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Disease activity trajectories in rheumatoid arthritis: a tool for prediction of outcome

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Objective: Predicting treatment response and disease progression in rheumatoid arthritis (RA) remains an elusive endeavour. Identifying subgroups of patients with similar progression is essential for understanding what hinders improvement. However, this cannot be achieved with response criteria based on current versus previous Disease Activity Scores, as they lack the time component. We propose a longitudinal approach that identifies subgroups of patients while capturing their evolution across several clinical outcomes simultaneously (multi-trajectories).

Method: For exploration, the RA cohort BARFOT (n = 2829) was used to identify 24 month post-diagnosis simultaneous trajectories of 28-joint Disease Activity Score and its components. Measurements were available at inclusion (0), 3, 6, 12, 24, and 60 months. Multi-trajectories were found with latent class growth modelling. For validation, the TIRA-2 cohort (n = 504) was used. Radiographic changes, assessed by the modified Sharp van der Heijde score, were correlated with trajectory membership.

Results: Three multi-trajectories were identified, with 39.6% of the patients in the lowest and 18.9% in the highest (worst) trajectory. Patients in the worst trajectory had on average eight tender and six swollen joints after 24 months. Radiographic changes at 24 and 60 months were significantly increased from the lowest to the highest trajectory.

Conclusion: Multi-trajectories constitute a powerful tool for identifying subgroups of RA patients and could be used in future studies searching for predictive biomarkers for disease progression. The evolution and shape of the trajectories in TIRA-2 were very similar to those in BARFOT, even though TIRA-2 is a newer cohort.

Huge efforts have been made to find predictive markers for disease prognosis in rheumatoid arthritis (RA) (1). Reducing disease activity is essential for decreasing the risk of joint destruction and development of RA-related comorbidities (2–4). However, finding the perfect predictive markers remains an elusive goal. This may be because the optimal biomarkers have not yet been discovered, along with the heterogenic nature of the disease: there are patients with or without shared

epitope or autoantibodies, with joint destructive versus non-destructive disease, with early or late disease onset in life, and with different responses to treatments. Differences in outcome depend also on gender and age (5). However, there are groups of patients with a similar disease evolution and similar treatment response, and identifying these groups may help to predict outcome in clinical studies.

An essential question is: what do we want to predict? First, we want to predict progression of disease activity and severity. Disease activity is commonly assessed through the composite Disease Activity Score (DAS28), consisting of swollen and tender 28-joint counts (SJC and TJC), erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), and patient's assessment of global health on a visual analogue scale (GH-VAS) (6). Other indices are the Clinical

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Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) (7). Disease activity can also be evaluated by ultrasound or magnetic resonance imaging (8) and disease severity as joint destruction or presence of extra-articular manifestations.

Secondly, we want to predict whether a patient responds to a specific intervention. The majority of clinical trials use the American College of Rheumatology (ACR) response criteria (9): a dichotomous indicator where the patient either is a responder or is not. This is decided according to a certain improvement in SJC or TJC, patient and physician assessment of VAS-GH, pain, disability, and acute-phase reactants. The European League Against Rheumatism (EULAR) response criteria (10) use defined cut-offs based on DAS28, which indicate a good, moderate, or poor response in relation to previous DAS28. Irrespective of which composite score or response criteria are used, they only give a snapshot of patients' health at a specific time-point. Further, hidden dynamics in the disease evolution cannot be captured by recorded average changes. Equally important is that there may be subgroups of patients with a different disease course. It is essential to identify such subgroups in order to find prediction factors of disease evolution or for treatment response. This heterogeneous progression of disease across patient subgroups can be captured by trajectories, which group patients based on their similar disease evolution over time.

Trajectory modelling has been used in other disciplines for prediction of disease risk or progression (11–13). Even in rheumatology, trajectories have started to be a well-known tool and have been used to identify psychological distress (14, 15), fatigue (16), disability (17), physical activity in RA (18) and ankylosing spondylitis (19), impact on work, disease progression, and treatment response (20, 21). Despite their gain in popularity over the past few years, it is less understood that trajectories can also build on simultaneous disease aspects, such as DAS28 and its components, quality of life, and physical function. Similarly, it is less understood how much data are required to reliably estimate trajectories.

This study aims to demonstrate the usefulness of a trajectory approach across multiple indicators of disease activity simultaneously in patients with early RA.

