Mortality Trends in Rheumatoid Arthritis: The Role of Rheumatoid Factor

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ABSTRACT. ***Objective***. We previously demonstrated a widening in the mortality gap between subjects with rheumatoid arthritis (RA) and the general population. We examined the contribution of rheumatoid factor (RF) positivity on overall mortality trends and cause-specific mortality.

Methods. A population-based RA incidence cohort (1955-1995, and aged ≥ 18 yrs) was followed longitudinally until death or January 1, 2006. The underlying cause of death as coded from national mortality statistics and grouped according to ICD-9/10 chapters was used to define cause-specific mortality. Expected cause-specific mortality rates were estimated by applying the age-, sex-, and calendar-year-specific mortality rates from the general population to the RA cohort. Poisson regression was used to model the observed overall and cause-specific mortality rates according to RF status, accounting for age, sex, disease duration, and calendar year.

Results. A cohort of 603 subjects (73% female; mean age 58 yrs) with RA was followed for a mean of 16 years, during which 398 died. Estimated survival at 30 years after RA incidence was 26.0% in RF+ RA subjects compared to 36.0% expected ($p < 0.001$), while in RF– RA subjects, estimated survival was 29.1% compared to 28.3% expected ($p = 0.9$). The difference between the observed and the expected mortality in the RF+ RA subjects increased over time, resulting in a widening of the mortality gap, while among RF– RA subjects, observed mortality was very similar to the expected mortality over the entire time period. Among RF+ RA subjects, cause-specific mortality was higher than expected for cardiovascular [relative risk (RR) 1.50; 95% confidence interval (CI) 1.22, 1.83] and respiratory diseases [RR 3.49; 95% CI 2.51, 4.72]. Among RF– RA subjects, no significant differences were found between observed and expected cause-specific mortality.

Conclusion. The widening in the mortality gap between RA subjects and the general population is confined to RF+ RA subjects and largely driven by cardiovascular and respiratory deaths. (First Release April 15 2008; J Rheumatol 2008;35:1009–14)

Key Indexing Terms:
SURVIVAL RHEUMATOID FACTOR RHEUMATOID ARTHRITIS
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Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder associated with increased mortality. Some studies reported improvements in mortality in patients with RA, suggesting that these improvements may be due at least in part to increased use of new antirheumatic treatment regimens and/or earlier diagnosis of RA in recent years[1-3]. Yet in order to fully understand mortality trends in RA, these must be examined considering the dramatic secular declines in overall mortality in the general population over the past decades[4]. For example, it may be reasonable to expect that mortality trends in the RA population follow patterns similar to those in the general population. Our recent analysis suggests that this is not the case[5]. RA subjects did not experience the same improvements in survival as their non-arthritic peers in the general population, resulting in a worsening in the relative mortality in recent years. Earlier studies suggested that rheumatoid factor (RF) positivity had a significant impact on mortality in RA[6-10].

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To determine the contributors of this widening of the mortality gap, we examined the influence of RF positivity on overall mortality trends and cause-specific mortality.

MATERIALS AND METHODS

The study was conducted within the population of Rochester, Minnesota (MN). This population is well suited for investigation of mortality trends because comprehensive medical records are available for all residents seeking medical care from all healthcare providers for over half a century[11,12]. Using the resources of the Rochester Epidemiology Project, virtually all clinically recognized cases of RA and their RF status can be identified along with complete vital status information.

The study population consisted of a previously described inception cohort of all subjects with RA first diagnosed between January 1, 1955, and January 1, 1995, among Rochester, MN residents ≥ 18 years of age[13,14]. All subjects fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA[15]. Incidence date was defined as the first date of fulfillment of (4 of the 7) ACR classification criteria. Data on RF status were collected based on laboratory results available both at baseline and at any time during followup. Subjects who seroconverted during followup were classified as RF+. All subjects were followed longitudinally through their entire medical records until death or January 1, 2006 (end of followup for the study).

