

Predicting outcomes in rheumatoid arthritis

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Abstract Biologic therapies have brought improved efficacy in the field of rheumatoid arthritis (RA), but their use in clinical practice may be limited by concerns over cost. Predictive models are, therefore, needed to identify those people with RA with the worst potential outcomes, who will benefit most from the use of these drugs. A variety of studies have investigated factors that will predict the onset of RA to allow preventative intervention and the identification of prognostic factors to guide the need for aggressive treatment at the time of diagnosis and prognostic factors in patients who have failed on optimal traditional therapies—all strategies to guide the cost-effective use of modern therapies. Prediction rules have been developed that are sensitive and specific, but many are limited by their complexity or the need for biomarkers that will never be routinely measured in the clinic. Most rules to date have therefore failed to have a major impact on clinical practice. Probably most interesting is the prediction of response to therapy based upon early treatment response, with outcomes at as early as 3 months predicting response at 12 months. Further work is needed, however, to identify the efficacy of current therapies in preventing disease onset and the long-term cost-effectiveness of appropriately targeted treatment with biologics.

Keywords Cost-effectiveness · Early · Intervention · Modelling · Outcomes · Prediction · Rheumatoid arthritis

Introduction

While there is universal agreement from individual physicians and international guidelines on early intervention for rheumatoid arthritis (RA), there is still no consensus on an optimal therapeutic strategy. In part, this is related to health economics as modern highly effective biologic therapies are relatively costly. Many physicians believe that all patients should be started on the best available drugs, with treatment stepped down once remission is achieved, while others feel that enough patients have good outcomes with traditional disease-modifying antirheumatic drug (DMARD) treatments that initial use of biologic therapies is not necessary. If we could better predict, either at diagnosis or following a period of therapy, which patients are likely to have poor outcomes, and if we could better predict which patients will respond to which therapies, we could better tailor the management of our patients. Predicting outcomes and response in this manner will help ensure that available therapies are utilised in the most cost-effective manner. This narrative review will attempt to summarise recent concepts and algorithms concerning prognosis in RA.

Prognosis and RA

Issues surrounding prognosis, including how prognosis can be determined, and how studies of prognosis can be undertaken, were recently discussed in a series of three articles in the *British Medical Journal* [1–3]. Moons et al. defined prognosis in medicine as ‘commonly relating to the

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probability or risk of an individual developing a particular state of health (an outcome) over a specific time, based on his or her clinical and non-clinical profile' [3]. They also noted that because of human and disease complexity, a single variable rarely provides an adequate estimate of prognosis, concluding that prognostic studies require a multivariate approach and should include desirable therapeutic goals.

A number of issues surround the concept of prognosis in RA. The use of terminology in relation to prognosis is not precise enough, and much of the literature uses the term inappropriately, referring to the course of the illness in general rather than the course of the disease in a given individual. Prognostic papers in the field of RA tend to fall into three groups:

- a growing number of reports that seek to predict the onset of RA, which could allow treatment to prevent the disease occurring;
- those that aim to determine poor prognosis at the time of diagnosis of RA, which would enable immediate treatment with the most appropriate therapies but overlook the fact that many patients initially do well on methotrexate alone and that modern biologics are expensive. This represents the bulk of RA prognostic studies, with predictors often derived from clinical trial cohorts; and
- those that predict poor prognosis in patients who have failed on optimal traditional therapies at an early stage, which would allow the cost-effective use of biologic therapies.

The ability to determine poor prognosis at diagnosis is likely to become increasingly important as recommendations advocate initiation of treatment as early in the disease process as possible [4]. Perhaps most interesting, however, is the possibility of being able to predict which patients will have a poor prognosis after failing on traditional therapy.

Considerations when developing prognostic models

To date, outcomes in RA have been largely based upon conventional radiographs that reflect structural damage. While arguably objective, these do not take into consideration the presence of inflammation, and patients with the worst radiographic progression often constitute only a small percentage of patients in trials. It is also increasingly difficult to see differences in structural damage, because modern treatment strategies (particularly tight control) have resulted in less radiographic progression. In addition, clinicians do not assess structural damage in a systematic way in clinical practice, so simple tools for assessment of relevant clinic-based outcomes are needed. However, there is a good chance

that within a few years, we will have image analysis tools that will enable automated structural assessments on X-rays within the clinic setting.

Moons et al commented that 'Prognosis studies should focus on outcomes that are relevant to patients'. In the field of RA, these outcomes would include function, disease activity and quality of life [3]. Aletaha et al. pooled data from several RA clinical trials in order to compare the value of reporting treatment effects in RA as relative change from baseline with the value of evaluating absolute disease activity states [5]. They concluded that not only is response rate important, but so too is the endpoint of the disease—the patient's final state—and this must be borne in mind when designing prognostic studies.