Method

Patients

The BARFOT (Better Anti-Rheumatic FarmacOTherapy) cohort (n = 2838) is an observational prospective multi-centre study, and was used as the exploration cohort. The patients met the ACR 1987 classification criteria (22) and were included consecutively at the time of RA diagnosis between 1992 and 2006. At baseline, patients had a disease duration of ≤ 12 months. They were assessed

according to a structured protocol at baseline, and 3, 6, 12, 24, and 60 months. At the 60 month visit, 2315 patients were available for examination and 80% had radiographic measurements. Causes for non-participation were death (48%), unwillingness to participate (5%), development of other rheumatic diseases (5%), relocation (4%), and unknown causes (39%). The patients lost to follow-up at 24 and 60 months, respectively, were more likely to be older at inclusion and rheumatoid factor (RF) negative. The patients missing at 60 months were more likely to be single.

Clinical disease assessments

Disease activity was measured by the DAS28 (6). ESR, CRP, anti-cyclic citrullinated peptide (CCP) antibodies, and RF were measured according to current laboratory standards at the hospitals. For the BARFOT patients, anti-CCP antibodies were analysed in stored serum from inclusion. Additional details are given elsewhere (23, 24). Patient characteristics are shown in Table 1.

The TIRA-2 (Swedish acronym for 'Early Intervention in Rheumatoid Arthritis') cohort was used as a validation cohort. A total of 504 patients with recent-onset RA (< 12 months' disease duration) were enrolled in 2006–2009 based on fulfilment of ACR 1987 (n = 422) or EULAR 2010 (n = 82) (22, 25) classification criteria. Patients were assessed according to a structured protocol at baseline, and 3, 6, 12, and 24 months. At the 24 month visit, 441 patients were examined and 59% had radiographic measurements. Patients missing at 24 months were more likely to be RF and anti-CCP negative. Patient characteristics are shown in Table 2.

The majority of patients in both cohorts did not receive disease-modifying anti-rheumatic drugs (DMARDs) or glucocorticosteroids prior to the first visit, but were subsequently treated with DMARDs in accordance with national guidelines.

Evaluation of radiographic changes

Conventional radiography of hands and feet was performed 24 and 60 months after inclusion. Certified assessors, blinded to clinical data, evaluated the images according to modified Sharp van der Heijde score (SHS) (26), which includes 28 areas for erosions and 27 for joint space narrowing (0–448). For dichotomy into two groups, the median value of the modified SHS (for BARFOT) or Larsen score (for TIRA-2) was used (27).

Ethics approval and consent to participate

The study complied with the Declaration of Helsinki and was approved by the Regional Ethical Review Boards at Lund University (398-01), Karolinska Institute (02-075, T2016/297-31/1), Linköping University

Table 1. Summary statistics of risk factors at inclusion in the BARFOT cohort for disease trajectories based on the composite measurement 28-joint Disease Activity Score (DAS28).

| Characteristic | Trajectory 1 Best outcome | Trajectory 2 Moderate outcome | Trajectory 3 Worst outcome | p |
|---|------------------------------|----------------------------------|-------------------------------|----------|
| N (%) | 1121 (39.5) | 1186 (41.8) | 531 (18.7) | - |
| Age (years) (n = 2838) | 57.7 ± 16.2 | 58.9 ± 15.4 | 56.6 ± 14.8 | 0.02* |
| Gender (n = 2838) | | | | < 0.001† |
| Female | 61.3 | 70.8 | 73.3 | |
| Male | 38.7 | 29.2 | 26.7 | |
| Marital status (n = 2238) | | | | 0.02† |
| Single | 26.1 | 31 | 32.3 | |
| Married/partner | 73.9 | 69 | 67.7 | |
| Smoking (n = 2698) | | | | 0.41† |
| Ever smoker | 59.9 | 59.2 | 62.6 | |
| Never smoker | 40.1 | 40.8 | 37.4 | |
| DAS28 (n = 2746) | 4.58 ± 1.14 | 5.50 ± 1.11 | 6.10 ± 1.08 | < 0.001* |
| CRP (mg/L) (n = 2769) | 27.1 ± 31.2 | 35.5 ± 39.3 | 37.0 ± 41.7 | < 0.001‡ |
| Rheumatoid factor (n = 2780) | | | | 0.54† |
| Positive | 59.3 | 61.4 | 61.2 | |
| Negative | 40.7 | 38.6 | 38.8 | |
| HAQ (n = 2654) | 0.8 ± 0.6 | 1.1 ± 0.6 | 1.3 ± 0.6 | < 0.001* |
| Medication: glucocorticosteroids (n = 2658) | | | | 0.04† |
| Yes | 40 | 40 | 46.1 | |
| No | 60 | 60 | 53.9 | |
| Medication: DMARD/biologics (n = 2830) | | | | 0.09† |
| Yes | 75.2 | 77.9 | 79.8 | |
| No | 24.8 | 22.1 | 20.2 | |

