Prediction of Mortality in Rheumatoid Arthritis Based on Disease Activity Markers

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ABSTRACT. ***Objective.*** The risks and predictors for mortality in patients with rheumatoid arthritis (RA) were examined in a cohort of 152 consecutive outpatients (119 women, 33 men) seen in a 2 month period.

Methods. We evaluated 4 measures of disease activity: erythrocyte sedimentation rate (ESR), physician and patient global assessment of disease activity, and the Ritchie Articular Index (RAI) as mortality predictors, adjusting for disease severity, treatment, and cardiovascular disease (CVD) comorbidity.

Results. During followup from 1978 through 1998, 111 patients (86 women, 25 men) died, and only one was lost to followup. The standardized mortality ratio for women was 161 (95% confidence interval 129–199), for men 152 (95% CI 99–223), and for both sexes combined 156 (95% CI 128–188). In a proportional hazards model adjusted for age and sex, at the beginning of the period and for the whole group, significant predictors of mortality were Steinbrocker functional class, Larsen index, CVD comorbidity, use of corticosteroids ever, ESR, and the physician and patient global assessment of disease activity; but the rheumatoid factor (RF), RAI, and use of disease modifying antirheumatic drugs were not significant predictors. When evaluating the 4 assessments of disease activity adjusting for confounders, only physician global assessment hazard ratio (HR) = 1.32 per 1 SD (95% CI 1.00–1.74) and ESR HR = 1.47 per 1 SD (95% CI 1.11–1.93) were significant predictors.

Conclusion. This longterm followup study of a single clinical patient cohort showed a significant increase in mortality among patients with RA compared to the general population in Malmö. In addition to disease damage and CVD comorbidity, measures of disease activity independently predicted mortality, which supports the hypothesis that improving these variables may also improve longterm outcome. (J Rheumatol 2005;32:430–4)

Key Indexing Terms:
RHEUMATOID ARTHRITIS MORTALITY PREDICTORS
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Rheumatoid arthritis (RA) is a chronic, inflammatory disease that results in various degrees of disability[1] as well as increased mortality[2], with a relative risk ranging from 1.1 to 3.0. To a large extent the increased mortality is caused by comorbidity in cardiovascular diseases (CVD)[2,3]. Apart from age and male sex, predictors for mortality in these studies were early functional disability, mostly according to the Health Assessment Questionnaire (HAQ) and modified HAQ (MHAQ)[2,4-7]. Other reported predictors are elevated erythrocyte sedimentation rate (ESR)[2,4], number of swollen joints[2,4], and in some[2,4,8,9] but not all[7] studies, rheumatoid factor (RF) seropositivity.

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In 1993 the American College of Rheumatology (ACR) published a consensus document of recommendations on what outcome measures to include in clinical trials of RA[10]. These measures include counts of swollen and tender joints, an estimate of the assessment of disease activity by patients and physicians, the acute phase response, measurement of disability, and the patient's assessment of pain. Selection of these factors was based on a consensus among physicians at an international workshop[11], and the ability of these factors to reflect significant improvement of disease activity in clinical trials with disease modifying antirheumatic drug (DMARD) therapy in patients with RA[12]. The validity of these measurements would be enhanced if they could be shown to predict longterm prognosis of RA, as reflected, for example, by mortality.

At the Department of Rheumatology in Malmö, consecutive patients presenting with RA in February and March 1978 were systematically evaluated with a battery of possible longterm predictors for mortality, including 4 of the variables that were later to constitute the ACR criteria for individual response. This study analyzes how these response criteria individually and multivariately predicted mortality in this clinically defined patient cohort.

MATERIALS AND METHODS

Patient cohort. From February through March 1978, 152 consecutive outpatients given a diagnosis of classical or definite RA according to the 1958 American Rheumatism Association (ARA) criteria for RA[13] were enrolled. At that time, the city of Malmö had a population of 230,000 inhabitants, and had only one outpatient clinic for secondary and tertiary rheumatological care in the only hospital in the city. The cohort consisted of 119 women (78%) and 33 men (22%), with a median age of 61 years (range 30–83). The median duration since initial symptoms of the disease when they were enrolled in 1978 was 12 years (range 1–52; Table 1). These patients were followed from 1978 until death or until March 31, 1998. The mean followup time was 12.4 years (SD ± 6.3). During this time, only one person was lost to followup (due to emigration to The Netherlands).

