The Impact of Functional Status and Change in Functional Status on Mortality Over 18 Years Among Persons with Rheumatoid Arthritis

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ABSTRACT. ***Objective***. To calculate mortality rate associated with rheumatoid arthritis (RA), to estimate the effect of initial functional status and of change in functional status on mortality among persons with RA, and to compare the mortality experience of such persons to that of the US population.

Methods. The study used a prospective panel of 1269 persons followed for a mean of 8.4 years (median 7 yrs, interquartile range 3–12, maximum 18). Mortality status was ascertained from contacts with next of kin, study physicians, and search of the National Death Index. The Kaplan-Meier method was used to calculate the proportion dying in each time interval, with and without stratification for initial functional status [Health Assessment Questionnaire (HAQ) score] or average change in functional status. Cox proportional hazards regression was used to establish the effect of functional status, demographic characteristics, and health status on mortality risk.

Results. There were 270 deaths among the 1269 persons with RA. After 18 years of followup the overall death rate was 39%. The death rates in the best through worst initial quartiles of HAQ score were 29, 33, 44, and 54%. The death rate was 51% among persons with declining HAQ score versus 31 and 32% among those with no change or improvement in this measure, respectively. Demographic and health status did not reduce the effect of HAQ or average change in HAQ on mortality risk. Compared to the US population, the persons with RA had a standardized mortality rate of 1.32.

Conclusion. The persons with RA in this study had elevated mortality rates. Poor initial functional status and declining functional status significantly increased mortality risk among these persons with RA. (J Rheumatol 2002;29:1851–7)

Key Indexing Terms:
MORTALITY RHEUMATOID ARTHRITIS

Mortality among persons with rheumatoid arthritis (RA) has been the subject of numerous publications, including several comprehensive literature reviews that summarize mortality information as of the mid-1990s[1-5] and a series of studies since then[6-13]. There is near unanimity among the studies in showing higher mortality rates among persons with RA. One set of authors concluded that persons with RA on average die between 10 to 15 years earlier than would be expected on the basis of their other characteristics[1]. In 2 studies that did not report elevated mortality, Kroot and colleagues[10] and Lindquist and Eberhardt studied persons with RA of very recent onset. Kroot and colleagues[10] speculated that the lack of association between RA and mortality in their study may be because mortality does not become elevated among persons with this condition until later in the course of disease. Ward tested this hypothesis directly, finding that mortality rates were lower in studies using inception cohorts, and that this factor, rather than actual improved mortality, probably accounted for the lower mortality rate in more recent studies[11].

Although almost all the studies report elevated mortality, RA is not commonly among the primary causes on the death certificates of persons with this condition. Instead, they would appear to die of the same mix of causes as the remainder of the population, albeit considerably earlier in life[1]. Low socioeconomic status, usually measured by extent of formal education, is a strong predictor of mortality risk among persons with RA[1,3,6,7]. Results with respect to the effect of age and sex are mixed, with only some studies showing men and older persons with RA with higher mortality rates[1,5]. However, several studies indict poor functional status as a substantial risk factor in mortality among persons with RA[1,6].

Our study is designed to characterize the mortality experience of a large cohort of persons with RA originally from the practices of a random sample of Northern California

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rheumatologists who have been followed prospectively for as long as 18 years. In contrast to 2 of the studies with similar longterm followup (e.g., 15 or more years)[12,14], our study has a much larger sample size, allowing more reliable estimates of mortality risk. The other mortality study with longterm followup was based on medical record review of a defined geographic area and therefore had the advantage of a community based sampling frame[9]. However, it did not have information on functional status at the point of incidence[15], precluding the analysis of functional status at one point on subsequent mortality, let alone change in functional status over time.