Statistics are given as column percentages by trajectory for categorical factors and as mean ± sd for continuous factors.

p Values are given according to: *ANOVA test of means, †Pearson's chi-squared test of independence, and ‡Kruskal–Wallis test. CRP, C-reactive protein; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying anti-rheumatic drug.

(01-263), and Linköping (TIRA-2 M168-05). Informed, written consent was obtained from the participants before enrolment.

Statistical methods

We used multi-trajectory modelling (28–30) to identify latent clusters of individuals who followed similar trajectories across multiple indicators of disease: DAS28, TJC, SJC, patient's VAS-GH, and ESR. The methodology for identifying trajectories for a single outcome is based on latent class growth modelling (31–34) and the multi-trajectory modelling extends that approach.

Since determining the number and shape of the trajectories would be challenging in a multiple-outcome context this was first done individually for each outcome. Specifically, the number of trajectories is chosen based on the model that fits the data best, according to the Bayesian information criterion (BIC), and on clinical relevance. Each trajectory can be linear or take more complex shapes described by the polynomial functions of time since diagnosis. The degree of the polynomial was found in an iterative manner, where a low degree is compared against a higher degree, such as quadratic versus cubic. Choosing the higher degree is based on a significant improvement in the

BIC and the statistical significance of all parameters of the higher-degree polynomial (34). Each trajectory can take a different mathematical shape and freely fluctuate over time – ascending, descending, or staying constant – to describe disease evolution.

DAS28, VAS-GH, and ESR followed censored normal distributions, while SJC and TJC followed zero-inflated Poisson distributions to allow for an excess of zeros. All trajectory analyses were conducted with the SAS macro PROC TRAJ, downloadable free from the developer's website (35). Risk factors (Table 1) for the association with trajectory membership were also investigated in the multi-trajectory model.

To assess the contribution of the components to the separation of the worst trajectory in DAS28, the following equation was used (6):

$$\text{DAS28} = 0.56 \cdot \sqrt{\text{TJC}} + 0.28 \cdot \sqrt{\text{SJC}} + 0.70 \cdot \ln(\text{ESR}) + 0.014 \cdot \text{VAS} - \text{GH} \quad (1)$$

Sensitivity analyses

The impact of the first 3 months after diagnosis on the DAS28 trajectories was investigated in a sensitivity analysis on DAS28 evolution from 3 to 24 months. The trajectories were adjusted for baseline DAS28 and

Table 2. Summary statistics of risk factors at inclusion in the TIRA-2 cohort for disease trajectories.

| Characteristic | Trajectory 1 Best outcome | Trajectory 2 Moderate outcome | Trajectory 3 Worst outcome | p |
|--|------------------------------|----------------------------------|-------------------------------|----------|
| N (%) | 205 (40.1) | 257 (50.3) | 49 (9.6) | – |
| Age (years) (n = 504) | 55.2 ± 15.2 | 60.5 ± 12.9 | 61.5 ± 13.0 | < 0.001* |
| Gender (n = 504) | | | | 0.002† |
| Female | 65.0 | 65.0 | 89.4 | |
| Male | 35.0 | 35.0 | 10.6 | |
| DAS28 (n = 469) | 4.0 ± 1.20 | 5.4 ± 1.02 | 6.2 ± 0.82 | < 0.001* |
| CRP (mg/L) (n = 488) | 5.0 (5.0; 20.0) | 15.0 (8.0; 35.0) | 20.0 (9.0; 50.0) | < 0.001§ |
| ACPA (n = 502) | | | | 0.96 ‡ |
| Positive | 71.9 | 71.0 | 70.2 | |
| Negative | 28.1 | 29.0 | 29.8 | |
| Rheumatoid factor (n = 504) | | | | 0.19 ‡ |
| Positive | 57.6 | 61.0 | 46.8 | |
| Negative | 42.4 | 39.0 | 53.2 | |
| HAQ (n = 453) | 0.74 ± 0.53 | 1.02 ± 0.62 | 1.30 ± 0.61 | < 0.001* |
| Medication: glucocorticosteroids (n = 498) | | | | 0.57 ‡ |
| Yes | 64.0 | 59.1 | 60.9 | |
| No | 35.0 | 40.9 | 39.1 | |
| Medication: DMARD/biologics (n = 498) | | | | 0.21† |
| Yes | 88.5 | 92.5 | 95.7 | |
| No | 11.5 | 7.5 | 4.3 | |

