



Original Article

Incidence and predisposing factors of extra-articular manifestations in contemporary rheumatoid arthritis

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ABSTRACT

Objective: Rheumatoid arthritis [RA] is a chronic inflammatory disease, with potential for extra-articular manifestations (ExRA). The incidence and predisposing factors for ExRA and the mortality were evaluated in an early RA inception cohort.

Methods: Patients ($n = 1468$; 69 % females, mean age (SD) 57.3(16.3) years) were consecutively included at the date of diagnosis, between 1 January 1996 and 31 December 2016, and assessed prospectively. In December 2016 development of ExRA was evaluated by a patient questionnaire and a review of medical records. Cumulative incidence and incidence rates were compared between 5-year periods and between patients included before and after 1 January 2001. Cox proportional hazard regression models were used to identify predictors for ExRA, and models with ExRA as time-dependent variables to estimate the mortality.

Results: After a mean (SD) follow-up of 9.3(4.9) years, 238 cases (23.3 %) had ExRA and 151 (14.7 %) had ExRA without rheumatoid nodules. Most ExRA developed within 5 years from diagnosis. Rheumatoid nodules (10.5 %) and keratoconjunctivitis sicca (7.1 %) were the most frequent manifestations, followed by pulmonary fibrosis (6.1 %). The ExRA incidence among more recently diagnosed patients was similar as to the incidence among patients diagnosed before 2001. Seropositivity, smoking and early biological treatment were associated with development of ExRA. After 15 years 20 % had experienced ExRA. ExRA was associated with increased mortality, HR 3.029 (95 % CI 2.177–4.213).

Conclusions: Early development of ExRA is frequent, particularly rheumatoid nodules. Predisposing factors were age, RF positivity, smoking and early biological treatment. The patients with ExRA had a 3-fold increase in mortality.

1. Introduction

Rheumatoid arthritis (RA) is the most prevalent of the chronic inflammatory joint diseases, with gradual destruction of joints and an increased risk of co-morbidity, predominantly cardiovascular disease. Some patients develop extra-articular manifestations (ExRA), affecting other tissues and organ systems, distinct from the co-morbidities occurring in the same organ systems [1]. In addition to increased mortality due to cardiovascular or pulmonary co-morbidity [2–4] ExRA can explain the excess mortality rates [5,6,7]. The recently defined concept of difficult-to-treat RA, affecting approximately 10 % of patients with RA, have been associated with ExRA [8,9,10]. ExRA are not limited to

rheumatoid nodules, but includes sicca syndrome, scleritis and episcleritis, pleuritis, pericarditis, cutaneous vasculitis, mononeuritis multiplex or polyneuropathy and interstitial lung disease [11].

Historically, 17.8–40.9 % of RA patients have been reported to develop ExRA [8–10] though a decline in recent years was reported in other cohorts [7,12]. A common belief has been that ExRA occur mainly in patients with long-standing and/or severe disease [13]. However, in recent studies, ExRA were shown to occur in early disease or even before the development of joint disease [1].

A history of smoking, early disability, joint erosions/destructive changes, and antinuclear antibody (ANA) or rheumatoid factor (RF) positivity, double dose of HLA-shared epitope (SE), age, higher C-

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reactive protein (CRP) and disease activity score (DAS28) at time of diagnosis have been identified as risk factors for ExRA [7,13–17].

Modern treatment strategies in RA, introduced around the turn of the millennium, with intensive treatment in early disease with the goal to rapidly achieve remission or low disease activity [18], could thus be expected to lower the incidence of ExRA. However, studies on the frequency of ExRA in patients receiving modern treatment are lacking.

The goal of this study was to provide up-to-date knowledge on the incidence of ExRA in a cohort of consecutive patients with early RA, to evaluate potential predictors for the development of ExRA and to determine if there is a decline in the incidence of ExRA as a result of modern treatment regimes. Further, the impact of ExRA on mortality was evaluated.

2. Materials and methods

2.1. Settings

The RA patients included in the study were diagnosed and followed at either one of the five rheumatology clinics in northern Sweden. All visits by the rheumatologist were registered in the same medical record at each clinic and all records were also available from all other departments, hospitals as well as visits to the general practitioners. There is only one private rheumatology practitioner in northern Sweden and the treatment and outcome of patients with RA are managed at rheumatology clinics.