Clinical data. The evaluation at baseline in 1978 included Steinbrocker functional class, which categorizes the patient's physical function into 4 classes (I–IV)[14], radiographic evaluation of hands and feet with the Larsen index, a method for numerical grading of joint damage (0–200 arbitrary units)[15], the physician's and patient's global assessment of disease activity on a 10-point scale (0–10) where 0 depicts best possible status and 10 the worst possible status, Ritchie Articular Index (RAI) for joint tenderness (0–78 units)[16], and duration of disease.

Blood samples were taken for ESR and IgM RF. ESR was analyzed by standard technique. RF was analyzed using the sheep cell agglutination test[17]. Patients were considered seropositive when the serum titer was ≥ 1/32.

Information on CVD comorbidity and present and previous medication with DMARD and corticosteroids was obtained through a structured review of all the clinical records. CVD was defined as inpatient care for acute myocardial infarction or a diagnosis of heart failure based on physical examination during the 2 years before examination in 1978.

Mortality data. Recording of deaths and causes of death was based on death certificates. We were able to find death certificates for all patients due to the national registration of all people in Sweden with a personal 4-digit code, attached to their birth date. Most (68%) of the death certificates were based on autopsies.

The observed numbers of deaths were also computed for cardiovascular (ICD9 codes 390-419, 423-448), infectious (ICD9 codes 001-139, 320-324, 420-422, 460-466, 473-476, 480-487, 510-511, 513), and malignant (ICD9 codes 140-208) causes of death. Standardized mortality ratios (SMR) and the corresponding 95% confidence intervals were calculated, comparing observed rates of death in the cohort with expected rates according to events in the general population of Malmö matched for sex, age, and calendar period of observation. The same procedure was performed for total and cause-specific mortality.

Statistical methods. Kaplan-Meier survival curves were computed and compared with the expected overall mortality in Malmö. SMR, the ratio between the observed number of deaths and the expected number of deaths times 100, matched for age and sex, was calculated.

Proportional hazards analysis was used for risk assessment within the RA cohort. To evaluate which measures of disease activity could predict mortality, we used 4 of the items of the ACR core set of outcome measures[10]. This core set of outcome measures consisted of tender joint count, patient and physician global assessments of disease activity, patient's assessment of physical function, laboratory evaluation of one acute-phase reactant, swollen joint count, and patient's assessment of pain.

In this cohort we evaluated 4 of these, namely RAI (as a tender joint count), patient and physician global assessments of disease activity, and ESR (as acute-phase reactant).

To control for disease severity we also evaluated the above measures of disease activity in a model containing age, sex, disease severity (Steinbrocker functional class, radiographic damage of the hands and feet according to the Larsen index, disease duration), corticosteroid treatment (ever), and cardiovascular comorbidity.

RESULTS

Of the original cohort of 152, 111 (86 women and 25 men) had died; one woman emigrated abroad and therefore was lost to followup. Patient characteristics are listed in Table 1. The median age at death was 74.7 years (45.5–92.7). Although 52 (46.8%) patients had the diagnosis of RA on their death certificates, in only one case was RA considered as the direct cause of death.

The observed number of deaths in the RA group (n = 111) exceeded the number of expected deaths (n = 71.2) in the community of Malmö during that 20 year period (Figure 1). This resulted in a SMR of 156 (95% CI 128–188). The SMR for women was 161 (95% CI 129–199) and for men 152 (95% CI 99–223).

The most common cause of death was CVD (n = 52,

Table 1. Patient characteristics at enrollment in 1978, presented as numbers and means (SD).

	N (%)	Means (SD)
Women	119	
Men	33	
Total	152	
Age, yrs		60 (12)
Disease duration, yrs		14 (11)
ESR, mm/h		43 (28)
RF positive (titer ≥ 1/32)	113 (85)	
Larsen index (0–200 units)		84 (46)
Ritchie Articular Index (0–78 units)		10 (9)
Physician global assessment (0–10)		3.6 (2.4)
Patient global assessment (0–10)		4.7 (2.6)
Cardiovascular disease (yes vs no)	23 (15)	
DMARD ever (yes vs no)	132 (87)	
DMARD at inclusion (yes vs no)	76 (50)	
Corticosteroids ever (yes vs no)	51 (30)	
Corticosteroids at inclusion (yes vs no)	20 (13)	

