Trajectories in early rheumatoid arthritis related fatigue over 10 years: results from the ESPOIR cohort

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Abstract

Objective

In a cohort of early rheumatoid arthritis (RA) patients, we aimed to determine and characterise fatigue trajectories over 10 years of follow-up and identify predictors of trajectory membership.

Methods

We selected patients fulfilling the 2010 ACR/EULAR criteria for RA included in the ESPOIR cohort. We used a cluster analysis to obtain fatigue (assessed by fatigue visual analogue scale) trajectories over the course of 10 years from enrolment. Chi-square tests or ANOVA were performed to evaluate differences of baseline variables between fatigue trajectories. Using a multinomial logistic regression we were able to identify predictors of trajectory membership.

Results

We analysed 598 patients with mean disease duration at enrolment of 26.2±40.9 days. Cluster analysis revealed 3 trajectories: high (18%), moderate (52%) and low fatigue (30%). Compared to patients with moderate or low fatigue trajectory, patients with high fatigue trajectory were predominantly women and reported significantly higher duration and intensity of morning stiffness, HAQ score, tender joints count, levels of pain, number of awakenings due to arthritis, frequency of fibromyalgic RA, levels of physician and patient global assessment, more frequent sleep problems, and increased psychological distress. Female patients with pain, psychological distress and presence of sicca symptoms had a higher risk of being in the high trajectory group.

Conclusion

These findings suggest that levels of fatigue are rather stable over time in each trajectory. Baseline clinical measures and baseline patient-reported measures of functional status better distinguished the three fatigue trajectories. We did not find any differences between trajectories in baseline laboratory measures. Inflammatory activity was not a predictor of being in the high trajectory fatigue group.

Key words

fatigue, persistent fatigue, early rheumatoid arthritis, VAS fatigue, depression, sicca syndrome

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Introduction

Fatigue is one of the most prevalent symptoms (40–80%) reported by persons with rheumatoid arthritis (RA) (1-6). RA-related fatigue is a complex concept with biological, psychological and social interactions (5, 7, 8).

It is recommended that RA-related fatigue should be measured in all RA studies, using a validated instrument (9-11). It is known that patients and clinicians have different priorities (12). From a patient perspective, fatigue is one of the most important manifestations to address and it is defined as an uncontrollable and overwhelming symptom (13-15). There are three aspects of impact disease that require assessment. This was developed by patients and researchers and termed the "impact triad"; the severity of an outcome, its importance to the patient, and patient ability to self-manage it. It is important to consider how symptom severity and self-management may influence patient priorities or the importance of outcomes for an individual (16).

However, no current treatment has been described other than standard pharmacological treatment (17).

Consistent with past analyses in established RA, the strongest correlates of RA related- fatigue were pain (1, 2, 18-20), psychological distress (2, 18, 21-24) and physical disability (1, 15).

It has been shown that fatigue in RA is correlated with disease activity (25-28). However, a recent systematic review found no link between fatigue and inflammatory activity (29). This association is thus complex and far from clear-cut (30)

To date, few longitudinal studies for fatigue starting in early-RA exist (24, 27, 28, 31). They showed that fatigue is present and related to female gender (27, 28, 31), younger age (27, 31), swollen and tender joint count (31), smoking (27), pain (28), disease activity (28) and mental health (28). To our knowledge, there has been no study that has characterised fatigue trajectories in early RA.

The present work set out to identify trajectories of long-term fatigue course in patients with early RA and to explain differences between theses subgroups. The identification of distinct longitudinal fatigue trajectories and their relation with specific patient or illness related aspects can provide the opportunity to know about fatigue in early RA and might provide indications for tailored interventions.

Materials and methods

Study population

We used data from the ESPOIR cohort. ESPOIR is a prospective observational cohort of patients with early arthritis promoted by the French Society of Rheumatology. A total of 813 patients (aged between 18–70 years) with early inflammatory arthritis (disease duration <6 months) and probable clinical diagnosis of RA or undifferentiated arthritis were enrolled between December 2002 and March 2005 in 14 French academic regional centres. Patients were naive to disease-modifying antirheumatic drugs. Corticosteroids were permitted only if prescribed for <2 weeks and with a maximum mean dose of 20 mg/week (32, 33).

Follow-up

Patients were followed with clinical and laboratory examinations at baseline and after 6, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108 and 120 months.

For the current study, we selected those patients fulfilling the 2010 ACR/EULAR criteria for RA at the 12-month (M12) visit.

