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# Predictive factors for outcome of rheumatoid arthritis

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# CHAPTER 9

## Long-term impact of delay in assessment of early arthritis patients

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## ABSTRACT

### Background

During the last decade rheumatologists have learned to initiate disease-modifying-antirheumatic-drugs (DMARDs) early to improve outcome of rheumatoid arthritis (RA). The effect of delay in referral to rheumatologists on the outcome of RA is scarcely explored. We studied the association between delay in assessment by rheumatologists, rates of joint destruction, and probability of achieving DMARD-free-remission in RA. Patient characteristics associated with the patient and general practitioner (GP)-components of overall delay were assessed.

### Methods

1674 early arthritis-patients from the Leiden EAC were studied on patient, GP-, and total delays. Within 598 RA patients, associations between total delay, achievement of sustained DMARD-free remission, and the rate of joint destruction over six years follow-up were determined.

### Results

The median patient, GP-, and total delays in early arthritis-patients were 2.4, 8.0 and 13.7 weeks respectively. From all diagnoses, early arthritis patients diagnosed with RA or spondylarthropathy had the longest total delay (18 weeks). 69% of RA patients were assessed in ≥12 weeks; this was associated with a hazard ratio of 1.87 for not achieving DMARD-free remission and a 1.3 times higher rate of joint destruction over six years compared to assessment <12 weeks. Older age, female gender, gradual symptom onset, small joint involvement, lower CRP levels, and autoantibody presence associated with longer total delay.

### Conclusion

Only 31% of RA patients were assessed <12 weeks. Assessment <12 weeks is associated with less joint destruction and a higher chance on DMARD-free remission compared to a longer delay in assessment. These results imply that attempts to diminish delay in seeing rheumatologists will improve disease outcome in RA.

## INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic disease, affecting 1% of the population. It is associated with significant morbidity, mortality and cost for the health service and society. The disease is characterized by inflammation of the synovium, most frequently in the small joints of hands and feet; this inflammatory process frequently leads to loss of cartilage and bone erosions. The level of joint destruction is correlated with the severity of inflammation.[1,2] At present, potent Disease Modifying Antirheumatic Drugs (DMARDs) and biological agents are available to treat RA synovitis. It has been unequivocally demonstrated that early initiation of aggressive treatment schedules results in less joint damage and disability.[3-6] This has led to the concept of the 'window of opportunity'.[7] Indeed it has been demonstrated that initiation of treatment within 12 weeks after disease onset results in lower levels of joint destruction[8] and increases the chance of achieving remission,[9] which is increasingly regarded as the targeted outcome in therapeutic trials. Many studies focused on the importance of diminishing delay between the diagnosis of RA and treatment initiation. However, shortening the time period between first symptoms and first visit to a rheumatologist might be equally important. Thus far the effect of delayed assessment by rheumatologists on disease outcome has scarcely been investigated.

We aimed to assess the association between delay in assessment and disease outcome in RA, measured by the rate of joint destruction and the chance of achieving sustained DMARD-free remission. Second, we also aimed to determine the patient characteristics associated with longer patient and GP-delay. Knowledge of these factors is of utmost importance. Rheumatologists nowadays are aware of the need to treat early. This implies that to further improve the outcome of RA, strategies should be put in place to ensure that delays in assessment are as short as possible. Understanding factors that associate with delayed assessment is the first step required to achieve this.

## PATIENTS AND METHODS

### Patients

All patients come from the Leiden Early Arthritis Clinic (EAC) cohort, a large inception cohort that enrolled all consecutive patients between 1993 and 2006.[10] This clinic is the only referral center in a health care region of about 300,000 inhabitants. Patients were referred by their general practitioners (GPs) when arthritis was suspected and GPs were encouraged to refer as soon as possible. Inclusion took place when synovitis was confirmed by physical examination and symptom duration was less than 2 years. At baseline, patients were asked about their joint symptoms and subjected to a physical examination, which included a 66 swollen and 68 tender joint count (Ritchie score). Blood samples were taken for routine diagnostic laboratory screening (including C-reactive protein (CRP) and IgM-rheumatoid factor (RF)) and stored to determine other autoantibodies (anti-CCP2) at a later time. Follow-up visits were performed on a yearly

basis and included radiographs of hands and feet.[10] Written informed consent was obtained from all participants. The study was approved by the local Medical Ethical Committee.