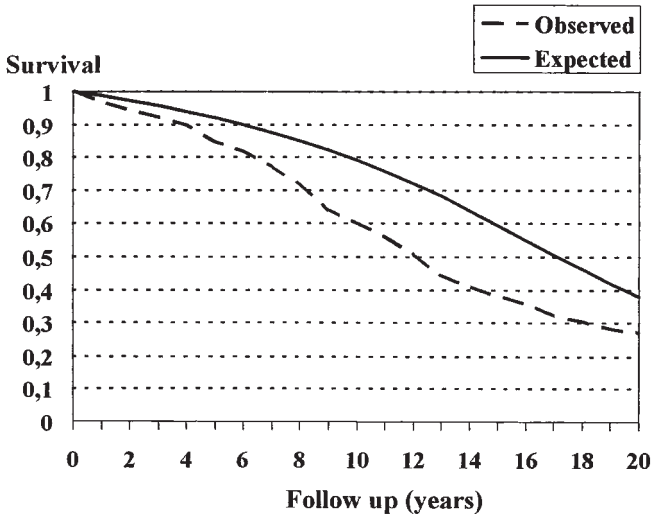

Figure 1. Kaplan-Meier survival curves for patients with RA and age and sex matched population of Malmö, Sweden.

47%). In 18 (33%) of these deaths, RA was mentioned on the death certificate. The expected number of deaths due to CVD for the whole group during these years was 33.2, corresponding to a 57% excess mortality (Table 2). The second most common cause of death was infectious diseases (209% excess mortality), which occurred in 21 patients (19%), of whom 17 (77%) had RA mentioned on their death certificates. Nine patients died from cancer, but RA was not noted on any of their death certificates. The cancer mortality was lower than expected, but not significantly.

To determine risk factors for mortality in this cohort, we used the Cox proportional hazards model and calculated a hazard ratio (HR) for each variable (Table 3). We found that Steinbrocker functional class, the Larsen index, CVD comorbidity, corticosteroid use, the physician and patient global assessment of disease activity, and the ESR were significant predictors for mortality using this model. In contrast, treatment with DMARD, RF, and RAI were not.

To elucidate whether ESR, RAI, and patient and physician global assessment were independent risk factors we used age and sex adjusted multivariate proportional hazards models including the Larsen index, Steinbrocker functional class, and disease duration to control for disease severity (Table 4). In all models, we also controlled for CVD comorbidity and corticosteroid use ever, since these were bivariate predictors for mortality (Table 3). In these models the HR for ESR per 1 SD increase was 1.47 (95% CI 1.11–1.93) and for physician global assessment 1.32 (95% CI 1.00–1.74). These 2 variables were the only independent risk factors for death among the 4 measures considered to reflect disease activity.

Table 2. Observed and expected cause-specific number of deaths, excess mortality, and standardized mortality ratio (SMR) for patients with RA.

	Expected Deaths, n	Observed Deaths, n	Excess Mortality, n	SMR (95% CI)
Cardiovascular disease	33.2	52	18.8	157 (117–205)
Infectious diseases	6.8	21	14.2	308 (190–470)
Malignancy	14.9	9	–5.9	60 (28–114)
Other	16.1	29	12.8	179 (120–257)

Table 3. Age and sex adjusted hazard ratio (HR) for death in patients with RA for various measures of disease activity and severity, treatment, and cardiovascular disease comorbidity.

Predictors of Mortality	HR	95% CI
Steinbrocker functional class*	2.21	1.66–2.96
Larsen index**	1.49	1.17–1.88
Disease duration, yrs **	1.13	0.94–1.36
RF seropositivity (positive vs negative)	0.94	0.53–1.67
DMARD ever (yes vs no)	1.04	0.58–1.87
DMARD at inclusion (yes vs no)	1.12	0.75–1.68
Corticosteroids ever (yes vs no)	1.88	1.25–2.83
Corticosteroids at inclusion (yes vs no)	1.98	1.18–3.32
Cardiovascular disease (yes vs no)	2.12	1.27–3.53
Measures of disease activity		
ESR**	1.54	1.23–1.93
Physician global assessment**	1.12	1.06–1.73
Patient global assessment **	1.27	1.02–1.54
Ritchie Articular Index**	1.20	0.98–1.48

* Per 1 stage Steinbrocker functional class increase. ** Per 1 SD increase.

DISCUSSION

We found that mortality was significantly increased among these consecutively-seen patients with RA, with excess mortality being due in particular to cardiovascular and infectious disease. In a multivariate model controlling for age, sex and disease severity, treatment and CVD comorbidity, the only activity measures that independently predicted death were ESR and physician global assessment.

It has been demonstrated repeatedly that mortality is increased in patients with RA[1-4,8,9,18-26], although 2 recent studies with patients initially given a diagnosis of RA in the 1980s and 1990s did not show any increased mortality[27,28]. The latter studies are based on inception cohorts and their results may be due to better treatment, or perhaps more likely to study of patients with milder or earlier RA[29].