2.2. Subjects and collection of clinical data

The inception cohort of 1468 patients diagnosed with early RA (symptom onset <12 months and fulfilling ACR classification criteria) [19] were consecutively included in the study at the time of RA diagnosis (index date) from 1 January 1996, when the systematic registration in the Swedish Rheumatology Register at diagnosis (index date) was opened, until 31 December 2016 [20]. Disease activity was assessed using the 28-joint count (DAS28) score, based on the number of swollen and tender joints, erythrocyte sedimentation rate, and the patients' self-reported global health [21]. In addition, C-reactive protein, Health Assessment Questionnaire (HAQ, a disability index) [22] and pharmacological treatment were systematically registered, at visits 6, 12, 18 and 24 months after diagnosis, and continuously thereafter at clinical visits scheduled at least once a year. DAS28-area under curve (AUC) were calculated using DAS28-recordings at index date, 6, 12, 18 and 24 months. Pharmacological treatment was registered from the index date and for 24 months, regarding corticosteroids and conventional synthetic disease modifying anti-rheumatic drugs csDMARDs; methotrexate, sulfasalazine, chloroquine, leflunomide, azathioprine, cyclosporine, mycophenolate mofetile, and oral or injectable gold salts, and biological (b)DMARDs; abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab, tocilizumab. The presence of RF and anti-citrullinated peptide antibody (ACPA; anti-CCP test) was analyzed in samples collected at the index date as previously described [20]. Radiographs of the hands and feet were obtained at index date ($n = 496$; 45.4 %) and at 24 months ($n = 458$; 41.9 %) and graded according to Larsen score [23]. Data on smoking habits was also collected at the index date and previous and current smoking was registered as smoking ever versus non-smoking. Demographic and clinical data are presented in Supplementary Table 1.

At the end of 2016, the patients were invited to complete a questionnaire regarding their disease progression and presence of extra-articular symptoms and signs. The questionnaire included questions and illustrations about the presence of rheumatoid nodules, keratoconjunctivitis sicca (KCS; described as dry eyes), other symptoms or signs in the eyes (e.g., red eye, pain or ache), difficulties breathing or chest pain, and different skin manifestations and/or burning pain or numbness in the legs or arms. If the answers in the questionnaires indicated any symptoms of ExRA, the patients' medical records from disease onset

were reviewed. Of the originally recruited 1468 early RA patients, 1008 early RA cases answered the questionnaire and were eligible for evaluation. Among the 460 (31.1 %) patients who did not answer the questionnaire, 200 (13.6 %) declined to participate, 247 (15.9 %) were deceased, 13 were lost to follow-up (due to wrong addresses, incorrect personal identification numbers, emigration and dementia). Thus, available medical records were reviewed for 539 of the 550 cases reporting any symptoms or signs of ExRA in the questionnaires. For approximately half of those patients reporting no symptoms, medical records were randomly chosen for review (258/458). Furthermore, medical records were available for review for 229 of the 247 deceased patients. This procedure resulted in a total of 1226 eligible individuals, and the medical records were reviewed for 1026. (The patient population is visualized in Fig. 1). The patients were followed until December 31 2016, or lost of follow-up or death. The mean (SD) follow-up for all included individuals was 9.3 (4.9) years.

The time point for any ExRA manifestation was continuously registered and evaluated from the medical records. To be confirmed as ExRA in the review of the medical records, rheumatoid nodules had to be registered by a rheumatologist, eye manifestations had to be diagnosed by an ophthalmologist, pleuritis was diagnosed by clinical symptoms and an X-ray confirming exudate, pericarditis by echocardiography, cutaneous vasculitis manifestations by a biopsy and involvement of peripheral nerves or muscles by neurography/electromyography. Interstitial lung disease and/or pulmonary fibrosis (PF) was diagnosed by a reduction in the vital capacity or diffusion capacity by >15 % from normal and findings from high resolution computed tomography [11, 24].

In the questionnaire 550 of 1008 (56.0 %) patients with early RA reported symptoms or signs of ExRA. The review of the medical records indicated over-reporting of all ExRA manifestations with the exception of PF (Supplementary Table 2). Among patients reporting no ExRA symptoms ($n = 458$), reviews of the medical records of 56 % of them revealed 11 (4 %) cases with ExRA: 4 with rheumatoid nodules, 6 diagnosed with KCS, and 1 pleuritis.

The study was approved by the Regional Ethics Committee of Umeå University, Umeå, Sweden (Dnr 2016–326–32 M).

