Rheumatoid arthritis severity: its underlying prognostic factors and how they can be combined to inform treatment decisions

Rheumatoid arthritis (RA) is a heterogeneous disease that varies markedly in its severity. There is, therefore, a key research need to develop methods that can predict an individual's likely RA severity at disease onset, which would enable treatment to be tailored accordingly. A number of different prognostic factors for RA severity have been identified. These include environmental (such as smoking and alcohol consumption), genetic (such as the *HLA-DRB1* alleles and polymorphisms in the *IL1* locus), serological (rheumatoid factor and antibodies to citrullinated protein antigens) and biochemical (such as matrix metalloproteinases) factors. In this review, the authors discuss these prognostic factors in detail, outlining the evidence supporting them and focusing on how they have been combined in prognostic modeling to predict the likely severity of an individual's RA phenotype.

KEYWORDS: environmental ■ genotype ■ prognosis ■ rheumatoid arthritis ■ risk factors

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Rheumatoid arthritis (RA) is a heterogeneous disease that ranges from a mild, non-erosive form to a severe phenotype characterized by persistent inflammation and rapid radiological progression (RRP). Adopting a uniform, as opposed to a stratified, approach for the management of all RA cases is, therefore, inappropriate and there is a requirement for methods to prospectively establish the likely severity of an individual's RA early in the course of their disease, so that treatments can be tailored accordingly. This 'personalized medicine' approach would limit the development of irreversible articular damage from aggressive RA and prevent exposing individuals with a mild disease course to the potentially toxic effects of multiple drug therapies.

A number of different factors have been shown to associate with RA severity. The evidence underlying many of these is, however, uncertain with environmental and genetic associations often not replicated in independent cohorts. Previous reviews of prognostic factors for RA have either focused on a single factor type, such as genetics [1], described risk factors for a single disease outcome, such as radiological erosions [2], or have not detailed how prognostic factors could be combined to predict RA outcomes [3]. In this review, the authors provide a comprehensive overview of RA severity, outlining the evidence underlying a wide range of prognostic factors – spanning environmental, epidemiological, biochemical, radiological and genetic domains – for multiple RA outcomes with a focus on how they have been combined in prognostic modeling to stratify an individual's risk of severe disease.

The relevance of predicting RA severity: facilitating early treatment in poor prognosis cases

Much evidence exists to support the notion that individuals with RA have better outcomes if treated early and aggressively. The benefits of early combination treatments are demonstrated in several randomized controlled trials (RCTs). These include the BeSt and COBRA studies, with individuals receiving initial combination treatments having significantly better radiographic outcomes compared with those receiving monotherapy or step-up combination therapy, although both RCTs included high-dose steroids or TNF inhibitors in their initial combination regimens, which could explain a significant proportion of their efficacy [4,5]. Evidence also exists that step-up combination disease-modifying antirheumatic drugs (DMARDs) may be as effective as initial combination DMARDs, when used without oral steroids or biologics [6]. Earlier treatment also improves longer-term outcomes: one meta-analysis of 12 observational studies reported a 33% reduction in rates of long-term radiographic progression in patients receiving early versus delayed DMARD therapy [7]. The beneficial effects of prompt aggressive therapies on the natural history of RA have lead to the concepts of 'a window of opportunity' and 'treat to target' in which outcomes are improved provided appropriate treatments are initiated prior

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to the end of this window and individuals have their treatment titrated until remission or low disease activity is attained [8,9].

However, despite the benefits of prompt combination therapies, a recent national UK audit of prescribing practices in early RA found that only 50% of 258 rheumatologists surveyed used initial combination treatments in newly diagnosed cases; 81% used sequential monotherapy in at least some patients [10]. The main reasons for this comprised concerns regarding side effects, monitoring requirements and patient acceptability. The capacity to stratify individuals' risks of RA severity at disease onset could facilitate aggressive treatment in the poor prognosis cases that are most likely to benefit from such a management strategy.

Defining RA severity

Although many criteria exist to define remission in RA [11], far fewer criteria have been developed that focus on the opposing end of the disease spectrum, which is defining severe RA. The most widely used criteria in clinical practice is a 28 joint count Disease Activity Score (DAS28) of more than 5.1 [12]. This cross-sectional assessment fails, however, to consider disease severity at more than one time point, disability, erosive disease and the extra-articular impacts of RA. Although several self-reported scales have been developed to assess RA activity, such as the RA Disease Activity Index [13] and the Rapid Assessment of Disease Activity in Rheumatology questionnaire, these do not have thresholds to define severe RA [14]. They also suffer from the same shortcomings as other cross-sectional assessments, and focus on disease activity. The Health Assessment Questionnaire (HAQ) – and more specifically one of its components, the HAQ Disability Index – is commonly used to assess RA severity indirectly through evaluating disability levels. The HAQ Disability Index is a self-reported questionnaire that evaluates functional ability using 20 questions spanning eight categories [15]. Scores of 0–1 are considered to represent mild-to-moderate disability, 1–2 moderate-to-severe disability and 2–3 severe or very severe disability. Separate from clinical criteria, many RCTs and observational studies use radiological damage as indices of RA severity. Two radiological assessments that are commonly used comprise the Sharp/van der Heijde score (SHS) and the Scott modification of the Larsen method, which give scores out of 448 and 250, respectively [16]. Consensus opinion suggests that a change in the SHS of at least 5.0 represents a minimal clinically important difference; the

minimal clinically important difference for the modified Larsen score is less clear [17]. A summary of these scoring systems is given in TABLE 1.

Serological predictors of RA severity

It is increasingly clear that RA is not a single disease entity, but represents a spectrum of clinical syndromes spanning distinct disease subsets [18]. Historically, RA has been stratified according to the presence or absence of rheumatoid factor (RF), termed RF-positive RA (when RF is present) and RF-negative RA (when RF is absent). A more contemporary stratification is by antibodies to citrullinated peptide antigens (ACPA), with ACPA-positive RA characterized by a more aggressive disease course with a greater number of swollen joints and more severe radiological destruction [19]. Interestingly, both ACPA-positive and -negative disease can appear similar at initial presentation [19]; they can also be phenotypically similar at other disease stages.

The role of RF as a predictor of disease severity is well established, with cohorts of RF-positive patients consistently having higher rates of joint damage and extra-articular manifestations. This is particularly true of the IgA RF isotype, which is often reported as having a stronger association with severe disease when compared with IgM and IgG RF [20]. In one longitudinal observational study of 135 women with early RA followed-up for a mean duration of 6 years, while all three RF isotypes were significantly associated with more radiological damage progression and a greater number of swollen joints, IgA RF titers were most strongly correlated with the number of erosions, swollen joint counts (SJCs), the Ritchie index and HAQ scores [21]. Other studies have also shown stronger correlations between IgA RF with radiological erosions [22,23] and extra-articular manifestations [24] in comparison with other RF isotypes.