Of all 1881 patients included in the EAC cohort, information on the dates of symptom onset was available for 1674 patients. There were no significant differences between baseline patient characteristics of patients with and without information on this date, apart from slightly lower titers of acute phase reactants in the group with missing data (data not shown). Among the 1674 patients who had information on the date of symptom onset available, 598 patients (35.7%) were diagnosed with RA according to the 1987 ACR criteria within the first year of follow-up and had radiographs available. These patients were consecutively included between 1993 and 2006. Treatment strategies for RA changed over time and became more aggressive in subsequent inclusion periods (1993-1996, 1996-1998 and 1999-2006).[10] Patients included before 1996 were treated initially with analgesics and subsequently with chloroquine or salazopyrin if they had persistent active disease (delayed treatment). Between 1996 and 1998 RA patients were promptly treated with either chloroquine or salazopyrin, and from 1999 onward patients were promptly treated with either salazopyrin or methotrexate.

## Delay

We studied delay at 2 levels. Level 1 related to the delay from the onset of symptoms to a patient being seen by their GP. This delay is a composite of the delay on the part of the patient in seeking an appointment with the GP and the time the patient has to wait to see the GP once they have approached the GP for an appointment. In practice, the Dutch healthcare system is such that the second component of this is almost always very short and for simplicity we have referred to level 1 delay as "patient delay". Level 2 delay related to the delay from when the patient first saw their GP to when they were seen in the Leiden Early Arthritis Clinic. This delay is also a composite; in this case of the time it takes a GP to decide to make a referral and the time it takes for the rheumatologist to see the patient once the referral is made. The average wait for a patient to be seen in the Leiden EAC, once a referral has been made, is short (~2 weeks) and for simplicity we have referred to level 2 delay as "GP-delay". The total delay was calculated as the sum of both patient and GP-delay. The duration of total delay was known for 1674 early arthritis patients. Data on the first visit to a GP was available for ~1100 early arthritis patients. There were no significant differences between characteristics of patients with and without information on the date of visiting the GP (data not shown). Analysis of associations between patient characteristics and delay were carried out for patient delay, GP-delay, and total delay. For all other analyses, the total delay was used. Since the literature indicates that the time period known as 'the window of opportunity' is about 12 weeks, the total delay was divided into two categories: <12 weeks and ≥12 weeks.[7-9]

### Radiographs

Radiographs of hands and feet of 598 RA patients were scored according to the Sharp-van der Heijde method.[11] Due to the study design (an inception cohort) not all patients had an equal duration of follow-up (median 4 years, IQR 2-6). Radiographic follow-up data were restricted to a maximum of 6 years because of increasing frequency of missing radiographs later on. All radiographs were scored by one experienced scorer (MPMvdL) who was blinded with respect to clinical and treatment data. 499 radiographs were rescored (149 baseline radiographs and 350 radiographs during follow-up from 60 randomly selected RA patients). Intraclass-observer correlation coefficients (ICC) were 0.91 for all radiographs, 0.84 for baseline radiographs, and 0.97 for the radiographic progression rate.

### Sustained DMARD-free remission in RA

Remission was defined in its most stringent form as the persistent absence of synovitis for at least one year after cessation of DMARD therapy and the identification of remission by the patient's rheumatologist.[12] As such, this definition approaches cure of the disease. The remission status could be reliably ascertained in 557 out of 598 RA patients. 72 Patients (12.9%) achieved sustained DMARD-free remission after a median follow-up of 3.33 years (IQR 2.02-5.48). Most patients who achieved remission had a synovitis-free follow-up longer than the minimum requirement of one year; the median time of observation after achieving sustained DMARD-free remission was two-and-a-half years.

### Statistical analysis

The duration of patient delay and GP-delay within a patient were compared using the Wilcoxon signed ranks test.

The association between delay and the rate of joint destruction during follow-up after the visit to a rheumatologist was assessed in 598 RA patients using repeated measurement analysis on log-transformed radiological data of subsequent yearly measurements. Log transformation was performed because of skewness of radiological data. Visit number and delay group were entered as categorical variables. Adjustments were applied for age, gender, and inclusion period (a proxy for treatment strategy) and their interaction with time as described before,[13] since these factors are known to influence the rate of joint destruction. Difference in the rate of joint destruction between the delay groups was assessed by testing the interaction between time and delay group. The association between delay and disease progression was also analyzed with the onset of symptoms as a starting point. This was done with a repeated measurement analysis with a random person and time effect, where the fixed effect of time was modeled with linear spline functions with knots at each year.

Analysis of sustained DMARD-free remission was performed by comparing Kaplan-Meier curves and by Cox regression analysis, taking into account the differences in follow-up times among patients. For patients who achieved remission, the dependent variable was "time-to-

event", indicating the time until reaching remission. For non-remission patients the time to last follow-up was used. Again two different starting points were considered: time from the onset of symptoms and time from the first visit to a rheumatologist. Cox regression for left truncated data was used for the analysis with time from onset of symptoms to account for the fact that remission status was only observed after the first visit to a rheumatologist.

