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Predictive factors for outcome of rheumatoid arthritis

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CHAPTER 14

Predicting arthritis outcomes - what can be learned from the Leiden Early Arthritis Clinic?

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ABSTRACT

Introduction

In order to allow personalized medicine, adequate prediction of the disease outcome is required. In early undifferentiated arthritis (UA) prediction of the development of rheumatoid arthritis (RA) is crucial and in case of RA predicting the severity of the disease course may guide individualized treatment decisions.

Methods

570 UA patients and 676 RA patients included in the Leiden Early Arthritis Clinic cohort were studied for baseline characteristics. The disease outcomes studied were fulfillment of the 1987 ACR RA criteria and arthritis persistency in UA patients and the rate of radiological joint destruction and achieving sustained DMARD-free remission in RA patients.

Results

Predictive factors for fulfillment of the 1987 ACR RA criteria and for persistent arthritis in UA were largely similar. Risk factors for a severe rate of joint destruction were: (p-value) older age (<0.001); male gender (<0.001); longer symptom duration at first visit (0.048), involvement of lower extremities (<0.001); BMI (<0.001); high acute phase reactants, presence of IgM-RF (<0.001); anti-CCP2 antibodies (<0.001); anti-MCV antibodies (<0.001) and HLA-SE alleles (0.001). A high BMI was associated with a lower rate of joint destruction but with a higher risk on disease persistency. The proportion of variance in joint destruction explained was 32%.

Conclusion

Predictors for RA development, previously used to develop a prediction rule in UA patients, are largely similar to predictors for arthritis persistency. Only part of the level of joint destruction in RA is explained by currently known risk factors. New factors need to be identified in order to guide pharmaceutical intervention at the level of individual RA patients.

INTRODUCTION

The outcome of early arthritis patients is highly variable. Approximately only one-third of the patients with a recent-onset undifferentiated arthritis (UA) progresses towards rheumatoid arthritis (RA). The severity of the progression of joint destruction in RA is highly variable as well, as only a minority will become severely destructed. In order to achieve individualized treatment decision making, the severity of the disease outcome needs to be estimated adequately. This is particularly relevant since it is widely acknowledged that early initiation of treatment of RA is effective in diminishing the level of joint destruction and disability.¹⁻³ Fewer studies are performed on the effects of early intervention in recent-onset UA, but available data suggest that early treatment strategies hamper progression in UA as well.⁴⁻⁶ Potent treatment strategies such as targeted therapies are generally not started in an early phase because of the risk of overtreatment. However, when the individuals who will have an unfavorable disease outcome can be identified at first presentation, the risk on overtreatment and undertreatment can be balanced, resulting in a personalized pharmaceutical regimen.

Observational studies of unselected patients are most appropriate to identify risk factors for a certain disease course. Following patients with and without risk factors allows direct assessments of absolute risks on a disease outcome. The Leiden Early Arthritis Clinic cohort is a population based inception cohort including early arthritis patients since 1993. Patients are being followed as long as they are seen at the rheumatologist and follow-up ends in case patients are discharged because of having a sustained DMARD-free remission or when patients die. During the past years several risk factors for a mild or progressive disease course, both in UA and RA, have been identified.

The present manuscript in this themed issue on Registries in Rheumatologic conditions reviews to what extent the disease outcome in early UA and early RA can be predicted, using data from the Leiden Early Arthritis Clinic cohort. The two disease outcomes studied in UA are fulfilling the 1987 ACR criteria for RA and having persistent arthritis. The disease outcomes studied in early RA patients are the progression in joint destruction over time and disease persistency. These evaluations allow comparison of risk factors for joint destruction and RA persistency. Since it is thus far unclear to what extent the processes underlying joint destruction are similar to the processes that mediate disease persistency, evaluation of overlapping and dissimilar risk factors may increase understanding and the subsequent elucidation of the underlying biological pathways leading to these phenotypic characteristics. Finally, the fraction of explained variance of progression in joint destruction by the currently known risk factors is determined to assess how complete our current understanding is.