Statistics are given as column percentages by trajectory for categorical factors and as mean ± sd for continuous factors, unless otherwise stated.

p Values are given according to: *ANOVA test of means, †Fisher's exact test, ‡Pearson's chi-squared test of independence, and §Kruskal–Wallis test.

||Presented as median and (25th; 75th) percentiles.

DAS28, 28-joint Disease Activity Score; CRP, C-reactive protein; ACPA, anti-citrullinated protein antibody; HAQ, Health Assessment Questionnaire; DMARD, disease-modifying anti-rheumatic drug.

ΔDAS28 at 3 months (i.e. the difference between DAS28 at baseline and at 3 months).

In a separate analysis with trajectory membership as the outcome and ΔDAS28 at 3 months as the independent factor, we examined how much ΔDAS28 contributes to trajectory membership.

The EULAR responses at 3, 6, 12, and 24 months were calculated to examine whether these could predict disease severity at 24 months as well as the trajectories.

A further sensitivity analysis was conducted in TIRA-2 including only the patients enrolled according to ACR 1987 (n = 422) to examine whether the different inclusion criteria could affect the disease trajectories in this cohort.

All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Identification of trajectories

In BARFOT, three multi-trajectories were identified, with 39.6% of the subjects in the lowest trajectory, 41.5% in the middle, and 18.9% in the highest trajectory (Figure 1). From a mathematical standpoint, all three trajectories of DAS28 were quartic functions of time since diagnosis (Figure 1A), whereas for the other components some

trajectories were linear, some cubic and some quartic (Figure 1B–E).

At inclusion, the patients in the highest (third) trajectory started with a mean TJC of 13, SJC of 6, and VAS-GH > 40 mm. After 24 months, they still had a TJC > 8. Using the max–min values of the highest trajectory of each of the four components (corresponding to the time at inclusion and 24 months' follow-up) and the DAS28 equation, it was estimated that the contribution range to DAS28 was 1.98–1.53 for TJC, 0.99–0.69 for SJC, 2.55–2.31 for ESR, and 0.71–0.60 for VAS-GH. This indicates that the most significant clinical component for DAS28 is the ESR, followed by TJC.

The evolution of DAS28 and the division of patients into three trajectories were validated in the independent TIRA-2 cohort (Figure 2). The patients in the highest trajectory represented 10% of the cases and had a mean DAS28 > 6 at inclusion and 4.5 after 24 months. Patients in the middle and lowest trajectories had mean DAS28 of 3 and 2, respectively, at 24 months. These remained unchanged in a sensitivity analysis including only patients enrolled according to ACR 1987. The evolution and shape of the trajectories in TIRA-2 were very similar to those in BARFOT, although BARFOT patients had slightly higher averages at 24 months.

In BARFOT, there was no difference in RF status across the three trajectories (Table 1). An increasing tendency