Data collection

Demographic variables: age (years), gender (male/female), smoking status (yes/no), educational level (university/primary or secondary school) and marital status (couple/single)

Laboratory measures: haemoglobin (mg/dL), C-reactive protein (CRP) (mg/L) erythrocyte sedimentation rate (ESR) (/mg/L), positivity or negativity of anti-cyclic citrullinated peptide antibody (anti-CCP) (enzyme-linked immunosorbent assay (ELISA), DiaSorin, positive 50 units/mL) and rheumatoid factor (RF) (ELISA, Menarini, positive 9 IU/mL)

Clinical history: number of awakenings due to arthritis, sleep problems (yes/no), initial pattern of joint involvement

(acute/chronic), joint symptoms (symmetric/asymmetric), oligo or polyarticular at onset of symptoms (yes/no), presence of fever at onset of symptoms (yes/no), menopausal status (yes/no), history of thyroid problems (yes/no), history of diabetes (yes/no) and presence of sicca symptoms at the time of assessment (as indicated by the rheumatologist) (yes/no)

Clinical examination and disease-related data: fatigue (fatigue VAS), functional capacity assessed by the Health Assessment Questionnaire (HAQ) (0–3 scale), Disease Activity Score in 28 joints (DAS28), swollen joint count (SJC), tender joint count (TJC) morning stiffness severity (range 0–100 VAS) and duration (min), and body mass index (BMI) (kg/m^2), pain (SF-36 pain scale transformed to a 0–100 score range), patient and physician global assessment (VAS 0–100), five-item Mental Health Inventory questionnaire (MHI-5) (a screening tool for identifying depressive or anxiety symptoms, lower scores indicate major psychological distress) (34). Fibromyalgic RA (defined as having TJC/SJC≥7) (35).

Radiological characteristics: presence or absence of erosions.

Statistical analysis

Patient characteristics: Descriptive data are presented as mean ± standard deviation (SD) or frequencies and percentage.

Fatigue trajectories: A hierarchical agglomerative clustering procedure with Ward's method was used to obtain fatigue trajectories over the course of 10 years from enrolment. Analysis was performed in all patients who completed four or more visits over 10-year period. To avoid the exclusion of patients with missing values in some visits, an imputation of missing data was made using the maximisation expectation algorithm. This method allows adjusting parametric models for incomplete data using maximum likelihood.

Description of baseline characteristics of fatigue trajectories: Bivariate analyses were performed to compare baseline variables between the 3 fatigue trajectories. Chi-square test and ANOVA were used for qualitative and quantitative variables respectively.

Table I. Demographic and clinical characteristics at baseline of the 598 patients with early RA.

Baseline characteristics	Values
Female*	459 (76.8)
Age at disease onset, years	48.7 (12.1)
Marital status (couple)*	434 (72.8)
Education level (secondary school)*	190 (31.8)
Menopausal*	219 (47.9)
Smoking status*	277 (46.5)
Initial pattern of the joint involvement (acute)*	456 (76.5)
Joint symptoms (symmetric)*	356 (59.7)
Oligo-polyarticular at onset*	484 (81.2)
Fever at RA onset*	53 (8.9)
Anti-CCP antibodies positive*	289 (48.5)
Rheumatoid factor-positive*	308 (51.7)
Haemoglobin (mg/dL)	12.9 (1.3)
CRP (mg/L)	23.5 (35.7)
ESR (mm/hour)	30.3 (25.0)
Morning stiffness, duration, minutes	100.57 (12.1)
Morning stiffness intensity (VAS 0-100)	52.4 (26.6)
DAS 28	5.3 (1.2)
HAQ score (0-3 scale)	1.0 (0.7)
Swollen joint count/28	8.4 (5.7)
Tender joint count/28	9.7 (7.4)
Physician global assessment (VAS 0-100)	53.4 (21.5)
Patient global assessment (VAS 0-100)	61.5 (24.5)
SF-36 bodily pain scale	55 (19.5)
Awakenings due to arthritis	1.8 (2.5)
Sleep problems*	274 (66.2)
MHI-5 score (psychological distress)	52.6 (19.8)
Body mass index	24.9 (4.5)
>3 comorbidity*	249 (41.8)
History of thyroid problems*	68 (11.4)
History of diabetes*	19 (32)
Sicca symptoms*	179 (29.9)
Radiographic changes*	93 (15.6)
Fibromyalgic RA*	105 (17.5)

The values are the mean (SD) unless otherwise indicated. *Frequencies (percentage)
Education level is missing in 2 patients, marital status in 2, smoking status in 2, initial pattern in 2, Morning stiffness (range 0–100) is missing in 2 patients, DAS28 in 11, Haemoglobin in 1, CRP in 10, ESR in 8, Sicca symptoms in 2, depression in 3, swollen joint count in 308, tender joint count in 308, physician VAS in 2, patient VAS in 2, joint pain at rest in 2, joint pain at movement in 2 and pain in 2. Menopausal woman: a total of 457 women.

Predictors of trajectory membership: A multinomial logistic regression analysis was used to search for the association between potential predictors of trajectory membership, with trajectory as the outcome. Variables that did not demonstrate significant group differences in the bivariate multinomial logistic regression at baseline were not included in the multivariable analysis. The final model was obtained after using a backward selection method. Adjusted odds ratio with 95% confidence intervals are presented for variables in the final model.