Univariate analyses of baseline patient characteristics associating with delay in early arthritis patients were performed using Mann-Whitney U and Kruskal-Wallis tests as delay data were not normally distributed. In order to identify baseline characteristics that independently associated with delay, variables that associated with delay in univariate analyses ($p<0.05$) were entered in a multivariate regression analysis with backward selection method. For these analyses delay data were log-transformed. To prevent exclusion of patients with missing data from the multivariate model, multiple imputations were performed (SPSS 17.0). The complete set of data was used to generate 10 imputations that were subsequently applied to the multivariate analysis.

SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and R (http://www.R-project.org) were used. P-values <0.05 were considered significant. All reported p-values are two-sided.

## RESULTS

### Duration of delay in assessment

Baseline characteristics of all early arthritis patients and the patients that were diagnosed with RA are presented in Table 1.

In all early arthritis patients the median total delay was 13.7 (IQR: 5.7-28.5) weeks, the GP-delay 8.0 (IQR: 2.7-18.4) weeks, and the patient delay 2.4 (IQR: 0.7-7.4) weeks. The GP-delay was significantly longer (median 8.0 weeks) than the patient delay (median 2.4 weeks) ($p<0.0001$). The total delay in the subgroup of early arthritis patients who developed RA within the first year of follow-up was 18.4 weeks (median, IQR: 10.4-35.0). Also here, the GP-delay was significantly longer than the patient delay (median 11.8 (IQR: 5.2-22.9) vs. 3.3 (IQR: 1.0-8.9) weeks; $p<0.0001$). The applied treatment strategies for the RA patients differed for three inclusion periods; the median total delays for patients in these inclusion periods were 22.1 weeks for 1993-1996, 18.3 weeks for 1996-1998, and 18.3 weeks for 1999-2006 ($p=0.38$). From all RA patients, only 186 patients (31.1%) were assessed within 12 weeks of symptom onset.

### Delay and outcome of RA

Within the 598 patients diagnosed with RA, we investigated whether the degree of delay in assessment has an effect on the disease outcome, measured by the progression in Sharp-van der Heijde score over a six year period of followup and the achievement of sustained DMARD-free remission. Those RA patients who saw a rheumatologist within 12 weeks after symptom onset had a lower rate of progression in Sharp-van der Heijde score (Figure 1A) than those with a delay of ≥12 weeks. Repeated measurement analysis comparing patient groups with delays of

**Table 1.** Baseline characteristics of all early arthritis patients and the subset of early arthritis patients that were diagnosed with RA

| Characteristics | Early arthritis patients (n=1674) | RA (n=598) |
|---|---|---|
| Female, n (%) | 989 (59.1) | 405 (67.7) |
| Age at inclusion (yrs), mean (SD) | 51.7 (17.5) | 56.8 (15.8) |
| SJC, mean (SD) | 7.1 (6.4) | 9.2 (7.0) |
| Ritchie score, mean (SD) | 7.2 (5.6) | 9.2 (6.0) |
| Anti-CCP2-positive, n (%) | 391 (28.5)[§] | 309 (53.3)[§] |
| IgM-RF-positive, n (%) | 480 (29.2)[‡] | 343 (58.0)[‡] |
| CRP (mg/l), mean (SD) | 28.9 (38.8) | 31.0 (35.3) |

SJC: 66-swollen joint count; Ritchie score: 68-tender joint count; CRP: C-reactive protein; IgM-RF: Rheumatoid factor. [§]Data on anti-CCP2 status was available for 1373/1674 early arthritis patients and 580/598 RA patients. [‡]Data on IgM-RF was available for 1645/1674 and 591/598 patients respectively