Our specific aims are: (1) to provide estimates of the mortality rate associated with RA as a function of duration of followup; (2) to estimate the effect of initial functional status and change in functional status [as measured by the Health Assessment Score (HAQ) score and change in HAQ score] on survivorship using the Kaplan-Meier method; (3) to estimate the effect of functional status and change in functional status on the proportion dying in each year when taking into account other medical and demographic characteristics of the individual using Cox proportional hazards regression; and (4) to compare the mortality experience of persons with RA to that of persons of similar age and sex in the nation as a whole.

MATERIALS AND METHODS

Data source. This report is based on analyses of the UCSF RA Panel Study, an observational data source in which 1278 persons with RA from the practices of a random sample of Northern California rheumatologists have been followed for as long as 18 years, from 1983 through 2000. Enrollment occurred in 4 waves. In 1982 and 1983, 822 persons with RA from the practices of 40 rheumatologists were enrolled; these 40 represented about half of the board certified rheumatologists in Northern California. In 1989, 203 persons from the practices of another 10 rheumatologists randomly sampled were enrolled; these 10 represented half of the rheumatologists who had entered practice between 1983 and 1989. In 1995, 131 persons from 10 of the 50 rheumatologists already involved in the study were enrolled; these 10 were those who had contributed the largest number of patients in the prior 2 waves. In 1999, 122 persons from the practices of Northern California rheumatologists with a high concentration of managed care patients were enrolled. Overall, as of the end of 2000, 511 persons were still alive and being interviewed as part of the RA Panel Study. At that time, the study's archive included 10,702 person-years of observation.

The data for the RA Panel derive from annual structured telephone interviews with the persons with RA conducted by a trained survey worker, periodic information from their physicians on the severity of disease, and, for select subsets, medical record information and/or physical examination and history data collected by a registered nurse in a home visit. The RA Panel Study has been reported in over 40 publications. Two reports provide greater details on this database and on the validity of the measures collected in the annual surveys[16,17].

The annual interview collects information on the current state of signs and symptoms; number and kind of comorbidities; functional status, with the HAQ as the principal measure; psychological status; and a list of all specific medications taken. In addition, the persons with RA report on their use of health care services in the 12 months prior to interview.

When we cannot reach an individual for his or her annual interview, we use several sources to attempt to find that individual, including contacting family members listed in the prior interview as likely to know the respondent's whereabouts, contacting all physicians listed in that interview, and searching the vital records of the State of California and, when it becomes available for a year, the National Death Index maintained by the National Center for Health Statistics. As of this writing, we have documented 272 deaths among the 1278 persons who have ever been in the UCSF RA Panel; 130 have been lost to followup and 367 have declined to continue in the study after completing at least one interview. Since data on variables used in the analyses described below were missing for 9 respondents, the analyses were conducted on 1269 persons with RA, in whom there were 270 deaths.

Following the suggested reporting requirements for longitudinal observational studies[18], the UCSF RA Panel has the following characteristics:

Study design: prospective.
Source of cases: consecutive cases presenting to a random sample of rheumatologists.
Timing of patient recruitment: mean of 11.1 years after disease onset (range 0–65).
Inclusion criteria: all persons rheumatologists certify as having RA.
Demographic data collected: sex, age, race/ethnicity, income, education, occupation, marital status.
Baseline clinical data: From rheumatologist: rheumatoid factor positivity, sedimentation rate, site of erosions; From patient: count of painful and swollen joints, HAQ score, global pain and RA status, extent of morning stiffness.
Followup data: patient-provided data updated annually.

Analyses. There are no randomized trials in RA with sufficient longterm followup to estimate mortality rates much beyond the period of the trial. Accordingly, out of necessity, researchers have turned to longitudinal observational studies to estimate mortality risks; such studies have also been used to estimate the longterm prognosis for persons with RA of varying severity[19]. Although there are risks attendant to the use of longitudinal studies, criteria for the design and use of such data have emerged[18,20,21]. Two of these criteria include prospective collection of data and the use of batteries that have been validated and accepted as core outcome measures in RA. In our study, the principal variable used to predict mortality risks — the HAQ score — was collected prospectively and has been accepted as a core outcome measure in RA clinical trials, as well as in observational databases[22].