The prognostic value of ACPA is also well described. In one cohort study of 93 early RA patients identified among Swedish blood donors, the presence of ACPA prior to and at disease onset was significantly associated with radiological outcomes [25]. The baseline and 2-year Larsen scores in cases positive for ACPA pre-disease onset were 8 and 14, respectively; for individuals negative for ACPA pre-disease onset they were 5 and 9. These differences were statistically significant (p < 0.001) at both time points. ACPA also predicts longer-term radiological damage. Lindqvist *et al.* demonstrated this point in 183 RA cases followed-up for 10 or more years [26]. In multilinear regression analyses, Larsen

Table 1. Examples of assessment criteria for rheumatoid arthritis severity.

Criteria name	Criteria type	Description	Ref.
DAS28 score	Clinical physician assessment	Composite score involving assessment of the number of swollen and tender joints on a 28 joint count, the ESR and a self-reported VAS of global RA activity A score of >5.1 indicates severe RA activity	[12]
HAQ-DI	Clinical self-reported assessment	Assesses function across eight categories. Following scores represent varying disability levels: 0–1: mild-to-moderate disability 1–2: moderate-to-severe disability 2–3: severe or very severe disability	[15]
Sharp/van der Heijde score	Radiological assessment	Assesses erosions and joint-space narrowing in 44 and 42 joints, respectively, alongside subluxation. The total score ranges from 0 to 448 Higher scores indicate worse disease	[16]
Scott modification of the Larsen method	Radiological assessment	Assesses changes of erosion and joint destruction in the hands, wrists and feet, providing a total score ranging from 0 to 250 Higher scores indicate worse disease	[16]

DAS28: 28 joint count Disease Activity Score; ESR: Erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire Disability Index; RA: Rheumatoid arthritis; VAS: Visual analog scale.

scores at 10 years were significantly associated with ACPA and C-reactive protein (CRP) levels, which accounted for 32% of the variance in the score.

The prognostic value of antibodies specific for citrullinated peptides in the joint is less certain. Current ACPA assays, such as the anti-CCP2 test, incorporate many peptides derived from proteins absent from the synovial joint; they are, therefore, unlikely to be pathogenic. Although assays specific for citrullinated peptides present within the joint could be more prognostic, current evidence does not support this with a systematic literature review reporting similar associations between antibodies to modified citrullinated vimentin (an intra-articular antigen) and ACPA with radiological progression [27].

Environmental & epidemiological risk factors for RA severity

A variety of environmental and epidemiological factors have been linked with RA severity. These are outlined in TABLE 2, which also provides examples of which studies have reported this relationship.

■ Smoking

Cigarette smoking is the dominant environmental risk factor for the development of seropositive RA. A recent systematic review on this topic demonstrated that smoking has a gender-related effect, being associated with RA in men who have smoked at any point, but only being associated with RA in women who have smoked heavily [28]. There is some evidence that cigarette smoking also influences the natural history of RA. In one prospective study of 100 early RA

patients followed-up for 24 months, baseline SJC, tender joint count and pain visual analog scale scores were all significantly higher in smokers compared with non-smokers [29]. The SJC at 6 months was also significantly associated with smoking status, with current smoking increasing the number of swollen joints by at least three on average in a regression model after the elimination of non-significant variables. Another observational study of 63 women with advanced RA of an average disease duration of 13.7 years showed that heavy smoking (defined as ≥20 pack-years) was significantly associated with the presence of rheumatoid nodules, higher rates of radiological damage as defined by modified Sharp scores and higher HAQ scores when compared with smokers of <20 pack years or or those who had never smoked [30]. Other studies have, however, failed to demonstrate a clear association between smoking and RA severity with the QUEST-RA study finding no relationship between smoking status and erosions, severe extra-articular disease or DAS28 scores [31]. Any impact of smoking on disease severity probably stems from the fact that it predisposes to the development of ACPA-positive as opposed to ACPA-negative RA in genetically predisposed individuals and, therefore, leads to the onset of a different, more aggressive clinical phenotype [32].

■ Alcohol consumption

There has been much interest in the role of alcohol consumption as a protective factor against RA development. Recent case–control studies have found lower rates of alcohol consumption in cases compared with controls, implying that it has a protective effect [33]. This relationship has not,

Table 2. Studies evaluating environmental and epidemiological prognostic factors for rheumatoid arthritis severity.

Risk factor	Study (year)	Size	Type	Severity outcome(s)	Main findings	Ref.
Smoking	Masdottir et al. (2000)	63 Ca	Cross-sectional	Nodules, modified Sharp score, SJC, HAQ, grip strength	Significant associations between ≥20 pack years and nodules, higher Larsen scores, higher HAQ scores and worse grip strength	[30]
	Manfredsdottir et al. (2006)	100 Ca	Longitudinal	Joint counts, pain VAS, CRP, van der Heijde score	Over 24 months current smokers had the highest and those who had never smoked the lowest SJC (p < 0.001) and TJC (p = 0.02) scores, respectively	[29]
Alcohol	Maxwell et al. (2010)	873 Ca	Cross-sectional	Larsen score, DAS28-CRP, modified HAQ, pain VAS	Significant trends for reducing Larsen scores, DAS28-CRP, CRP, modified HAQ and pain VAS with increasing alcohol intake	[34]
	Nissen et al. (2010)	2908 Ca	Longitudinal	Ratingen score (radiographic damage), HAQ	Non-significant reduced radiographic progression in drinkers: 1-year mean progression 0.99% (95% CI: 0.89–1.09) in drinkers vs 1.13% (95% CI: 1.01–1.26) in non-drinkers	[35]
OCP	Spector and Hochberg (1990)	1407 Ca 181,081 Co	Meta-analysis	ORs for RA using hospital- or population-derived cases	Pooled OR for studies using hospital cases showed significant protective effect of OCP use on RA development; not observed in studies using population cases	[37]
Periodontitis	Abou-Raya et al. (2008)	100 Ca	Cross-sectional	DAS28, HAQ, Larsen score	Periodontitis severity significantly correlated with DAS28 score, ESR and CRP	[40]
	Mercado et al. (2001)	65 Ca	Cross-sectional	Joint counts, VAS for physician global/early morning stiffness/pain, ESR/CRP, HAQ	Periodontitis severity significantly associated with higher SJCs, higher HAQ scores and higher CRP/ESR levels	[41]
Gender	Jawaheer et al. (2010)	292 Ca	Longitudinal	DAS28, HAQ, pain/fatigue VAS, global health scores, CRP, Sharp scores	Females had worse disease progression reflected by DAS28, physician global and TJC scores	[46]
	Ahlmén et al. (2010)	549 Ca	Longitudinal	DAS28, HAQ, SOFI instrument, SHS	Females had significantly higher DAS28 and HAQ scores at all time points	[47]
Social deprivation	McEntegart et al. (1997)	814 Ca	Longitudinal	Pain score, articular index, ESR, CRP, HAQ	Cases from deprived areas had significantly higher HAQ scores	[43]
	ERAS Study Group (2000)	869 Ca	Longitudinal	Joint counts, HAQ, pain VAS, grip strength, ESR, erosive radiological changes	Significantly worse HAQ and joint scores, and grip strength in individuals with higher deprivation scores	[44]