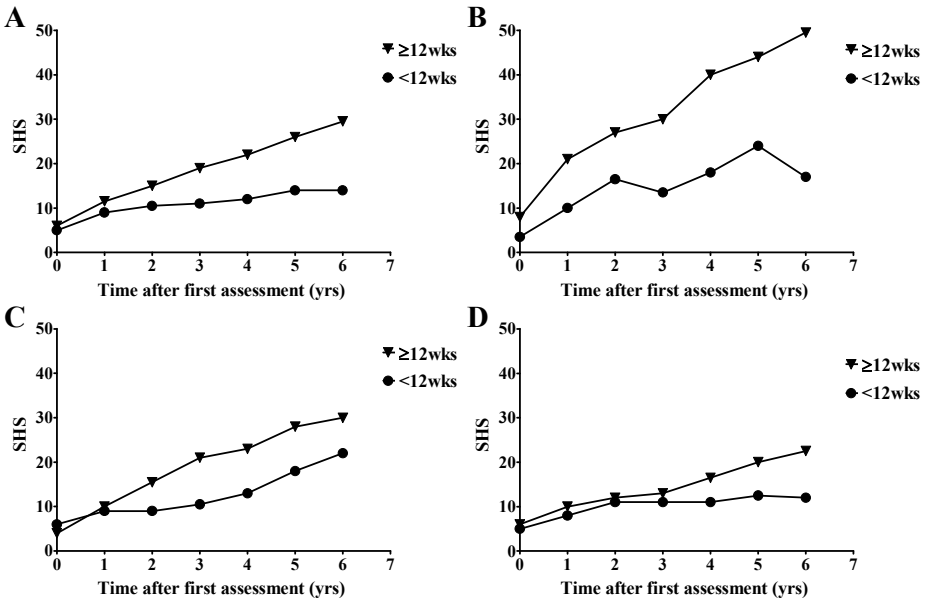


**Figure 1.** The rate of joint destruction during 6 years of follow-up after first assessment by a rheumatologist for RA patients in different delay categories (A), and separated by treatment strategy after inclusion (B-D). Because of a non-normal distribution of radiological data median Sharp van der Heijde scores are presented. Figure 1A presents data on the total RA group and in Figure 1B-D data were separated for different treatment strategies which became more aggressive over time. The applied treatment strategies were (B) initial treatment with analgesics and subsequently with chloroquine or salazopyrin if they had persistent active disease (delayed treatment), (C) prompt treatment with either chloroquine or salazopyrin, and (D) prompt treatment with either salazopyrin or methotrexate. SHS: Sharp-van der Heijde Score; Time after first assessment (yrs): follow-up time in years after the first visit to a rheumatologist

<12 weeks and ≥12 weeks showed that the difference in progression rate was statistically significant (p=0.001). Because of skewness of the data, radiological data were log transformed before analysis; back transforming the regression coefficient showed that over a period of six years after the first visit to the rheumatologist, patients with a delay ≥12 weeks had a 1.34 fold larger rate of progression in Sharp-van der Heijde score than patients with a delay <12 weeks. In this analysis adjustments were made for age, gender, and the different treatment periods. Plotting the observed median radiological scores over time for the different treatment periods separately (Figure 1B-D), illustrated that RA patients assessed within 12 weeks of symptom onset had lower progression rate, irrespective of the treatment period. Thus although the increase in aggressiveness of treatment after assessment reduced the overall level of Sharp-van der Heijde scores, this did not diminish the effect of delay in referral on progression in Sharp-van der Heijde scores.

The lower progression rate in the patients with a short delay (<12 weeks) could have been due to the fact that these patients presented in an earlier phase of the disease course, with concomitantly less severe joint damage. To investigate whether this explained the observed difference, a second analysis of the progression in Sharp-van der Heijde score was performed while taking into account the symptom duration before the first radiograph, i.e. before presentation. Thus, the follow-up time for all patients now commenced at the (self-reported) first date of symptoms. In this analysis, patients with a delay <12 weeks had a significantly lower progression rate during six years after the onset of the first symptoms, compared to patients with a delay ≥12 weeks (p<0.001 after adjustment for age, gender, and treatment period).

Reports in literature suggest that anti-CCP positive and anti-CCP negative RA are two subsets of RA with differences in the underlying pathophysiological mechanisms and disease course.[14,15] To explore whether the effect of delay was different in anti-CCP positive and negative RA, stratified analyses were performed. Although stratification resulted in reduced power, a statistically significant association of a delay <12 weeks with a lower progression in Sharp-van der Heijde score was observed in anti-CCP negative RA (test for interaction p=0.002 without and p<0.001 with adjustments for age, gender, and treatment period). In anti-CCP positive RA a similar, though not significant, tendency was seen with an observed lower rate of destruction in the <12 weeks delay group (test for interaction p=0.07 without, and p=0.18 with adjustments for age, gender, and treatment period).

Similar results were seen for the achievement of sustained DMARD-free remission as were observed for the progression in Sharp-van der Heijde scores. Sustained DMARD-free remission was achieved most frequently in patients with a total delay of <12 weeks (Figure 2). In the <12 weeks delay group, 18.5% (31/168) of patients achieved remission, and in the >12 weeks delay group, 10.5% (41/389) achievement of remission was observed. The hazard ratio for not achieving sustained DMARD-free remission was 1.87 (95%CI 1.18-2.99, p=0.008) for a total delay of ≥12 weeks compared to <12 weeks. The difference did not change after adjusting for age, gender, and treatment period (HR 1.87 (95%CI 1.17-3.00, p=0.009)). Similar results comparing patients with a total delay of <12 weeks and ≥12 weeks were obtained when the analysis was repeated

with the date of the first symptoms as a starting point, both without (HR 1.90, 95% CI 1.19-3.03) and with (HR 1.90, 95%CI 1.18-3.05) correction for age, gender, and year of inclusion. Since in the anti-CCP2 positive subset only 8 patients achieved DMARD-free remission, no stratified analysis was performed.