We used the Kaplan-Meier method to estimate survival rates for quartiles of HAQ scores in the year of enrollment and 3 strata of a measure of total change in HAQ score averaged over the number of years the respondent was interviewed. In these analyses, the dependent variable was time until death occurred, with those surviving and/or those lost to followup (but not known to have died) constituting censored observations. For the record, the range of baseline HAQ scores in the first quartile were 0 through 0.500, in the second were 0.501 through 1.125, in the third were 1.126 through 1.750, and in the fourth were 1.751 through 3.000. The number of cases included in the quartiles was not precisely one-fourth of the total number of cases because of ties. (Since there are a limited number of different HAQ scores, many cases have the same scores, thus requiring the researcher to place the borders between quartiles at the next highest score.) We also analyzed survival for the continuous baseline HAQ score. Since the findings did not materially differ from the results presented below, they are omitted.

The average change in HAQ score was calculated by dividing the change in HAQ between the baseline year and final interview year by the number of years a respondent was interviewed; the scores on this measure had a mean value of 0.021 per year, a standard deviation of 0.124 per year, a range of from –0.813 to 0.938 per year, and an interquartile range of from –0.021 to 0.063 per year. Following the suggestion in the literature that a HAQ score of 0.25 represents a clinically meaningful change in functional status[23,24], we defined 3 strata in the average change measure according to whether a respondent would have achieved such a clinically meaningful change over the average number of years in which respondents were inter-

viewed in this study (8.4), or 0.03 per year. The 3 strata of the measure of change used in the analyses included all those for whom HAQ score had declined (improved) by 0.03 per year, stayed relatively stable (neither declining nor increasing by more than 0.03 per year), or increased (worsened) by 0.03 per year.

We used the log-rank test to establish whether mortality differed by HAQ or average change in HAQ strata overall. In a separate set of analyses, we used the log-rank test to compare dyads of HAQ quartiles (for example, the first, or best, vs the second quartile of function) and average HAQ strata (for example, persons experiencing no change vs those experiencing improvement) for their effect on mortality.

In addition to the Kaplan-Meier survival analyses, we used SAS (Version 8.01) Proc PHREG to estimate Cox proportional hazards models of the effect of select variables on the proportion dying in each year of followup. As in the Kaplan-Meier analyses described above, in the Cox regression analyses the dependent variable was time until death occurred, with those surviving and/or those lost to followup but not known to have died constituting censored observations.

Five separate Cox regressions were run. In the first, we estimated the effect of the baseline HAQ score on the probability that respondents died in each year. In the second, we included the baseline HAQ score and the measure of average change in HAQ score. In the third, we added the following demographic covariates to the model, including the baseline and average change HAQ score measures: age (yrs, entered as a continuous measure), sex, race (white vs nonwhite), extent of formal education, marital status (indicator variables for married, widowed, separated, divorced, with never married as the reference), and household size. In the fourth model, the following health measures were added to the variables in the preceding model: duration of RA (in yrs), number of swollen joints, pain rating (0–100 scale, with increased rating indicating higher levels of pain), the respondent's assessment of overall health status (fair or poor vs excellent or good), the number of comorbid conditions, and the number of disease modifying antirheumatic drugs (DMARD) taken. In the final model, we added the following measures of change in health status to the variables included in the fourth model: whether a decline in overall health status had occurred, average change in the count of swollen joints and in pain rating, and whether an increase in the number of comorbid conditions and DMARD taken had occurred.

As an alternative to this final model, we estimated a model that also included an interaction term for the baseline and average change in HAQ measures. The latter variable assesses whether the effect of the average change in HAQ score differs for persons in the 4 quartiles of baseline HAQ score.

