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BRIEF REPORT

# Predicting Functional Disability: One-Year Results From the Scottish Early Rheumatoid Arthritis Inception Cohort

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***Objective.*** **To identify baseline prognostic indicators of disability at 1 year within a contemporary early inflammatory arthritis inception cohort and then develop a clinically useful tool to support early patient education and decision-making.**

***Methods.*** **The Scottish Early Rheumatoid Arthritis (SERA) inception cohort is a multicenter, prospective study of patients with newly presenting RA or undifferentiated arthritis. SERA data were analyzed to determine baseline predictors of disability (defined as a Health Assessment Questionnaire [HAQ] score of ≥1) at 1 year. Clinical and psychosocial baseline exposures were entered into a forward stepwise logistic regression model. The model was externally validated using newly accrued SERA data and subsequently converted into a prediction tool.**

***Results.*** **Of the 578 participants (64.5% female), 36.7% (n = 212) reported functional disability at 1 year. Functional disability was independently predicted by baseline disability (odds ratio [OR] 2.67 [95% confidence interval (95% CI) 1.98, 3.59]), depression (OR 2.52 [95% CI 1.18, 5.37]), anxiety (OR 2.37 [95% CI 1.33, 4.21]), being in paid employment with absenteeism during the last week (OR 1.19 [95% CI 0.63, 2.23]), not being in paid employment (OR 2.36 [95% CI 1.38, 4.03]), and being overweight (OR 1.61 [95% CI 1.04, 2.50]). External validation (using 113 newly acquired patients) evidenced good discriminative performance with a C statistic of 0.74, and the calibration slope showed no evidence of model overfit ($P = 0.31$).**

***Conclusion.*** **In the context of modern early inflammatory arthritis treatment paradigms, predictors of disability at 1 year appear to be dominated by psychosocial rather than more traditional clinical measures. This indicates the potential benefit of early access to nonpharmacologic interventions targeting key psychosocial factors, such as mental health and work disability.**

The primary concern for many patients with newly diagnosed rheumatoid arthritis (RA) or undifferentiated inflammatory arthritis is the functional impact of their disease. Rheumatologists recognize the importance of

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targeting functional needs and appreciate that early, more aggressive intervention is likely to reduce long-term disability (1). However, the heterogeneous nature of the disease and its prognosis means a good outcome will be achieved with usual care alone in some patients but not in others. Identifying those patients at high risk of disability at a sufficiently early stage of their disease course presents a major challenge. Knowledge of baseline predictors of future disability would not only inform decision-making, for example, regarding the implementation of stratified therapeutic approaches, but also empower patients. Patients would be better able to understand their condition and options; this increases self-management, adherence, and satisfaction with consequent improvements in overall outcome (2).

Previous studies have identified a few baseline predictors of future disability, for example, high disease activity and erosive disease (3). Those studies have largely modeled putative clinical predictors and have rarely considered psychosocial factors, such as depression, which are considered common predictors of disability in other populations (4). Furthermore, previous models were derived from either historic cohorts (3,5,6), which generally used more conservative management approaches, or clinical trials, raising concerns regarding their generalizability. Finally, almost all limited their analyses to predictions of long-term disability (disability at 5–10 years) (3,7). Patients need more immediate prognostic information when first diagnosed in order to inform shorter-term personal decisions.

Ultimately, such models must be user-friendly if they are to be implemented. Clinical prediction tools can translate the output of statistical models into formats (e.g., scoring algorithms) suitable for general use. To the best of our knowledge, no 1-year RA disability clinical prediction tools have previously been developed.

In this study we aimed to identify baseline predictors of disability at 1 year within a prospective, generalizable, inception cohort of RA patients receiving modern standards of care. We adopted a holistic modeling approach, considering psychosocial as well as traditional clinical variables, and subsequently developed a clinical prediction tool with a view to facilitating future decision-making for both patients and clinicians.