Ca: Case; Co: Control; DAS28: 28 joint count Disease Activity Score; ESR: Erythrocyte sedimentation rate; HAQ: Health assessment questionnaire; OCP: Oral contraceptive pill; OR: Odds ratio; RA: Rheumatoid arthritis; SJC: Swollen joint count; SHS: Sharp/van der Heijde score; SOFI: Signals of Functional Impairment; TJC: Tender joint count; VAS: Visual analog scale.

however, been observed in earlier cohort studies. There is also evidence that alcohol intake may associate with a less severe disease course. In one study of 873 erosive RA cases, more frequent alcohol consumption correlated significantly with lower DAS28-CRP, Larsen and modified HAQ scores [34]. These trends are shown in Figure 1. The median DAS28-CRP, Larsen and modified HAQ scores in individuals drinking no alcohol in the month prior to assessment comprised 4.29, 38 and 1.0, respectively; these scores in individuals drinking on more than 10 days in the month prior to assessment comprised 3.72, 27 and 0.63. All of these differences were statistically significant

(p < 0.05) when evaluated by trend tests across alcohol intake categories. A protective effect of alcohol intake on radiographic progression was also demonstrated in a large Swiss observational study evaluating 2908 RA cases nested within a national database of RA patients [35]. This study evaluated the impact of drinking alcohol on the progression of x-ray damage, scored according to the Ratingen method [36]. It found that in a model adjusting for multiple variables (comprising baseline radiological damage scores, DAS28, HAQ, presence of RF, sex, age, disease duration, tobacco smoking, education level and medications) radiographic damage at 12 months had progressed by an average of 0.99% (95% CI: 0.89–1.09) in drinkers and 1.13% (95% CI: 1.01–1.26) in non-drinkers. Interestingly, as with the beneficial effects of drinking on cardiovascular disease, a J-shaped dose–response effect was seen with occasional and daily alcohol consumers having less radiographic progression at 12 months compared with non-drinkers and heavy drinkers.

■ Oral contraceptive pill use

Although the oral contraceptive pill (OCP) has often been considered to protect against RA development, a meta-analysis of nine studies evaluating this topic by Spector and Hochberg indicated that OCP use may protect against the progression to a severe RA phenotype as opposed to protecting against disease onset [37]. While an overall protective effect of OCP use on RA risk was observed in case–control studies, when their meta-analysis was subdivided by studies using cases enrolled from hospitals or the community different impacts on disease risk were observed. In case–control studies evaluating hospital-based cases, the odds ratio (OR) for RA in OCP users was 0.49 (95% CI: 0.39–0.63); in those evaluating population-derived cases the OR was 0.95 (95% CI: 0.78–1.16). The authors considered that the most likely explanation for this discrepancy was that rather than preventing RA development, OCP use modified the disease process, maintaining it as a mild or transient disorder.

■ Periodontitis

Periodontitis, a destructive inflammatory disease of the supporting tissues of the teeth, is prevalent in RA patients [38]. The best characterized causative organism for periodontitis is *Porphyromonas gingivalis*, but there are others, including the *Prevotella* species. *P. gingivalis* is the only known bacterium to express its own functional peptidylarginine deiminase enzyme, the orthologs of the peptidylarginine deiminase family of enzymes responsible
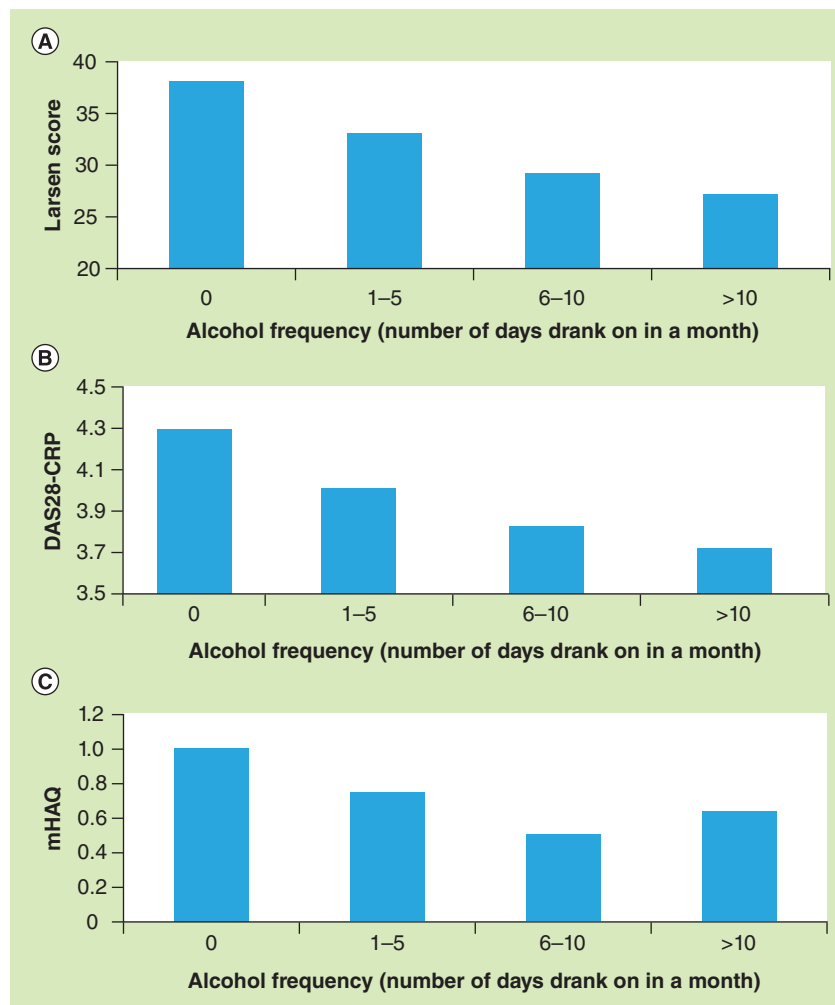

Figure 1. The relationship between alcohol consumption and disease outcomes in a case–control study. p-values for trend tests are all p < 0.0001.
DAS28: 28 joint count Disease Activity Score; mHAQ: Modified Health Assessment Questionnaire.
Data taken from [34].

for the citrullination of arginine residues in mammals [39]. It has, therefore, been hypothesized that it contributes to ACPA formation in pre-RA individuals. It follows from this that, as with smoking, periodontitis could affect disease severity through promoting ACPA. This relationship was evaluated in a cross-sectional study of 100 patients with active RA, which reported significant correlations between periodontitis severity and DAS28 scores (p < 0.001), erythrocyte sedimentation rate (ESR; p < 0.005) and high sensitivity CRP levels (p < 0.003) [40]. Another small observational study of 65 RA patients found that individuals with moderate-to-severe periodontitis had significantly more swollen joints, higher HAQ scores and higher CRP levels when compared with patients with no or mild periodontitis [41]. Further work is required with large longitudinal studies to better establish this relationship, and to explore the

impact of aggressive treatment of periodontitis on disease onset and/or severity.