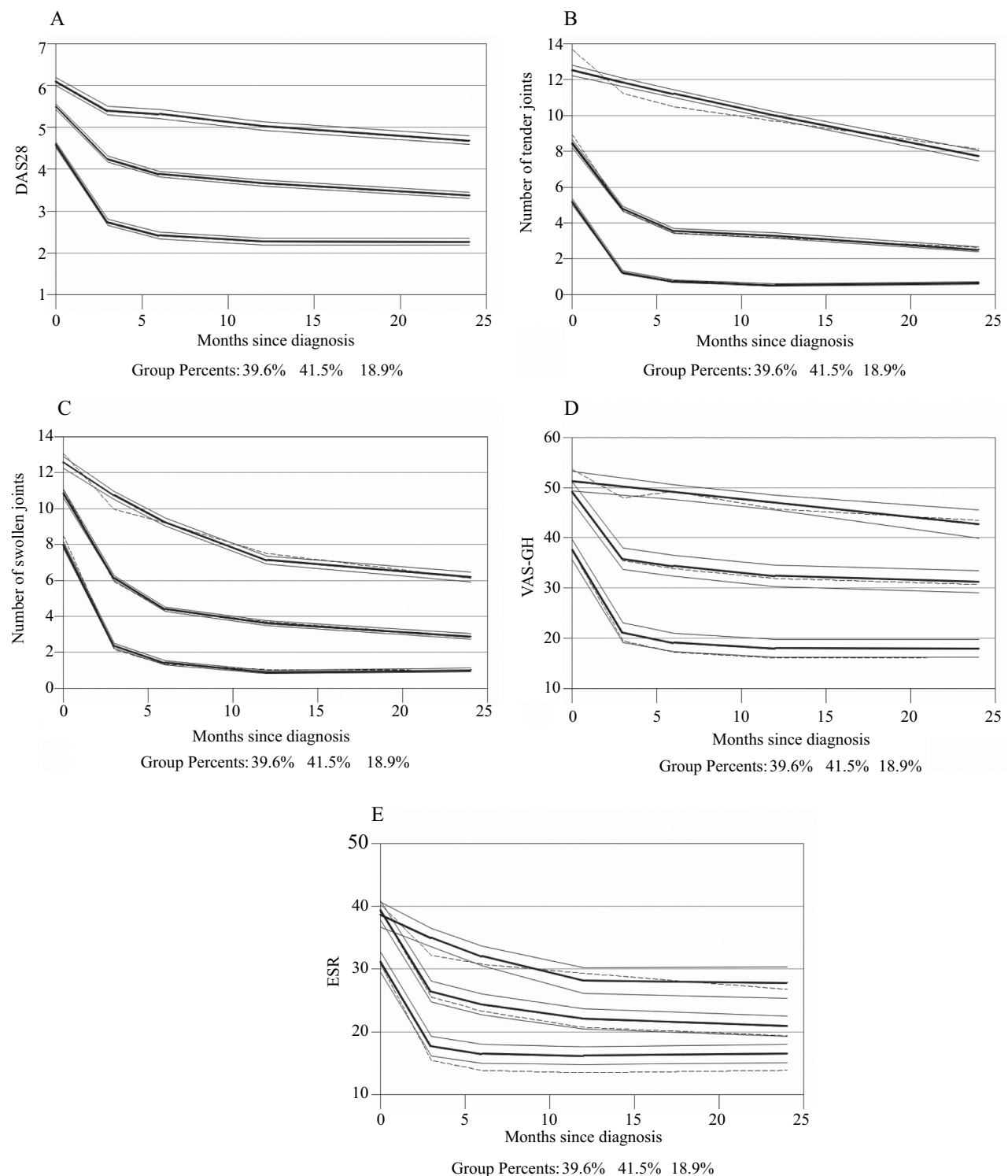
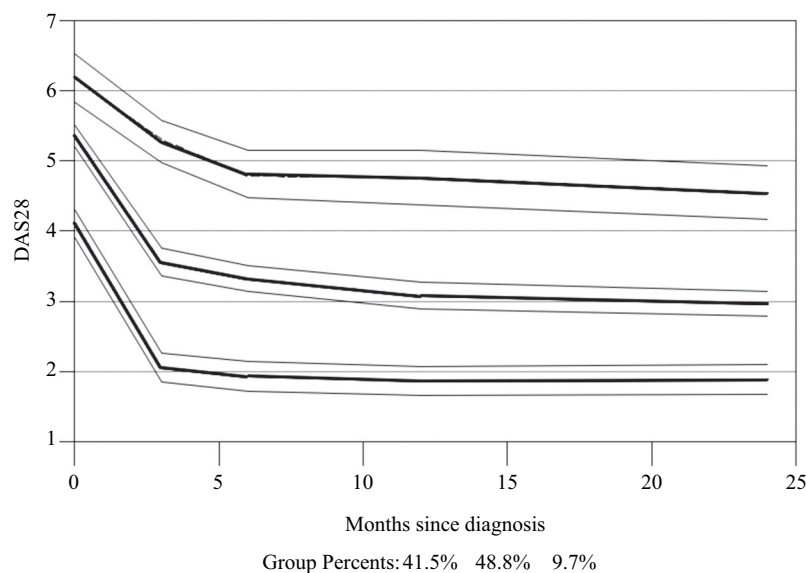