## PATIENTS AND METHODS

**Study population.** The Scottish Early Rheumatoid Arthritis (SERA) inception cohort, which began in 2011, is an ongoing multicenter, prospective study of patients with newly diagnosed RA or undifferentiated arthritis. In Scotland, patients with RA or undifferentiated arthritis are primarily cared for at hospital-based rheumatology departments. Almost all departments (16 of 17) contribute to SERA, so coverage is excellent.

Eligible patients are required to have a minimum of 1 swollen joint. Patients are excluded if they have previously received disease-modifying antirheumatic drug (DMARD) treatment for more than 4 weeks or have an alternative rheumatic disease diagnosis.

**Data collection.** Patients are followed up every 6 months, and a comprehensive set of clinical, biologic, and psychosocial variables are evaluated. For this study, data extraction took place on October 23, 2014 (model development cohort) and again on April 27, 2015 (temporal validation cohort).

*Outcome of interest.* The outcome of interest was functional ability, as defined by the Health Assessment Questionnaire (HAQ) disability index, a self-report instrument describing physical function (scores range from 0 to 3 for each item). For this analysis, a HAQ score of ≥1 indicated moderate to high disability (8).

*Psychosocial predictor variables at baseline.* In addition to baseline HAQ, information on demographic characteristics and socioeconomic status were obtained, including age, sex, ethnicity, marital status, and employment status. The latter incorporated an assessment of absenteeism and was categorized as either "in paid employment without absenteeism during the last 7 days," "in paid employment with absenteeism during the last 7 days," or "not in paid employment" (including unemployed, retired, or homemaker patients). Lifestyle variables included current alcohol intake in units per week and smoking history, categorized as "current smoker," "ex-smoker," or "never smoker." Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) questionnaire, scored 0–3 for 14 items (total range 0–21 for either anxiety or depression) with a cutoff of 11 (i.e., patients with scores of ≥11 were considered more likely to have anxiety or depression) (9).

*Clinical predictor variables at baseline.* Weight was measured as the body mass index, dichotomized at 25 kg/m$^2$ (the World Health Organization–defined cut point for being overweight). Disease activity was assessed using the Disease Activity Score in 28 joints using the C-reactive protein level (DAS28-CRP). Early morning stiffness was assessed, and the duration of morning stiffness was classified as ≤30 minutes, 31–60 minutes, or ≥60 minutes. Time to referral was defined as the time from symptom onset to first referral. Laboratory measures included rheumatoid factor (RF; >15 units/ml), anti–cyclic citrullinated peptide (anti-CCP) antibodies (>7 units/ml), inflammatory response (neutrophilia [$>5.8 \times 10^9$/liter] and CRP level [>10 mg/liter]). Cutoffs were set according to local laboratory ranges.

The study was reviewed and approved by the West of Scotland Research Ethics Committee, and written informed consent was obtained from all participants.

**Statistical analysis.** Logistic regression models were used to examine the relationship between baseline characteristics (i.e., predictors) and the outcome variable (HAQ) at 1 year. Continuous predictors that are generally presented as categorical with clinically recognized cutoffs were included in the model as such. Baseline HAQ and DAS28-CRP, which can be presented clinically as either continuous scores or categories, were included in the model in continuous form since this increases statistical power. The relationship between continuous predictors and the observed log odds were assessed for linearity. In the absence of linearity, either a suitable transformation was used or the predictor was categorized.

First, a univariable logistic regression analysis was conducted to examine the association between each of the candidate

predictor variables and the outcome. Those variables with $P < 0.2$ were entered into a forward stepwise regression model. The entry and exit criteria for the model were $P \leq 0.1$ and $P > 0.15$, respectively. The exit criteria of $P > 0.15$ was chosen so that important predictors that were not statistically significant, but may have been if the sample size was larger, could be included in the model. Associations were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). To assess model performance, discrimination, which measures how well the model discriminates between patients at high risk and those at low risk, was evaluated using the C statistic. The agreement between observed and predicted probabilities was assessed using a calibration plot. The model sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were also calculated.