■ Social deprivation

Several studies have highlighted that individuals from socially deprived areas have poorer disease outcomes [42,43]. This association was evaluated in 869 patients from the Early Rheumatoid Arthritis Study (ERAS), which is a large prospective cohort study of individuals with RA of less than 2 years duration [44]. The authors reported that the Carstairs score (a composite score of male unemployment, social class, overcrowding and car access that represents an index of deprivation) was associated with more severe disease at presentation, as reflected by HAQ and joint scores; this association persisted and remained after 3 years of follow-up. The precise underlying mechanism for this association is unclear; it may represent an association between low socioeconomic status and lifestyle factors such as smoking.

■ Gender

Gender differences in RA are well described, with the incidence of RA greater amongst women compared with men [45]. There is also evidence that RA outcomes are worse in females. Jawaheer *et al.* found that in a longitudinal prospective study of 225 women and 67 men with early seropositive DMARD-naive RA, women had worse disease progression over 2 years as reflected by DAS28 scores, physician global scores and tender joint counts; this was in spite of similar treatments [46]. Men were also more likely to attain remission. Similarly, the Swedish BARFOT study reported that women had significantly higher DAS28 and HAQ scores compared with males at all time points over a 5-year follow-up period; the authors attributed this DAS28 discrepancy to a higher number of tender joints and general health scores in women compared with men, which suggested that gender differences may exist in pain experiences in RA [47]. Other studies have reported similar female gender influences on RA progression [48].

Evidence for a genetic component to disease severity

In contrast to the identification of genetic susceptibility variants for RA – with 46 loci identified [49] – there is substantially less information on which genetic markers influence RA severity. The dominant reason for this is a lack of adequately sized cohorts containing detailed genotypic and longitudinal disease outcome data. Studies on this topic have been inadequately powered to detect genome-wide significant single nucleotide polymorphisms (SNPs), relying on candidate gene approaches instead to identify loci. While these have had some successes, a candidate gene approach fails to consider the entire genome and important loci may be overlooked. Despite these problems, there is accumulating evidence that genetics play an important role in determining radiological progression in RA. A twin study found that the variance in radiographic joint destruction was highest in unrelated patients, followed by dizygotic and finally monozygotic twins [50]. A more recent study has replicated the association between relatedness and radiological damage in 325 Icelandic patients with RA; this study quantified the heritability of radiological joint destruction to be between 45 and 58% [51].

Genetic risk factors for RA severity
■ *HLA-DRB1* alleles

The *HLA-DRB1* alleles, in particular those encoding the shared epitope (SE), are the best established genetic risk factors for seropositive RA, explaining approximately 36% of the heritability of RA [49]. They also associate with a more severe phenotype [52]. In one case–control study of 309 Caucasian RA patients and 283 controls, heterozygous/homozygous SE carriers used significantly more DMARDs – an indirect marker of disease severity – compared with non-SE carriers [53]. Similarly, Wagner *et al.* found that in a prospective study of 55 early RA cases, those positive for the SE on *HLA-DR4* had an OR for erosive disease of 13.75 (p = 0.00083) [54].

More recent studies have employed the classification system for *HLA-DRB1* alleles proposed by du Montcel *et al.* [55]. This broadly divides *HLA-DRB1* alleles into two groups: S alleles and X alleles, which have or do not have the RAA sequence at position 72–74, respectively. Some S alleles – such as S_2 (containing *HLA-DRB1*04:01*) – are associated with an increased disease risk; other S alleles – such as S_1 (containing *HLA-DRB1*13:01*) – are associated with a reduced risk [56]. Using this classification system one observational study of 962 RA cases found that S_2 allele carriage significantly correlated with higher Larsen scores, with the median Larsen score for individuals carrying one and two S_2 copies comprising 29 and 41, respectively [57]. Carriage of S_1 alleles associated with less radiological damage (p = 0.011). Similar findings come from a prospective study of 144 French–Caucasian early RA patients in which S_2 allele carriers had greater radiographic damage progression compared with noncarriers (p = 0.004); in addition, S_{3D} allele carriers had less

radiographic damage progression compared with noncarriers (p < 0.0001) [58]. In both instances significant gene–dose effects were observed.

It therefore appears that, as with disease susceptibility, some *HLA-DRB1* alleles are risk factors for, and some protect against, radiological progression in RA. The association with severity may arise from the fact that carrying SE alleles predisposes individuals to developing ACPA-positive RA [57].

▪ PTPN22

There is limited evidence that *PTPN22* – the dominant non-MHC susceptibility allele – contributes to radiological progression. This allele encodes a lymphoid-specific tyrosine phosphatase, Lyp, which is an important regulator of kinases and signaling intermediates that mediate antigen receptor signal transduction and T-cell activation [59]. It has been suggested that the RA-associated variant represents a gain-of-function mutation that predisposes to autoimmune disease through excessive suppression of T-cell receptor signaling leading to the survival of autoreactive T cells [60], but this remains controversial.

In a cross-sectional study of 964 RA cases, Marinou *et al.* reported a trend towards higher rates of x-ray damage in *PTPN22* minor allele carriers compared with non-carriers. Median modified Larsen scores for individuals with zero, one or two minor allele copies comprised 25.5, 33.0 and 50.0, respectively [61]. This finding was, however, only of borderline statistical significance (p = 0.04) and has not been replicated in other cohorts. These include the BRASS in which the adjusted OR (95% CI) for an erosive phenotype in *PTPN22* T allele carriers was 1.14 (0.77–1.71) [62] and the Leiden Early Arthritis Clinic and North American Rheumatoid Arthritis Consortium in which no association was demonstrated between the *PTPN22* susceptibility risk variant and joint destruction rates in RA patients, even when restricting analyses to ACPA-positive RA [63].

▪ IL1B & IL1RN

IL-1 is an important proinflammatory cytokine in RA, as demonstrated by the relative efficacy of anakinra, an IL-1β receptor antagonist [64]. IL-1 induces T-cell activation, promotes lymphocyte and monocyte chemotaxis and facilitates pannus formation. It is, therefore, an ideal candidate gene to examine its role in RA progression. IL-1 comprises three inflammatory mediators, encoded by the *IL1* locus on chromosome 2 [65].

These comprise IL-1α, IL-1β and the IL-1 receptor antagonist (IL-1Ra); all bind to the IL-1 receptor with the initial two mediators stimulating signal transduction and the latter acting as a competitive signaling inhibitor.

Cantagrel *et al.* evaluated the relationship between two polymorphisms in the *IL1B* gene and one polymorphism in the *IL1RN* gene amongst 108 patients with early RA [66]. Although none independently associated with erosion development at 2 years, when *IL1B* exon 5 allele E2 carriage was combined with the presence of SE alleles an increased risk of erosive disease was observed: the OR for erosions was 8.20 (95% CI: 2.59–25.84). This implies that epistasis (gene–gene interactions) contributes to radiological progression. Buchs *et al.* also examined the association between radiological damage and polymorphisms in the *IL1B* (within the promoter region at -511 and in exon 5 at +3954) and *IL1RN* (in exon 2 at position +2018) genes amongst 297 RA cases [67]. They found a significant relationship between destructive RA and the carriage of the rare *IL1B* (+3954) allele 2. The association of the exon 5 +3953 A2 allele with more active RA – defined by higher DAS28 scores and ESR levels – was demonstrated in a smaller study of 93 RA patients [68].