In order to avoid colinearity; DAS28, SCJ, TJC and fibromyalgic RA were not entered in the same statistical model, they were analysed separately with the other variables.

The significance level was set at 0.05. All analyses were conducted using SAS v. 9.4, SAS Institute Inc., Cary, NC, USA.

Results

Patient characteristics

Of the 813 ESPOIR patients, 677 (83.3%) fulfilled the 2010 ACR/EULAR criteria for RA at M12. The number of patients with complete data regarding fatigue assessments was 598 (Table I): 76.8% women, mean age at disease onset of 48.7±12.1 years. As expected, at baseline, levels of disease activity (mean ± SD 5.3±1.2) and disability (mean ± SD 1.0±0.7) were high.

Identification of fatigue trajectories

Cluster analysis of fatigue VAS scores

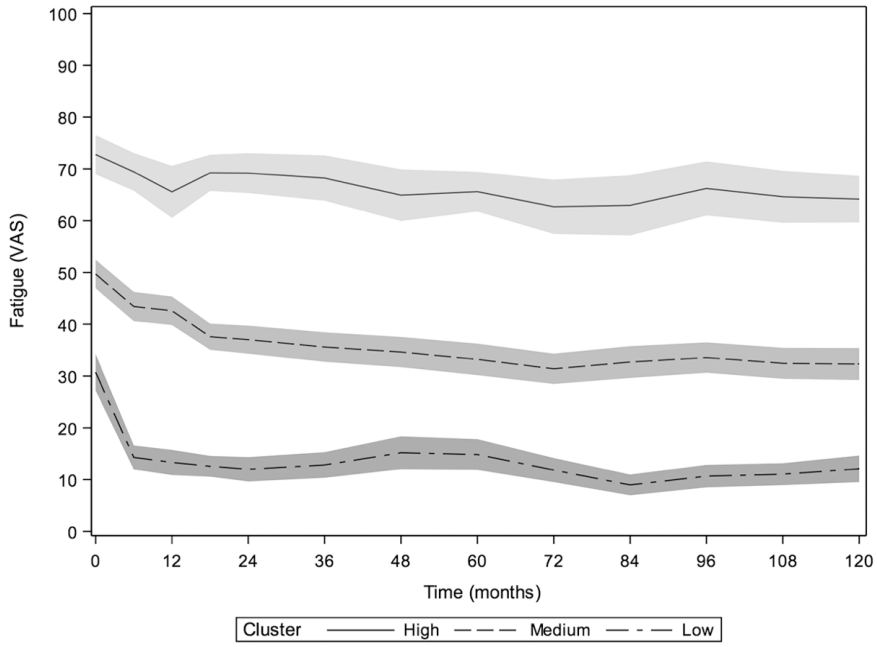

Fig. 1. Trajectories of fatigue in early RA patients over 10 years of follow-up.

revealed 3 trajectories over 10 years (Fig. 1): high (18%), moderate (52%) and low (30%) fatigue trajectories. For each trajectory group, fatigue shows a stable trajectory over time.

Description of baseline characteristics of fatigue trajectories

The key characteristics of each trajectory were as follows:

The high fatigue group (18%) had the lowest number of patients and were predominantly females with low MHI-5 levels (major probability of psychological distress) ($p<0.001$), greater duration ($p=0.009$) and higher levels of morning stiffness ($p<0.001$). Levels of pain ($p<0.001$), HAQ score ($p<0.001$), DAS 28 ($p=0.004$), number of awakenings due to arthritis ($p<0.017$), percentage of sleep problems ($p<0.001$), number of tender joints ($p=0.0164$), fibromyalgic RA ($p=0.001$) and levels of physician and patient assessment ($p<0.001$) were the highest among the three fatigue trajectories (Table II).

The moderate fatigue group (52%) was the largest, with more than a half of all subjects in our study. This group had significantly the highest number of patients with sicca symptoms (53.6%) at baseline and the highest number of patients with high IMC. Among the three fatigue trajectories groups, this group had the highest percentage of patients presenting with an oligo or polyarticular onset.

The low fatigue group (30%) was characterised by patients with high MHI-5 levels (minor probability of psychological distress) ($p<0.001$) and high education level. They had lowest frequency of fibromyalgic RA, lowest levels of pain ($p<0.001$), HAQ score ($p<0.001$), number of awakenings due to pain ($p<0.017$), number of tender joints ($p=0.0164$), levels of physician and patient global assessment ($p<0.001$) among the three fatigue trajectories.

No differences between the three trajectories were found for age, history of thyroid problems, SJC, positivity of Anti-CCP, RF, baseline levels of CRP, ESR and haemoglobin.

Importantly, there were no significant differences between the trajectory groups for the proportion of people lost to follow-up by the 10-year follow-up (data not shown).

Predictors of trajectory membership

The results from the multinomial logistic regression analysis, with odds ratios for all potential predictors of being in the high trajectory *versus* low and moderate trajectory *versus* low trajectory are presented in Table III. We did not find differences analysing DAS28, SJC, TJC nor fibromyalgic RA separately.