PATIENTS AND METHODS

Design of Leiden Early Arthritis Clinic

This Leiden EAC is a population-based prospective cohort that was started in 1993 in order to detect and treat inflammatory disorders early in the disease state, especially early RA. In order to obtain early referrals by general practitioners (GPs), a campaign was started among GPs to refer patients with suspected arthritis as soon as possible to the rheumatology department of the Leiden University Medical Center. This is the only centre for rheumatic diseases in a semi-rural area with more than 400,000 inhabitants. Patients are seen within 2 weeks. Inclusion took place when arthritis was confirmed at physical examination and symptom duration was less than two years. Written informed consent was obtained from all participants. The study was approved by the local Medical Ethical Committee. At the first visit, the rheumatologist completed a questionnaire regarding the presenting symptoms, as reported by the patient: type, localization and distribution of initial joint symptoms, symptom duration, and course of the initial symptoms. The patient's smoking history and family history were assessed. Patients rated morning stiffness on a visual analogue scale (VAS; range 0-100 mm); the duration of morning stiffness was also assessed. The Health Assessment Questionnaire (HAQ) was used to provide an index of disability. A 66-joint count for swollen joints (SJC) was performed. Blood samples were taken for routine diagnostic laboratory screening (including C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR) and immunoglobulin (Ig)M-rheumatoid factor (RF)) and stored to determine other serum markers (amongst others antibodies against citrullinated peptide antibodies) at a later time. Blood samples were taken for DNA extraction as well. Follow-up visits with standard clinical assessments (including a SJC and a HAQ) were performed 3 months after the first presentation and yearly thereafter. Radiographs of the hands and feet were taken at baseline and yearly thereafter. Two weeks after inclusion, when results of laboratory investigations and radiography were known, patients that had a form of arthritis that could not be classified according to American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria were documented as having UA. The diagnosis RA was established in case patients fulfilled the 1987 ACR criteria for RA. The initial treatment of RA patients had changed in time and differed according to the inclusion period.⁷ Patients included between 1993 and 1995 were initially treated with analgesics and were subsequently treated with hydroxychloroquine or sulfasalazine if they had persistent active disease. Between 1996 and 1998, patients who were included were promptly treated with chloroquine or sulfasalazine, while after 1998, the initial treatment strategy consisted of either methotrexate or sulfasalazine.⁷ Treatment of UA patients was not protocolized.

Definition of outcome measures

Patients with UA were assessed on two outcomes. First, after one year of follow up, the fulfillment of the 1987 ACR criteria for RA was evaluated. As previously described, 31% of UA patients pro-

gressed to RA during 1 year of follow-up. The majority of the patients (94%) had been followed up for more than 1 year (mean follow-up 8 years, SD 3 years) and 4.4% of UA patients developed RA later than one year after inclusion.⁸ The second disease outcome was disease persistency. As a generally accepted definition for persistency is lacking, we defined persistent arthritis as the absence of sustained DMARD-free remission. Sustained remission was diagnosed when patients had no swollen joints for at least one year after cessation of eventual DMARD therapy. The absence of swollen joints had to have been observed by a rheumatologist for at least one year to ensure that remission was not temporary, but rather sustained. When remission was not obtained after 5 years of disease, a patient was classified as having persistent disease in the present study.

The RA patients were studied for the rate of radiological joint destruction and for achieving sustained DMARD-free remission or having persistent RA, also during a five years period of follow-up. In order to study the progression rate in a sensitive way all serial radiographs were scored by one experienced reader (MvdL) according to the Sharp-van der Heijde method (SHS) in chronological order. Four hundred and nine radiographs belonging to 60 randomly selected RA patients were rescored. The intraclass-observer correlation coefficient was 0.91 for all scored radiographs, and 0.97 for the radiographic progression rate. The means (\pm SEM) at the subsequent time points were 9.15 (0.43) at baseline; 15.65 (0.72) at one year follow up; 20.0 (0.93) at two years; 24.79 (1.36) at three years; 34.83 (2.14) at four years and 34.8 (2.14) at five years of follow-up. Persistent RA was defined as the absence of a sustained DMARD-free remission. A sustained DMARD free remission in RA was defined as the absence of swollen joints for at least one year after cessation of DMARDs and classification as DMARD-free remission by the rheumatologist. To ensure that remission was not temporary but rather sustained and long-lasting, the absence of swollen joints had to have been observed by a rheumatologist for at least 1 year after discontinuation of DMARD therapy. Corticosteroids were here considered to be equivalent to DMARDs. The majority of patients with disease in remission were discharged from the outpatient clinic at any time, however most patients who achieved remission were followed up longer than the minimum requirement of 1 year; the median time of observation after discontinuation of DMARDs in the absence of swollen joints was 2.5 years. Patients who had a recurrence of their arthritis after discharge could easily return to the Leiden University Medical Center. The frequency of disease relapse was 6%; these patients were included in the persistency group. We observed previously that sustained DMARD-free remission was obtained by 15% of RA patients after a median disease duration of 43 months.⁹ Therefore, for the present study, patients that within the first 5 years did not achieve a sustained DMARD-free remission were classified as having persistent RA.