Figure 1. Disease evolution (trajectories) during 24 months after diagnosis, representing (A) 28-joint Disease Activity Score (DAS28), (B) number of tender joints, (C) number of swollen joints, (D) patient's assessment of global health on a visual analogue scale (VAS-GH), and (E) erythrocyte sedimentation rate (ESR) in the BARFOT cohort ($n = 2838$). Estimated trajectories are shown as thick lines with surrounding 95% confidence bands (thin lines). Mean statistics are shown as dashed lines, unless they are concealed by the trajectories owing to overlap.

towards more treatment with synthetic and biological DMARDs and glucocorticoids was observed from the lowest to the highest trajectory, which was borderline significant for glucocorticoids use ($p = 0.04$) but not for DMARDs

and biological medication. At inclusion, more patients in the highest trajectory were women, single, and younger; and had significantly higher DAS28, higher CRP, and higher Health Assessment Questionnaire (HAQ) scores compared



to the lowest two trajectories. Similar observations were obtained in TIRA-2, except that in the highest trajectory patients were significantly older at inclusion (Table 2). In addition, no difference regarding anti-CCP positivity at inclusion was observed in TIRA-2. As anti-CCP was not routinely analysed at the time of enrolment into BARFOT, we had available anti-CCP information for only 68% of the participants. In a sensitivity analysis of this group, we found no association between anti-CCP status and trajectory membership ($p = 0.23$).

Joint destruction predicted by trajectory

Mean joint narrowing score and the total SHS at 24 months were significantly increased from the lowest to the highest trajectory (Table 3). Similarly, the total SHS at 60 months was significantly increased across the trajectories where the joint narrowing score contributed more than the erosion score.

For comparison, we examined whether the EULAR responses at 3, 6, 12, 24, and 60 months could predict the radiographic severity at 24 and 60 months (Supplementary table S1). The median SHS differed across the 3 month EULAR response categories and in a similar manner to those in the three trajectories. However, beyond 3 months there was no association between EULAR response and radiographic changes.

Figure 3 shows the evolution of the DAS28 trajectories from 3 to 24 months while accounting for baseline DAS28 and Δ DAS28 at 3 months. Both factors were significantly associated with trajectory membership ($p < 0.001$), with higher baseline DAS28 resulting in increased risk of belonging to a higher trajectory and larger Δ DAS28 associated with lower risk. This shows that both initial DAS28 and the magnitude of Δ DAS28 play a role in the DAS28 evolution. In addition, there was an interesting change in the shape of the lowest trajectory, which became a straight line with DAS28 around 2.2, suggesting a highly stable group of patients after the initial 3 months.

Table 3. Radiographic measurements by trajectory in the BARFOT cohort.

| Radiographic evaluation | N | Trajectory 1: Best outcome | N | Trajectory 2: Moderate outcome | N | Trajectory 3: Worst outcome | p* |
|-------------------------|-----|-----------------------------------|-----|-----------------------------------|-----|-----------------------------------|-------|
| | | Median (25th; 75th) percentile | | Median (25th; 75th) percentile | | Median (25th; 75th) percentile | |
| ES 24 months | 840 | 1 (0; 4) | 857 | 1 (0; 5) | 348 | 1 (0; 8) | 0.07 |
| JNS 24 months | 840 | 2 (0; 9) | 858 | 4 (0; 12) | 349 | 4 (0; 16) | 0.002 |
| Total SHS 24 months | 842 | 4 (0; 15) | 859 | 6 (0; 17) | 349 | 7 (0; 23) | 0.002 |
| ES 60 months | 787 | 2 (0; 7) | 802 | 1 (0; 7) | 316 | 1.5 (0; 8.5) | 0.84 |
| JNS 60 months | 788 | 5 (0; 14) | 802 | 7 (0; 18) | 317 | 8 (0; 22) | 0.001 |
| Total SHS 60 months | 788 | 7.5 (1; 21) | 802 | 9 (2; 24) | 317 | 12 (0; 31) | 0.01 |

Statistics are presented as number of people in the respective trajectory, together with the median and percentiles (25%; 75%) of the radiographic measurements.

*p Values are given according to the Kruskal–Wallis test.

ES, erosion score; JNS, joint narrowing score; SHS, modified Sharp van der Heijde score.