Being in the high trajectory *versus* the moderate or low trajectory was predicted by female sex, pain, psychological distress and sicca symptoms at baseline.

Discussion

We found three fatigue trajectories over 10 years of follow-up. Although a majority of our sample belonged to the moderate fatigue trajectory group, almost 20% of patients reported high levels of fatigue over time.

Interestingly, we found that trajectories are rather stable over time (just slightly decreasing).

Gender, clinical measures of disease activity, patient-reported measures of functional status and history of psychological distress better distinguished the three fatigue groups at baseline.

The different fatigue trajectories groups also increase our knowledge of why certain patients with RA are more susceptible than others to experience a high fatigue trajectory. To our knowledge, the present work is the largest to study the longitudinal course of fatigue in early RA patients.

Druce *et al*. (30) previously reported in a cohort of established RA, the presence of 3 trajectories: which consisted of Improved or persistent moderate-high paths for both sexes (and further included a persistent high trajectory in women). Participants who followed persistent trajectories were best distinguished from improvers by patient-reported measures rather than demographic or clinical variables.

Our results indicate that psychological distress; pain and presence of sicca symptoms at onset are more likely to show a high fatigue pattern *versus* moderate or low trajectory.

Interestingly, we did not find that measures of disease activity (clinical or analytical) were predictors to have a worst fatigue trajectory. This is in accordance with the findings suggesting that fatigue is not driven by inflammatory disease factors (1-5, 29, 30, 38). The DAS-28 has failed to demonstrate a significant correlation with fatigue in RA. A direct association between

Table II. Baseline chactereristics by fatigue trajectory groups.

	Trajectory groups						
	High fatigue	n	Moderate fatigue	n	Low fatigue	n	*p*
Female*	94 (87.9)	107	245 (78.3)	313	120 (67.4)	178	0.003
Age at disease onset, years	47.0 (12.1)	107	49.3 (11.7)	313	48.7 (12.7)	178	0.230
Marital status (couple)*	77 (72.6)	106	226 (72.4)	312	131 (73.6)	178	0.961
Education level (secondary school)*	22 (20.8)	106	91 (29.2)	312	77 (43.3)	178	0.001
Menopausal*	42 (45.2)	93	120 (49.2)	244	57 (47.5)	120	0.800
Smoking status*	52 (49.1)	106	136 (43.6)	312	89 (50.0)	178	0.330
Initial pattern of the joint involvement (acute)*	78 (73.6)	106	244 (78.2)	312	134 (75.3)	178	0.562
Joint symptoms (symmetric)*	68 (64.2)	106	184 (58.9)	312	104 (58.4)	178	0.588
Oligo-polyarticular at onset*	88 (83.0)	106	264 (84.6)	312	132 (74.2)	178	0.015
Fever at RA onset*	14 (13.2)	106	24 (7.7)	312	15 (8.4)	178	0.219
Anti-CCP antibodies (positive)*	43 (40.6)	106	155 (49.7)	312	91 (51.1)	178	0.189
Rheumatoid factor-(positive)*	49 (46.2)	106	161 (51.6)	312	98 (55.1)	178	0.354
Haemoglobin (mg/dL)	13.0 (1.3)	107	12.9 (1.3)	313	12.9 (1.2)	177	0.473
CRP (mg/L)	21.1 (32.6)	105	22.4 (36.7)	310	26.9 (35.6)	173	0.312
ESR (mm/hour)	28.5 (22.9)	106	30.1 (25.5)	309	31.7 (25.5)	175	0.568
Morning stiffness, duration, minutes	144.4 (303.0)	107	102.2 (193.7)	313	71.4 (78.1)	178	0.009
Morning stiffness intensity (VAS 0-100)	57.7 (26.8)	107	54.5 (26.8)	313	45.6 (28.0)	178	<0.001
DAS 28	5.6 (1.16)	106	5.4 (1.2)	308	5.1 (1.3)	173	0.004
HAQ score (0-3 scale)	1.3 (0.75)	107	1.1 (0.67)	308	0.85 (0.63	178	<0.001
Swollen joint count/28	8.5 (5.2)	57	8.4 (5.9)	150	8.4 (5.8)	83	0.9874
Tender joint count/28	11.9 (8.0)	57	9.6 (7.2)	150	8.3 (6.9)	83	0.0164
Physician global assessment (VAS 0-100)	59.9 (20.3)	107	54.7 (20.6)	312	47.2 (22.2)	177	<0.001
Patient global assessment (VAS 0-100)	71.7 (21.1)	107	62.9 (22.6)	312	52.7 (26.8)	177	<0.001
SF-36 bodily pain scale	64.7 (18.9)	107	55.9 (18.3)	313	55.9 (18.3)	178	<0.001
Awakenings due to arthritis	2.4 (2.9)	107	1.9 (2.6)	313	1.5 (1.9)	178	0.017
Sleep problems*	60 (76.9)	78	155 (70.8)	219	59 (50.4)	117	<0.001
MHI-5 score (psychological distress)	41.9 (19.5)	107	51.8 (19.1)	313	60.5 (17.9)	178	<0.001
Body mass index	24.9 (4.5)	106	25.3 (4.5)	309	24.1 (4.3)	177	0.015
>3 comorbidity *	47 (44.3)	106	135 (43.3)	312	67 (37.6)	178	0.402
History of thyroid problems*	10 (9.4)	107	36 (11.5)	313	22 (12.4)	178	0.730
History of diabetes*	3 (2.8)	106	10 (3.2)	312	6 (3.4)	178	0.969
Sicca symptoms*	51 (47.6)	107	96 (30.7)	313	32 (17.9)	178	<0.001
Radiographic changes *	12 (11.3)	106	47 (15.0)	312	34 (19.1)	178	0.202
Fibromyalgic RA*	30 (28.3)	107	55 (17.7)	313	20 (11.3)	178	0.001