Finally, to compare the mortality rate of the UCSF RA Panel members to the remainder of the US population, we estimated a standardized mortality ratio (SMR)[25] for 1990, the approximate mid-point of the UCSF RA Panel Study; we also estimated SMR for men and women. In order to assess the extent to which the estimate of the SMR for all RA Panel members is sensitive to the selection of 1990 as the comparison year, we also calculated SMR for 1985 and 1995.

RESULTS

Table 1 shows the baseline characteristics of the 1269 persons from the UCSF RA Panel with complete data and who were, therefore, included in the analyses. The panel members were about 57 years of age on average; slightly more than three-quarters were female. These individuals had had their RA for just over 11 years on average. Almost four-fifths had taken a DMARD in the year prior to interview. Their average HAQ scores of 1.2 are indicative of moderate disability. Over the years that they were followed, 40% of panel members experienced declining function, 38% had no substantive change in their HAQ scores, and 22% experienced improved function.

Table 1. Baseline Characteristics of UCSF RA Panel Members (n = 1269).

Characteristic	Categorical Variables, %	Continuous Variables Mean	SD	Range
Age, yrs		56.7	14.0	16–94
Female, %	77			
White, %	81			
Marital status, %				
Married	63			
Widowed, separated, divorced	29			
Never married	9			
No. of persons in household		2.4	1.3	0–24
Education, yrs		12.7	3.1	0–21
Number of comorbid conditions, %		0.5	0.7	0–5
With no conditions	62			
With 1 condition	29			
With 2+ conditions	9			
Duration of RA, yrs		11.1	10.2	0–65
No. of painful joints		7.6	3.6	0–13
No. of swollen joints		4.7	2.9	0–10
Pain rating		37.9	27.2	0–100
In fair or poor health, %	49			
Taking 1 or more DMARD, %	79			
HAQ score		1.2	0.8	0–3
Change in HAQ score*, %				
Declining function	40			
No substantive change	38			
Improved function	22			

* Averaged over number of years in study. Substantive change is considered to be 0.25 point.

Figure 1 presents an estimate of a life table for the UCSF RA Panel members without stratification for HAQ score. Overall, about 2% of the 1269 panel members had died by the second year after followup; this percentage increased to 11% by the fifth year, to 23% by the tenth year, to 34% by the fifteenth year, and to 39% by the eighteenth year, the maximal period of followup as of the end of 2000. By the eighteenth year, the 95% confidence interval for the proportion dying ranged from 35 to 44% (data on confidence interval not shown).

The baseline HAQ score had a substantial and (by log-rank test) statistically significant effect on the time until mortality (Figure 2). By the fifth year of followup, fewer than 5% of persons in the first (best) quartile of HAQ score had died, while more than 20% in the fourth (worst quartile) had. By the tenth year, the percentage dying in the first through fourth quartiles of baseline HAQ were about 15, 16, 25, and 37%, respectively. By the fifteenth year, the percentage dying was similar between those who had been in the first and second quartiles of HAQ at baseline (26 and 25%, respectively), but both groups had lower mortality than those in the third and fourth quartiles (of whom about 39 and 48% had died, respectively). By the eighteenth year of follow-up, about 29% of those in the first quartile of func-