2.3. Statistical analysis

Statistical analyses were performed using R software [25] version 3.5.0, and SPSS 25.0 (IBM USA). Descriptive data were presented as proportions, means (standard deviation (SD)), and medians (Inter quartile range (IQR)) as appropriate. Frequencies were compared using chi-squared test. The Student's *t*-test and non-parametric tests were used for continuous data. The exact date when an ExRA appeared was difficult to define; thus, the calendar year when it was diagnosed was used in the analyses and event was set to December 31 that particular year for the presence of ExRA. Censoring times were treated similarly. As death is a competing risk for ExRA, all Cox proportional hazard (CPH) models described are cause-specific models. Probability-in-state estimates were obtained using the Aalen-Johansen estimator, accounting for death as competing risk. Two definitions of ExRA were used: one including all manifestations (ExRA), and one not including the presence of rheumatoid nodules as ExRA (ExRA except nodules). Associations between different ExRA and predictors in the CPH regression analysis are presented as hazard ratio (HRs) with 95 % confidence intervals (CIs). As an initial illustration, simple CPH regression models were fitted for each predictor separately using ExRA as outcome, before fitting multivariable models. All multivariable models included sex, smoking habits, RA onset age, ACPA, RF, disease activity during the first 24 months summarized by the calculated area under the curve for DAS28 (DAS28-AUC₂₄), disability (HAQ-AUC₂₄) and treatment with bDMARDs during the first 24 months after index date (bDMARDs₂₄) as predictors. The multivariable models were investigated for violations of the proportional-hazards assumption and time-stratified if needed. Collinearity was investigated

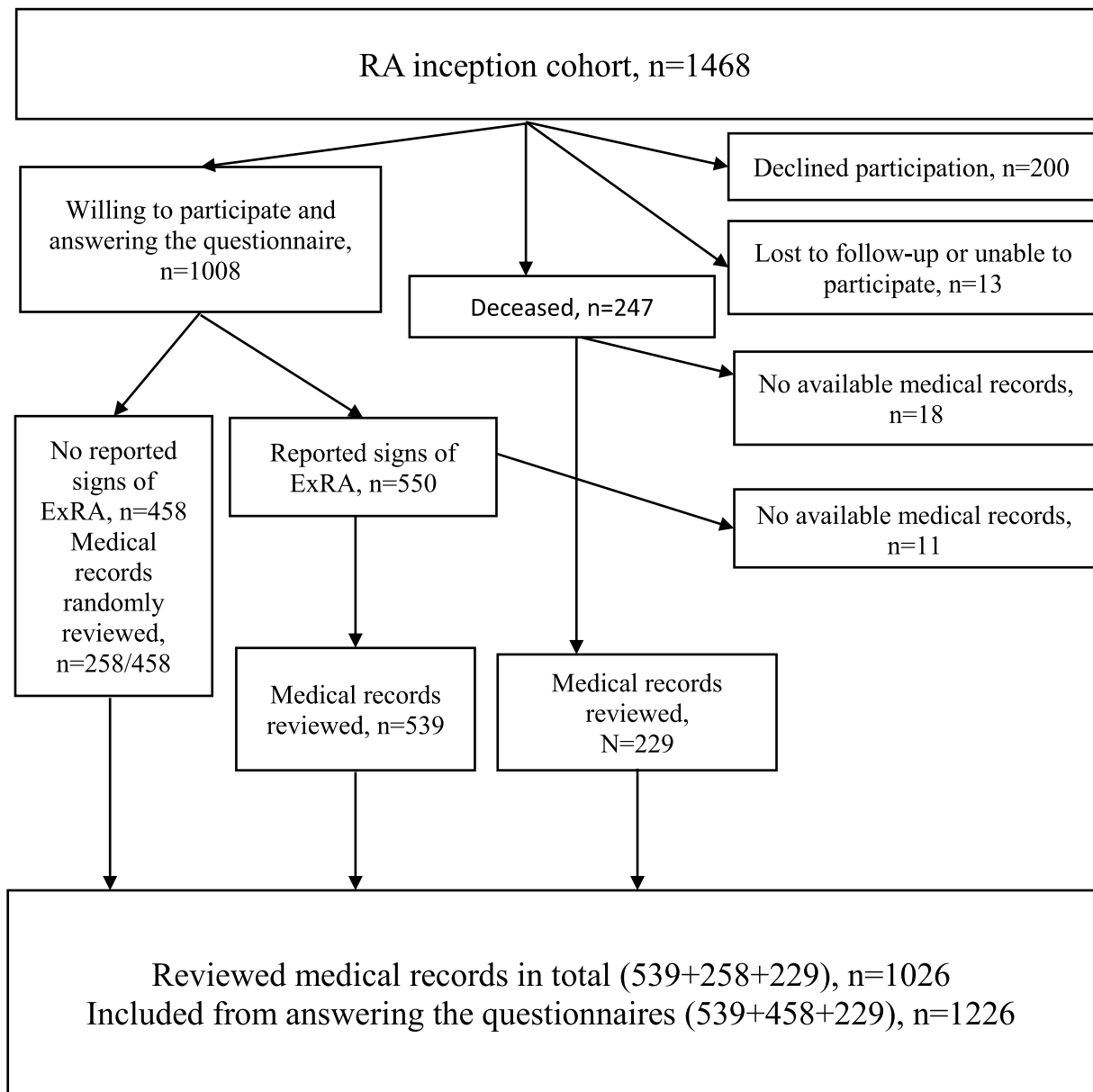


Fig. 1. Flow chart of the cases included from the inception cohort 1 Jan 1996 until 31 Dec 2016.

