues [8] demonstrated a positive RF as one of the best predictors of outcome after 6 yr follow-up. In a prospective study of early RA over 15 yr, Corbett and co-workers [9] confirmed seropositivity as one of the early indicators of a poor outcome. Finally, in a review of the literature by van der Heijde *et al.* [10] in 1988, they concluded that most reports state the presence of RF as a strong predictor of an unfavourable course.

In contrast to many other studies on RF in which comparisons are undermined by discrepancies in methodology, the measurement of the IgM-RF in the present study was performed at one centre and with WHO standard reference RF preparations, thus ensuring reliable RF measures. In this study of 706 patients with early RA, neither the presence nor the titre of RF was able to explain current disability. The probable explanation for this lack of correlation between disability and the RF is the short disease duration of the present sample (range 0-4 yr, mean 2.0 yr). This implies that the well-documented link between the RF and an accelerated deterioration in physical function may be impossible to identify early in the course of the disease. Another possible contribution to the lack of correlation between the RF and disability is that seropositive patients in the study were treated more aggressively with DMARDs, thus theoretically reducing their level of disability.

The second variable which failed to explain disability in both regression models was the level of formal education. This is opposite to the findings of Callahan and Pincus [17], who demonstrated that education serves as a significant marker of clinical status in RA. Their results are in keeping with a study by Leigh *et al.* [13], who found that education was negatively associated with rapid deterioration in physical function. However, Corbett *et al.* [9] found no difference in functional deterioration between patients of different socioeconomic classes; a measure which overlaps with educational level to a considerable extent.

Age as a risk factor of increased disability is a controversial issue in the rheumatological literature [10]. This is reflected in the present study where age at inclusion was significantly related to disability in the Norwegian sample, whereas it failed to be identified as a significant correlate of disability in the second regression model with French, Dutch and Northern Irish patients. In a study by Sherrer *et al.* [12], age was the most powerful single predictor of disability, whereas Suarez-Almazor and colleagues [7] did not find any relationship between age at onset and prognosis of RA. Some authors have argued that disability in older individuals probably includes the effects of co-morbid conditions and senescence itself [13], as opposed to a more severe disease in the elderly.

Based on the first regression model with Norwegian patients, we hypothesized that hand X-ray changes would not correlate with disability. As this variable was not available for the rest of the sample, we were not, however, able to test this hypothesis. The lack of a relationship between erosive changes and disability is contrary to several studies of long-lasting disease [9, 12]. Although the mean disease duration of our sample may be too short to identify a relationship between erosions and disability, X-ray changes were actually present in 55% of the 237 patients. Furthermore, there is evidence that erosive changes occur within the first 2 yr of the disease [15, 16], thus supporting the relevance of examining the correlation between X-ray changes and disability even early in the course of RA.
The Ritchie score and the ESR were significantly correlated with disability in both of the regression models. Since disease activity and impairment drive the HAQ [33], these findings are not surprising. There is substantial evidence in the literature that measures reflecting the disease process are related to disease outcome in RA [6, 8–10]. Furthermore, disease duration was consistently correlated with functional disability even in this sample of patients with a maximum disease duration of 4 yr. Our finding is in agreement with a study on disability and disease duration by Leigh and colleagues [13], in which a significant association between disease duration and HAQ score was found.

In the present study, females consistently scored higher than males on functional disability. Theoretically, the current measure of disability, i.e. the HAQ, may be biased against women, thus augmenting the impression of severity of RA in women. However, most studies relate female sex to a poorer disease prognosis, which may be biased against women, thus augmenting the clinically, the current measure of disability, i.e. the HAQ, may be biased against women, thus augmenting the impression of severity of RA in women. However, most studies relate female sex to a poorer disease prognosis, whereas sex, only the latter was significantly correlated with disability in this cross-sectional study of early RA. These results indicate that while the disease duration of the present sample was too short to demonstrate increased disability among seropositive individuals, it was sufficiently long to demonstrate elevated levels of disability among females. Indirectly, this gives evidence for the relative strength of these two variables as early correlates of disability, indicating that the effect of sex on disability is more pronounced than the effect of the RF at an early stage of the disease.

CONCLUSION

Early identification of risk factors of disability in RA is a challenge to clinicians and researchers. In this cross-sectional study of early RA, the RF, traditionally considered as a predictor of a bad prognosis, was not significantly correlated with disability, whereas female sex, disease activity measures and duration of disease were. Early identification of high-versus low-risk patients with RA implies that aggressive and potentially toxic treatment can be reserved for those individuals who are most likely to fare badly, whereas low-risk patients may be candidates for less, rather than more, aggressive therapy.

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REFERENCES