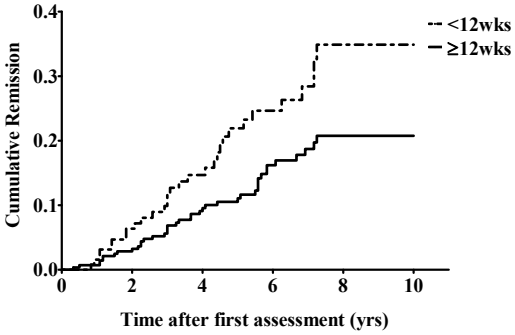


**Figure 2.** The probability of achieving sustained DMARD-free remission for the different delay categories. Remission as outcome measure for the amount of total delay. Remission was defined as the persistent absence of synovitis for at least one year after cessation of DMARD therapy and the identification of remission by the patient's rheumatologist.[12] Time after first assessment (yrs): follow-up time in years after the first visit to a rheumatologist

## Characteristics associated with delay in assessment

Subsequently, patients characteristics associating with an increased delay in assessment were investigated in early arthritis patients (n=1674). Univariate analysis showed that female gender, gradual symptom onset, older age at inclusion, symmetric distribution of symptoms, involvement of small joints and joints of the upper extremities, presence of RF and anti-CCP antibodies, and lower levels of CRP were all significantly associated with a longer duration of total delay ($p<0.001$) (Table 2).

Multivariate regression analysis identified the following variables as independently associated with a longer duration of total delay: older age, gradual symptom onset, involvement of small joints, presence of anti-CCP2 and RF, and lower CRP-levels. As regression analysis was performed on log transformed delay data, the relative estimated progressions were back transformed to the original scale (Table 3). Patient characteristics associated with patient delay and GP-delay showed comparable findings (Table 2 and Table 3).

The findings that the presence of autoantibodies (anti-CCP2 and RF), symmetric involvement of small joints and a gradual onset of symptoms were associated with a longer delay, leads to the presumption that the delay in assessment differs for early arthritis patients with different diagnoses. To study this, early arthritis patients were grouped according to the diagnoses that were achieved within the first year of follow-up and the total delay durations were compared. This showed that reactive arthritis, sarcoidosis and crystal arthritis have the shortest delay in assessment (Figure 3). In contrast, RA patients and patients with psoriatic arthritis and spondylarthropathy had the longest delay in assessment.

**Table 2.** Baseline characteristics of early arthritis patients associated with patient, GP and total delay in a univariate analysis

