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Predicting functional disability: One year results from the Scottish Early Rheumatoid Arthritis Inception Cohort

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Objective. To identify baseline prognostic factors of one year disability within a contemporary early inflammatory arthritis inception cohort and then develop a clinically useful tool which may support early patient education and decision making.

Methods. The Scottish Early Rheumatoid Arthritis (SERA) inception cohort is a prospective multicentre study of newly presenting RA and undifferentiated arthritis patients. SERA data were analysed to determine baseline predictors of disability (defined as a Health Assessment Questionnaire [HAQ] score ≥ 1) at one year. Clinical and psychosocial baseline exposures were submitted to 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 one year. These were independently predicted by baseline disability (OR 2.67; 95%CI 1.98 – 3.59), depression (2.52; 1.18 – 5.37), anxiety (2.37; 1.33 – 4.21), in paid employment with absenteeism during the last week (1.19; 0.63 – 2.23), not in paid employment (2.36; 1.38 – 4.03) and being overweight (1.61; 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 over-fit (p=0.31).

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

The primary concern for many newly diagnosed rheumatoid and undifferentiated inflammatory arthritis (RA/UA) patients is the functional impact of their disease.

Rheumatologists recognise the importance of 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 some patients will achieve a good outcome with usual care alone, while others will not. Identifying those patients at high risk of disability at a sufficiently early stage of their disease course presents a major challenge. Baseline predictors of future disability would not only inform decision-making, for example the implementation of stratified therapeutic approaches, but also empower patients. Patients will be better placed to understand their condition and options; this increases self-management, adherence and satisfaction with consequent improvements in overall outcome (2).

Studies have previously identified a few baseline predictors of future disability; for example, high disease activity and erosive disease (3). These studies have largely modelled 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) – that generally used more conservative management approaches – or clinical trials, so raising concerns regarding their generalizability. Finally, almost all limited their analyses to predictions of long-term (5-10 years) disability (7,3). Patients require more immediate prognostic information when first diagnosed in order to inform shorter-term personal decisions.

Ultimately, such models require to 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 one year RA disability clinical prediction tools have previously been developed.

In this study we aimed to identify baseline predictors of one year disability within a prospective, generalizable, inception RA cohort receiving modern standards of care. We adopted a holistic modelling 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 is an ongoing prospective multicentre study of patients with new RA/UA, which began in 2011. In Scotland, RA/UA is primarily managed by hospital based rheumatology departments. Almost all departments (16/17) contribute to SERA, so providing excellent coverage.

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

Data collection. Patients are followed-up every six months when a comprehensive set of clinical, biological and psychosocial variables are collected. For this study, data extraction took place on the 23/10/14 (model development cohort) and again on 27/04/15 (temporal validation cohort).

The following variables were considered in this analysis:

Outcome of interest. Functional ability, as defined by the Health Assessment Questionnaire Disability Index (HAQ), a self-report instrument describing physical function (range 0-3 for each item). For this analysis, a HAQ score ≥ 1 defined moderate to high disability (8).

Predictor variables at baseline.

Psychosocial.

In addition to baseline HAQ:

- (i) Demographics and socio-economic status: age, gender, ethnicity, marital status and employment information. The latter incorporated an assessment of absenteeism and was categorised as either “in paid employment without absenteeism during the last seven days”, “in paid employment with absenteeism during the last seven days” or “not in paid employment” (including unemployed, retired or homemaker patients).
- (ii) Lifestyle: current alcohol intake in units per week, smoking history categorised as “current smoker”, “ex-smoker” or “never smoker”.
- (iii) Depression and Anxiety: the Hospital Anxiety and Depression Scale questionnaire (HADS), scored from 0-3 for 14 items (total range 0-21) and a cut off of 11 (9).

Clinical.

- (iv) Weight: body mass index (BMI) dichotomised at 25 kg/m² (WHO defined cut-point for being overweight)
- (v) Disease activity: 28 joint count disease activity score (DAS28-CRP)

- (vi) Early morning stiffness: duration of morning stiffness (cut off for analyses: ≤ 30 min, 31-60 min or ≥ 60 min)
- (vii) Time to referral: symptom onset until first referral
- (viii) Laboratory measures: rheumatoid factor (>15 U/mL), anti-CCP antibodies (>7 U/mL), inflammatory response [neutrophilia ($>5.8 \times 10^9/L$) and CRP (>10 mg/L)]. Cuff offs were chosen according to local laboratory ranges.

This 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 one year. Continuous predictors that are generally presented as categorical with clinically recognised cut-offs 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 then either a suitable transformation was used or the predictor was categorised.

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 a p-value <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 we could include important predictors in the model which were not statistically significant but may have been if the sample size was larger. Associations were expressed as odds ratios (OR) with

95% confidence intervals (CI). For model performance, discrimination, which measures how well the model discriminates between patients at high and 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 over-optimistic 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 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 two c-statistics for each sample was calculated and the average 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 clinical prediction tool performance 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 non-systematic differences between the predicted and observed probabilities.

RESULTS

Study population (table 1). Of the 1140 patients recruited to the study, 592 participants had completed one year follow up. Among these, 578 reported HAQ results (13 persons missing one year HAQ and one missing baseline HAQ) and, of these, 80.6% (466/578) fulfilled the 2010 ACR/EULAR classification criteria for RA during the first year of follow up.