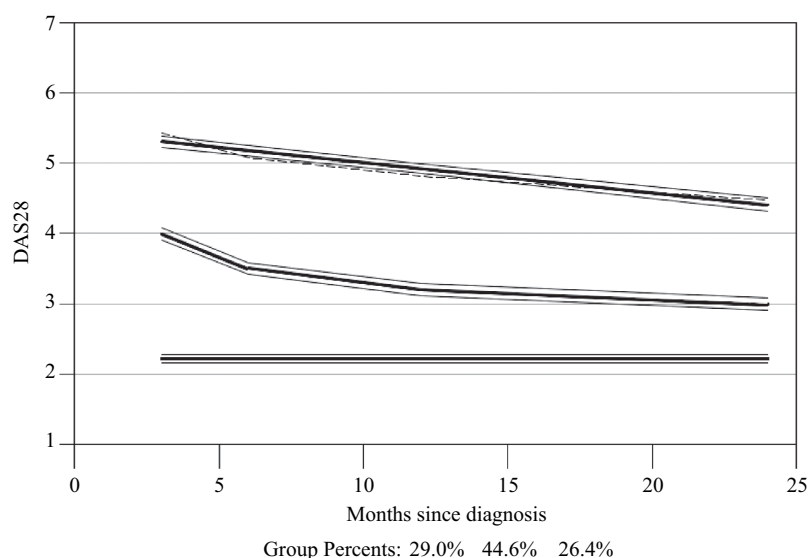


Figure 3. Evolution in 28-joint Disease Activity Score (DAS28) score from 3 to 24 months with adjustment for DAS28 at baseline and Δ DAS28 at 3 months (calculated as the difference between DAS28 at baseline and DAS28 at 3 months) in the BARFOT cohort.

Discussion

In this study, we show that clinically relevant groups of patients with RA with distinct disease evolution over time can be identified by the trajectory approach, and that trajectories predict radiographic damage after 24 and 60 months. Patients in the highest trajectory had the most destruction as measured by SHS. Taking advantage of the multi-trajectory approach, we also examined how each of the DAS28 components contributed to the composite score over time and found that, after ESR, TJC was driving the DAS28 evolution.

Trajectories have been used to describe evolution in various diseases including RA (11, 15, 20, 21), but to our knowledge, the contribution of the different DAS28 components and a comparison to EULAR response have not previously been shown. The multi-trajectory approach accounts for the interrelationship between multiple outcomes, which is very useful in our setting as we simultaneously illustrate the trajectories for DAS28 and each component (28). We identified three significantly different trajectories for patients with early RA in BARFOT, and validated these in TIRA-2 with respect to DAS28 evolution. A Canadian study (11) found a similar evolution and percentage of participants in the top (worst) DAS28 trajectory (11%) over 24 months after diagnosis, as in TIRA-2. The percentage is lower than the 19% belonging to the top DAS28 trajectory found in BARFOT. This is not surprising; the time of enrolment was very similar to that in TIRA-2, while BARFOT is an older cohort that was collected earlier. Another cohort study of early RA participants enrolled slightly earlier than BARFOT (1986–1997) found that, in term of psychological distress, 23% of the participants were on a high–stable or low–increasing stress trajectory over the course of 10 years (14). In a relatively small study of 370 patients with early axial

spondyloarthritis followed for 3 years, 34% were on a high persistent disease activity trajectory (19).

In our study, patients who belonged to the highest trajectory in both cohorts had higher CRP and HAQ at inclusion and a higher percentage were women. These patients had also a higher DAS28 at inclusion, which was expected, even though theoretically it would be possible to identify a group that starts off with an average DAS28 that increases after diagnosis, without going into remission. In addition, in BARFOT, the patients in the top trajectory were more often single and younger at inclusion, and had the highest percentage of glucocorticoids users at inclusion, which could reflect a more aggressive disease at baseline. Noticeably, the opposite was true in TIRA-2, where patients in the worst trajectory were older. These findings agree with previous knowledge on predictors of poor disease outcome, such as gender and age (36, 37). One of our aims was to disentangle which component is driving DAS28, which is of special concern for the group of patients that are not in remission after several years from diagnosis. This group corresponds to the highest trajectory and we found that after ESR, the major driving force was TJC. The finding confirms the long-standing notion that the disease is driven by inflammation and characterized by joint-specific pain. A combination of TJC, ESR, and HAQ has been shown to predict persistent disease activity during the first year after diagnosis (38). The mathematical weight of TJC is double [$0.56 \times \sqrt{\text{TJC28}}$] that of SJC [$0.28 \times \sqrt{\text{SJC28}}$] in the DAS28 equation, which may very well influence our findings. Moreover, TJC is a difficult variable and can be a part of a chronic pain syndrome, but might also be due to sub-clinical inflammation (38). However, tender joints and an elevated DAS28 may also be due to a chronic pain syndrome and not associated with joint inflammation (39). Thus, we cannot exclude that TJC gives misleading information in this scenario, but because of the increased ESR

levels we believe that it is more likely that a majority of these patients suffer from subclinical inflammation, as it could be indicated by TJC.