To test for overfitting, which arises when the model predicts well for patients within the development cohort but leads to overoptimistic predictions for new patients, a bootstrap resampling technique was used. One hundred samples were randomly drawn with replacement from our original development cohort. For each bootstrapped sample, the same stepwise procedure used to develop our original model was conducted. The C statistic was calculated for each of the 100 bootstrapped models and for each of the 100 models applied to the original development cohort. The difference between the 2 C statistics for each sample was calculated, and the average was taken over the 100 samples. This value subtracted from the original C statistic gives the optimism-corrected C statistic and is an estimate of internal validity. To aid decision-making and accessibility in clinical practice, we created a prediction tool using coefficients from the final logistic regression model (10). We assessed the performance of the clinical prediction tool by comparing probabilities given by the logistic regression model to probabilities estimated by the tool.

As a method of external validation we used temporal validation. The final logistic regression model was applied to the validation cohort. Model discrimination and calibration were assessed. Calibration was examined using calibration-in-the-large, which tests whether predictions are systematically too low or too high, and the calibration slope, which tests for nonsystematic differences between the predicted and observed probabilities.

## RESULTS

**Study population.** Characteristics of the study population are shown in Table 1. Of the 1,140 patients recruited to the study, 592 had completed 1 year of follow-up. Among these, 578 patients had HAQ results available for both baseline and 1 year (13 were missing 1-year HAQ scores and 1 was missing baseline HAQ score), and of these, 80.6% (466 of 578) fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 criteria for RA (11) during the first year of follow-up.

There was a wide age distribution in the study population (median 60.5 years, interquartile range [IQR] 22.6–86.9), and 64.5% of the patients were women. Initially, most patients received methotrexate monotherapy (54.7%), with the remainder receiving either sulfasalazine (10.6%), hydroxychloroquine (5.7%), leflunomide (0.4%), or a standard DMARD combination (25.9%). None of the patients were receiving biologic agents at baseline. The majority (60.7%; 351 of 578) reported baseline functional disability (HAQ score of ≥1), which fell to 36.7% (212 of 578 patients) at 1 year.

**Table 1.** Characteristics of the study population at baseline (n = 578)*

| | |
|---|---|
| Demographic and socioeconomic characteristics | |
| Age, median (IQR) years | 60.5 (22.6–86.9) |
| No. (%) female | 373 (64.5) |
| No. (%) white† | 571 (99.5) |
| Employment status, no. (%) | |
| Full-time employment | 181 (31.3) |
| Part-time employment | 93 (16.1) |
| Self-employed | 23 (4.0) |
| Student | 4 (0.7) |
| Homemaker | 16 (2.8) |
| Retired | 225 (38.9) |
| Unemployed seeking work | 12 (2.1) |
| Unemployed not seeking work | 24 (4.2) |
| In paid employment without absenteeism during the last 7 days | 162 (28.0) |
| In paid employment with absenteeism during the last 7 days | 139 (24.1) |
| Not in paid employment | 277 (47.9) |
| Lifestyle and referral factors | |
| Time from symptom onset until first referral, median (IQR) months | 5.1 (0.6–250.1) |
| Alcohol intake per week, median (IQR) units | 1 (0–35) |
| Smoking status, no. (%) | |
| Never smoker | 228 (39.5) |
| Ex-smoker | 200 (34.6) |
| Current smoker | 146 (25.3) |
| Clinical and biologic factors | |
| BMI, mean ± SD kg/m$^2$ | 28 ± 5.2 |
| Morning stiffness, no. (%) | |
| ≤30 minutes | 150 (26.0) |
| 31–60 minutes | 63 (10.9) |
| ≥60 minutes | 356 (61.6) |
| DAS28-CRP score, mean ± SD | 4.7 ± 1.3 |
| HAQ score, median (IQR) | 1.1 (0–2.9) |
| HADS depression score, median (IQR) | 5 (0–17) |
| HADS anxiety score, median (IQR) | 6 (0–18) |
| Neutrophils, mean ± SD ×10$^9$/liter | 5.7 ± 2.2 |
| Rheumatoid factor >15 units/ml, no. (%)‡ | 238 (68.8) |
| Anti-CCP >7 units/ml, no. (%)§ | 306 (64.2) |
| CRP >10 mg/liter, no. (%)¶ | 273 (54.2) |