Prospective cohort studies are probably the best design when developing prognostic models, or they can be used to validate models derived from randomised control trials. Clear predictors of outcome need to be identified from the myriad of potentially predictive markers for RA that have been used in different studies (Table 1). It is of particular importance that study designs differentiate between predictors and outcomes. In addition, validation studies are needed as potential prognostic models are developed. In RA, it may be of importance to differentiate between early and established disease cohorts, both in the context of prognostic model development, and in terms of validation of such models. Finally, it is of the foremost importance that any models developed for use in daily clinical practice are simple to use.

Prognostic model for the onset of RA

There has been an extensive literature examining why inflammatory arthritis persists or may become RA [6]. Recently, Huizinga et al. developed a prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis from a large inception cohort of patients, most with 1-year follow up [7]. The defined outcome was the American College of Rheumatology (ACR) 1987 diagnosis of RA; clinical characteristics were identified by logistic regression, and the results were validated in an independent cohort of patients. The resultant prognostic model (Table 2) had positive predictive value (PPV) of 84% and negative predictive value (NPV) of 91%, using upper and lower cut-offs of 8 and 6, respectively. Recent validation of this work in cohorts from the UK, Germany and the Netherlands, with outcome of RA diagnosis after 1 year, found NPVs for scores ≤ 6 of 83% to 86% and PPVs for scores ≥ 8 of 93% to 100% [8]. This model does not require unusual markers and is practical enough to be useful in the clinic, but there are concerns about the potential for misdiagnosis. Further validation has recently been reported from a Canadian group [9].

Table 1 Potential predictive markers for rheumatoid arthritis

<ul style="list-style-type: none"> • <i>Disease activity score (DAS)</i> • <i>Simplified disease activity index (SDAI)</i> • <i>Clinical disease activity index (CDAI)</i> • <i>Health assessment questionnaire (HAQ)</i> • <i>Radiological progression</i> • <i>Rheumatoid factor (IgM RF, IgA RF)</i> • <i>Swollen joint count</i> • <i>Anti-citrullinated protein/peptide antibody (ACPA)</i> • <i>C-reactive protein (CRP)</i> • <i>Erythrocyte sedimentation rate (ESR)</i> • <i>MRI and ultrasound signs of inflammation</i> • Interleukin-6 (IL-6) • Tumour necrosis factor receptor type 1 (TNFR1) • Calcium binding protein (S100A8/A9) • Soluble intercellular adhesion molecule 1 (sICAM-1) • Matrix metalloproteinase 3 (MMP-3) • C-telopeptide of type II collagen (CTX-II) • Tumour necrosis factor α (TNFα) • Fibrinogen • Interleukin 1 α (IL-1α) • Anti-perinuclear factor (APF) • B lymphocyte chemokine (BLC/CXCL13) • Myeloid progenitor inhibitory factor 1 (CCL23/MPIF1) 	<ul style="list-style-type: none"> • Transforming growth factor α (TGFα) • Tumour necrosis factor receptor superfamily member 9 (TNFRSF9) • Macrophage colony stimulating factor (M-CSF) • Female gender alleles (<i>DRB1*04</i>) • Cartilage oligomeric matrix protein (COMP) • Pyridinoline (Pyr) • Tissue inhibitor of metalloproteinases 1 (TIMP) • Deoxyypyridinoline glycosylated Pyr (Glc-Gal-Pyr) • Oncostatin M • Matrix metalloproteinase 10 (MMP-10) • Matrix metalloproteinase 8 (MMP-8) • CCL8/Myeloid progenitor inhibitory factor 1 (MPIF-1) • CCL8/monocyte chemotactic protein 2 (CCL8/MCP-2) • Chemokine (C-X-C motif) ligand 11 (CXCL11/I-TAC) • Lymphotactin • Fibroblast growth factor 4 (FGF-4) • Ciliary neurotrophic factor receptor α (CNTFRα) • Follistatin • Interleukin 9 (IL-9) • Lymphotoxin β receptor • Interleukin 2 (IL-2) • Apolipoprotein A-I (Apo-AI)—biomarker for Infliximab response in RA • Platelet factor 4 (PF-4)—biomarker for Infliximab response in RA
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Items in italics indicate the markers most commonly investigated

Predicting structural outcomes in RA

The definition of progression of radiographic damage differs between studies but, despite this, a number of baseline markers are indicative of subsequent radiographic damage in RA [10–12]:

- Autoantibodies: RF is perhaps the most commonly identified predictive factor, although recent long-term work has highlighted that, of the common clinical variables, anti-cyclic citrullinated peptide (ACCP) antibody may be a strong independent predictor of radiographic progression [13].
- Inflammatory markers/acute-phase reactants: ESR and CRP, as well as cytokines, such as TNF α or IL-6, are involved in multiple reports predicting progression.
- Genetic markers: Clearly there are important race-related associations, but HLA-DR4 and HLA-DRB1 are probably the best identified markers.
- Radiographs: Baseline radiographic damage is a reported predictor of subsequent structural progression.
- Soluble and genomic biomarkers: The most evaluated are collagen breakdown products as markers of cartilage degradation, but bone and synovial markers have also been examined. Particular problems arise with such markers owing to individual variance in excretion and

diurnal variation. Recently, a model combining matrix MMP-3 and type II collagen (CTX-II) provided prediction of radiographic progression in a large early RA cohort [14].

- Modern imaging: MRI and ultrasound have a role in predicting structural damage. For example, the area under the curve for inflammation in four metacarpophalangeal joints and the progression in joints with new erosions on MRI scans show that people who have more inflammation develop more damage (Fig. 1) [15]. Results are similar for wrist joints. Bone marrow erosion, which can be observed on MRI scans, also predicts later structural damage and preceded MRI erosion in 40% of patients at 1 year, preceded MRI erosion with an odds ratio of 6.5 and predicted the 6-year Sharp score [16–19]. Some evidence also indicates that BME predicts long-term physical function according to the short-form 36-item survey (SF-36) score [18].

A variety of predictive models, utilising a combination of clinical and laboratory biomarkers, have predicted radiographic progression in RA. For example, a model combining ACCP antibody, sex, ESR and immunoglobulin M RF has an accuracy of 74% in predicting radiographic progression [13]. In an attempt to increase utility for

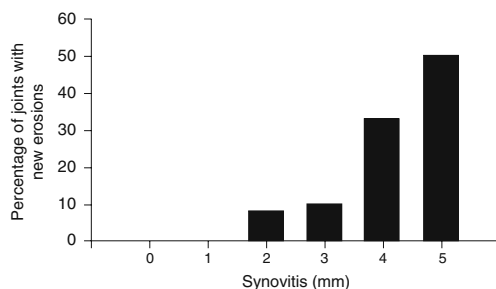
Table 2 Prognostic model for developing RA [7]. Reproduced with permission

Question	Points
1. What is the age in years? • Multiply by 0.02	
2. What is the sex? • In case female:	1
3. What is the distribution of involved joints? • In case small joints hands/feet: • In case symmetric: • In case upper extremities: • In case upper and lower extremities:	0.5 0.5 1 1.5
4. What is the score for morning stiffness on a 100 mm visual analogue score (VAS)? • In case 26–90 mm: • In case >90 mm:	1 2
5. What is the number of tender joints? • In case 4–10: • In case 11 or higher:	0.5 1
6. What is the number of swollen joints? • In case 4–10: • In case 11 or higher:	0.5 1
7. What is the C-reactive protein level? • In case 5–50 mg/L • In case 51 mg/L or higher:	0.5 1
8. Is the patient rheumatoid factor positive? • If yes:	1
9. Are the anti-CCP antibodies positive? • If yes:	2

clinicians, a recent report presented two preliminary matrix models that included 28 swollen joint count, RF and CRP or ESR to predict *rapid* radiographic progression, as defined by an increase in van der Heijde/Sharp score of ≥ 5 units per year [20]. Such a matrix presentation allows clinicians to have a visual colour-coded matrix to assess an individual's risk of progression.

Predicting functional outcomes in RA

In terms of disability, the best known and most commonly used outcome is the Health Assessment Questionnaire (HAQ)