The EULAR response and ACR improvement criteria perform equally well (40, 41). They are both based on the difference in disease activity between two defined time-points. However, disease activity is not an 'on or off' phenomenon, and it may be beneficial to assess the development of disease activity over time even in clinical studies, which can be done using the trajectory approach. We found that the trajectories could predict joint damage at 24 and 60 month follow-up in BARFOT. Joint damage at 24 and 60 months could also be predicted by EULAR response at 3 months, but not by EULAR response at later time-points. This indicates that classifying a patient according to the EULAR response is highly dependent on the time-point at which it is calculated and is not as reliable as the trajectories in predicting disease prognosis. Another disadvantage of the EULAR response classification is that patients migrate in and out of categories over time, so it is a less stable classification system than the trajectories.

Onset DAS28 is an important negative prognostic factor (37, 42) and a rapid reduction in disease activity is important for positive treatment response (43, 44, 45). Not surprisingly, we showed that a good EULAR response at 3 months was associated with better prognosis. Similarly, Δ DAS28 at 3 months was associated with the entire disease evolution, and we believe that increased attention should be given to the initial 3 months in order to affect the evolution positively. However, other factors aside from Δ DAS28 impact disease evolution, as this explained only 6–7.5% of the risk of belonging to the top two trajectories.

Despite differences in inclusion criteria, age, and medication between the cohorts, the DAS28 trajectories from BARFOT could be validated in TIRA-2. Similar findings were obtained with respect to patient characteristics in the different trajectories and Δ DAS28. However, TIRA-2 is a considerably smaller cohort, which is why we focused on DAS28 trajectory validation, as the power was insufficient for estimating multi-group trajectories based on DAS28 and its components.

The multi-trajectory approach is a powerful tool for finding hidden groups of patients with RA while considering the interrelationship between multiple clinically relevant outcomes. A simplified version of this approach is available for modelling single outcomes. Another advantage is that the number or shape of the trajectories does not have to be known beforehand, which means that the method allowed us to find hidden dynamics in disease activity over time based on statistical tests (32) and correlate these with radiographic changes. A disadvantage is that a minimum of 300–500 patients is required to obtain trajectories for single outcomes (34) and even higher numbers are needed for the multi-trajectory modelling (we were not able to use the multi-trajectory approach in TIRA-2,

which includes 504 participants). Also, trajectories including less than 5% of the data cannot be reliably estimated.

Our study has several limitations. Information for BARFOT was collected in 1992–2006 and treatment strategies changed over that period. The missing data at 60 months may complicate the correlation between DAS28 and radiographic changes, although 50% of the loss to follow-up was due to death. Data for TIRA-2 were collected in 2006–2009 and this was a smaller study, which rendered insufficient power for the multi-trajectory analysis or to correlate the DAS28 trajectories to radiological joint damage. Information on smoking, which previously was shown to be an important predictor for disease activity, is lacking in TIRA-2. Information on anti-CCP antibodies is lacking in 32% of the BARFOT participants, as it was not routinely analysed at disease onset in these patients, included until 2006, but instead analysed in stored serum, when available. In a sensitivity analysis performed in the group with anti-CCP antibody ($n = 1936$), there was no association between anti-CCP status and trajectory membership, which is in line with the finding in TIRA-2.

Conclusion

Multi-trajectories constitute a powerful tool for identifying hidden groups of patients with RA patients and could be used in future studies searching for predictive biomarkers for disease progression. In our study, we used multi-trajectories to investigate which of the DAS28 components drives long-term disease severity, and found that after ESR, TJC was driving the DAS28 evolution 24 months post-diagnosis. We found no association between EULAR response beyond 3 months and radiographic changes, although trajectories could predict joint destruction at 24 and 60 months after diagnosis.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supporting information

Additional Supporting Information may be found in the online version of this article.

Supplementary table S1. Radiographic measurements at 24 and 60 months in the BARFOT cohort by EULAR response at different time-points.

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