Occurrence of Extraarticular Disease Manifestations Is Associated with Excess Mortality in a Community Based Cohort of Patients with Rheumatoid Arthritis

CARL TURESSON, W. MICHAEL O'FALLON, CYNTHIA S. CROWSON, SHERINE E. GABRIEL, and ERIC L. MATTESON

ABSTRACT. ***Objective.*** To investigate the occurrence of extraarticular manifestations (ExRA) in a well defined community based cohort of patients with rheumatoid arthritis (RA), and to examine their effect on mortality.

Methods. Using the resources of the Rochester Epidemiology Project, a retrospective medical record review was conducted of a cohort of 424 cases of RA in Olmsted County, MN, USA, diagnosed during the period 1955–1985. These cases had been classified using the American College of Rheumatology 1987 criteria for RA. Patients were followed 1955–1998 (median followup 14.8 yrs; range 0.2–42.8 yrs), and incident ExRA manifestations were recorded according to predefined criteria. Data on comorbidities were extracted using the definitions of the Charlson comorbidity index. Survival was compared to the general population using Kaplan-Meier estimates.

Results. ExRA occurred in 169 patients, corresponding to an incidence rate of 3.67/100 person-yrs. Compared to the general population, survival among patients with RA was decreased. Survival among patients with ExRA was markedly decreased compared to the general population and to patients without ExRA ($p < 0.001$). A particularly poor prognosis was noted in a subgroup of 63 patients (incidence rate 1.04/100 person-yrs) who fulfilled predefined criteria for severe ExRA (i.e., vasculitis, pericarditis, pleuritis, and/or Felty's syndrome). For RA patients who did not fulfill these criteria, there was no significant increase of mortality ($p = 0.09$). In a multivariate model of mortality, including age, sex, and the presence of known comorbidities, the presence of one or more of these ExRA was the strongest predictor of mortality.

Conclusion. In this first community based study of extraarticular manifestations in RA, virtually all the excess mortality occurred in a subgroup of patients with severe extraarticular disease, suggesting that extraarticular disease is the major predictor of mortality in patients with RA. (J Rheumatol 2002; 29:62–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
MORTALITY
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Rheumatoid arthritis (RA) is a chronic disease characterized by inflammatory polyarthritis and systemic features. It is associated with an increased mortality compared to the general population[1-6]. A high number of involved joints and poor functional status have consistently been found to predict mortality in RA[6-8], whereas response to methotrexate treatment may be associated with improved survival[9]. Mortality in patients with extraarticular manifestations (ExRA) has been reported to be increased compared to RA patients in general in most[10-15] but not all studies[16]. The problem of referral bias when studying this aspect at major research centers has been underlined[17].

Previous surveys of ExRA have studied consecutive RA patients from clinical centers. Due to the variations in case definitions and in selection of the patients studied, comparisons between different studies are of limited value. Investigations using previously applied criteria in new, well defined populations are of major importance.

We investigated the occurrence of extraarticular manifestations in RA and their impact on mortality in a well defined population. We studied a community based cohort of RA patients from Rochester, Minnesota, utilizing inclusion criteria for extraarticular RA that have been used in part in other studies[15,18].

MATERIALS AND METHODS

The population of Rochester, Minnesota, is well suited for investigation of the epidemiology of RA and associated extraarticular features, because comprehensive medical records for all residents seeking medical care are available.

From Malmö University Hospital, Lund University, Malmö, Sweden; and Mayo Clinic and Mayo Graduate School of Medicine, Rochester, Minnesota, USA.

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C. Turesson, MD, Department of Rheumatology, Malmö University Hospital; W.M. O'Fallon, PhD; C.S. Crowson, BS; S.E. Gabriel, MD, MSc, Department of Health Sciences Research; E.L. Matteson, MD, MPH, Divison of Rheumatology, Mayo Clinic and Mayo Graduate School of Medicine.

Address reprint requests to Dr. C. Turesson, Department of Rheumatology, Malmö University Hospital, S-205 02 Malmö, Sweden.
E-mail: Carl.Turesson@telia.com

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A record linkage system allows ready access to the medical records from all health care providers for the local population, including the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Group, the Olmsted Community Hospital, local nursing homes, and the few private practitioners. The potential of this data system for use in population based studies has been described[19,20]. This system ensures virtually complete ascertainment of all clinically recognized cases of RA among the residents of Rochester, Minnesota.