There are a number of studies, however, that show no relationship between *IL1B* loci variants and RA outcomes. In one report of 756 RA patients, three SNPs tagging *IL1B* (rs16944, rs1143623 and rs4848306) and one tagging *IL1A* (rs17561) did not correlate with the presence of rheumatoid nodules, joint replacement need or radiographic progression [69]. Another report found no robust association between 24 SNPs from *IL1A* and *IL1B* and hand radiograph erosions in 712 cases [70].

▪ IL6

IL-6 is another prominent cytokine in RA. It is abundant in the synovial fluid and serum of RA patients; its titers positively correlate with disease activity and joint damage [71]. An association between an *IL6* tagging SNP and radiographic severity was reported by Marinou *et al.* [61]. In this cross-sectional evaluation of 964 RA cases, the SNP, rs1800795, that tags the promoter region of the *IL6* gene (referred to as the '-174' polymorphism) significantly associated with radiological damage in seropositive RA. The modified Larsen scores in ACPA-positive RA risk allele non-carriers, heterozygotes and homozygotes comprised 29, 32 and 41 (trend test p-value = 0.004), respectively. As this finding has not been validated in other cohorts its prognostic relevance is uncertain.

■ IL10

While many genetic associations in RA are restricted to seropositive disease, one research group identified a polymorphism in *IL10* -592C (tagging SNP, rs1800872) specific for erosive damage in ACPA-negative RA [61]. In this study, ACPA-negative individuals homozygous for the risk allele had more severe radiographic damage compared with non-carriers/heterozygous individuals (pooled due to small numbers); the median modified Larsen score was 6.0 in non-carriers/heterozygotes and 16.0 in homozygotes (p-value for trend = 0.002). This suggests that, as with susceptibility alleles, genetic risks for severity differ serologically. This discrepancy by ACPA status is highlighted in Figure 2, which also demonstrates an *IL6* polymorphism associated with x-ray damage in ACPA-positive, but not ACPA-negative disease. Another *IL10* locus polymorphism was shown to influence the rate of radiological progression in 91 patients in The Netherlands [72]. Although this study did not subdivide its analysis by ACPA status, the presence of the *IL10* -1082GG genotype was associated with significantly greater increases in the Sharp radiographic damage scores at 3 and 6 years when compared with individuals with the -1082AA genotype. Other studies have, however, failed to demonstrate an association between these polymorphisms and radiographic damage in RA [73–75].

■ IL15

IL-15 is an innate immune system cytokine. It is present in the RA synovium where it plays a functional role, inducing neutrophil activation, granule release from natural killer cells, endothelial cell activation and preventing fibroblast apoptosis [76]. Clinical trials suggest that anti-IL-15 monoclonal antibody treatments may be effective in RA [77], offering further evidence for a pathogenic role. A meta-analysis of 1418 RA patients from four independent data sets evaluated the relationship between polymorphisms in the *IL15* locus and radiographic progression [78]. This involved an initial exploratory analysis in 600 patients from the largest cohort; significant SNPs were subsequently evaluated in the remaining cohorts, with a final combined assessment undertaken. In the initial analysis, five SNPs significantly associated with joint destruction rates. Although not independently replicated in the other data sets (possibly due to limited power in these smaller cohorts) the meta-analysis revealed significant associations for four SNPs. These comprised rs6821171 (protective effect on joint destruction) and rs7667746,

rs7665842 and rs4371699 (deteriorative effects). p-values after multiple testing correction comprised rs6821171 (p = 0.03), rs7667746 (p < 0.01), rs7665842 (p < 0.01) and rs4371699 (p = 0.02).

■ TRAF1/C5

TRAF1 encodes an intracellular protein member of the TNF receptor-associated factor family involved in TNF-α signaling [79]; the complement component 5 has been associated with RA in animal models [80]. In the Norfolk Arthritis Register (NOAR) – a primary care-based inception cohort of recent-onset inflammatory polyarthritis patients – two SNPs mapping to the *TRAF1/C5* locus (rs2900180 and rs10760130) were associated with erosions at 5 years; this was independent of ACPA [81]. At 5 years, the ORs for developing erosions in inflammatory polyarthritis after adjusting for ACPA positivity comprised 1.65 (95% CI: 1.13–2.42; p = 0.01) for individuals carrying the risk allele for rs2900180 and 1.52 (95% CI: 1.00–2.29; p = 0.05) for those carrying the rs10760130 risk allele. The SNP rs2900180 has also been associated with RA patient Larsen scores in ERAS [82]. Although another study of 278 cases reported a significant association between a SNP in this locus (rs10818488), which is in high linkage disequilibrium with rs10760130, and radiological progression [83], this was not reproduced in a meta-analysis of seven data sets (evaluating 2666 RA patients) [84].

■ CD40

The CD40 protein is expressed on the surface of multiple immune cells; it plays a pivotal role in providing CD4+ T-cell helper activity in immune reactions [85]. The association of the *CD40* locus with RA outcomes was shown in 250 and 393 ACPA-positive RA cases from the Leiden Early Arthritis Clinic cohort and North American Rheumatoid Arthritis Consortium, respectively [86]. In this analysis, the SNP rs4810485 yielded a 1.12-times (95% CI: 1.04–1.21) greater increase in the Sharp score per year in those carrying the risk genotype in the Leiden Early Arthritis Clinic (a significant association remained after correcting for multiple testing). Using a perfect SNP proxy the risk genotype from the Leiden Early Arthritis Clinic cohort also revealed a higher estimated radiological progression rate in the North American Rheumatoid Arthritis Consortium cohort.

Ultrasound imaging & MRI as predictors of RA severity

Advances in imaging technology have lead to an increased use of MRI and, in particular,

musculoskeletal ultrasound scanning (USS) in routine clinical practice. The key advantages that USS has over MRI are that many peripheral joints can be examined multiple times during a consultation with the patient thus improving clinical accuracy, prosthetic joints do not interfere with imaging, and USS is less costly [87]. In early RA, there is evidence that both techniques are able to predict longer-term radiological outcomes.

■ Ultrasound

Synovial inflammation involves peri-articular vasodilation, synovial proliferation and angiogenesis; this process can be detected by the USS power Doppler (PD) modality [88]. USS, and more specifically PD, assessments have been shown to correlate with radiographic progression in several studies. In 42 early RA patients (with disease duration of less than 12 months) followed-up at 0, 3, 6 and 12 months, time-integrated values of USS PD parameters had stronger correlations with radiographic progression at 1 year ($r = 0.59$; $p < 0.001$) than clinical and laboratory parameters ($r < 0.5$) [87]. In another RCT in which 24 methotrexate-treated RA cases were randomized to either placebo or infliximab, in the placebo arm there were significant positive correlations between both baseline synovial thickness and vascularity as measured by USS and progression in radiographic severity scores at 54 weeks [89].