Statistical analysis

Predictors for RA development and arthritis persistency were analyzed univariately with a logistic regression analysis. Since the aim of the present study was to review predictive factors

and not to develop a prediction rule for the outcome of UA, which has been done before,¹⁰ no multivariate regression analysis was performed in UA patients.

Associations between baseline factors and rate of joint destruction were analyzed with a linear multivariate regression model see ref. for detailed description.⁷ This was done for each variable separately, but all analyses were adjusted for the applied treatment strategy. In a previous study we showed that the inclusion period is an adequate proxy for the different treatments strategies that were applied over time.⁷ The baseline characteristics were tested with an interaction term of a linear function of time. The risk estimate (β) resulting from these analyses reflected the relative difference in slopes between the groups over five years of follow-up. To test for a difference that is not progressive but stable over time, a model without interaction term was fitted; the overall effect of the risk factor then reflected a constant effect in time. This model does not exclude patients in case of missing radiographs and can deal with missingness provided that it is missingness at random.⁷ Patients with complete datasets are weighted more heavily in the analysis than patients with missing radiographs.

All factors that were associated with the progression of joint destruction were entered in a multivariate analysis to determine the variance of joint destruction explained by these factors. This variance was defined by comparing the residual variance of the analysis including all risk factors with the residual variance of the analysis including only the adjustment factor for treatment strategy (inclusion period). The proportional reduction of the residual variance was the explained variance of the risk factors analyzed.

P-values <0.05 were considered significant. Since the aim was to review baseline characteristics in relation to the disease outcome, p values were presented without corrections for multiple testing. Analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

Predictors for disease outcome in UA

177 UA patients developed RA (31%). An overview of baseline characteristics associating with RA development and persistency of arthritis is presented in Table 1. Part of the variables predictive for the development of RA was described previously.¹⁰⁻¹² Identified variables associating with the development of RA were patients' characteristics (age, gender, having a positive family history of RA), morning stiffness, inflammatory characteristics (CRP, ESR, number of swollen joints), localization of involved joints, and presence of auto-antibodies (RF, anti-CCP2, and anti-MCV). The environmental factors smoking and BMI were not associated with progression from UA to RA. The acuteness of the start of the complaints was associated with RA development; UA patients with a gradual onset of symptoms had a 1.5 higher odds ratio to develop RA than patients with a subacute symptom onset. A longer duration of symptoms at first presentation was associated with a higher risk on the development of RA as well.

Table 1. Baseline characteristics of patients with undifferentiated arthritis in relation to the outcome measures RA development and persistency of arthritis