The values are the mean (SD) unless otherwise indicated. *frequency (percentage).

raised inflammatory markers and fatigue has not been demonstrated (1-3, 14, 36, 39-41).

Moreover, fatigue can persist even after successful treatment of inflammation (19, 20, 22, 27, 36). However, it has been shown in recent trials that fatigue in RA is correlated with disease activity (24-26) and that treatment, in particular with biologic drugs, has shown improvement in fatigue (2, 26, 42-44).

Given these conflicting data, it is not possible to generate conclusions about the relationship between fatigue and disease activity in RA.

Pain is a commonly reported symptom in RA, our results showed that pain is a predictor of the high fatigue trajectory group. These findings were expected and there were in line with the pre-existing studies (1, 2, 18-20, 23, 24, 27, 45). Some authors have contended that it is pain, not disease activity, that drives fatigue in RA (2, 22); other authors have showed that, despite disease remission fatigue and pain persist (20, 37). It is clear that the two symptoms are associated; their link could be explained because the existence of a common aetiology.

We found that sicca symptoms were predictors of being in the high fatigue trajectory group. This might be related to the relation between RA with secondary Sjögren's syndrome, as fatigue is a major aspect of the disease as pain and dryness.

Perhaps the most consistent finding across studies is the correlation between fatigue and depression in RA (1, 2, 18, 21, 24, 25, 29, 46-50). Our work support that psychological distress is a predictor of been in a worst fatigue trajectory in this cohort of early RA patients. Furthermore, cause and effect have not been established, it is not possible to confirm if depression influences fatigue or *vice versa* and maybe there is a synergy between both (50, 51-55).

A major strength of this study is that it presents real-world data in early rheumatoid arthritis patients, its large, well-defined sample and its longitudinal design. These findings must be viewed in the context of some limitations.

First, we used no definite diagnostic criteria for Sjögren's syndrome (only the assertion of the rheumatologist). It is not possible to determine the impact of fibromyalgia on our results. Tender points have been traditionally used to diagnose fibromyalgia, however, this measure is not always performed in RA clinics. As Pollard *et al*. (35), we used TJC/SJC>7 to identify fibromyalgic RA. It shows a sensitivity of 80%

Table III. Predictors of trajectory membership.

	Bivariate analysis				Final model			
	High *vs*. low		Moderate *vs*. low		High *vs*. low		Moderate *vs*. low	
	OR	*p*	OR	*p*	OR	*p*	OR	*p*
Female	3.49	<0.001	1.74	0.008	3.0	0.0002	1.60	0.033
Age at disease onset, years	0.99	0.261	1.00	0.585				
Marital status (couple)	1.04	0.861	1.06	0.782				
Education level (secondary school)	2.91	<0.001	1.85	0.0017				
Menopausal	0.91	0.743	1.07	0.763				
Smoking status	1.03	0.877	1.29	0.171				
Initial pattern of the joint involvement (acute)	0.91	0.750	1.18	0.458				
Joint symptoms (symmetric)	1.27	0.340	1.02	0.958				
Oligo-polyarticular at onset	1.74	0.0859	1.92	0.0051				
Fever at RA onset	1.65	0.201	0.91	0.772				
Anti-CCP antibodies (positive)	1.53	0.085	1.06	0.758				
Rheumatoid factor (positive)	1.43	0.150	1.15	0.461				
Haemoglobin (mg/dL)	1.12	0.236	1.02	0.760				
CRP (mg/L)	0.99	0.218	0.97	0.199				
ESR (mm/hour)	0.99	0.298	0.99	0.503				
Morning stiffness, duration, minutes	1.00	0.009	1.00	0.065				
Morning stiffness intensity (VAS 0-100)	1.02	0.001	1.01	0.001				
DAS 28	1.39	0.001	1.18	0.037				
HAQ score (0-3 scale)	2.68	0.001	1.62	0.001				
Swollen joint count/28	1.01	0.876	1.00	0.912				
Tender joint count/28	1.07	0.005	1.03	0.189				
Physician global assessment (VAS 0-100)	1.03	0.001	1.02	0.001				
Patient global assessment (VAS 0-100)	1.04	0.001	1.02	0.001				
SF-36 bodily pain scale	1.05	0.001	1.02	0.001	1.03	0.001	1.02	0.005
Awakenings due to arthritis	1.16	0.006	1.09	0.044				
Sleep problems	3.28	<0.001	2.38	<0.001				
Psychological distress (MHI-5 score)	0.95	0.001	0.98	0.001	0.96	0.001	0.9	0.013
Body mass index	1.05	0.096	1.67	0.004				
>3 comorbidity	1.32	0.26	1.26	0.232				
History of thyroid problems	1.36	0.436	1.085	0.771				
History of diabetes	1.19	0.801	1.05	0.921				
Sicca symptoms	4.15	0.001	2.01	0.002	2.93	0.001	1.71	0.025
Radiographic changes	1.84	0.080	1.33	0.248				
Fibromyalgic RA	3.09	0.0018	1.68	0.0018				