In a previous survey[21], all cases of RA diagnosed in the period January 1, 1955, to January 1, 1985, (N = 425) were identified using the computerized diagnostic index and a revision of the complete medical record in each potential case. The incidence date was defined as the earliest date at which the patient fulfilled ≥ 4 of the 1987 American College of Rheumatology (ACR) classification criteria for RA[22]. This study was undertaken as part of further characterization of the RA cohort.

Using a structured protocol, the complete medical records of 424/425 of these patients (one patient refused research authorization) were reviewed by one of the authors (CT), and extraarticular manifestations were identified according to predefined criteria (Table 1). The criteria for severe disease manifestations (Table 1; criteria 1–8) were based on those used in a previous study of occurrence of ExRA[15], in which they were found, as a group, to identify patients with a poor survival. To assess the occurrence of rheumatoid pericarditis during the time period before echocardiography was available, the criteria for pericarditis were modified to include other methods of investigation, in accord with the definitions used in another longterm study of pericarditis[12]. In the present study, further ExRA manifestations (Table 1; criteria 9–17) were also investigated. The criteria for Sjögren's syndrome have been used to identify cases of primary and secondary SS in epidemiological surveys[23,24]. All cases of suspected ExRA were separately reviewed by a second investigator (EM), with concordant results. In addition, a random sample of 30 cases from the source cohort were independently revised by 2 investigators (CT and EM), also with concordant results. The patients were followed from January 1, 1955, until December 31, 1998, or until death or loss to followup (median followup 14.8 yrs, range 0.2–42.8). For patients who moved away from the area, the date of the last physical examination noted in the case record was used as the date of loss to followup. The date of fulfillment of the criteria for ExRA was noted, as well as the date of death according to the death certificate. The cumulative incidence of ExRA was calculated, adjusted to the followup time, and presented as 30-year cumulative incidence data. Data on comorbidities were extracted using the Charlson comorbidity index[25].

The Kaplan-Meier product limit method was used to estimate survival from diagnosis of RA in this cohort[26]. Overall survival analysis involved fol-

Table 1. Criteria for inclusion as extraarticular manifestations of RA.

1. Pericarditis	A. Clinical judgment and exudation verified by echocardiography If ultrasound not available: Criteria according to Hara, *et al*[12]. B. Clinical criteria (1 required): Typical pericardial pain, peripheral edema, dyspnea/orthopnea, ascites, dysrythmia (heart rate > 140/min, atrial flutter/fibrillation, 2–3 degree atrioventricular block, ventricular tachycardia Objective criteria compatible with pericarditis (1 required): Physical examination, cardiac catheterization findings, histologic examination Other causes improbable, such as tuberculosis or other infection, metastases, primary tumor, postoperative status, or other trauma
2. Pleuritis	Clinical suspicion and exudation verified by radiograph Other causes improbable, such as tuberculosis or other infection, metastases, primary tumor, postoperativer status, or other trauma
3. Felty's syndrome	Splenomegaly (clinically evident or measured by ultrasound) and neutropenia ($< 1.8 \times 10^9$/l) on 2 occasions Other causes improbable, such as drug side effect or infection
4. Major cutaneous vasculitis	Diagnosed biopsy or clinical judgment by dermatologist
5. Neuropathy	Clinical judgment by physician and signs of polyneuropathy/mononeuropathy at electromyography/electroneurography
6. Scleritis, episcleritis, or retinal vasculitis.	Clinical judgment by ophthalmologist
7. Glomerulonephritis	Clinical judgment by nephrologist and positive biopsy
8. Vasculitis involving other organs	Clinical judgment by organ specialist and biopsy compatible with vasculitis
9. Amyloidosis	Clinical judgment and positive biopsy from affected organ
10. Keratonconjunctivitis sicca	Clinical judgment; positive Rose-Bengal staining or result of Schirmer's test < 5 mm/min
11. Xerostomia	Clinical judgment; abnormal sialometry, sialography, or salivary scintigraphy, or salivary gland biopsy with lymphocytic infiltrate
12. Secondary Sjögren's syndrome	Two of three criteria: Keratonconjunctivitis sicca (see above), xerostomia (see above), serological evidence: rheumatoid factor, ANA, anti-Ro (SS-A)/anti-La (SS-B) positive, or hypergammaglobulinemia
13. Pulmonary fibrosis	Clinical judgment *and* decreased vital capacity or DLCO by 15% from normal
14. Bronchiolitis obliterans organizing pneumonia	Clinical judgment by pulmonologist
15. Cervical myelopathy	Clinical judgment and increased atlantoaxial movement—verified by radiograph
16. Subcutaneous rheumatoid nodules	Clinical judgment
17. Rheumatoid nodules in other locations	Positive biopsy