The study population characteristics indicated a wide age distribution (median 60.5 years, interquartile range (IQR) 22.6 - 86.9), with 64.5% female. Initially, most patients received methotrexate (54.7%) monotherapy, with the remainder receiving either sulfasalazine (10.6%), hydroxychloroquine (5.7%), leflunomide (0.4%) or a standard DMARD combination (25.9%). No one received a biological therapy at baseline. The majority (60.7%, 351/578) reported baseline functional disability ($\text{HAQ} \geq 1$) which fell to 36.7% (212/578 patients) at one year.

Model development. Following univariable analysis (supplementary table 1), 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). On univariable analysis (Supplementary table 1) RF and CCP were not statistically significant and so were not considered for inclusion in the forward stepwise modelling process. Whilst neutrophils and CRP were borderline significant on 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 (supplementary figure 1).

The bootstrap resampling technique evidenced a reliable optimism-corrected c-statistic of 0.75.

Clinical prediction tool (figure 1). The multivariable model informed the development of a user-friendly prediction tool with scores ranging between 0 - 26. Higher scores corresponded to higher probabilities of reporting a high HAQ score at one year (supplementary figure 2).

External validation. The validation cohort contained 113 patients (supplementary table 2) of which 38 (33.6%) reported high disability at one year. 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 over- or under-estimation 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 over-fitting in the model.

Supplementary figure 3 presents two clinical vignettes to illustrate the relationship between the estimated risks of the prediction tool and those from the logistic regression model.

DISCUSSION

Our findings demonstrate that, within a contemporary RA/UA cohort, baseline predictors of one year disability are dominated by psychosocial rather than clinical factors. In addition to high baseline disability, these included work disability, depression, anxiety and being overweight. A clinical prediction tool has been developed based on these prognostic markers which in the future may provide valuable personalised information for patients and support stratified approaches to

their care. The latter may involve holistic non-pharmacological approaches, which maybe effective in the modification of psychosocial factors.

There are some methodological issues to consider when interpreting these results. Firstly, despite the comprehensive nature of data collection in SERA, not all putative predictors were collected (e.g. chronic pain) or usable (e.g. comorbidities captured in free text only). Radiological scoring was only captured in a sub-set of patients, prohibiting its assessment within the full model.

However among those of our participants with baseline radiological information (n=329), erosions were not found to be individually associated with one year disability (data not shown).

Secondly, although the identified baseline predictors could serve as targets to reduce or prevent future disability, such an interpretation should be made cautiously. Our pre-specified analysis was designed to stratify patients, receiving current standard care, according to prognosis rather than better understand the mechanisms of our outcome of interest. To fully address the latter distinct question would ideally require consideration of data from all interim time points (not just baseline) in order to characterise the putative mediators of the changes in outcome. The effect of drug therapies is a prime example and we recognise that the observed heterogeneity in treatment may impact differentially on functional disability.

Thirdly, not all patients fulfilled current ACR/EULAR RA classification criteria. We, however, intentionally designed this study to take the perspective of the clinician and patient at first presentation of inflammatory arthritis. Due to the recognised need for early treatment, this is the time point where some of the most critical therapeutic decisions are made. Waiting to fulfil classification criteria (which were developed for research purposes) before instituting treatment leads to unacceptable delays. It is therefore at this juncture that pragmatic prognostic information

is most valuable. In actual fact, and despite the broad inclusion criteria, most patients did ultimately fulfil RA criteria and this explains why the baseline characteristics indicated levels of disability and sero-positivity similar to RA classified cohorts (3) and higher than other early inflammatory arthritis cohorts which, unlike our 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.

Finally, the model performance is good but lacks sensitivity. Again from a clinical perspective, rheumatologists would welcome certainty in the prognostic information if it is to support additional therapy above and beyond standard care and so 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, unsurprising for baseline levels of the outcome of interest to be longitudinally predictive. Age is a predictor, which is less consistently reported. It appears that older age may be more relevant for predicting longer term (5,11) rather than short term disability and this serves as reminder that predictors of outcome may vary between different follow-up times. Otherwise, our results are dissimilar to previously reported prediction studies in 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. In keeping with bio-psychosocial 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 disease activity (a significant predictor on univariable analysis alone). This observation likely reflects the success of modern pharmacological strategies that specifically target disease activity. Thus high

presenting levels of disease activity are promptly and effectively addressed leading to a weaker association with functional disability later in the course of disease. In contrast, psychosocial issues remain inadequately targeted in standard care. It is widely recognised 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 (13). We are the first to also identify the predictive importance of work absenteeism and excessive weight. Early identification of these problems by the rheumatology team and subsequent channelling towards other relevant health services is considered ideal practice (14), but does not commonly occur due to limited resources (15).

To our knowledge, such prognostic information has only been translated into a clinically usable format on two previous occasions. Bansback et al. developed a nomogram which aimed to predict RA disability at five years (7) and Dirven et al. have recently reported a matrix model of six month disability (6). The former is based on historic data (recruitment began 1986), the latter on clinical trial data (BeSt) and neither have been externally validated.

The RA landscape has been transformed by changes in therapeutic approach and so we have sought to re-evaluate the baseline predictors of one year disability 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 identified predictors are potentially modifiable by common non-pharmacological approaches underpinned by educational, exercise and behavioural interventions. Those at greatest risk of disability may benefit from such preventative strategies. The compilation of these predictors into a user friendly tool will aid the stratification of patients according to their needs, a first step towards personalised treatment, and a valuable method to better inform patients of their future disease journeys’.

AUTHORS CONTRIBUTIONS

CK, NB and GJM conceptualised and designed the study. Analysis was performed by CK and DM. CK and NB drafted the manuscript. All authors contributed to data collection, interpretation, critically reviewed and edited the manuscript.

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