**Fig. 1** Correlation between synovitis and prediction of erosions on MRI [15]. Reproduced with permission

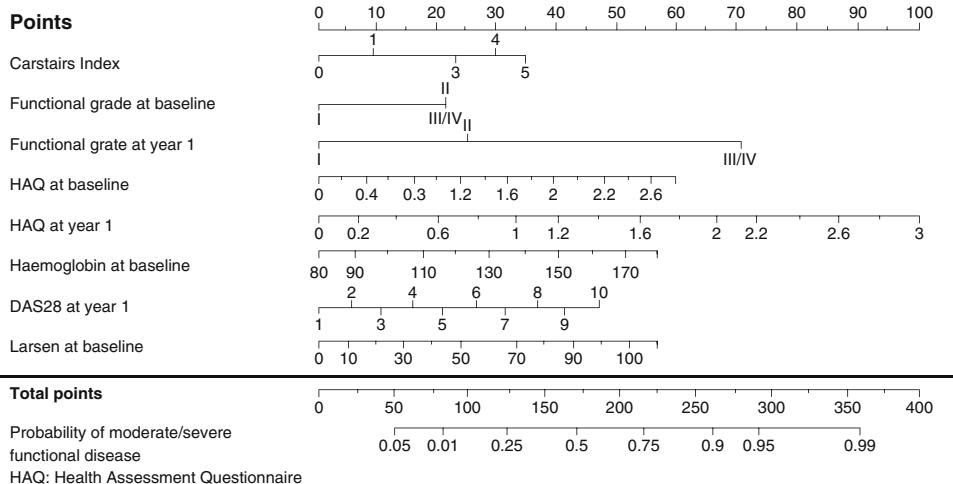
score. Clinical variables that predict poor HAQ include elevated baseline HAQ scores and RF positivity [10]. Few papers looking at prognostic factors for functional outcome in patients with early RA have been published recently, perhaps reflecting a declining interest in this area. Bansback et al. constructed a prognostic algorithm to predict 5-year functional outcome in RA based on HAQ [21]. The study population involved a typical RA inception cohort treated with conventional care in the UK in a period before modern aggressive methotrexate-based therapies and biologics were used. Potential prognostic factors included standard clinical, radiological and laboratory features measured at baseline and 1 year. Multivariate analysis was performed using logistic regression to identify factors predicting functional outcome (HAQ) at 5 years (HAQ score ≥ 1.5 at 5 years is considered moderate/severe disease). Patients were aged 17–93 (median 55) years, 66% were female, 74% were seropositive at baseline, 24% had erosions at baseline and 92% displayed functional grade I or II disease. The median HAQ score decreased from 1.00 to 0.63 in the first year of treatment, from 0.92 to 0.55 in patients with mild disease (60%) and from 1.51 to 1.41 in those with moderate/severe disease (30%), as might be expected with the use of pre-modern aggressive therapies. Of the 32 potential prognostic factors

included in the analysis, six consistently predicted moderate/severe functional outcome. The most important were functional grade III or IV disease at 1 year (odds ratio 6.7) and HAQ at 1 year (odds ratio 2.4). Others included Carstairs deprivation index, haemoglobin and Larsen score at baseline and DAS28 at 1 year. Reasonably large values for the c-index (0.82) and Nagelkerke r^2 (0.39) indicate that the set of prognostic factors explains the variation in outcome to a degree that implies good prediction for individual patients. Figure 2 shows the resultant nomogram for predicting moderate or severe functional outcome at 5 years, and Table 3 summarises the implications of using the prediction rule in clinical practice. Depending on the cut-off values used, 7–34% of patients identified as at risk by the algorithm would be eligible for anti-TNF therapy according to current UK guidance. This model is probably too complex for clinicians to use in practice and requires measurement of values not routinely collected; however, it was a constructive attempt to predict functional outcome scientifically using common measures and is an interesting model for how rheumatologists might look at cohort data in the future.

In a long-term study of an inception cohort, Drossaers-Bakker et al. found that similar baseline variables (swollen joint count, Ritchie score, RF, presence of erosions and HAQ) predicted both radiographic and functional (HAQ) outcomes [22]. These, combined in an algorithm, were highly predictive of long-term (12-year) outcomes, but HLA status added little.

Although predictive markers have been the subject of many papers over a long period, none, individually, has had a major impact on the clinical practice of rheumatologists, simply because most of these predictors are useful when employed at the trial/group level, but there are problems with translating this into useful predictors for individuals. Some of these models, employing combinations of biomarkers, may prove to be useful, but others involve biomarkers that will never be available to clinicians in their daily practice.

Fig. 2 Nomogram for prediction of risk of moderate/severe functional outcome [21]. Reproduced with permission



Predicting response to treatment

Determining predictors of radiographic progression can be difficult from modern trials in which biologic therapy substantially inhibits progression [23]. There are clear difficulties in examining predictors of response to therapy in real-world cohorts, and registries are one way of collecting such data. One report on predictors of response to anti-TNF therapy came from the British Society of Rheumatology Biologics Registry [24]. In this large cohort with established RA (disease duration 14 years), Hyrich et al. reported that higher baseline HAQ correlated with a poorer DAS28 response at 6 months. Age, disease duration, RF and prior number of DMARDs did not predict response.

Modern studies have also sought to use proteomic and biomarker approaches to predict responses to anti-TNF therapies; this remains a highly active research field. In a relatively small number of patients, Hueber et al. reported that a 24-biomarker signature (using antigen arrays, cytokine assays and ELISAs) provided modest prediction of clinical response [25].