lowing all patients from diagnosis of RA to death or loss of followup. The expected survivorship was based on the sex and age of the study population and death rates from the United States (Caucasian populations) life tables. To estimate survival among patients without ExRA, followup of those patients who developed ExRA prior to death was censored at diagnosis of ExRA. Estimation of survival from RA diagnosis of patients who developed ExRA began with those few who had such manifestations at diagnosis of RA, with those who developed ExRA subsequently entering the Kaplan-Meier calculations at a followup time corresponding to the number of days from RA diagnosis to ExRA diagnosis[26]. As the analysis considered the effect of extraarticular disease on subsequent survival, the patients remained in the ExRA group at all times after first presentation of ExRA, regardless of the duration of signs and symptoms of ExRA. Cox proportional hazards modelling was used to examine the effects of age, sex, and rheumatoid factor (RF) positivity on survival. ExRA (criteria 1–8), nodules, and comorbidities (heart disease, liver disease, chronic obstructive pulmonary disease, malignancy, and dementia) were examined in these models as time-dependent covariates. Bootstrap sampling[27] was used to validate variable selection and interaction among the significant main effects examined.

RESULTS

The RA cohort consisted of 312 women and 112 men. The median age at diagnosis was 60.0 years. The median followup period was 14.8 years (range 0.2–42.8). During the followup period, 169 patients developed extraarticular manifestations, corresponding to an overall incidence rate of 3.67/100 person-years at risk (3.65/100 person-years in male patients and 3.68/100 person-years in females). The 30-year cumulative incidence of any ExRA was 57.1% (standard error 3.8%). The 30-year cumulative incidence of rheumatoid nodules was 39.4% (SE 3.6%), secondary Sjögren's syndrome 17.1% (SE 3.0%), and pulmonary fibrosis 9.4% (SE 2.1%). The cumulative incidence of each ExRA is noted in Table 2. A subgroup of 63 patients (30-year cumulative incidence 26.8%, SE 3.6%) fulfilled the criteria for severe ExRA (ExRA Malmö) used in the Malmö ExRA study[15], corresponding to an incidence rate 1.04/100 patient-years (1.33/100 in men, 0.94/100 in women). There was no significant change in the incidence of ExRA Malmö over the decades studied (data not shown).

There were 288 deaths during the followup period. Mortality was increased in the RA cohort as a whole compared to the general US population ($p < 0.001$). A particularly poor survival was noted in the subgroup of patients with ExRA Malmö ($p < 0.001$ vs expected) (Figure 1). There was no significant increase of mortality in RA patients without ExRA ($p = 0.9$) or in the group of RA patients who did not fulfill the Malmö ExRA criteria as a whole ($p = 0.09$) compared with the general US population. Excess mortality in the ExRA Malmö patients was markedly increased within the first 2 years of followup, and survival continued to be severely impaired during the entire study period. In particular, mortality was increased in patients with neuropathy [age and sex adjusted conditional risk ratio (CRR) 8.09; 95% confidence interval (95% CI) 3.92–16.70], cutaneous vasculitis (CRR 5.67; 95% CI 3.05–10.52), pericarditis (CRR 5.26; 95% CI 3.12–8.84), pleuritis (CRR 3.72; 95% CI 2.10–6.57), and Felty's syndrome (CRR 3.36; 95% CI 1.64–6.89). Among the ExRA not included in the Malmö criteria, pulmonary fibrosis and rheumatoid nodules were associated with a smaller but significant increase of mortality. The risk ratios for individual ExRA are listed in Table 3.