and specificity of 83% for fibromyalgia (36, 37). Another limitation was the use of VAS-fatigue (the measure available at the ESPOIR cohort); VAS fatigue did not take into account the different fatigue dimensions. For futures studies, perhaps as proposed by Santos, the use of single item toll followed by multidimensional instruments could be appropriate (51).

As expected in a long-term cohort, the loss to follow-up (36% of patients at the last visit of follow-up) was a limitation of the study.

In conclusion, in a cohort of early AR patients, we identified three trajectories groups of fatigue with monotonous trajectory over 10 years of follow-up. Baseline clinical measures and baseline patient-reported measures of functional status better distinguished the three fatigue trajectories. Inflammatory activity (clinical or analytical) and positivity of Anti CCP or RF were not predictors of being in the high trajectory fatigue group.

The identification of these trajectories and its predictors in the early course of RA may warrant tailored interventions for early RA-related fatigue. Differences in specific patient or illness related aspects should be taken into consideration in formulating treatment strategies in the early course of the disease, when interventions are mosts likely to benefit the patient.

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References

1. WOLFE F, HAWLEY DJ, WILSON K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-17.
2. POLLARD LC, CHOY EH, GONZALEZ J, KHOSHABA B, SCOTT DL: Fatigue in rheumatoid arthritis reflects pain, not disease activity. *Rheumatology* (Oxford) 2006; 45: 885-9.
3. BELZA TACK B: Fatigue in rheumatoid arthritis: conditions, strategies, and consequences. *Arthritis Care Res* (Hoboken) 1990; 3: 65-70.
4. BELZA BL, HENKE CJ, YELIN EH, EPSTEIN WV, GILLISS CL: Correlates of fatigue in older adults with rheumatoid arthritis. *Nurs Res* 1993; 42: 93-9.
5. REPPING-WUTS H, VAN RIEL P, VAN ACHTERBERG T: Fatigue in patients with rheumatoid arthritis: what is known and what is needed. *Rheumatology* (Oxford) 2009; 48: 207-9.
6. OVERMAN CL, KOOL MB, DA SILVA JA, GEENEN R: The prevalence of severe fatigue in rheumatic diseases: an international study. *Clin Rheumatol* 2016; 35: 409-15.
7. PILGAARD T, HAGELUND L, STALLKNECHT SE, JENSEN HH, ESBENSEN BA: Severity of fatigue in people with rheumatoid arthritis, psoritic artrhitis and spondyoarthritis. Results of cross-sectional study. *Plos One* 2019; 14: e0211831
8. HEWLETT S, CHALDER T, CHOY E *et al*.: Fatigue in rheumatoid arthritis: time for a conceptual model. *Rheumatology* (Oxford) 2011; 50: 1004-6.
9. KIRWAN JR, MINNOCK P, ADEBAJO A *et al*.: Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. *J Rheumatol* 2007; 34: 1174-7.
10. KIRWAN JR, HEWLETT SE, HEIBERG T,