A highly important concept in defining prognostic models is whether initial response to conventional DMARD therapy predicts subsequent disease activity. Aletaha et al. looked for associations between disease activity measures at 0, 1, 2, 3 and 6 months and disease activity at 12 months using data from patients treated with methotrexate, anti-TNF drugs or combination therapy [26]. Data from early RA trials were used for primary analyses, and data from late RA trials were used for validation. They found significant correlations between the simplified disease activity index (SDAI) scores (an additive score of swollen tender joint counts, patient and physician global assessment and CRP) at baseline and at 12 months, but more importantly, the correlation was stronger ($r=0.6$) at 3 months (Fig. 3). Results were similar for DAS28 and the clinical disease activity index (CDAI).

Table 3 Implications of using the rule for predicting the risk of moderate/severe functional outcome in clinical practice [21]. Reproduced with permission

Predicted probability (risk threshold) at which aggressive treatment is given	Sensitivity (%) ^a	Specificity (%) ^b	Patients to be treated aggressively using algorithm (%)	Patients identified at risk by algorithm who meet current BSR criterion for treatment with TNF inhibitors (%) ^c
≥0	100	0	100	7
≥10	97	25	83	8
≥20	90	51	65	11
≥30	82	67	51	13
≥40	73	79	40	16
≥50	63	88	31	20
≥60	51	94	23	20
≥70	42	96	18	23
≥80	29	99	12	27
≥90	12	100	5	34

BSR: British Society of Rheumatology; TNF: tumour necrosis factor

^a Probability that a patient with moderate/severe functional outcome will be identified positive

^b Probability that a patient with good functional outcome will be identified negative

^c Trial of minimum of two disease-modifying antirheumatic drugs, one of which is methotrexate, and a disease activity score 28 > 5.1 before a TNF inhibitor can be used

The authors concluded that the level of disease activity at baseline, and particularly over the first 3 months of treatment, is significantly related to disease activity at 12 months. In other words, outcomes at as early as 3 months already indicate the likely response to a given therapy at 12 months.

Conclusion

Biologic therapies have brought improved efficacy in the field of RA, but their use in clinical practice may be limited by concerns over cost. To guide the most cost-effective use

of these agents, predictive models are needed to identify those patients with the worst potential outcomes, such as those who will benefit most from their use.

Prognostic papers in the field of RA tend to fall into three groups. Firstly, studies seeking to predict the onset of RA to allow preventative intervention. Whilst a model for identifying new cases of RA is now available, data regarding the efficacy of current therapies in preventing disease onset are still needed. Secondly, studies to determine prognosis at the time of diagnosis to guide the need for immediate treatment. Large numbers of predictors and some models for poor outcomes (radiographic progression and function) in early RA are available, but their clinical utility remains unknown. Finally, studies predicting poor prognosis in patients who have failed on relatively inexpensive traditional therapies to allow the cost-effective use of biologic therapies. Models to predict poor outcomes after initial standard therapy are needed to demonstrate the long-term cost effectiveness of appropriately targeted treatment with biologics.

Future efforts should focus on analyses of clinical trial data, by academia and the pharmaceutical industry to further broaden our understanding of which patients are most likely to respond to different therapies, to better help in decision making. In addition, registries of early disease and biologic-treated cohorts are well placed to examine the relationships between the identification of different patient types, e.g. those identified as likely responders to a particular therapy, and their long-term outcome. In so doing, we will be able to expand our knowledge around predicting outcomes in RA.

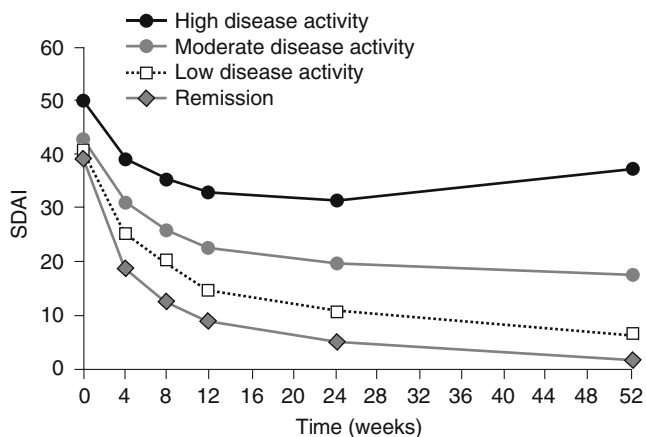


Fig. 3 Simplified disease activity index score over first 12 months in patients with early RA [26]. Reproduced with permission

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