All subjects (irrespective of residency status) were tracked nationally to ascertain vital status, and death certificates were obtained from the respective states for subjects who died outside Minnesota. The underlying cause of death was coded from national mortality statistics and grouped according to International Classification of Diseases, 9th Revision (ICD-9) and ICD-10 chapters. The cause-specific death rates from the Minnesota population from 1979 to 2002 were used for comparison.

Statistical methods. The distribution of survival times following RA incidence date was estimated using the Kaplan-Meier method[16]. The log-rank test was used to compare survival between RF– and RF+ RA subjects[17]. Overall and cause-specific expected mortality rates were estimated by applying the age-, sex-, and calendar-year-specific mortality rates from the Minnesota Caucasian population (1979–2002) to the RA cohort[18]. At the time of the analyses, Minnesota life tables were available until the end of 2002. Therefore, we carried forward the 2002 expected mortality rates to 2006. We conducted additional analyses by truncating followup in the RA cohort at the end of year 2002. This resulted in exclusion of 331 person-years of followup and 30 deaths in the RA cohort and had no effect on results reported here.

Ninety-five percent confidence intervals for the standardized mortality ratios (SMR) were calculated assuming that the expected rates were fixed and the observed rates followed a Poisson distribution[19]. Chapters of causes from ICD-9 and ICD-10 were combined for analyses of cause-specific mortality. Poisson regression was used to model the observed mortality rates[20] according to RF status, and accounting for calendar year of followup, age, sex, and disease duration. In these models, natural splines were used to model the age and calendar year relationships to allow for nonlinearity. Predicted mortality rates (shown in Figure 2) were direct-standardized to the age and sex distribution of the entire RA cohort.

RESULTS

The overall study population comprised a cohort of 603 subjects with incident RA (73% female; mean age 58 yrs). All subjects were followed for a mean of 16 years, during which 398 died. The distribution and characteristics of the study population by RF status are shown in Table 1. For the 393 RF+ subjects, the mean age of the cohort at RA incidence was 56.8 years, and 73.0% were women. Median followup for the RF+ RA cohort was 13.9 years for a total of 6267 person-years. For the 210 RF– subjects (Table 1), the mean age at RA incidence was 60.2 years, and 73.3% were women. Median followup for the cohort was 14.2 years for a total of 3410 person-years. At baseline, RF+ subjects were younger (p = 0.998), more likely to be smokers (0.012), and more likely to have nodules (p = 0.009). All other baseline characteristics were similar (Table 1). Only 32 (5.3%) RA subjects were lost to followup in our study and of these, 18 were RF+.

Table 1. Baseline characteristics of the 603 subjects with incident rheumatoid arthritis.

Characteristic	RF+ RA	RF– RA	p
Subjects, no.	393	210	
Followup, median, yrs	13.9	14.2	
Deceased subjects, n (%)	260 (66.1)	138 (65.7)	
Age at RA incidence, mean, yrs	56.8	60.2	0.008
Female, n (%)	287 (73)	154 (73)	0.94
Caucasian, n (%)	384 (98)	207 (99)	0.47
Current smoking, no. (%)	124 (32)	46 (22)	0.012
Disease characteristics			
Nodules, no. (%)	30 (8)	5 (2)	0.009
Erosions, no. (%)	25 (8)	9 (6)	0.34
Decalcification, no. (%)	15 (5)	9 (6)	0.71
Large-joint swelling*, no. (%)	152 (42)	81 (42)	1.00
Hand/wrist swelling, no. (%)	344 (93)	185 (93)	0.84

* Elbow, shoulder, hip, and knee joints.

During the followup period, 260 RF+ RA subjects died, yielding an age-adjusted overall mortality rate of 4.94 (95% CI 4.32, 5.56) per 100 person-years. Overall mortality for RF+ RA subjects was significantly higher than the mortality in the general population, with a SMR of 1.81 (95% CI 1.60, 2.05). Among the RF– RA subjects, 138 subjects died during the followup period, yielding an age-adjusted overall mortality rate of 3.18 (95% CI 2.62, 3.74) per 100 person-years. Overall mortality in the RF– RA cohort was not different from the general population, with a SMR of 0.99 (95% CI 0.83, 1.17).