* IQR = interquartile range; BMI = body mass index; DAS28-CRP = Disease Activity in 28 joints using the C-reactive protein level; HAQ = Health Assessment Questionnaire; HADS = Hospital Anxiety and Depression Scale; anti-CCP = anti–cyclic citrullinated peptide antibody.
† Information was available for 574 patients.
‡ Data were available for 346 patients.
§ Data were available for 477 patients.
¶ Data were available for 504 patients.

**Model development.** Following univariable analysis (data are available from the corresponding author upon request), 10 eligible predictor variables were submitted to the stepwise logistic regression model. Five remained statistically significant and were retained: work disability, overweight, high disability score, depression, and anxiety

**Table 2.** Multivariable explanatory model for functional disability at 1 year in patients with RA or undifferentiated arthritis*

| Explanatory baseline variable | OR (95% CI) | Coefficient (95% CI) |
|---|---|---|
| Employment | | |
| In paid employment without absenteeism during the last 7 days | 1.0 | |
| In paid employment with absenteeism during the last 7 days | 1.19 (0.63, 2.23) | 0.17 (−0.46, 0.80) |
| Not in paid employment | 2.36 (1.38, 4.03) | 0.86 (0.32, 1.39) |
| Weight | | |
| BMI <25 kg/m$^2$ | 1.0 | |
| BMI ≥25 kg/m$^2$ (high) | 1.61 (1.04, 2.50) | 0.48 (0.04, 0.91) |
| Depression | | |
| HADS depression score <11 | 1.0 | |
| HADS depression score ≥11 (high) | 2.52 (1.18, 5.37) | 0.92 (0.16, 1.68) |
| Anxiety | | |
| HADS anxiety score <11 | 1.0 | |
| HADS anxiety score ≥11 (high) | 2.37 (1.33, 4.21) | 0.86 (0.29, 1.44) |
| HAQ score (continuous) | 2.67 (1.98, 3.59) | 0.98 (0.68, 1.28) |

* Functional disability was defined as a Health Assessment Questionnaire (HAQ) score of ≥1. RA = rheumatoid arthritis; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; HADS = Hospital Anxiety and Depression Scale.

(Table 2). RF and CCP were not statistically significant in univariable analysis and therefore were not considered for inclusion in the forward stepwise modeling process. While neutrophilia and CRP level were borderline significant in univariable analysis, they were included in the stepwise process but were excluded from the final model since their *P* values were greater than the exit *P* value of 0.15.

Good discriminative performance of the model was demonstrated by a C statistic of 0.78, with a sensitivity of 46.8%, specificity of 87.1%, PPV of 67.2%, and NPV of 74.4%. The model showed excellent agreement between observed and predicted probabilities (data are available from the corresponding author upon request). The bootstrap resampling technique evidenced a reliable optimism-corrected C statistic of 0.75.

**Clinical prediction tool.** The clinical prediction tool for estimation of disability at 1 year is shown in Figure 1. The multivariable model informed the development of a user-friendly prediction tool with scores ranging from 0 to 26. Higher scores corresponded to higher probabilities of reporting a high HAQ score at 1 year (results are available from the corresponding author upon request).

**External validation.** The validation cohort consisted of 113 patients, 38 (33.6%) of whom reported high disability at 1 year (data are available from the corresponding author upon request). When the final model was applied to the validation cohort, the C statistic was 0.72. Calibration-in-the-large showed no evidence of systematic overestimation or underestimation of the predicted probability of functional disability ($P = 0.99$). The calibration slope was not significant ($P = 0.31$), i.e., there was no evidence of overfitting in the model. (Two clinical vignettes illustrating the relationship between the estimated risks of the prediction tool and those from the logistic regression model are available from the corresponding author upon request.)