In a multivariate model including age, sex, and the presence of various comorbidities (heart disease, chronic pulmonary disease, liver disease, malignancy, and dementia), ExRA according to Malmö criteria was the strongest predictor of death (RR 4.25; 95% CI 2.88–6.30) (Table 4). The presence of subcutaneous rheumatoid nodules was also modestly associated with increased mortality in this model (RR 1.51; 95% CI 1.06–2.16), as was the presence of RF (Table 4). The inter-

Table 2. Cumulative incidence at 30 years' followup of extraarticular disease manifestations.

Extraarticular Manifestation	No. of Patients	30-year Cumulative Incidence, % (± SE)
Pericarditis	18	10.9 (± 3.0)
Pleuritis	19	9.4 (± 2.7)
Felty's syndrome	9	2.7 (± 1.0)
Major cutaneous vasculitis	14	5.1 (± 1.6)
Neuropathy	8	2.8 (± 1.0)
Scleritis	3	1.0 (± 0.6)
Episcleritis	3	0.8 (± 0.5)
Retinal vasculitis	0	0.0
Glomerulonephritis	4	2.9 (± 1.7)
Other vasculitis	0	0.0
Amyloidosis	3	1.0 (± 0.6)
Keratoconjunctivitis sicca	41	15.4 (± 2.6)
Xerostomia	3	1.0 (± 0.6)
Sjögren's syndrome	42	17.1 (± 3.0)
Pulmonary fibrosis	25	9.4 (± 2.1)
Bronchiolitis obliterans	3	1.2 (± 1.0)
Cervical myelopathy	9	3.5 (± 1.3)
Subcutaneous nodules	114	39.4 (± 3.6)
Other nodules	0	0.0

Table 3. Extraarticular manifestations and associated mortality.

Manifestation	Conditional Risk Ratio*	95% CI	p
Pericarditis	5.26	3.12–8.84	≤ 0.0001
Pleuritis	3.72	2.10–6.57	≤ 0.0001
Felty's syndrome	3.36	1.64– 6.89	≤ 0.0001
Major cutaneous vasculitis	5.67	3.05–10.52	≤ 0.0001
Neuropathy	8.09	3.92–16.70	≤ 0.0001
Scleritis	1.30	0.32–5.25	0.71
Episcleritis	2.89	0.71–11.76	0.14
Glomerulonephritis	1.55	0.38–6.38	0.54
Amyloidosis	2.52	0.62–10.20	0.20
Keratoconjunctivitis sicca	1.43	0.92–2.23	0.12
Secondary Sjögren's syndrome	1.47	0.95–2.28	0.08
Pulmonary fibrosis	2.80	1.65–4.72	≤ 0.0001
Cervical myelopathy	0.94	0.30–2.95	0.91
Subcutaneous rheumatoid nodules	2.08	1.58–2.74	≤ 0.0001

*Adjusted for age and sex.

Table 4. Multivariate analysis of predictors of mortality in RA.

Predictor	Conditional Risk Ratio	95% CI	p
Age	1.07	1.06–1.09	< 0.0001
Male sex	1.46	1.08–1.98	0.014
Cardiovascular disease	2.34	1.72–3.20	< 0.0001
Dementia	2.44	1.60–3.71	< 0.0001
Malignancy	1.94	1.28–2.93	0.002
Severe extraarticular manifestations*	4.25	2.88–6.30	< 0.0001
Rheumatoid factor positivity	1.94	1.45–2.60	< 0.0001

*According to criteria 1–8, Table 1.

action between ExRA Malmö and RF was borderline, but did not withstand "bootstrap" validation (see Materials and Methods), suggestive but not conclusive evidence that patients who have both ExRA Malmö and positive RF have an even worse prognosis than those who do not.