Figures 1A and 1B illustrate observed and expected survival in RF+ (Figure 1A) and RF– RA (Figure 1B) subjects up to 30 years after RA incidence. Estimated survival at 30 years after RA incidence was 26.0% in RF+ RA subjects compared to 36.0% expected (p < 0.001), while in RF– RA subjects, estimated survival was 29.1% compared to 28.3% expected (p = 0.9; Figures 1A, 1B).

Figure 2 illustrates mortality rates in RF+ and RF– subjects and expected mortality based on the Minnesota Caucasian population over calendar-years of followup. Over the entire time period, the overall mortality rate in RF+ RA subjects was relatively constant at 3.0–3.2 per 100 person-years. The difference between the observed and the expected mortality rates in the RF+ RA subjects increased over time, resulting in a widening of the mortality gap. In contrast, among RF– RA subjects the observed mortality rate was very similar to the expected mortality over the entire time period (Figure 2).

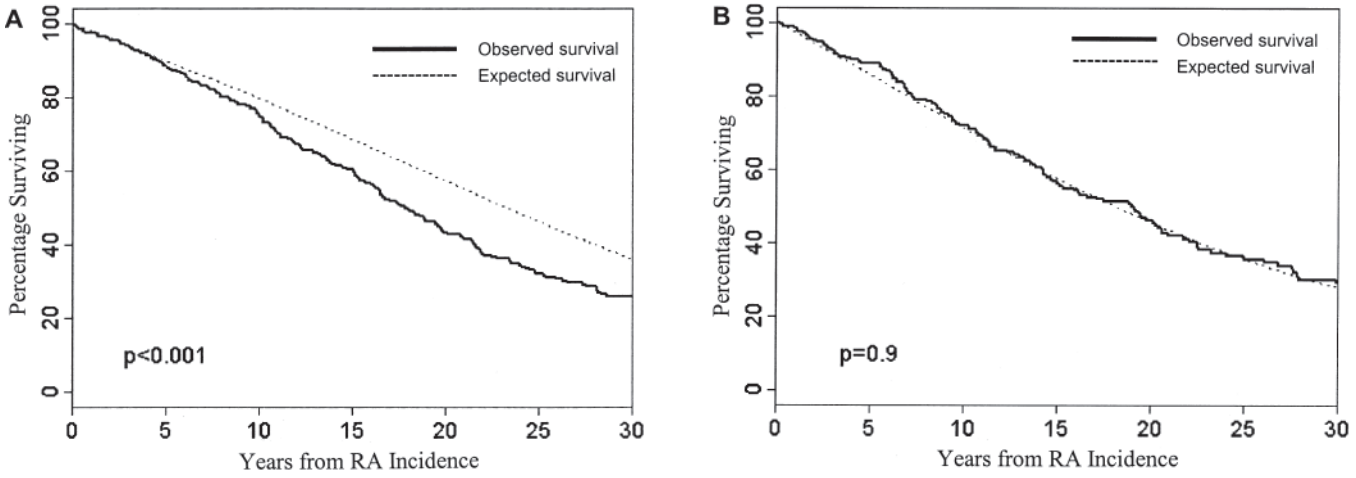

Figure 1. Observed survival in subjects with rheumatoid factor-positive rheumatoid arthritis (RF+ RA) (A) and RF– RA (B) compared with expected survival based on the Minnesota Caucasian population.