HUGHES RA, CARR M, HEHIR M: Incorporating the patient perspective into outcome assessment in rheumatoid arthritis: progress at OMERACT 7. *J Rheumatol* 2005; 32: 2250-6.
11. GOSSEC L, DOUGADOS M, RINCHEVAL N *et al*.: Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. *Ann Rheum Dis* 2009; 68: 1680-5.
12. HEWLETT SA: Patients and clinicians have different perspectives on outcomes in arthritis. *J Rheumatol* 2003; 30: 877-9.
13. RIEMSMA RP, RASKER JJ, TAAL E, GRIEP EN, WOUTERS JM, WIEGMAN O: Fatigue in rheumatoid arthritis: The role of self-efficacy and problematic social support. *Br J Rheumatol* 1998; 37: 1042-6.
14. HEWLETT S, COCKSHOTT Z, BYRON M *et al*.: Patients' perceptions of fatigue in rheumatoid arthritis: overwhelming, uncontrollable, ignored. *Arthritis Rheum* 2005; 53: 697-702.
15. REPPING-WUTS H, UITTERHOEVE R, VAN RIEL P, VAN ACHTERBERG T: Fatigue as experienced by patients with rheumatoid arthritis (RA): a qualitative study. *Int J Nurs Stud* 2008; 45: 995-1002.
16. SANDERSON TC, HEWLETT SE, FLUREY C, DURES E, RICHARDS P, KIRWAN JR: The impact triad (severity, importance, self-management) as a method of enhancing measurement of personal life impact of rheumatic diseases. *J Rheumatol* 2011; 38: 191-4.
17. REPPING-WUTS H, FRANSEN J, VAN ACHTERBERG T, BLEIJENBERG G, VAN RIEL P: Persistent severe fatigue in patients with rheumatoid arthritis. *J Clin Nurs* 2007; 16: 377-83.
18. FELDTHUSEN C, GRIMBY-EKMAN A, FORSBLAD-D'ELIA H, JACOBSSON L, MANNERKORPI K: Explanatory factors and predictors of fatigue in persons with rheumatoid arthritis: a longitudinal study. *J Rehabil Med* 2016 28; 48: 469-76.
19. MADSEN SG, DANNESKIOLD-SAMSØE B, STOCKMARR A, BARTELS EM: Correlations between fatigue and disease duration, disease activity, and pain in patients with rheumatoid arthritis: a systematic review. *Scand J Rheumatol* 2016; 45: 255-61.
20. OLSEN CL, LIE E, KVIEN TK, ZANGI HA: Predictors of fatigue in rheumatoid arthritis patients in remission or in a low disease activity state. *Arthritis Care Res* (Hoboken) 2016; 68: 1043-8.
21. WOLFE F, MICHAUD K: Predicting depression in rheumatoid arthritis: the signal importance of pain extent and fatigue, and comorbidity. *Arthritis Rheum* 2009; 61: 667-73.
22. DRUCE K, JONES GT, MACFARLANE GJ, VERSTAPPEN SMM, BASU N: The longitudinal course of fatigue in rheumatoid arthritis: results from the Norfolk Arthritis Register. *J Rheumatol* 2015; 42: 2059-65.
23. TREHARNE GJ, LYONS AC, HALE ED, GOODCHILD CE, BOOTH DA, KITAS GD: Predictors of fatigue over 1 year among people with rheumatoid arthritis. *Psychol Health Med* 2008; 13: 494-504.
24. MANCUSO CA, RINCON M, SAYLES W, PAGET SA: Psychosocial variables and fatigue: a longitudinal study comparing individuals with rheumatoid arthritis and healthy controls. *J Rheumatol* 2006; 33: 1496-502.
25. JUMP RL, FIFIELD J, TENNEN H, REISINE S, GIULIANO AJ: History of affective disorder and the experience of fatigue in rheumatoid arthritis. *Arthritis Rheum*. 2004; 51: 239-45.
26. MINNOCK P, BRESNIHAN B: Fatigue is related to poor pain outcomes in women with established rheumatoid arthritis. *Clin Exp Rheumatol* 2008; 26: 707-8.
27. RAT AC, POUCHOT J, FAUTREL B, BOUMIER P, GOUPILLE P, GUILLEMIN F: Factors associated with fatigue in early arthritis: results from a multicenter national French cohort study. *Arthritis Care Res* (Hoboken) 2012; 64: 1061-9.
28. THYBERG I, DAHLSTROM O, THYBERG M: Factors related to fatigue in women and men with early rheumatoid arthritis: the Swedish TIRA study. *J Rehabil Med* 2009; 41: 904-12.
29. NIKOLAUS S, BODE C, TAAL E, VAN DE LAAR MA: Fatigue and factors related to fatigue in rheumatoid arthritis: a systematic review. *Arthritis Care Res* (Hoboken) 2013; 65: 1128-46.
30. DRUCE KL, BASU N: Predictors of fatigue in rheumatoid arthritis. *Rheumatology* (Oxford) 2019; 58 (Suppl. 5): v29-v34
31. VAN STEENBERGEN HW, TSONAKA R, HUIZINGA TW, BOONEN A, VAN DER HELM-VAN MIL AH: Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. *RMD Open* 2015; 1: e000041.
32. COMBE B, RINCHEVAL N: Early lessons from the recent-onset rheumatoid arthritis cohort ESPOIR. *Joint Bone Spine* 2015; 82: 13-7.