DISCUSSION

In this community based study of extraarticular manifestations in rheumatoid arthritis (ExRA), mortality was increased in the RA cohort, and virtually all the excess mortality occurred in patients with severe ExRA (i.e., neuropathy, vasculitis, serositis, and Felty's syndrome), confirming previous findings indicating a particularly poor prognosis in this group of patients[15]. Pulmonary fibrosis and subcutaneous rheumatoid nodules were also associated with increased mortality.

We also examined the effect of comorbid conditions on survivorship in patients with ExRA and considered the possibility that ExRA may in fact be markers of other diseases. We considered whether the increased mortality in ExRA is due to fatality from comorbidities. In the multivariate analysis, the presence of known heart, liver or chronic pulmonary disease, dementia, or malignancy was associated with increased mortality, but ExRA according to the Malmö criteria (ExRA Malmö) remained the most important predictor of mortality. This indicates that ExRA Malmö predict mortality independently of known comorbidities, and that it is unlikely that the increased mortality in ExRA Malmö patients is due to selection of patients with other, preexisting diseases. Even after adjustment for age and sex, the ExRA Malmö remained strong independent predictors of premature mortality.

In this series, systemic features of RA occurred in a substantial proportion of patients at some time, but the incidence of some extraarticular manifestations was less than that reported from organ-specific studies of referral based patients. For instance, in consecutive RA outpatients from a single center serving a defined area in Denmark, an annual incidence of pleuritis of 1.54% in men and 0.34% in women was observed[28]. In a hospital based inpatient study from Malmö, Sweden[15], the cumulative incidence of pleuritis in RA was 3.0% during a followup period of 4.5 years. These figures would correspond to a 30-year cumulative incidence of more than the 9.4% observed in the present series. Similarly, the cumulative incidence of Felty's syndrome (2.1% per 30 years' followup) was less than that reported by Sibley and co-work-

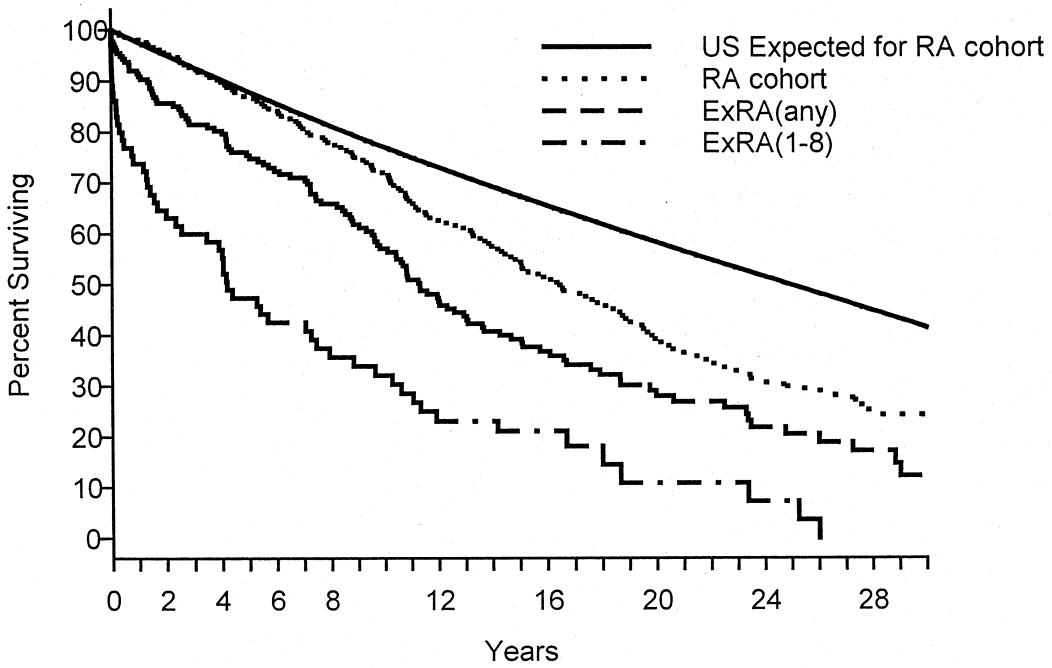

Figure 1. Survival of patients with RA after first presentation of extraarticular manifestation according to the criteria used in the Malmö study (Table 1; criteria 1–8), and after first presentation of any of the extraarticular manifestations (Table 1; criteria 1–17); and survival in the entire RA cohort, compared to the expected survival from the general population.