Baseline characteristic	Frequency	RA development		Arthritis Persistency	
		OR (95%CI)	P	OR (95%CI)	P
Age, mean (SD), years	60.0 (16.8)	1.03 (1.01-1.04)	<0.001	1.00 (0.99-1.01)	0.90
Female gender, n (%)	329 (57.7)	2.00 (1.35-2.86)	<0.001	1.47 (1.03-2.08)	0.034
Pos. family history for RA, n (%)	135 (23.7)	1.65 (1.11-2.45)	0.013	1.32 (0.87-1.98)	0.20
Chronic symptom vs. (sub)acute, n (%)	244 (42.8)	1.54 (1.11-2.23)	0.010	1.19 (0.84-1.69)	0.34
Symptom duration at fist visit, mean (SD), weeks	23.3 (23.6)	1.012 (1.004-1.019)	0.002	1.011 (1.002-1.019)	0.012
Morning stiffness severity - VAS (0-100), mean (SD)	41.3 (31.1)	1.02 (1.01-1.03)	<0.001	1.00 (1.00-1.01)	0.19
BMI, mean (SD)	26.0 (12.0)	1.03 (0.99-1.08)	0.18	1.07 (1.01-1.13)	0.013
Localization initial joint symptoms					
Small vs. large joints, n (%)	266 (57.5)	2.48 (1.63-3.79)	<0.001	0.95 (0.65-1.40)	0.80
Large & small vs. large joints, n (%)	107 (35.2)	4.18 (2.50-6.97)	<0.001	1.25 (0.76-2.06)	0.38
Upper vs. lower extremities, n (%)	248 (43.5)	2.21 (1.36-3.57)	0.001	1.02 (0.68-1.53)	0.92
Upper & lower vs. lower extremities, n (%)	161 (50.0)	6.07 (3.63-10.10)	<0.001	2.13 (1.31-3.46)	0.002
Symmetric vs. asymmetric, n (%)	265 (46.5)	2.82 (1.98-4.03)	<0.001	1.20 (0.85-1.71)	0.29
Past or present smoker vs. non-smoker, n (%)	271 (48)	1.0 (0.9-1.4)	0.98	0.7 (0.5-1.1)	0.10
SJC, mean (SD)	3.8 (4.0)	1.17 (1.11-1.23)	<0.001	1.07 (1.02-1.13)	0.01
CRP (mg/L), mean (SD)	21.4	1.01 (1.00-1.02)	0.001	1.01 (1.00-1.01)	0.03
ESR (mm/1hr), mean (SD)	29.5 (24.8)	1.02 (1.01-1.02)	<0.001	1.01 (1.00-1.02)	0.003
IgM-RF positive, n (%)	140 (24.6)	5.10 (3.39-7.66)	<0.001	3.55 (2.18-5.76)	<0.001
Anti-CCP2 positive, n (%)	121 (21.2)	8.74 (5.51-13.84)	<0.001	5.97 (3.30-10.78)	<0.001
Anti-MCV positive, n (%)	172 (33.9)	6.48 (4.32-9.71)	<0.001	4.53 (2.87-7.17)	<0.0001
HLA-SE positive, n (%)	309 (55.9)	1.96 (1.36-2.81)	<0.001	1.76 (1.23-2.51)	0.002

Age, BMI, ESR, CRP, SJC, symptom duration at first visit and morning stiffness were analyzed as continuous variables; this means that the presented OR indicates the odds per unit. For instance, an OR of 1.03 for age in relation to the risk on RA development means that per year increase in age, the OR is 1.03. Morning stiffness is displayed in millimetres. From all 570 patients data on RA-development was present, the remission/persistency state could be reliably determined in 538 patients and was not clear recorded in the medical file in 43 cases. CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BMI: Body Mass Index; SJC: swollen joint count; HLA-SE: HLA-DRB1 shared epitope alleles; RF: rheumatoid factor; anti-CCP2: anti-cyclic citrullinated peptide antibody; anti-MCV: anti-modified citrullinated vimentin antibodies

As the outcome measure of fulfilling the 1987 ACR criteria for RA might be subject to discussion (because these criteria were not designed to identify RA in an early phase) and to circular reasoning (because the presence of hand erosions are part of the ACR criteria), we also tested these baseline characteristics in relation to arthritis persistency, defined as the absence of sus-

tained remission. During the five year period of follow up, 210 UA patients achieved remission (39%). The median disease duration till remission was achieved was 17 months (IQR 6.3-37). Factors significantly associated with disease persistency were inflammatory markers (the number of swollen joints, CRP and ESR) and presence of auto-antibodies. Other characteristics such as the distribution of involved joints, the acuteness of the onset of the complaints, and morning stiffness were not predictive for having a persistent form of arthritis.

Predictors for outcome of RA

Baseline characteristics of RA patients associated with the severity of joint destruction over time are presented in Table 2. The strongest association with the rate of joint destruction was seen for presence of anti-cyclic citrullinated peptide 2 (anti-CCP2). Anti-CCP positive RA patients had over the 5 year period a 2.4 times higher progression rate than anti-CCP negative patients. A similar effect was seen for presence of IgM-RF. Higher levels of acute phase reactants at first presentation were also associated with more severe joint damage over time. RA patients whom initial joint symptoms were located at the lower extremities had a higher rate of joint destruction. Interestingly, the severity of morning stiffness at first presentation was not associated with the severity of joint destruction over time. The body mass index (BMI) was inversely correlated with the progression of joint destruction over time. Few genetic factors are convincingly reported to associate with progression of joint destruction. Here we studied the HLA-Shared Epitope (SE) alleles and *CD40*, both are identified risk factors for anti-CCP positive RA only.^{11,13} Although presence of the HLA-SE alleles associated with the progression of joint destruction in RA, *CD40* did not reveal such an association in a cohort consisting of both anti-CCP positive and anti-CCP negative RA patients. All the analyses on the rate of joint destruction were adjusted for the treatment strategy applied; this variable was significantly associated with the rate of joint destruction in all performed analyses.