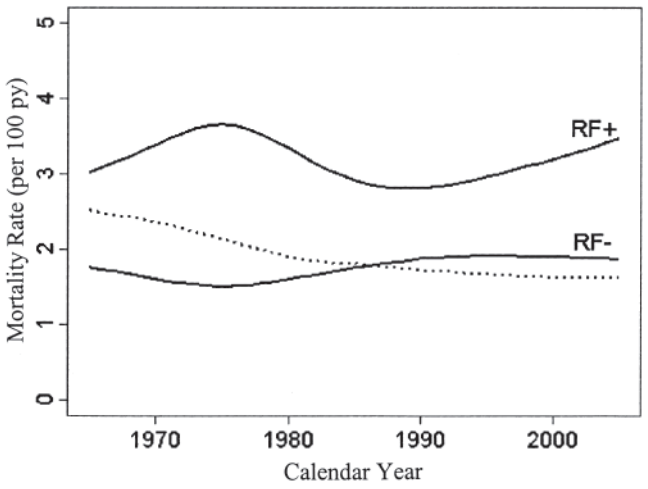

Figure 2. Observed and expected mortality in subjects with rheumatoid factor-positive (RF+) and rheumatoid factor-negative (RF–) rheumatoid arthritis (RA). Expected mortality is based on the Minnesota Caucasian population (broken line). py: patient-years.

We then examined the cause-specific mortality in the 2 groups in order to determine whether increased mortality was associated with specific causes of death. Among RF+ RA subjects (Table 2), cause-specific mortality was higher than expected for circulatory diseases (ICD-9 390-459 and ICD-10 I00-I99), SMR 1.50 (95% CI 1.22, 1.83), and for respiratory diseases (ICD-9 460-519 and ICD-10 J00-J99), SMR 3.49 (95% CI 2.51, 4.72). Cause-specific mortality among RF+ RA subjects was also higher than expected for diseases of blood and blood-forming organs, infectious diseases, and genitourinary and gastrointestinal system disorders, but the number of observed and expected events was small. In contrast, no significant differences in cause-specific mortality were found for the RF– RA subjects when compared to expected cause-specific mortality (Table 3). Because the number of observed and expected events was small (≤ 3) and no significant difference was apparent for infectious and parasitic diseases, endocrine disorders, diseases of blood and blood-forming organs, diseases of digestive system, and diseases of genitourinary system, data were not included in Table 3.

We then examined the specific causes of death for circulatory and respiratory diseases since these causes were the major drivers of excess deaths with the highest number of cases. Under circulatory causes, ischemic heart disease (ICD-9 410-414, ICD-10 I20-I25, including myocardial infarction) was the main driver of mortality in both RF+ and RF– RA subjects, with 47 and 32 deaths, respectively. The SMR for ischemic heart disease among RF+ RA subjects was 1.41 (95% CI 1.04, 1.88) and among RF– RA subjects was 1.00 (95% CI 0.68, 1.41). Among respiratory causes, chronic obstructive pulmonary diseases (ICD-9 490-494, 496 and ICD-10 J40-J47) were the most common with 19 and 2 deaths, respectively, among RF+ and RF– RA subjects. The SMR for chronic obstructive pulmonary diseases among RF+ RA subjects was 3.36 (95% CI 2.02, 5.24), and among RF– RA subjects 0.49 (95% CI 0.06, 1.77).

DISCUSSION

We examined the overall and cause-specific mortality trends in subjects with RF+ and RF– RA as compared to mortality trends in the population at large. Our results indicate that the widening in the mortality gap between RA subjects and the general population is confined to RF+ RA subjects. In contrast, mortality trends for RF– RA subjects are essentially identical to the general population. Further, excess mortality in RF+ RA subjects is due not only to cardiovascular conditions but to various other disorders, including respiratory, hematologic and hematopoietic disorders, infectious diseases, and genitourinary and gastrointestinal system disorders. Nevertheless, since cardiovascular and respiratory

Table 2. Cause-specific mortality among subjects with RF+ RA.