using the Variance Inflation Factor (VIF). The patients were stratified according to index date; patients included between 1 January 1996 and 31 December 2000 (Cohort 1) or inclusion 1 January 2001 and end of study 31 December 2016 (Cohort 2) based on the introduction and general use of treatment with bDMARDs. Of the cases answering the questionnaires ($n = 1226$), 1023 belonged to Cohort 2.

For analysis of mortality in relation to ExRA, we use extensions of the Cox regression model to allow for time-dependent covariates and multi-state models, respectively. Both extensions rely on the so-called counting process formulation of time-to-event data, for thorough theoretical treatment [26] and Meira-Machado et al. [27] for an introduction using medical applications. The multi-state model treats ExRA as an intermediate step in progression to the “deceased” state and allows us to investigate transition intensities between states. In a complementary analysis we treat ExRA as a time-dependent covariate to investigate the direct association between ExRA and mortality.

Investigating missingness patterns revealed that 15 % of our subjects had incomplete data for at least one covariate. Consequently, we performed the CPH regression analysis using multiple imputation of

missing covariates as outlined in White & Royston [28] using the cumulative hazard function instead of time-to-event along with all other available information in the imputation models. Multiple imputation was performed using the *mice* package, version 3.14 [29], in R, (v.4.0.2). We performed 20 imputations using default settings. Results were considered significant if $p < 0.05$.

3. Results

In this longitudinal study of an inception cohort with patients with early RA and a mean follow-up from disease onset of 9.3 (SD 4.9) years ExRA was confirmed in 19.4 % ($n = 238$) of the 1226 cases with 1–4 manifestations per patient. The corresponding frequency of ExRA except nodules was 12.3 % ($n = 151$). A total of 238 first events of ExRA resulted in an incidence rate of 23.5/1000 person-years at risk (pyar) and a corresponding incidence rate for ExRA except nodules ($n = 151$) of 17.2/1000 pyar.

Patients treated with bDMARDs within the first 24 months had higher DAS28-AUC₂₄ (94.2 vs. 81.6, $p < 0.001$). We found no significant

differences in demographic or clinical data between those answering the questionnaires, confirmed from medical records, or declining to participate except for lower age at diagnosis in the latter group (Supplementary Table 1).

Analyses of incidence rates for intervals of disease duration after RA onset showed the numerically highest incidence rate for ExRA during the first 5 years of disease, 29.7/1000 pyar. During the second time period, >5–10 years after RA onset, the incidence rate for ExRA was 6.7/1000 pyar, and for the time period >10 years after RA onset, the incidence rate was 4.4/1000 pyar. The corresponding incidence rates for ExRA except nodules were; 16.8/1000 pyar, 4.9/1000 pyar, and 2.8/1000 pyar (data not shown).

Evaluation of the cumulative incidence of ExRA in 5-year periods of disease duration showed that already during the first 5 years after disease onset of RA, ExRA was present in 12.1 % of patients (Fig. 2). During the second 5-year period (>5–10 years of disease duration), 16.0 % of the early RA patients had developed ExRA and during the third 5-year period (>10–15 years), 18.7 %. Among patients followed for 15 years after disease onset the cumulative incidence of ExRA increased up to 23.3 % and of ExRA except nodules, up to 14.7 % (Fig. 2).

At first presentation of ExRA 10.9 % (26/238) had more than one manifestation, and 4.2 % (10/238) developed other manifestation(s) during a mean of 4 years after the first manifestation. Rheumatoid nodules, KCS and PF were the most frequent ExRA manifestations and were also the earliest to be observed during the disease course, 6.5–13.9% were present already at index date (Table 1). The cumulative incidence of the each ExRA manifestation is visualized in Fig. 2.

Early development of rheumatoid nodules diagnosed within the first 5 years after the index date, 78/228 (34.2 %), did not predict later development of other ExRA (OR=1.16, 95 %CI 0.57, 2.36). However, the presence of rheumatoid nodules and pleuritis was significantly more frequent in patients with PF (20.8% vs. 10.1 %, $p = 0.016$ and 5.9% vs. 1.1 %, $p = 0.005$, respectively).