33. COMBE B, BENESSIANO J, BERENBAUM F *et al*.: The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. *Joint Bone Spine* 2007; 74: 440-5.
34. RUMPF HJ, MEYER C, HAPKE U, JOHN U: Screening for mental health: validity of the MHI-5 using DSM-IV axis I psychiatric disorders as gold standard. *Psychiatry Res* 2001; 105: 243-53.
35. POLLARD LC, KINGSLEY GH, CHOY EH, SCOTT DL: Fibromyalgic rheumatoid arthritis and disease assessment. *Rheumatology* (Oxford) 2010; 49: 924-8.
36. VAN HOOGMOED D, FRANSEN J, BLEIJENBERG G, VAN RIEL P: Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. *Rheumatology* (Oxford) 2010; 49: 1294-302.
37. DRUCE KL, JONES GT, MACFARLANE GJ, BASU N: determining pathways to improvements in fatigue in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Arthritis Rheumatol* 2015; 67: 2303-10.
38. MINNOCK P, VEALE DJ, BRESNIHAN B, FITZGERALD O, MCKEE G: Factors that influence fatigue status in patients with severe rheumatoid arthritis (RA) and good disease outcome following 6 months of TNF inhibitor therapy: a comparative analysis. *Clin Rheumatol* 2015; 34: 1857-65.
39. HUYSER BA, PARKER JC, THORESON R, SMARR KL, JOHNSON JC, HOFFMAN R: Predictors of subjective fatigue among individuals with rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 2230-7.
40. BERGMAN MJ, SHAHOURI SH, SHAVER TS *et al*.: Is fatigue an inflammatory variable in rheumatoid arthritis (RA)? Analyses of fatigue in RA, osteoarthritis, and fibromyalgia. *J Rheumatol* 2009; 36: 2788-94.
41. STEBBINGS S, TREHARNE GJ: Fatigue in rheumatic disease: an overview. *Int J Clin Rheumatol* 2010; 5: 487-502.
42. GENTY M, COMBE B, KOSTINE M, ARDOUIN E, MOREL J, LUKAS C: Improvement of fatigue in patients with rheumatoid arthritis treated with biologics: relationship with sleep disorders, depression and clinical efficacy. A prospective, multicentre study. *Clin Exp Rheumatol* 2017; 35: 85-92.
43. CHAUFFIER K, SALLIOT C, BERENBAUM F, SELLAM J: Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. *Rheumatology* (Oxford) 2012; 51: 60-8.
44. WALTER MJM, KUIJPER TM, HAZES JMW, WEEL AE, LUIME JJ: Fatigue in early, intensively treated and tight-controlled rheumatoid arthritis patients is frequent and persistent: a prospective study. *Rheumatol Int* 2018; 38: 1643–50.
45. VAN DARTEL SA, REPPING-WUTS JW, VAN HOOGMOED D, BLEIJENBERG G, VAN RIEL PL, FRANSEN J: Association between fatigue and pain in rheumatoid arthritis: does pain precede fatigue or does fatigue precede pain? *Arthritis Care Res* (Hoboken) 2013; 65: 862-9
46. KATZ PP: The stresses of rheumatoid arthritis: appraisals of perceived impact and coping efficacy. *Arthritis Care Res* (Hoboken) 1998; 11: 9-22.
47. COVIC T, TYSON G, SPENCER D, HOWE G: Depression in rheumatoid arthritis patients: demographic, clinical, and psychological predictors. *J Psychosom Res* 2006; 60: 469-76.
48. TOURNADRE A, PEREIRA B, GOSSEC L, SOUBRIER M, DOUGADOS M: Impact of comorbidities on fatigue in rheumatoid arthritis patients: results from a nurse-led program for comorbidities management (COMEDRA). *Joint Bone Spine* 2019; 86: 55-60.
49. DEMMELMAIER I, PETTERSSON S, NORDGREN B, DUFOUR AB, OPAVA CH: Associations between fatigue and physical capacity in people moderately affected by rheumatoid arthritis. *Rheumatol Int* 2018; 38: 2147-55.
50. ZALLI A, JOVANOVA O, HOOGENDIJK WJ, TIEMEIER H, CARVALHO LA: Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology* (Berl) 2016; 233: 1669-78.
51. SANTOS EJF, DUARTE C, DA SILVA JAP, FERREIRA RJO: The impact of fatigue in rheumatoid arthritis and the challenges of its assessment. *Rheumatology* (Oxford) 2019; 58 (Suppl. 5): v3-v9.
52. IYENGAR RL, GANDHI S, ANEJA A *et al*.: NSAIDs are associated with lower depression scores in patients with osteoarthritis. *Am J Med* 2013; 126: 1017.e11-8.
53. SLAVICH GM, IRWIN MR: From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. *Psychol Bull* 2014; 140: 774-815.
54. DOWLATI Y, HERRMANN N, SWARDFAGER W *et al*.: A metaanalysis of cytokines in major depression. *Biol Psychiatry* 2010; 67: 446–57.
55. DIRENZO DD, CRAIG ET, BINGHAM III CO, BARTLETT SJ: Anxiety impacts rheumatoid arthritis symptoms and health-related quality of life even at low levels. *Clin Exp Rheumatol 2020*; 38: 1176-81.