| | | Early arthritis patients | | | | | |
|---|---|---|---|---|---|---|---|
| | | *Total delay(n=1674)* | | *GP-delay(n=1111)* | | *Patient delay(n=1078)* | |
| | | Weeks (IQR) | p | Weeks (IQR) | p | Weeks (IQR) | p |
| Gender | *Male* | 11.9 (4.4-26.3) | <.001* | 6.9 (2.0-16.9) | .001* | 2.1 (0.6-6.4) | .049* |
| | *Female* | 15.3 (6.4-30.7) | | 8.9 (3.3-19.4) | | 2.9 (0.8-8.4) | |
| Age at Inclusion (yrs) | *<52.5*[§] | 12.6 (4.0-28.7) | <.001* | 6.9 (2.0-18.4) | .001* | 2.4 (0.7-8.4) | .907 |
| | *≥52.5*[§] | 15.0 (7.9-28.1) | | 8.9 (3.9-18.4) | | 2.6 (0.9-6.6) | |
| Family history of RA | *No* | 13.6 (5.5-28.2) | .119 | 7.6 (2.6-17.7) | .099 | 2.4 (0.7-6.9) | .185 |
| | *Yes* | 14.9 (6.0-30.6) | | 9.3 (3.6-20.9) | | 2.9 (0.9-8.8) | |
| Onset of symptoms[‡] | *Acute* | 5.6 (1.9-15.9) | <.001* | 3.4 (1.0-13.0) | <.001* | 0.9 (0.1-2.9) | <.001* |
| | *Subacute* | 11.8 (5.9-22.0) | | 7.7 (3.0-14.8) | | 2.1 (0.9-5.3) | |
| | *Gradual* | 26.0 (13.6-47.4) | | 13.0 (6.3-29.4) | | 5.9 (2.6-16.7) | |
| Affected Joints | *Small* | 16.9 (8.7-32.3) | <.001* | 9.1 (3.9-20.6) | <.001* | 3.9 (1.0-8.9) | <.001* |
| | *Large* | 9.7 (2.9-23.4) | | 4.4 (1.2-15.6) | | 1.4 (0.3-4.6) | |
| | *Both* | 13.1 (6.1-26.9) | | 8.4 (3.0-18.4) | | 2.0 (0.7-4.6) | |
| Affected extremities | *Upper* | 15.1 (7.6-30.1) | <.001* | 8.8 (3.3-19.0) | <.001* | 3.1 (1.0-9.1) | <.001* |
| | *Lower* | 8.6 (2.9-24.6) | | 4.4 (1.0-15.4) | | 1.3 (0.3-4.4) | |
| | *Both* | 14.6 (7.1-27.8) | | 8.4 (3.0-17.3) | | 3.0 (0.7-7.9) | |
| Symmetric distribution affected joints | *Yes* | 14.6 (6.9-28.4) | <.001* | 9.1 (3.4-19.1) | <.001* | 3.0 (1.0-8.4) | .005* |
| | *No* | 12.6 (4.2-27.8) | | 6.3 (1.6-16.1) | | 2.0 (0.4-6.9) | |
| SJC | *≤5.0*[§] | 15.4 (7.9-31.4) | .725 | 9.1 (3.9-19.2) | .053 | 3.0 (0.9-8.4) | .286 |
| | *>5.0*[§] | 17.1 (9.7-31.1) | | 11.1 (4.9-22.5) | | 2.7 (1.0-7.1) | |
| Ritchie Score | *<6.0*[§] | 15.4 (8.5-30.8) | .674 | 10.0 (4.4-20.4) | .894 | 2.9 (0.9-6.8) | .351 |
| | *≥6.0*[§] | 16.9 (8.4-31.3) | | 10.5 (4.3-21.5) | | 3.6 (1.0-8.5) | |
| Anti-CCP2 | *Positive* | 20.3 (11.6-36.9) | <.001* | 12.4 (6.1-22.7) | <.001* | 4.3 (1.0-10.9) | <.001* |
| | *Negative* | 12.7 (4.6-27.1) | | 6.7 (2.3-16.4) | | 2.3 (0.7-6.6) | |
| IgM-RF | *Positive* | 18.6 (10.1-35.7) | <.001* | 12.3 (5.6-22.7) | <.001* | 3.9 (0.9-9.3) | .005* |
| | *Negative* | 12.3 (4.4-26.6) | | 6.3 (2.1-16.5) | | 2.3 (0.7-6.5) | |
| C-reactive Protein (mg/l) | *<13.0*[§] | 16.7 (7.4-32.7) | <.001* | 10.0 (3.6-21.9) | <.001* | 3.9 (1.0-9.3) | <.001* |
| | *≥13.0*[§] | 12.1 (4.5-24.1) | | 7.1 (2.1-15.1) | | 2.0 (0.6-4.7) | |

Delay durations are presented in weeks, median (IQR). The shown p-values reflect the difference within each delay group (total, GP- or patient delay), thus the comparison made is for instance whether the total delay is different between males and females. [§]The continuous variables age, CRP, SJC and Ritchie score were analyzed by creating two groups based on median values. [‡]Defined durations of symptom onset: acute <24 hours; subacute <1 week and gradual ≥1 week. IgM-RF: Rheumatoid factor; CRP: C-reactive protein; SJC: 66-swollen joint count; Ritchie score: 68-tender joint count. *P-value <0.05; Mann-Whitney U/Kruskal-Wallis tests

**Table 3.** Baseline characteristics of early arthritis patients associated with patient, GP and total delay in a multivariate analysis

| *Total delay* | | | | |
|---|---|---|---|---|
| | | 95%CI | | |
| Variable | ratio | lower | upper | p-value |
| Age at inclusion (yrs)‡ | 1.004 | 1.002 | 1.007 | <.001 |
| Female gender§ | 1.12 | 1.02 | 1.22 | .014 |
| Gradual onset§ | 2.22 | 2.02 | 2.44 | <.001 |
| Involvement of small joints vs. large§ | 1.31 | 1.18 | 1.46 | <.001 |
| Involvement of both small and large joints vs. large§ | 1.16 | 1.02 | 1.32 | .021 |
| Anti-CCP2§ | 1.31 | 1.13 | 1.51 | <.001 |
| IgM-RF§ | 1.20 | 1.04 | 1.37 | .010 |
| CRP-level‡ | 0.995 | 0.993 | 0.995 | <.001 |
| *GP-delay* | | | | |
| | | 95%CI | | |
| Variable | ratio | lower | upper | p-value |
| Age at inclusion (yrs) ‡ | 1.004 | 1.002 | 1.009 | .004 |
| Female gender§ | 1.14 | 1.01 | 1.29 | .040 |
| Gradual onset§ | 1.93 | 1.69 | 2.20 | <.001 |
| Symmetric distribution of complaints§ | 0.79 | 0.69 | 0.90 | <.001 |
| Anti-CCP2§ | 1.33 | 1.09 | 1.63 | .006 |
| IgM-RF§ | 1.22 | 1.01 | 1.47 | .039 |
| CRP-level‡ | 0.995 | 0.993 | 0.995 | <.001 |
| *Patient delay* | | | | |
| | | 95%CI | | |
| Variable | ratio | lower | upper | p-value |
| Gradual onset§ | 2.38 | 2.09 | 2.70 | <.001 |
| Involvement of joints of lower extremities vs. upper§ | 0.73 | 0.63 | 0.84 | <.001 |
| Involvement of joints of both extremities vs. upper§ | 0.90 | 0.77 | 1.04 | .155 |
| Anti-CCP2§ | 1.21 | 1.04 | 1.39 | .010 |
| CRP-level‡ | 0.995 | 0.995 | 0.998 | <.001 |