No significant differences in the frequencies of ExRA were observed after stratification by year of inclusion: In Cohort 1 (included between 1 January 1996 and 31 December 2000, $n = 203$) 12.3 % developed ExRA during the first 5 -years after inclusion vs. 13.0 % in Cohort 2 (included 1 January 2001 or later). The corresponding results for ExRA except nodules were 4.9 % in Cohort 1 and 7.0 % in Cohort 2. Comparisons of clinical and demographic data between Cohort 1 and Cohort 2 showed a higher frequency of RF and of DAS28-AUC₂₄ in Cohort 1. Patients included in Cohort 2 were more extensively treated compared with

Table 1

Duration since diagnosis for the observation of extra-articular manifestations (ExRA) in patients with early RA ($n = 238$) with the time point for the manifestations to appear, at the index date and after index date. Presented as median (IQR) time for extra articular manifestations.

	N total	ExRA present at index date, n (%)	Disease duration at observation after index date, median (IQR), years
Rheumatoid nodules	108	7 (6.5)	3.5 (6)
KCS	72	10 (13.9)	4 (6.25)
Pulmonary fibrosis	53	6 (11.3)	4 (6)
Pleuritis	15	1 (6.7)	5.5 (9.25)
Neuropathy/ Polyneuropathy	12	1 (8.3)	4.5 (6.25)
Episcleritis/scleritis	7	–	8 (7)
Painful ulcers/ vasculitis	7	1 (14.3)	8 (8)
Pericarditis	2	–	0.38 (0.25)

earlier included patients; treatment with corticosteroids at the index date was noted in 62.5 % of the patients versus 50.8 % in Cohort 1, and methotrexate was started at the index date in 82.6% vs. 62.0 %. Treatment with bDMARDs within 24 months from the index date was noted in 5.3 % of patients in Cohort 1 and 13.0 % in Cohort 2 (Supplementary Table 3).

In simple Cox regression models in Cohort 2, age at onset, RF or ACPA positivity, ever being a smoker, DAS28-AUC₂₄, bDMARD₂₄ treatment started within the first 24 months, and HAQ-AUC₂₄ were associated with ExRA (Table 2). In the corresponding analyses of the patients included in Cohort 1 only age at index date was significantly associated with the development of ExRA (HR=1.027, 95 %CI 1.008, 1.046, $p = 0.006$, data not shown).

In multiple Cox proportional hazard regression analysis, (Table 2), development of ExRA was associated with age at onset, RF positivity at index date, being ever smoker and bDMARDs within the first 24 months of the disease (Table 2). For the corresponding analyses of the development of ExRA except nodules, associations were observed with age at onset, and bDMARDs₂₄ (Table 2). ACPA was only significantly associated with ExRA in the simple model (Table 2). For the validated cases the same predictors were identified in the multiple Cox proportional hazard regression analysis for ExRA and ExRA except nodules in Cohort 2 (Supplementary Table 4). For ExRA, the proportional hazards test indicated a deviation from proportionality for the bDMARD variable.

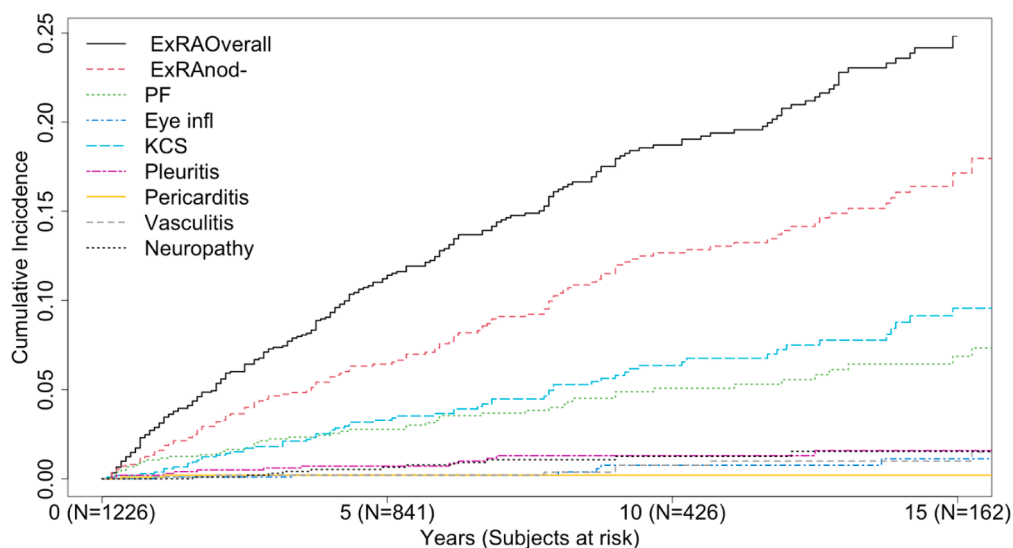


Fig. 2. Cumulative incidence of ExRA (ExRAOverall), ExRA except nodules (ExRA nod-) and each manifestation separately in patients with early RA ($n = 1226$). The number of individuals at risk during the follow up is presented on the X-axis.