Since it is unclear whether the processes driving joint destruction are the same that drive RA persistency, predictive factors for both outcomes of RA were compared. The proportion of patients that achieved a sustained DMARD-free remission was 0.157, thus 84.3% of the patients were classified as having persistent RA. The median disease duration till remission was 40 months (IQR 25.5-66.5). The factors that were clearly associated with RA persistency were presence of auto-antibodies, the HLA-SE alleles and the duration of symptoms at the first visit. A high BMI was associated with a higher chance on RA persistency. Although the characteristics indicative for the level of inflammation (CRP, ESR, and SJC) were associated with severity of joint destruction, they were not predictive for having a persistent form of RA.

Fraction of variance of progression in joint destruction explained

The total variance of joint destruction at 5 years explained by the baseline characteristics studied was 32%. Subsequently we aimed to study the contribution of the individual risk factors to the explained variance. This was accomplished by calculating the proportion of the effect size of the

Table 2. Baseline characteristics of patients with rheumatoid arthritis in relation to the outcome measures rate of joint destruction and RA persistency

Baseline characteristic	Frequency	Rate of joint destruction over 5 years of follow-up		RA Persistency	
		β (95%CI)	P	OR (95%CI)	P
Age, mean (SD), years	56.4 (15.7)	1.14 (1.11-1.16)	<0.001*	0.99 (0.97-1.00)	0.070
Female gender, n (%)	459 (67.9)	0.74 (0.63-0.86)	<0.001*	0.85 (0.50-1.45)	0.553
Pos family history for RA, n (%)	173 (26.5)	1.079 (0.92-1.27)	0.354	2.27 (1.18-4.36)	0.014
Chronic symptom vs. (sub)acute, n (%)	287 (44.6)	1.10 (0.94-1.27)	0.234	1.55 (0.93-2.59)	0.095
Symptom duration at fist visit, mean (SD), weeks	26.4 (22.4)	1.00 (1.00-1.00)	0.048	1.02 (1.01-1.03)	0.007
Morning stiffness severity - VAS (0-100), mean (SD)	55.2 (28.7)	1.00 (1.00-1.00)	0.874	1.00 (0.99-1.01)	0.827
BMI, mean (SD)	25.8 (3.8)	0.96 (0.94-0.98)	<0.001	1.11 (1.01-1.23)	0.034
Localization initial joint symptoms					
Small vs. large joints, n (%)	356 (75.7)	1.01 (0.83-1.24)	0.923	0.66 (0.34-1.28)	0.216
Large & small vs. large joints, n (%)	177 (60.8)	0.92 (0.74-1.15)	0.470	0.96 (0.45-2.06)	0.911
Upper vs. lower extremities, n (%)	268 (39.2)	0.62 (0.50-0.76)	<0.001	0.76 (0.35-1.62)	0.468
Upper & lower vs. lower extremities, n (%)	222 (44.6)	0.72 (0.57-0.92)	0.009	1.01 (0.46-2.26)	0.972
Symmetric vs. asymmetric, n (%)	415 (69.6)	0.93 (0.79-1.10)	0.396	0.89 (0.51-1.55)	0.687
SJC, mean (SD)	9.5 (7.4)	0.99 (0.98-1.00)	0.010	0.99 (0.96-1.02)	0.379
CRP (mg/L), mean (SD)	30.4 (34.7)	1.01 (1.00-1.01)*	<0.001	1.005 (1.997-1.013)	0.210
ESR (mm/1hr), mean (SD)	39.7 (27.4)	1.01 (1.01-1.01)*	<0.001	1.005 (0.995-1.015)	0.314
IgM-RF positive, n (%)	378 (58.0)	1.76 (1.50-2.02)	<0.001	6.66 (3.69-12.02)	<0.001
Anti-CCP2 positive, n (%)	217 (32.1)	2.31 (2.00-2.67)	<0.001	11.46 (5.85-22.46)	<0.001
Anti-MCV positive, n(%)	373 (54.6)	1.97 (1.68-2.30)	<0.001	6.13 (3.48-10.79)	<0.001
HLA-SE positive, n (%)	393 (63.8)	1.31 (1.12-1.52)	0.001	2.25 (1.35-3.74)	0.002
CD40 (rs4810485) non-G carrier, n (%)	22 (4.4)	1.02 (0.67-1.58)	0.915	0.78 (0.17-3.54)	0.751