The linear regression analysis was performed on log-transformed delay data and the regression coefficients were back transformed for comprehensible results. The inverse log-transformed coefficients represent the estimated relative progression in delay. §In a categorical variable for instance, a ratio of 1.31 (Involvement of small joints vs. large) represents a 1.31 times longer delay. ‡In a continuous variable, a ratio of 1.004 (age at inclusion) indicates a 1.004 times longer delay when there is an increase in age of one year. 95CI: 95% confidence interval; lower: lower bound; upper: upper bound; IgM-RF: Rheumatoid factor; CRP: C-reactive protein

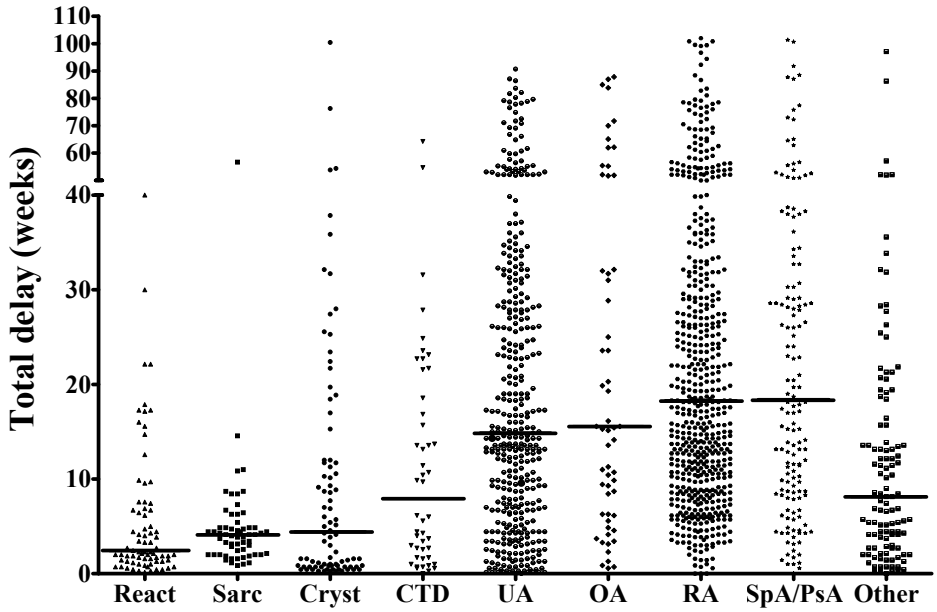


**Figure 3.** Total delay in assessment by rheumatologists for separate diagnoses. Total delay before visiting a rheumatologist divided per disease category. Depicted are the distribution and median of the total delays per diagnosis (at one year). React: reactive arthritis; Sarc: sarcoidosis; Cryst: crystal arthritis; CTD: connective tissue disease (including SLE and scleroderma); UA: undifferentiated arthritis; OA: Inflammatory osteoarthritis; RA: Rheumatoid arthritis; SpA/PsA: spondylarthropathy/psoriatic arthritis; Other. Horizontal bars represent median delays

## DISCUSSION

Early initiation of treatment dramatically improves clinical outcomes in patients with RA. In the last decade, rheumatologists have developed growing awareness of the need to treat early, and this, together with the availability of newer therapies and improved predictive algorithms for patients with early arthritis,[16,17] has improved the outcome of arthritis patients considerably.[18] The present study shows that RA patients who have a delay longer than 12 weeks between first symptoms and visiting a rheumatologist have a worse disease outcome, measured by two outcomes, the rate of joint destruction, and achievement of sustained DMARD-free remission. The effect of delay did not disappear when a more potent treatment strategy was applied after assessment by the rheumatologist. Importantly, amongst all early arthritis patients, patients diagnosed with RA had the longest delay in assessment and the majority of RA patients were assessed after 12 weeks of symptoms, a period which has been referred to as the window of opportunity. These results suggest that, to further improve the outcomes of RA patients, an important challenge is to get patients with arthritis to see a rheumatologist as early as possible after symptom onset.