USS can also play a role in the pre-RA stage by predicting which individuals with an undifferentiated arthritis will develop a persistent disease that may progress to a full RA phenotype. In a study of 50 patients with inflammatory hand symptoms for up to 12 weeks, the presence of a PD score in any joint of at least 2 had a similar predictive value for developing a persistent inflammatory arthritis to that of serology [90]. In this study, the sensitivities/specificities for RF, ACPA and a PD score ≥2 in any joint were reported as 31.6/100.0, 44.7/100.0 and 50.0/100.0, respectively. Similar findings come from a study by Filer *et al.*, who reported that the addition of a 10-joint PD index to the Leiden clinical prediction score for RA development significantly improved the model's predictive capabilities in individuals with very early synovitis (as demonstrated by an area under the curve increase from 0.905 to 0.962; $p < 0.05$) [91].

■ MRI

Several studies have shown that the presence of MRI-detected bone marrow edema at disease onset predicts joint damage progression years later. In one RCT of 130 early RA patients, baseline
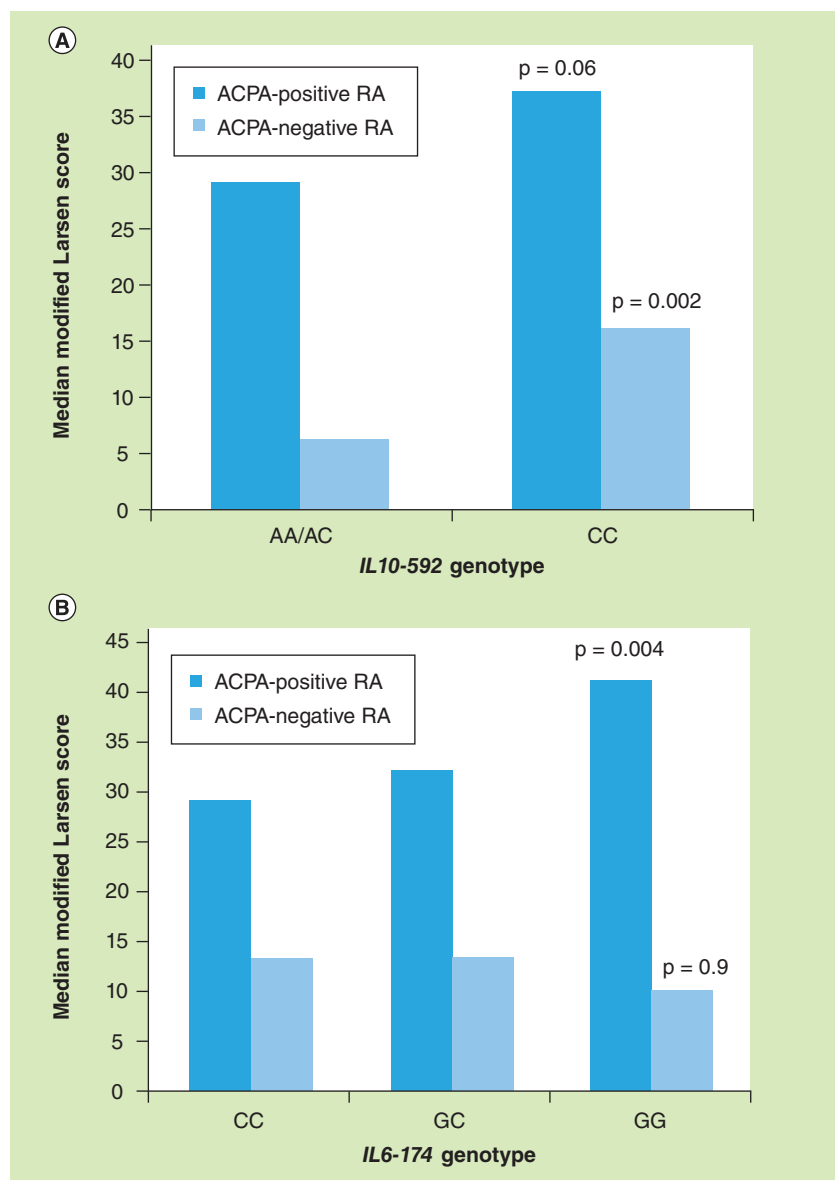

Figure 2. The effects of *IL6* and *IL10* gene polymorphisms on modified Larsen scores when evaluated by ACPA status in a recent case–control study. p-values are for the comparison of median scores across genotype groups. ACPA: Antibodies to citrullinated peptide antigens; RA: Rheumatoid arthritis. Data taken from [61].

MRI bone marrow edema was the only significant predictor (in a multiple linear regression analysis) of radiological progression at the wrist and metacarpophalangeal joints, explaining 41% of the variation in the SHS [92]. Similarly, in a smaller prospective study of 42 RA patients the baseline MRI bone edema score was predictive of the 6-year total Sharp score ($p = 0.01$) [93]. Palosaari *et al.* also demonstrated the predictive value of bone marrow edema on MRI; in 27 early RA patients the baseline MRI bone edema score was the only baseline variable that predicted erosive progression at 24 months in a multivariate model (OR: 4.2; 95% CI: 1.3–13.8) [94].

Biochemical markers

The best established and most commonly used prognostic biomarkers for RA comprise the acute phase response indices ESR and CRP, both of which correlate with disease severity [26]. A number of other markers have been evaluated for their prognostic implications in RA. One example is the matrix metalloproteinases (MMPs), which are zinc-dependent proteases that regulate extracellular matrix proteolysis and are involved in the cleavage of cytokines, chemokines and their receptors; they are thus considered to play important roles in inflammation [95]. Other examples include the bone turnover marker urinary C-telopeptide of type II collagen (CTX-II), which is an immunoassay that uses antibodies specific for the C-terminal cross-linking telopeptide of type II collagen in the urine [96] and the osteoclast activation markers RANKL and osteoprotegerin (OPG). RANKL is an essential osteoclastogenesis cytokine; OPG is a decoy receptor for RANKL that inhibits osteoclast function by interrupting RANKL's interaction with its receptor [97].

Young-Min et al. evaluated the role of several serum biomarkers comprising MMP-1, MMP-13, MMP-3, TIMP-1 and COMP and urinary biomarkers including CTX-II in predicting radiographic progression in 132 early RA patients [98]. They found that although multiple biomarkers including MMP-3, COMP and TIMP-1 correlated significantly with radiographic progression by multivariate analysis, a model consisting of baseline MMP-3 and CTX-II provided the best prediction of radiographic progression at study entry (area under the curve: 0.76; 95% CI: 0.66–0.85). Other research groups have shown MMP-3 to be predictive of radiographic progression in other RA cohorts. In 48 RA patients without radiological damage at presentation, serum MMP-3 levels at study entry significantly correlated with Sharp scores at 6 and 12 months and joint space narrowing at 6, 12 and 24 months [99]. Similarly, in 26 patients with early RA baseline serum MMP-3 levels were significantly associated with Larsen scores at 6 and 12 months after study entry; furthermore, when the relationship between percentage increases in serum MMP-3 in the first 12 months after entry and the percentage increase in Larsen scores in each year were evaluated, a significant correlation was observed between the increase in serum MMP-3 during the first 12 months and the increase in the Larsen score in the subsequent 12–24 months after entry [100].