*Outcome of analysis without interaction with time, evaluating whether a factor has an effect on the progression rate that is stable over time. Age, BMI, ESR, SJC, CRP, symptom duration at first visit and morning stiffness were analyzed as continuous variables; this means that the presented OR indicates the odds per unit. For instance, a beta of 1.01 for CRP indicates a 1.01 times higher progression of SHS-score per mg/L CRP. From all 676 patients data on the rate of joint destruction was available, the remission/persistency state was reliably determined in 491 patients

individual factors in the multivariate analysis to the total effect. The proportional effect size of these variables is depicted in Figure 1.

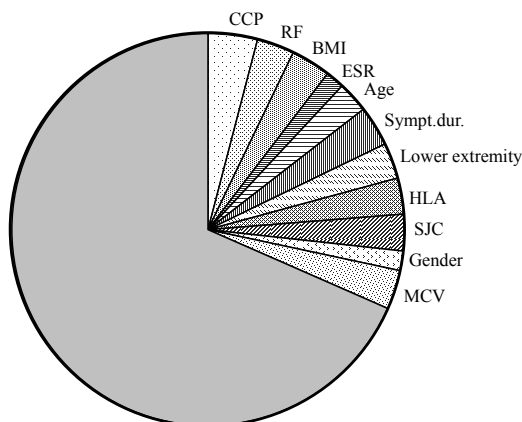


Figure 1. Contribution of baseline variables to the explained variance of Sharp-van der Heijde score over five years. Presented is the explained variance at 5 years of baseline variables that were associated with the progression of joint destruction. CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; BMI: Body Mass Index; ESR: erythrocyte sedimentation rate, sympt.dur.: symptom duration at first visit; lower extremity: initial complaints at lower extremity versus upper extremities; HLA: HLA-DRB1 shared epitope alleles; SJC: swollen joint count; MCV: anti-modified citrullinated vimentin antibodies. All continuous variables were categorized in two groups in order to derive this figure: BMI was grouped in lower or higher than 25; Symptom duration at first visit (sympt.dur.) was grouped in lower or higher than 12 weeks; SJC was grouped lower and above 6 swollen joints; Age under and above the median of 57 years; ESR normal or elevated according to reference value

DISCUSSION

Cumulating evidence supports the relevance of initiating DMARD therapy as early as possible. Individualized treatment decision making is hampered by the variability of the outcome of early arthritis. In case of early undifferentiated arthritis, the question is when DMARD therapy should be initiated. In early RA it would be beneficial to recognize the patients who will have a severe disease course, since in these patients the benefits of early combination therapy with potent targeted therapies will outweigh the associated costs and risks on side effects. In this themed issue risk factors for the outcome of UA and RA patients are explored based on data of the Leiden EAC.

With regards to early UA it was observed that predictive factors for the fulfillment of the 1987 ACR RA criteria and for having a persistent arthritis were largely similar. A predictive tool for RA development was derived before using a combination of identified risk factors.¹⁰ This prediction rule is now well-validated.¹⁴⁻¹⁶ Since the present study did not intend to re-derive or improve this predictive tool, no multivariate regression analyses were performed in UA patients. Some studies tried to improve this prediction rule and assessed the additive value of baseline erosiveness and genetic markers.^{8,17} Unfortunately, these attempts did not result in an increased prognostic performance of this model. Further improvements of the model may be expected to come from ultrasound and MR imaging studies. Although at present not much data on US and MRI in unselected populations of UA patients are available, initial results are promising.¹⁸

Fulfilling the 1987 ACR criteria as outcome of UA has the disadvantage that it may introduce some circle reasoning; in contrast the difficulty with the outcome measure disease persistency is that classification depends on the duration of follow-up. In UA patients included in this study remission was achieved after a median period of 17 months, whereas in the RA patients the median disease duration till remission was 40 months. A too early comparison of disease outcomes may result in misclassification of potential remission patients into the persistent disease category. In order to diminish the risk on misclassification, in this study we chose to classify patients with ≥ 5 years of arthritis as being persistent. This follow-up duration is arbitrary and results may have been slightly different in case a shorter or longer follow-up period was chosen.