ers from a cohort of RA patients from a university based referral center in Saskatchewan, Canada (3.9% cumulative incidence; mean followup 16.8 years)[29]. Data on the occurrence of rheumatoid leg ulcers are scarce, but Wilkinson reported 22 cases among a total of 324 patients seen in a rheumatology clinic in 6 years[30], corresponding to a cumulative incidence of 6.8%, which is considerably more than the 30-year cumulative incidence of 5.1% for cutaneous vasculitis in our study. These differences are probably explained in part by selection of RA patients with complicated disease in clinic based studies, compared to a population based cohort.

Pulmonary fibrosis also occurred to a lesser extent than reported in other studies. For example, in a cross sectional examination of RA patients seen at the University of Iowa, Iowa, USA, pulmonary function tests or radiological findings suggestive of interstitial lung disease were seen in 32.4%[31]. Detection of rheumatoid lung disease depends to a great extent on the method of investigation[32]. In general, a retrospective study may give a lower estimate of the incidence of conditions that have to be actively searched for, in contrast to disease manifestations that are easily detectable in the clinic, such as rheumatoid nodules. The incidence of nodules in the present series was similar to that reported by others[33,34].

The Malmö ExRA, which include pericarditis, pleuritis, Felty's syndrome, cutaneous vasculitis, neuropathy, episcleritis, scleritis, retinal vasculitis, other types of rheumatoid vasculitis, and glomerulonephritis, were found, in accord with the Malmö study[15], to identify a group of RA patients with a very poor survival. In other studies of ophthalmological manifestations[13], pericarditis[12], and various types of ExRA (i.e., vasculitis, neuropathy, scleritis)[11], an increased mortality compared to RA patients in general has also been shown. The group of ExRA patients identified by the Malmö criteria may be characterized by systemic inflammation of a kind that has a particular influence on mortality.

As in our series, increased mortality in patients with pulmonary fibrosis has been described in hospitalized patients with RA[35]. Rheumatoid nodules have been found to predict mortality in a large study of RA[6]. In a study of Sjögren's syndrome (SS)[23], using the same criteria as our study, mortality was increased in patients with secondary SS, most of whom had RA. In the present study, there was a trend toward increased mortality in patients with SS, although it was not significant.

The marked increase of mortality within 2 years after diagnosis of ExRA may be interpreted as suggesting a very direct link between extraarticular disease and death. Although RA is associated with increased mortality, RA is rarely noted as the cause of death[3]. In the first study to find poor survival in RA, the excess mortality was mainly attributed to infectious disease[1]. Later studies have shown the major cause of excess mortality is cardiovascular disease[5,36,37]. In studies of ExRA where causes of death were evaluated, a higher than expected number of cardiovascular deaths was noted[15,38], although the number of deaths was too small to allow any definite conclusions.

Serological markers of inflammation have been shown to be independent predictors of cardiovascular mortality[39-42], and the importance of inflammation in vascular disease is supported by histological and immunohistochemical studies[43-45]. The association between systemic features of RA and mortality may thus be an example of the importance of systemic inflammation in cardiovascular disease.

The major strength of this study is the community based approach, utilizing a well defined RA cohort, which limits selection of severe RA cases and enables an estimate of the true burden of extraarticular disease and the associated mortality in the community. It is not a case finding study. One limitation is due to the retrospective method, which limits analysis to the case record data collected by the managing physician. This might lead to underestimation of some forms of ExRA. However, the case definitions used were primarily developed for the identification of clinically relevant ExRA in retrospective studies involving review of medical records, and similar results have previously been found using these criteria[15].

In this first community based study of extraarticular disease manifestations in RA, such manifestations were present at some time in a substantial proportion of patients, but the incidence of some extraarticular manifestations was less than that reported from organ-specific studies of referral based patients. Virtually all excess mortality in the RA cohort occurred in a subgroup of patients with severe extraarticular disease, suggesting that extraarticular manifestations are the major predictors of mortality in RA.

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