Cause	No. Observed Events	No. Expected Events	SMR (95% CI)
All causes*	260	143.2	1.81 (1.60, 2.05)
Circulatory system	97	64.7	1.50 (1.22, 1.83)
Respiratory system	42	12.0	3.49 (2.51, 4.72)
Neoplasms	39	(35.0)	1.12 (0.79, 1.52)
Musculoskeletal	18	0.8	21.4 (12.7, 33.9)
Digestive system	11	4.7	2.35 (1.17, 4.21)
Genitourinary system	10	2.4	4.20 (2.01, 7.73)
Injury and poisoning	7	3.6	1.94 (0.78, 4.00)
Mental	6	3.2	1.85 (0.67, 4.02)
Endocrine	5	4.4	1.13 (0.37, 2.63)
Infectious and parasitic	5	1.2	4.10 (1.33, 9.56)
Hematological	4	0.55	7.27 (1.98, 18.62)
Nervous system	4	4.1	0.98 (0.27, 2.50)

* Includes 11 deaths of unknown cause and 1 death due to congenital abnormality. SMR: standardized mortality ratio.

Table 3. Cause-specific mortality among subjects with RF– RA.

Cause-specific Mortality	No. Observed Events	No. Expected Events	SMR (95% CI)
All causes*	138	139.8	0.99 (0.83, 1.17)
Circulatory system	75	64.5	1.16 (0.91, 1.46)
Respiratory system	10	11.0	0.91 (0.44, 1.68)
Neoplasms	23	24.5	0.94 (0.60, 1.41)
Injury and poisoning	5	3.0	1.65 (0.53, 3.83)
Mental	5	3.0	1.67 (0.54, 3.90)
Endocrine	4	3.5	1.16 (0.32, 2.96)
Nervous system	5	3.1	1.60 (0.52, 3.74)

* Includes 3 deaths of unknown cause, 3 digestive system, 3 genitourinary system, 1 musculoskeletal, and 1 death due to an ill-defined condition. SMR: standardized mortality ratio.

deaths constitute the majority of deaths (58%) in RA, their influence on excess mortality is greater.

Improvements in life expectancy in the general population during the last few decades have been attributed mainly to reductions in mortality due to cardiovascular diseases and unintentional injury[21]. Reductions in major cardiovascular risk factors and evidence-based medical therapies for primary and secondary prevention of heart disease were the major contributors of improvements in cardiovascular mortality[22]. Given these trends in the general population, there are at least 2 potential explanations for lack of improvements in mortality in RF+ RA subjects. First, RA subjects may not have received the same level of primary and secondary prevention interventions as their non-arthritic peers. This is conceivable, since underdiagnosis and undertreatment of comorbidities in RA patients have been reported, especially in the setting of unrecognized coronary heart disease and heart failure in RA subjects[23-25]. The second potential explanation is failure of the primary and secondary preventive interventions to provide the same level of beneficial effects in RF+ RA subjects as in the general population or the RF– RA subjects. If true, this would suggest different biological pathways for cardiovascular disease in RF+ and RF– RA subjects that would in turn require different approaches to prevention and treatment. Although earlier studies reported seropositivity as a significant predictor of mortality in RA[6-10], none addressed trends over time in comparison to the general population.

Pulmonary involvement is common in RA, including pleural disease, interstitial lung disease, nodular lung disease, bronchiolitis, pulmonary hypertension, and small-airway diseases[26,27]. However, contribution of these conditions to excess mortality in RA is not well defined. In Finland, Sihvonen, *et al* reported an SMR of 2.5 for respiratory diseases, but they also acknowledged the difficulties in distinguishing deaths due to respiratory infections (pneumonia, bronchitis) by relying only on the underlying causes of death[28]. In a more detailed analysis of mortality data from England[29], Thomas, *et al* examined cause-specific mortality in a large cohort of hospitalized subjects with RA, which reported SMR for respiratory diseases to be 2.94 for males and 2.37 for females. With respect to individual causes of