Table 2

Cox hazard regression analyses of disease related factors in patients in Cohort 2 (1 Jan 2001–31 Dec 2016) for the development of ExRA with and without nodules as dependent variable in simple Cox regression (a) and in multiple variable model (b).

ExRA with nodules								
Variables	a) Simple models				b) Multiple model			
	HR	95 % lower	95 % upper	p	HR	95 % lower	95 % upper	p
Age at onset, Years	1.022	1.009	1.035	0.001	1.030	1.014	1.046	<0.001
Sex, female	0.951	0.684	1.321	0.765	1.076	0.728	1.592	0.712
RF positivity	2.444	1.596	3.743	0.000	2.080	1.242	3.481	0.005
ACPA positivity	1.918	1.319	2.790	0.001	1.487	0.940	2.352	0.090
Ever smoker, yes/no	1.507	1.082	2.098	0.015	1.730	1.174	2.550	0.006
DAS-AUC ₂₄ ¹	1.009	1.002	1.015	0.012	1.001	0.993	1.009	0.849
bDMARDs ₂₄ ²	2.027	1.415	2.904	<0.001	2.230	1.445	3.443	<0.001
HAQ-AUC ₂₄ ³	1.017	1.002	1.032	0.027	1.007	0.988	1.027	0.464
ExRA except nodules								
Variables	a) Simple models				b) Multiple model			
	HR	95 % lower	95 % upper	p	HR	95 % lower	95 % upper	p
Age at onset, Years	1.032	1.015	1.050	<0.001	1.043	1.022	1.064	<0.001
Sex, female	1.212	0.777	1.891	0.397	1.359	0.806	2.293	0.250
RF positivity	1.504	0.939	2.411	0.090	1.373	0.717	2.629	0.339
ACPA positivity	1.289	0.833	1.995	0.255	1.151	0.624	2.121	0.653
Ever smoker, yes/no	1.257	0.834	1.895	0.274	1.548	0.947	2.531	0.082
DAS-AUC ₂₄ ¹	1.014	1.006	1.022	0.001	1.002	0.991	1.012	0.743
bDMARDs ₂₄ ²	2.268	1.426	3.607	0.001	2.621	1.485	4.627	0.001
HAQ-AUC ₂₄ ³	1.026	1.009	1.042	0.002	1.013	0.989	1.036	0.292

RF=rheumatoid factor. ACPA= anti- citrullinated peptide antibody. 1 DAS28-AUC₂₄ = DAS28 during the first 24 months summarized by the calculated area under the curve. 2 bDMARDs₂₄ = biological treatment during the first 24 months after the diagnosis of RA. 3 HAQ-AUC₂₄=HAQ during the first 24 months summarized by the calculated area under the curve.

Looking at the martingale residual plot, the departure from proportionality appeared to occur at 10 years (120 months). Thus, we performed a control analysis where the effect of bDMARD was stratified at below or above 120 months. The resulting HRs for below and above 120 months were 2.241 (95 %CI: 1.445–3.474) and 3.344 (95 %CI: 1.340–8.345) respectively.

Results from the analyses with multiple imputation data of covariates are presented in Supplementary Table 5. We found similar association patterns as the complete case analyses except for smoking, which was not significantly associated with any of the outcomes.

Separate analysis for PF identified only age at onset and bDMARD₂₄ as being associated with development of PF, and borderline significance for being ever smoker presented in Table 3. Separate analysis for KCS identified bDMARD₂₄ as being associated with development of KCS.

ExRA was associated with a three-fold increase of mortality, HR 2.952 (95 %CI: 2.188–3.982) in a model adjusted for age and sex, and HR 3.029 (95 %CI: 2.177–4.213) in a fully adjusted model (RF and ACPA positivity, ever being a smoker, DAS28-AUC₂₄, bDMARD₂₄, and HAQ-

AUC₂₄). In a visualisation of the multi-state model (Fig. 3a) the mortality curve after ExRA describes a steeper increase than the mortality without previous ExRA (Fig. 3b).

4. Discussion

In this cohort study of patients with early RA, up-to 20 years, more than 20 % of the patients developed ExRA over a mean (SD) follow-up of 9.3 (4.9) years. The highest incidence rate of ExRA was observed early, already within the first 5-years of disease. We found no evidence of a decreasing incidence of ExRA in patients diagnosed with RA after 2001. Age at disease onset, RF and ACPA positivity, smoking habits and early treatment with bDMARD were associated with ExRA development, and ExRA was associated with an increased risk of death.