The most potent predictors for having a persistent course of arthritis in UA patients and a persistent course of RA were the presence of auto-antibodies. Inflammatory markers (the number of swollen joints, ESR and CRP) were associated with the development of RA and a persistent form of arthritis in UA patients as well as the severity of joint destruction in RA patients, which is in line with findings in older studies. However, no significant association between these inflammatory markers and disease persistency was found in RA patients.^{19,20} This may be due to the fact that the number of patients with sustained DMARD-free remission in RA was low, thereby reducing the power to identify significant associations with this outcome measure.

It is interesting to note that morning stiffness is strongly associated with the development of RA but not with disease persistency or the severity of joint destruction. Several explanations may account for this feature. One of them is that morning stiffness is mainly related to RA according to the 1987 criteria because of circle reasoning. Morning stiffness is not part of the 2010 EULAR/ACR criteria for RA and it would be an interesting subject for further studies to see whether the association between morning stiffness and the risk on RA is still present when the new definition of RA is used.

Other intriguing findings concern the observations on BMI. Obese RA patients are found to have less severe joint destruction. This observation was not only observed in the present study but also in other populations.²¹⁻²³ The present study revealed that BMI was not associated with progression from UA to RA, but it was associated with having a persistent arthritis or persistent RA. Thus this indicates that obese patients have more often a persistent disease than non-obese arthritis patients. This observation is highly fascinating and may point to the notion that the role of fat tissue in rheumatoid arthritis is incompletely clear. Fat tissue secretes pro-inflammatory as well as anti-inflammatory adipocytokines.²⁴ It is clear that some of the mechanisms of joint destruction like osteoclast activation are different than inflammatory pathways and as such it is tempting to speculate that diverse adipocytokines may have different preferential effects on arthritis persistency and on joint destruction.

The associations between disease outcomes and involvement of the joints of the lower or upper extremities were different for patients with UA and RA. Whereas within UA presence of arthritis on lower extremities was associated with a lower OR on RA, within RA patients it was associated with a higher rate of joint destruction. This finding is in line with previous findings demon-

strating that patients presenting with knee arthritis had a more severe rate of joint destruction compared to patients without knee arthritis, when measured using destruction of small feet and hands joint.²⁵

Emerging evidence indicates that anti-CCP positive and anti-CCP negative RA are subsets of RA with differences in the underlying pathologic mechanisms.^{26,27} The present study addressed all UA patients and RA patients; stratified analyses on anti-CCP positive and anti-CCP negative patients were not performed. This may be an explanation why *CD40*, a genetic risk factor joint destruction in anti-CCP positive RA is not associated with the rate of joint destruction in the whole RA population.¹³

The baseline characteristics associated with the severity of joint destruction in RA were mainly auto-antibodies and other patient characteristics and to a lower extend factors expressing the level of inflammation. Although the present study did not evaluate the contribution of inflammation over time on the final level of joint destruction, such analyses have been performed before. Some of these studies also suggested that the largest part of joint destruction is not directly related to cumulative inflammatory markers.²⁸

The data presented are limited to data of the Leiden Early Arthritis Clinic cohort. However, many of the associating risk factors for UA and RA are observed in individual studies originating from different early arthritis cohorts as well.²⁹⁻³⁴

The proportion of the explained variance in progression of joint destruction by the identified risk factors was 32%. Although no clear guidelines are available what the level of variance explained is required in order to derive a prediction model with an adequate discriminative performance, previous investigations and experience^{10,35} are highly suggestive that the explained variance is insufficient to proceed with a derivation of a prediction rule for the rate of joint destruction in RA. This notion is exemplified by recent attempts to derive prediction models; with the current prediction rules about 50% of the RA patients could not be adequately classified.³⁵⁻³⁷

In conclusion, although the processes determining the persistency and severity of arthritis are incompletely understood, the identification of risk factors may help in individualization of therapy in patients with recent-onset UA. In RA, in contrast, the currently known risk factors for a progressive destructive disease course explain only part of the individual differences in level of joint destruction and more risk factors need to be identified in order to achieve at individualized treatment decision making.

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