The risk factors consistently observed for total mortality in patients with RA are decreased physical function according to HAQ and other self-report variables, and comorbidity[2,4-7,22], extraarticular disease[2,30,31], RF seropositivity[2,4,8,9], and, in a few studies, number of swollen joints[2,4,32] and serological acute phase reaction[2,4]. Our findings with ESR and physician global assessment as predictors for death are in accord with this, whereas absence of predictivity for RF seropositivity is in contrast with other studies[2,4,8,25]. Possible explanations of the latter include differences in patient enrollment, type of RF analysis, and chance. On the other hand several recent studies have identified patient questionnaire scores as far better predictors for mortality than RF or other more objective measures of disease activity[5-7,22]. However, patient global assessment in our cohort was not a significant independent predictor.

The major aim of our study was to evaluate if measures

Table 4. Hazard ratio (HR) for mortality for the 4 measures of disease activity adjusted for age, sex, disease severity (Steinbrocker functional class, Larsen index, disease duration), corticosteroid treatment (ever), and cardiovascular comorbidity.

	HR	95% CI
ESR*	1.47	1.11–1.93
Physician global assessment*	1.32	1.00–1.74
Patient global assessment*	1.15	0.90–1.47
Ritchie Articular Index*	1.08	0.84–1.41

* Per 1 SD increase.

of disease activity used in clinical trials were predictive for longterm prognosis as indicated by mortality. The global assessment by the patient and the RAI did not have any independent predictive power, although the first univariately predicted death. This may not be surprising, since they are intended to reflect a point estimate of disease activity and may not reflect any longterm effect of disease. In this study, there were no specific measurements of the patient's perception of pain. The RAI, being a measurement of joint tenderness, correlates with pain (unpublished data). It is well known that joint inflammation predicts joint damage[33], which in our study univariately predicted mortality. Further, the number of swollen joints, using repeated assessment, was in a recent population based study in Pima Indians found to be an independent predictor of CVD mortality[32]. In light of this it may seem surprising that RAI did not predict mortality. Possible explanations include the lack of repeated assessments and that it only partly reflects joint inflammation.

A major proportion of the excess mortality in RA in this and other studies is CVD[18,21,23,26]. Serological markers of inflammation such as highly sensitive C-reactive protein[34-36] and soluble intercellular adhesion molecule-1[37] have also been found to predict cardiovascular death in population studies. In our study, ESR was an independent predictor of mortality, which may support the hypothesis that serological evidence of inflammation is a stronger predictor of such death than clinical signs such as synovial inflammation.

Very few studies have addressed the effect of the ACR core set of outcome measures as predictors for death. A recent mortality study over 5 years included most outcome measures of the ACR core set, and found that MHAQ, age, and comorbidity were the best predictors of death[5]. Chehata, *et al* showed in a mortality study with 14 years' followup of patients having participated in pharmacological trials that age, rheumatic nodules, and RF seropositivity, but not disease activity, were predictors of death[38].

Excess mortality was greatest in deaths from cardiovascular and infectious diseases, which is in accord with previous reports[3,18,21,26,39]. Contributing factors to the excess mortality from infectious diseases could be extraarticular features and the well documented increased frequency of smokers in RA[40]. Unfortunately we do not have baseline information for this cohort on several possible predictors for cardiovascular or infectious complications such as hypertension, hyperlipidemia, diabetes, smoking, or extraarticular RA.

Some strengths of our study are the long period of followup with a large number of deaths and the low frequency of loss to followup. One possible concern with the study is left-censorship and selection, since it is a study of prevalent cases at a hospital clinic. On the other hand the mortality caused by RA may not, according to some studies, be apparent until after several years of disease duration[27,28]. To control for disease severity we controlled the multivariate analyses with radiographic joint damage. Further, the short period of recruitment may have enriched the cohort with cases frequently attending the outpatient clinics and consequently having more severe disease. Second, it may not be fair to compare the predictive power of factors that obviously reflect the cumulative burden of disease, such as Steinbrocker functional class, with those that merely reflect a point estimate of disease activity, although this is the approach that in general has been taken in previous studies. A more viable approach might be to compute the area under the curve for such variables; this approach demands repeated assessments. Despite this problem of only reflecting disease severity for a limited period and not cumulatively, the ESR and the physician global assessment of disease activity were found to be independent predictors for death.

We found a significant increase in mortality among patients with RA compared to the general population. Since disease activity, reflected by ESR and physician global assessment, is the most important mortality risk factor, interventions to improve these variables are especially important to improve the longterm prognosis in patients with RA.

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