The role of urinary CTX-II in RA prognostic stratification has also been reproduced in several studies. The association between baseline urinary CTX-I and CTX-II levels and the mean annual progression of joint destruction over a median of 4 years was examined in the COBRA study. In two multivariate logistic regression analyses that included each marker separately due to their high correlation, baseline urinary CTX-I and CTX-II levels both predicted long-term radiologic progression independently of treatment, disease activity and RF status at baseline [101]. In addition, Hashimoto et al. reported that in 145 patients with active RA of less than 5 years duration baseline urinary CTX-II levels correlated significantly with radiological progression at week 52 [102].

The prognostic value of the RANKL:OPG ratio (representing osteoclast activation) was also shown in the COBRA study. In a univariate analysis examining the relationships between disease activity measures/bone markers and annual radiographic progression, the baseline RANKL:OPG ratio was the strongest predictor of radiological deterioration [103].

Combining prognostic markers to predict RA severity

Several research groups have attempted to combine information on the aforementioned prognostic factors into models that are capable of identifying individuals at a high risk of radiological progression. Some have used simple clinical parameters and others have integrated these with biomarkers and radiological indices. Genetic markers have rarely been used.

Brennan et al. developed one such prediction model for the presence of radiological erosions in the hands and/or feet after 12 months within the NOAR cohort [104]. In this study of 175 patients with early RA, the study population was randomly split into a prediction sample of 105 patients – in which predictor variables for radiological progression were sought – and a validation sample of 70 patients – in which the prediction algorithm was tested. A simple algorithm using a combination of three variables, comprising a positive RF test, swelling of at least two large joints and disease duration of more than 3 months, was best able to predict erosions. This prediction model was able to classify eight risk groups, with a probability of developing erosions that ranged from 0.13 (if all variables were absent) to 0.89 (if all were present). It was able to correctly predict the development of erosive disease in 79% of cases; its negative and positive predictive values were 80 and 76%,

respectively. Its predictive abilities are illustrated in FIGURE 3. This model demonstrates that even simple clinical measurements used in routine practice can be useful in estimating disease progression.

Drossaers-Bakker *et al.* demonstrated that prognostic modeling can be undertaken to predict longer-term disease outcomes at 12 years [105]. This study evaluated 112 female RA patients with symptoms of less than 5 years' duration (median 1 year) at recruitment. It developed prediction models for three different disease outcomes: first, radiographic damage (measured by the SHS method); second, disability (measured by the HAQ); and third, a severe disease course (measured by calculating the area under the curve of all DAS assessments alongside the radiographic disease course). Individuals in the highest tertile of each outcome measure were defined as 'severe' for that outcome and individuals in the lowest tertile were defined as 'mild'. Using a model that contained the baseline parameters of the SJC, RF, the presence of erosions, the Ritchie index, ESR, HAQ and SHS, the accuracy of the model for predicting mild radiographic damage, severe radiographic damage, mild HAQ, severe HAQ and a severe disease course comprised 87, 84, 88, 84 and 83%, respectively. Surprisingly additional information on HLA typing added little to the modeling, improving the correct prediction of radiographic damage by only 3%. This finding highlights the limitations of including current genetic markers, which explain only a minor proportion of the heritability of radiological progression, in prognostic models.

More recently, two research groups have developed matrix risk models for RRP, which are organized into color-coded matrixes similar to that which is widely used in predicting the 10-year risk of fatal cardiovascular disease [106]. One of these matrixes was developed using data from 465 RA patients enrolled to the BeST RCT. As previously described, this study randomized patients to four treatment arms comprising two arms treated with initial monotherapy that could be switched or extended to other DMARDs, a third arm treated with initial combination DMARDs and tapering high-dose corticosteroids and a fourth arm treated with initial methotrexate and infliximab [107]. Patients were treated with an aim of attaining a DAS of ≤2.4. RRP was defined as an increase in the SHS of ≥5 after 12 months. Predictors of RRP were identified by multivariate logistic regression with backward selection. Different models were developed for different treatment groups and included the variables CRP,

erosion score and serology (RF and ACPA). The highest risk group was those individuals in the initial monotherapy treatment arm with a CRP ≥35mg/l, erosion score ≥4 and both RF and ACPA positivity; their risk of RRP was 78%. The lowest risk groups were those individuals in the initial combination with prednisolone or
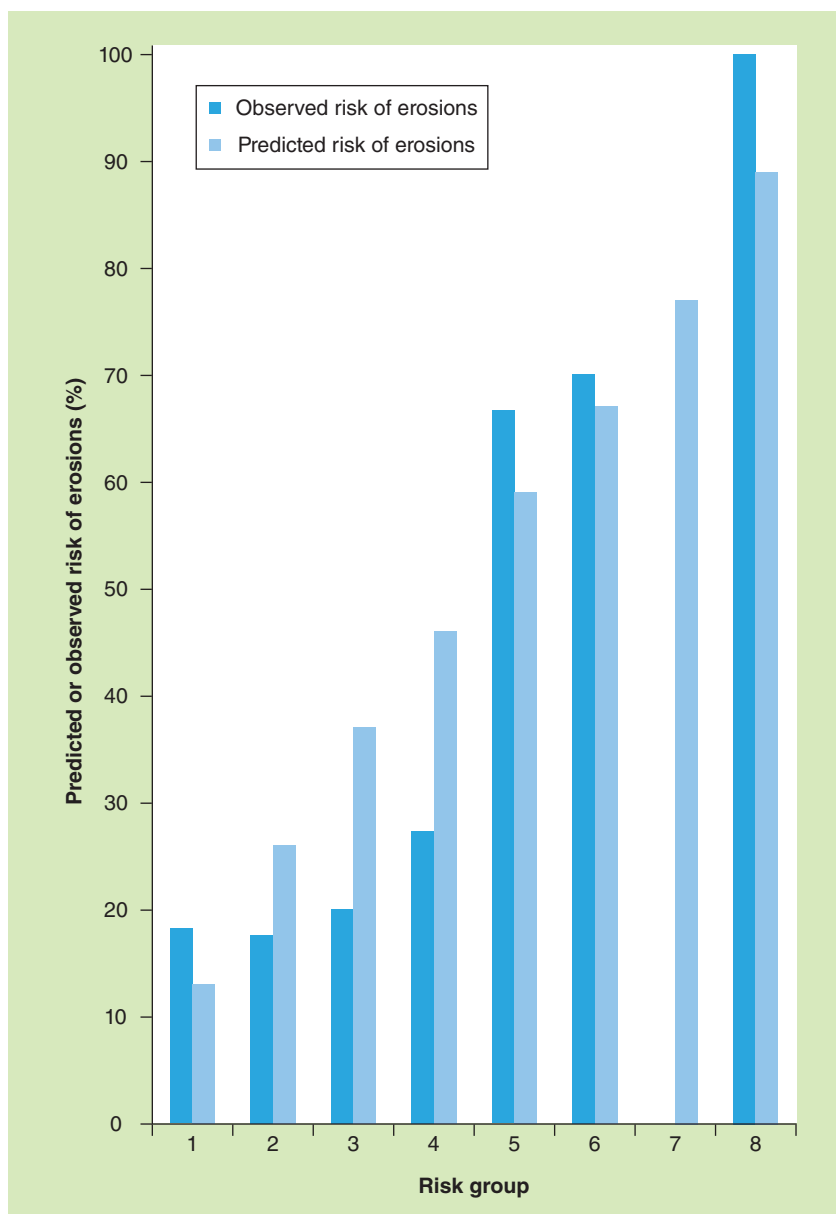