The frequency of ExRA in this study was in line with previous publications [12,21,30] but most previous studies were retrospective and included cases diagnosed during the 1980 and until 2007 [7,12,14,30]. Furthermore, only a few of the studies included patients at the time of

Table 3

Cox hazard regression analyses of disease related factors in patients in Cohort 2 (1 Jan 2001–31 Dec 2016) for the development of the two most frequent ExRA, pulmonary fibrosis and keratoconjunctivitis sicca, (besides rheumatoid nodules) in multiple variable model in 1223 subjects.

Variables	Pulmonary Fibrosis Multiple model				Keratoconjunctivitis sicca Multiple model			
	HR	95 % lower	95 % upper	p	HR	95 % lower	95 % upper	p
Age at onset, years	1.080	1.047	1.114	<0.001	1.038	1.007	1.069	0.016
Sex, female	1.411	0.639	3.119	0.394	2.499	0.950	6.578	0.064
RF positive	1.986	0.706	5.588	0.193	1.767	0.755	4.136	0.189
ACPA positive	1.018	0.409	2.531	0.970	0.829	0.406	1.694	0.608
Ever smoker, yes/no	2.336	0.955	5.713	0.063	1.736	0.845	3.569	0.133
DAS28-AUC ₂₄ ¹	1.002	0.986	1.018	0.806	0.989	0.971	1.007	0.218
bDMARDs ₂₄ ²	3.737	1.472	9.486	0.006	3.697	1.706	8.010	0.001
HAQ-AUC ₂₄ ³	1.011	0.979	1.045	0.501	1.040	1.009	1.072	0.010

RF=rheumatoid factor. ACPA= anti- citrullinated peptide antibody.

¹ DAS28-AUC₂₄=DAS28 during the first 24 months summarized by the calculated area under the curve.

² bDMARDs₂₄ = biological treatment during the first 24 months after the diagnosis of RA.

³ HAQ-AUC₂₄=HAQ during the first 24 months summarized by the calculated area under the curve.

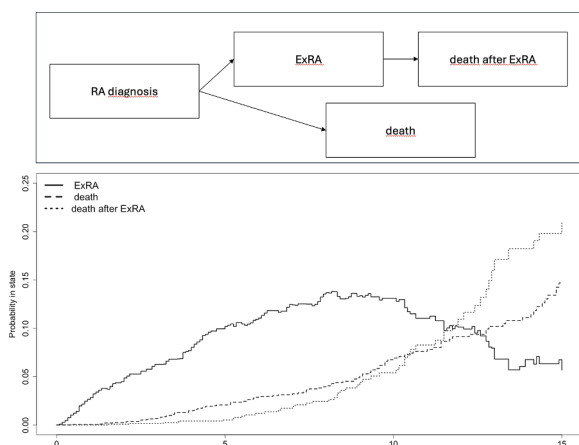


Fig. 3. a. Schematic description of the states in the multi-state model for mortality in the cohort.
b. Multi-state model for mortality in the cohort describing the probability in state at each time-point until 15 years after RA diagnosis.

RA onset and, in some of the studies, comorbidities were also included. In this study, we focused on ExRA defined according to Turesson et al. [11,24] including PF but not manifestations generally defined as comorbidities. A 15-years follow-up study reported much higher cumulative incidence (64.1) as two other reports (40.6 % and 47.5 %, respectively) [11,31,32]. The highest incidence of ExRA already during the first 5-years of disease has not been evident in previous studies. In contrast to others [33], the presence of rheumatoid nodules early during the disease course in our cohort did only predict the development of a second ExRA later (mean 4 years) in 4.2 %. 10.9 % had more than one manifestation at the same time of first ExRA. However, patients with PF had rheumatoid nodules or pleuritis significantly more often than expected. Clustering of rheumatoid nodules with other ExRA manifestations have been suggested [34]. We think that patients with early, less severe ExRA, such as rheumatoid nodules, benefitted from the intensive treatment strategies of modern rheumatology, and that the development of more severe ExRA had been halted. This may not be the case for PF, which seems to occur at the same frequency throughout different early studies [7]. The frequencies of the different ExRA were lower in our cohort than in others [7], with the exception of PF. It is unclear whether this difference can be explained by differences in the cohorts as such or the methods to capture the outcomes, but there was also a difference in treatment strategies, as our population had a higher exposure rate for both methotrexate and bDMARDs [7]. The disease activity as measured by DAS-AUC₂₄ was significantly related to treatment with bDMARDs, and bDMARDs were significantly associated with ExRA. The high intensity of treatment early in the disease course in our cohort indicates good compliance with the Swedish National RA treatment guidelines [35]. The use of advanced therapeutic treatments has been suggested to affect the occurrence of ExRA, such as vasculitis [36,37], and more intense therapy could have affected the pattern of ExRA occurrence in recent years. Interestingly, we also found an indication of early bDMARD treatment being associated with an increased risk of ExRA later in the disease course.