## DISCUSSION

Our findings demonstrate that, within a contemporary cohort of patients with RA or undifferentiated arthritis, baseline predictors of disability at 1 year are dominated by psychosocial rather than clinical factors. In addition to high baseline disability, predictors included work disability, depression, anxiety, and being overweight. We developed a clinical prediction tool based on these prognostic markers that in the future may provide valuable personalized information for patients and support stratified approaches to their care. The latter may involve holistic nonpharmacologic approaches, which may be effective in the modification of psychosocial factors.

There are some methodologic issues to consider when interpreting these results. First, despite the comprehensive nature of data collection in SERA, not all putative predictors were collected (e.g., chronic pain) or usable (e.g., comorbidities that were indicated in patient records but were not accessed using any instrument and therefore could not be quantified and analyzed). Radiologic scoring was only captured in a subset of patients, prohibiting its inclusion in the full model. However, among the participants with baseline radiologic information (n = 329), erosions were not found to be individually associated with 1-year disability (data not shown).

Second, although the identified baseline predictors could serve as targets to reduce or prevent future disability,

| Predictors | Categories and corresponding score | | | | | Score |
|---|---|---|---|---|---|---|
| HAQ score | <1 | ≥1 | ≥1.5 | ≥2 | ≥2.5 | |
| | **0** | **4** | **6** | **9** | **11** | |
| HADS depression score | <11 | ≥11 | | | | |
| | **0** | **5** | | | | |
| HADS anxiety score | <11 | ≥11 | | | | |
| | **0** | **4** | | | | |
| Employment & Absenteeism | In paid employment without absenteeism during the last seven days | In paid employment with absenteeism during the last seven days | Not in paid employment | | | |
| | **0** | **1** | **4** | | | |
| BMI | <25 kg/m$^2$ | ≥25 kg/m$^2$ | | | | |
| | **0** | **2** | | | | |
| | | | | | Total score | |

| Total Score | 1 year risk of HAQ ≥1 in % | Total Score | 1 year risk of HAQ ≥1 in % |
|---|---|---|---|
| 0 | 9 | 14 | 62 |
| 1 | 11 | 15 | 66 |
| 2 | 13 | 16 | 71 |
| 3 | 15 | 17 | 75 |
| 4 | 18 | 18 | 78 |
| 5 | 21 | 19 | 81 |
| 6 | 25 | 20 | 84 |
| 7 | 29 | 21 | 87 |
| 8 | 33 | 22 | 89 |
| 9 | 37 | 23 | 91 |
| 10 | 42 | 24 | 92 |
| 11 | 47 | 25 | 94 |
| 12 | 52 | 26 | 95 |
| 13 | 57 | | |

**Note**: For each risk factor enter the corresponding score in the box on the right hand side. Add up the scores and enter the total. Look for the total score in the lower table and read off the percentage risk of HAQ within one year.

**Figure 1.** Clinical risk tool for estimation of functional disability (defined as a Health Assessment Questionnaire [HAQ] score of ≥1) in rheumatoid arthritis or undifferentiated arthritis. Scores range from 0 to 26 points. HADS = Hospital Anxiety and Depression Scale; BMI = body mass index.

such an interpretation should be made cautiously. Our prespecified analysis was designed to stratify patients who were receiving current standard care according to prognosis rather than to better understand the mechanisms of our outcome of interest. To fully address the latter distinct question would require consideration of data from all interim time points (not just baseline) in order to characterize the putative mediators of the changes in outcome. The effect of drug therapies is a prime example, and we recognize that the observed heterogeneity in treatment may impact differentially on functional disability.