Figure 3. Predicted versus observed risks of developing erosions using a prediction model with three clinical variables in the Norfolk Arthritis Register cohort. The eight risk groups are defined by the presence or absence of the three variables included in the prediction model. The combination of the variables comprising a positive rheumatoid factor, disease duration of ≥3 months and ≥two large joints involved in risk group 1 is negative/no/no; in group 2 is negative/yes/no; in group 3 is negative/no/yes; in group 4 is positive/no/no; in group 5 is negative/yes/yes; in group 6 is positive/yes/no; in group 7 is positive/no/yes; and in group 8 is positive/yes/yes. In risk group 7 there were no individuals with this combination of variables in the Norfolk Arthritis Register validation cohort. Data taken from [104].

infliximab arms with a CRP <10mg/l, erosion score of 0 and negative serology; their risk of RRP was 1%. The area under the curve of the receiver operating curve was 0.81 (95% CI: 0.77–0.86), indicating a moderate ability to correctly classify individuals who will develop RRP.

The other research group to develop a risk matrix for RRP developed prediction models in two different cohorts [106]. The first cohort was the ASPIRE study, which comprised 1049 methotrexate-naive early RA patients randomized to receive methotrexate with or without infliximab; and the second cohort was the ATTRACT trial, which comprised 428 patients with established RA and active disease treated with either methotrexate and infliximab or placebo. They identified risk factors from the early RA cohort (the ASPIRE study) and in order to ensure this combination of risk factors had similar predictive capabilities in a more advanced RA population undergoing similar treatment generated a prediction model in the ATTRACT trial using the same variables. RRP was defined as a change in the modified SHS of ≥5 units/year. Spearman's rank analysis was used to identify baseline risk factors for RRP. Two prediction matrixes were developed, which contained either the ESR or CRP alongside information on the 28 SJC, RF and treatment (monotherapy or combination therapy). The highest risk group was those individuals in the ATTRACT study receiving methotrexate monotherapy with a 28 SJC >17, RF titer >200 U/ml and an ESR >50 mm/h; their risk of RRP was 65%. The lowest risk group was those individuals in the ASPIRE study receiving methotrexate and infliximab with a 28 SJC <10, RF <80 U/ml and an ESR <21 mm/h; their risk of RRP was 2%. Individuals treated with methotrexate monotherapy had higher predicted rates of RRP when compared with those receiving infliximab.

The latter three studies evaluating prognostic modeling that we have described developed and validated their models within the same patient cohorts [105–107]. It is, therefore, expected that they could predict disease outcomes with relative accuracy and their models require further assessment in alternative cohorts to better define their prognostic capabilities.

Conclusion

Research evaluating the prognostic factors for RA has lagged substantially behind that evaluating the underlying risk factors for RA susceptibility. This is particularly true of genetic factors; although 46 RA susceptibility loci of genome-wide significance have been identified, only a handful of risk loci for radiological progression are known. Furthermore, identified loci mainly stem from candidate gene studies of limited sample sizes and have rarely been replicated in independent data sets. Although some evidence suggests an overlap between RA susceptibility and severity loci, for the most part there appears to be little commonality between the two. One key impediment to research in this area is the lack of a consistent definition of what represents 'severe disease' with marked heterogeneity present in the disease severity markers used between studies. We consider that a better classification of severe RA is required to facilitate comparability across studies in this important research field. Another barrier is the lack of large data sets of RA patients with detailed genetic and disease outcome data; this greatly limits the evaluation of genetic predictors of RA outcomes.

Despite these problems prognostic modeling for RA severity has shown some promise, with disease severity prediction models incorporating variables routinely used in clinical practice, such as the ESR and SJCs, showing relative accuracy at identifying those individuals at a high risk of radiological progression. The inclusion of genetic prognostic markers that explain only a minor proportion of the heritability of radiological progression, have added only minor improvements to current prognostic models, highlighting the limited clinical application of current genetic research in this field.

Further work is needed to better define what markers are relevant in predicting RA prognosis. Ideally large longitudinal cohort studies are required that recruit patients at disease onset and capture detailed environmental, genotypic and disease outcome data. Such an approach should identify factors associated with adverse disease outcomes. As many of these factors (such as age, gender and genotypes) will be non-modifiable, the main benefit of their identification lies in their incorporation within prognostic modeling, although it is only factors of large effect sizes that would significantly improve upon existing models. Effective prognostic modeling would facilitate the advent of personalized medicine, allowing treatments to be tailored according to an individual's likelihood of developing severe disease, which is an attractive prospect for both clinicians and patients.

Future perspective

An increased appreciation of the heritability of radiological progression in RA tied in with the

rapid advances in genotyping techniques, such as next-generation sequencing, has placed a key research focus on identifying the genetic variants that influence disease outcomes, such as rapid radiological progression, in RA. We, therefore, envisage that the main area in which this research field will progress is in the identification of novel risk loci for severe RA, which may substantially improve the predictive capabilities of current prognostic models. This could allow the prediction of an individual's risk of severe RA at disease onset, enabling their treatments to be tailored according.

Executive summary

Requirement for prognostic models to predict rheumatoid arthritis severity

- Rheumatoid arthritis (RA) is a heterogeneous disease that varies markedly in its severity. There is, therefore, a requirement to develop methods that can prospectively stratify an individual's risk of severe disease, enabling treatments to be tailored accordingly.

Prognostic factors for RA severity

- Probable environmental and epidemiological prognostic factors for RA severity include smoking, periodontitis, social deprivation and female gender, which are associated with more severe disease, and drinking alcohol and oral contraceptive pill use, which are associated with less severe disease.
- The most reproduced genetic markers for RA severity comprise the *HLA-DRB1* alleles.
- Power Doppler signal on ultrasound and the presence of bone marrow edema on MRI both correlate with subsequent radiological joint damage.
- Biochemical markers such as MMP-3 and urinary C-telopeptide of type II collagen have shown modest capabilities in predicting joint damage.

Current prediction models for RA severity

- Models incorporating clinical prognostic factors have shown some promise in identifying individuals at a high risk of radiological progression.
- Many of these models require validation in separate cohorts of RA patients.

Future work

- A globally accepted definition of 'severe RA' is required to allow comparability across studies examining prognostic factors for RA.
- Further work is needed to better define what markers are relevant in predicting RA prognosis: large, longitudinal cohort studies are required that recruit patients at disease onset and capture detailed environmental, genotypic and disease outcome data.

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▪   **Outlines a matrix risk model for rapid radiographic progression using routinely available clinical variables. It does, however, require evaluating in a separate cohort of rheumatoid arthritis patients having been developed and validated in a single randomized controlled trial.**