There were some differences regarding possible predictors of ExRA between analyses including all patients answering the questionnaires and analyses limited to patients for whom the presence/absence of ExRA was validated. Similarly, the associations between ExRA except nodules and RF in simple models could not be observed in the smaller cohort of validated absence/presence of ExRA. The probable lower frequency of ExRA among the patients with no reported ExRA in Cohort 2, and with lower frequencies of RF, increased the power when also these patients were included in the models.

These findings are partly in line with previously reported risk factors,

as RF, smoking, and high disease activity, as well as male sex and positivity for ANA in some studies, have been found to be associated with ExRA [14,30,33,37,38]. In this study no significant association was found with sex. We lack data on ANA for comparisons between the studies. Positivity for ACPA, a marker of more severe disease, was related to ExRA in simple analysis and lost in multiple analysis. However, development of ExRA in our study, as well as in other studies, was clearly related to the presence of active and severe RA [14], although the association with HAQ-AUC₂₄ was lost in the multiple variable analysis. We found a significant relationship between disease activity measured as DAS-AUC₂₄ and treatment with bDMARDs.

In coherence with previous studies [5–7] we found ExRA to be associated with increased mortality. The numerically higher risk of death in our study could be related to methodological differences, but also a slower decrease in mortality over the years among patients with a more severe RA compared with patients with a more favourable disease course.

In this study we found higher age at disease onset to be a strong risk factor associated with ExRA. Due to the designs of other studies, age at onset has hardly ever been evaluated. We and others have also shown that older patients receive less intensive treatment for RA [39]. In the present study, younger individuals were more often treated with bDMARDs compared with the elderly. If less intensive treatment strategies result in more active disease, this could explain the importance of age. However, we cannot rule out that higher age increases the risk of ExRA due to a higher frequency of comorbidities and increased vulnerability for ExRA.

The agreement between patients reporting ExRA and confirmed medical records of manifestations of ExRA varied. For most manifestations, the patients reported much higher rates of signs and symptoms of ExRA than what was later confirmed in a review of the medical records, except for PF, which was underestimated. We used an extensive and illustrated questionnaire, but from the reporting pattern we draw the conclusion that patient reporting of ExRA through forms cannot be recommended to identify ExRA and does not make thorough record reviews any less necessary.

A strength of the present study was that the cohort of early RA patients being unselected subsequently included, originate from a homogenous population of northern Sweden. Almost all individuals, (84 %) of those diagnosed with early RA since 1996 and who were younger than 80 years of age within the catchment area of northern Sweden were willing to participate in this study. Another strength is that we have chosen a rather strict definition of ExRA [11,24] and have not included all types of co-morbidities.

There are also limitations to this study. The ExRA were not registered continuously but had to be confirmed retrospectively through the medical records. This also made complementary analyses or in-depth and targeted interviews impossible. The quality of clinical ascertainment of ExRA was high but the diagnosis is dependent on awareness from the patients and/or treating physician. Better awareness of ExRA in later years, as well as a risk for under reporting due to recall bias by patients with long disease duration, could affect the rate of ExRA, which in part was compensated by the review of medical records. The use of a questionnaire for identification of ExRA was not as helpful as expected. Furthermore, not all medical records were available for review. These limitations may influence the number of ExRA, especially less severe manifestations.

In conclusion, in our cohort of patients with RA diagnosed 1996–2016 more than one out of five patients developed ExRA, with the highest incidence rate within 5 years from the diagnosis. Factors related to disease severity such as RF, ACPA, smoking habits, and age, were risk factors for ExRA, as was early treatment with bDMARDs. The incidence rates were similar for patients diagnosed with RA before and after 1 January 2001. The results of this study indicate that ExRA are still an important cause of morbidity and mortality in RA and the risk of ExRA development needs to be taken into consideration from the time of

diagnosis in patients with negative prognostic factors.

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Statement of ethics and consent

The study was approved by the Regional Ethics Committee of Umeå University, Umeå, Sweden (Dnr 2016–326–32 M).

The participants have given their written consent to the participate in the study.

Declaration of competing interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ejim.2024.04.026](https://doi.org/10.1016/j.ejim.2024.04.026).

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