Third, not all patients fulfilled current ACR/EULAR classification criteria for RA. However, we intentionally designed this study to take the perspective of the clinician and patient at first presentation of inflammatory arthritis. Due to the recognized need for early treatment, this is the time point at which some of the most critical therapeutic decisions are made. Waiting until classification criteria (which were developed for research purposes) are fulfilled before instituting treatment leads to unacceptable delays. It is therefore at this juncture that pragmatic prognostic information is most valuable. In fact, and despite the broad inclusion criteria, most patients did ultimately fulfill RA criteria. This explains why the baseline characteristics indicated levels of disability and seropositivity similar to those in cohorts classified as having RA (3) and higher than those in other early inflammatory arthritis cohorts. Those studies, unlike the present study, tended to sample from primary care and so captured more self-limiting illness which would not routinely require specialist care (5). The wide variation observed in time from symptom onset to referral substantiates this likely distinction.

Fourth, the model performance is good but lacks sensitivity. Again, from a clinical perspective, rheumatologists would welcome certainty in prognostic information indicating that additional therapy above and beyond standard care is needed. Therefore, high specificity (in this case 87.1%) is quite desirable. Other prognostic studies of RA disability also consistently identify baseline disability as a significant predictor (3,6,7,12). It is, however, not surprising for baseline levels of the outcome of interest to be longitudinally predictive. Age is a less consistently reported predictor. It appears that older age may be more relevant for predicting longer-term (5,13) rather than short-term disability, and this is a reminder that predictors of outcome may vary with different follow-up times. Otherwise, our results are dissimilar to those of previously reported prediction studies in that we found that psychosocial factors dominate over clinical factors. This primarily relates to our unique decision to consider factors such as depression, anxiety, and work disability in addition to traditional measures.

Consistent with biopsychosocial models of health care delivery, our results highlight the importance of holistic patient evaluations. For example, poor mental health status seems to better predict functional disability than does disease activity (a significant predictor in univariable analysis alone). This observation likely reflects the success of modern pharmacologic strategies that specifically target disease activity. Thus, high levels of disease activity at presentation are promptly and effectively addressed, leading to a weaker association with functional disability later in the course of the disease. In contrast, psychosocial issues remain inadequately targeted in standard care. It is widely recognized that problems such as depression are strongly associated with, and can predict, functional disability in RA (12), but these problems remain poorly addressed, as reflected by their ongoing burden within RA populations (14). Our group also is the first to identify the predictive importance of work absenteeism and excessive weight. Early identification of these problems by the rheumatology team and subsequent channeling toward other relevant health services is considered ideal practice (15), but does not commonly occur due to limited resources (16).

To our knowledge, such prognostic information has been translated into a clinically usable format on only 2 previous occasions. Bansback et al developed a nomogram that aimed to predict RA disability at 5 years (7), and Dirven et al have published a matrix model of disability at 6 months (6). The former is based on historic data (recruitment began in 1986), the latter on clinical trial data (from the Behandelstrategieën voor Reumatoide Artritis [BeSt] study), and neither have been externally validated.

The RA landscape has been transformed by changes in therapeutic approach, and therefore we sought to re-evaluate the baseline predictors of disability at 1 year within a generalizable and contemporary national RA cohort. Psychosocial rather than traditionally clinical prognostic factors have been identified to be important in this new era. The predictors identified are potentially modifiable by common nonpharmacologic approaches underpinned by education, exercise, and behavioral interventions. Patients at greatest risk of disability may benefit from such preventive strategies. The compilation of these predictors into a user-friendly tool will aid in the stratification of patients according to their needs, which is a first step toward personalized treatment and a valuable method to better inform patients of their future disease journeys.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Basu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Kronisch, Ralston, Reid, Munro, Siebert, McInnes, Porter, Macfarlane, Basu.

**Acquisition of data.** Dale, Paterson, Ralston, Tierney, Harvie, McKay, Wilson, Munro, Saunders, Richmond, Baxter, McMahon, Kumar, McLaren, Siebert, McInnes, Porter, Basu.

**Analysis and interpretation of data.** Kronisch, McLernon, Dale, Ralston, Reid, McInnes, Macfarlane, Basu.

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