respiratory deaths, SMR for respiratory infections were 1.9 and 2.4, respectively, for males and females. SMR for chronic obstructive pulmonary disease were 1.8 and 2.1, respectively, for males and females. Our estimates for RF+ RA patients are within the same range as these earlier studies. Our results indicate that chronic obstructive pulmonary diseases constitute almost half of all respiratory disorder mortality, with a SMR of 3.36 (95% CI 2.02, 5.24) for RF+ and 0.49 (95% CI 0.06, 1.77) for RF– RA subjects. However, changes in the classification of respiratory diseases make it difficult to interpret these findings. Importantly, conversion from ICD-9 to ICD-10 in 1999 affected both the total number of deaths assigned to the respiratory disease chapter (22% decrease) and the numbers assigned to individual causes within this chapter, such as pneumonia, chronic obstructive pulmonary diseases, and influenza[30]. Therefore, these results must be considered only hypothesis-generating, and more in-depth analyses are warranted to fully understand the contribution of specific respiratory conditions to excess mortality in RA.

Cause-specific mortality in RF+ RA subjects was higher than expected for various other diseases that are relatively well known comorbidities in RA, such as infections, gastrointestinal disorders (e.g., ulcers), and diseases of the blood and blood-forming organs and of the genitourinary system. Although the SMR are as high as 6-fold for some comorbidities, the relative influence of these conditions on mortality is low due to the limited number of deaths they each contribute.

The observed differences in mortality trends between RF+ and RF– RA subjects could possibly be explained by differences in smoking rates over time in the 2 groups. Poorer survival among the RF+ RA subjects relative to the general population could potentially be due to an increased prevalence of smoking and smoking-related diseases among RA subjects only if (A) the prevalence of smoking in RA patients remained stable, despite a significant decline in the general population, or (B) improvements in survival in the general population are largely due to decline in prevalence of smoking. We examined the prevalence of smoking over time in our RA cohort and compared it to population-based matched controls. Among RF+ RA subjects, the prevalence of smoking declined from 35.2% between 1955 and 1984 to 22.0% after 1985. Among matched non-RA controls, the prevalence of smoking declined similarly, i.e., from 28.6% 1955-1984 to 17.3% after 1985. Therefore, although the prevalence of smoking in RF+ RA subjects is higher than in non-RA control subjects, there was a proportionate decline in prevalence of current smokers in both RA and non-RA subjects. Further, only 12% of the decline in overall mortality in the general population is attributed to decline in smoking prevalence[22]. Therefore, smoking is unlikely to be a major determinant of the observed trends.

Several potential limitations should be considered when interpreting our results. Misclassification of causes of death is a potential limitation when relying on only the underlying cause of death. A detailed analysis of individual causes of death, rather than ICD chapters, would provide more accurate information on contributors of excess mortality in RF+ RA subjects. Yet this study spans over 50 years, a period that includes major switches in coding systems for mortality data. During this period, comparable cause-specific mortality rates for the general population are available only for the underlying causes of death. Our findings may not be generalizable to non-Caucasian individuals because the Rochester population during the calendar years under investigation was predominantly Caucasian. The local population is socioeconomically similar to American Caucasians[11] and the incidences of RA and cause-specific mortality rates in local residents resemble those for other Caucasian populations[31]. Nevertheless, the generalizability of the study findings to populations with more diverse sociodemographic populations is unknown. Although followup for RA subjects extended to 2005, the incident RA subjects are limited to those diagnosed prior to 1995. Therefore, we cannot extrapolate our findings to subjects diagnosed after 1995, who may have been treated earlier, more aggressively, and with newer medications. Although we report on RF positivity as the major determinant of mortality, RF status may simply be an indicator of pathological processes causally associated with mortality in RA subjects. Our population-based design, standardized approach for case ascertainment, long and complete followup of all subjects, and availability of general population cause-specific mortality rates throughout the entire study period are major strengths of this study.

The widening in the mortality gap between subjects with RA and the general population is confined to RF+ RA subjects and is driven largely by cardiovascular and respiratory disorders. The reason for the marked difference between mortality of RF+ and RF– RA subjects should be addressed in future studies to determine the clinical and biological implications of RF status and to identify the therapeutic strategies that have the potential to reduce excess mortality in RA.

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