Diminishing the delay in assessment requires awareness on the part of both patients and their GPs. For that reason, the present study also evaluated which factors associate with the duration of the delay in assessment by a rheumatologist. This revealed that one of the important factors for early presentation to both the GP and to hospital was the acuteness of the start of the complaints. Patients with a gradual symptom onset had a longer delay than patients with an acute or subacute onset of symptoms. Other patient characteristics associated with a longer delay were female gender and an older age. A gender specific delay in referral has been reported before.[19,20] Thus to prevent a worse outcome of arthritis, our findings suggest that attention needs to be focused on the education of patients, in particular the older and female patients, about the significance of their symptoms and the education of GPs to rapidly refer patients, in particular older, female patients with a gradual onset of symptoms.

Several of the patient characteristics that were associated with the duration of delay in assessment of early arthritis patients belong to clusters of variables that are characteristic for specific diagnoses. For instance, an acute onset of symptoms and involvement of large joints of the lower extremities frequently occur in reactive arthritis or sarcoidosis; patients in these diagnostic groups had a short delay. In contrast, a gradual symptom onset and symmetrical involvement of small joints is more common in patients with RA. Both these characteristics and this diagnosis were associated with a longer delay in presentation and referral. Altogether, patients with chronic destructive diseases such as RA, but also psoriatic arthritis and spondylarthropathy, who should be seen particularly early by rheumatologists, had the longest delays in assessment. Therefore the present results underline the importance of putting in place strategies to tackle reasons underlying delay that have been identified at the level of the patient and the GP.[21,22]

Although our findings provide insight into delay in assessment and its association with patient characteristics and disease outcome, the present study has several limitations. Patients were included in the EAC only if they had a symptom duration of <2 years; patients who at first presentation had symptoms for more than 2 years were not studied. However, patients with such a long delay are observed to be very infrequent in our outpatient clinic. Secondly, data were obtained from a single country. In the present study the largest contribution to the total delay was delay in referral by the GP. This is in line with a study from the US[23] and in contrast to recent findings in British cohorts, where the largest contribution to total delay was delay on the part of the patient.[24,25] Differences in health care systems, but also cultural differences[26] could, at least partially, provide an explanation for the contrasting observations. Nevertheless, the median total delay for RA patients was well over 12 weeks in the UK, Canada and in the Netherlands (23 weeks,[24] ~17 weeks[27] and 18.4 weeks respectively) and the present study highlights the consequences of that delay.

The findings that RA patients with a longer delay had more severe joint destruction and less sustained DMARD-free remission are in line with findings that an early initiation of treatment is beneficial to the disease outcome.[8,9] It was questioned whether the patients with a shorter delay had a truly better disease course or were just seen earlier in the disease course, resulting in

a seemingly lower level of joint destruction. Therefore, analyses were repeated with the date of the first complaints as a starting point. This showed that patients who had a delay of <12 weeks indeed developed less severe disease compared to patients with a longer delay.

There are two potential explanations for the observed difference in severity between the <12 weeks and ≥12 weeks delay groups. First, it may be that RA patients that were assessed in a short time constitute a subset of RA that by itself is characterized by a better outcome. It is known that the subset of RA characterized by the absence of anti-CCP antibodies has a better disease outcome than the anti-CCP positive subset,[14] and in our data anti-CCP positive patients had more often a gradual onset of complaints (49.3% vs. 38.2%) and more delay (22.0 vs. 14.3 weeks, median) than anti-CCP negative RA patients. To account for such differences between RA patients, the effect of delay was studied in both the anti-CCP positive and anti-CCP negative subset. This showed a significant association between delay in assessment and joint destruction in anti-CCP2 negative RA patients and a similar tendency in anti-CCP positive RA patients. The present data however do have insufficient power for these sub-analyses and more specifically do not allow making definite conclusions on the effect of delayed assessment on joint destruction in the subset of anti-CCP positive patients. Alternatively, patients assessed within 12 weeks were treated earlier which may have contributed to a less severe course of RA which is in line with previous data,[4] and supports the hypothesized existence of a window of opportunity. Nonetheless, regardless of the explanation of the findings (better outcome in anti-CCP negative patients with a more acute symptom onset or better outcome due to early initiation of treatment) the main argument to refer as early as possible is that it provides the opportunity to modify RA in an early phase with potential beneficial effects on the future disease course.

In conclusion, a shorter time to assessment by a rheumatologist is associated with more DMARD-free remission and less joint destruction in RA. Despite this association, among all early arthritis patients, those diagnosed with RA had one of the longest delays in assessment and only one third was assessed within the so-called window of opportunity. Since rheumatologists are nowadays aware on the importance to treat early, our results suggest that in order to further improve disease outcomes in RA it will be crucial to diminish the delay in assessment by a rheumatologist. Further work could test whether accelerated treatment strategies indeed leads to improve disease outcomes in RA.

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