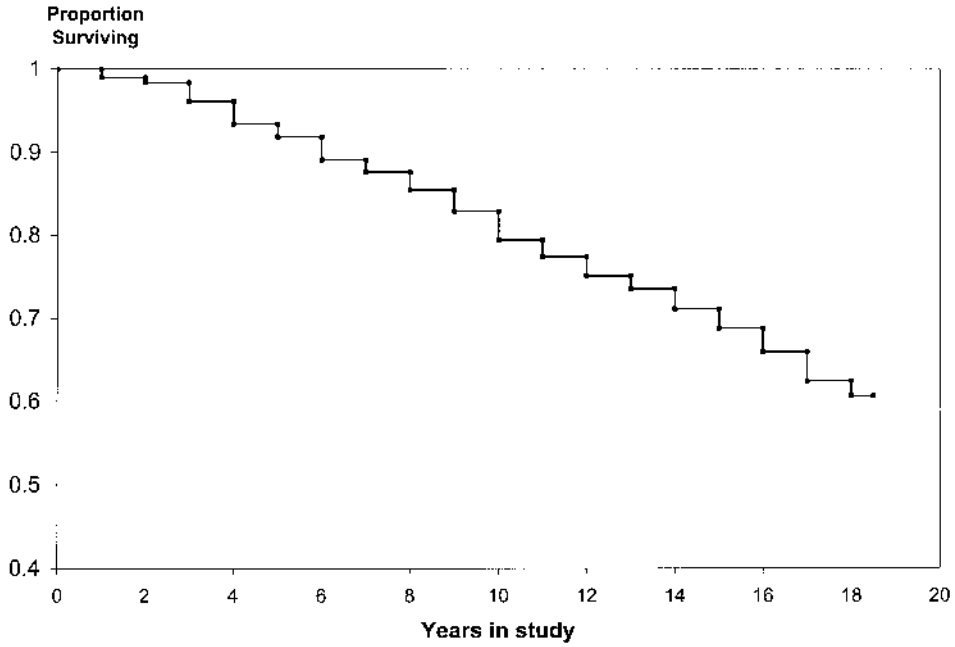

Figure 1. Survival rate of UCSF RA Panel members.

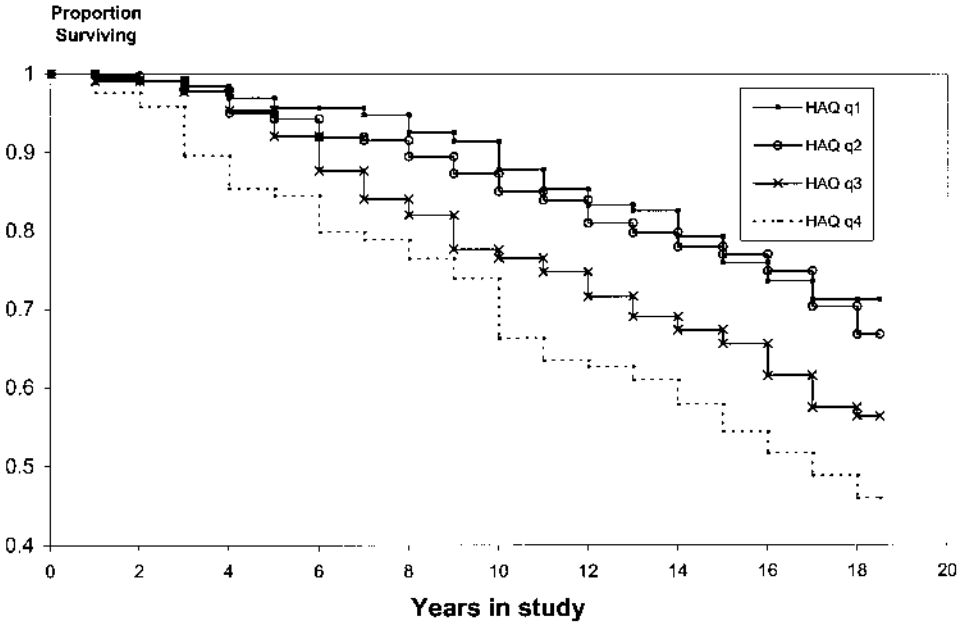

Figure 2. Survival rate among UCSF RA Panel members, by baseline HAQ score (quartiles).

tion had died; the corresponding figures for those in the second through fourth quartiles were 33, 44, and 54%, respectively. Thus, poor initial function results in a lower probability of survival. In a separate analysis (data not shown), we used the log-rank test to compare dyads of baseline quartiles of HAQ for their effect on the probability of dying in each interval. Persons in the first and second quartiles of baseline HAQ did not differ significantly in the proportion dying in each interval, but in every other case, those in a higher (worse) HAQ quartile were significantly more likely to die in each interval.

In addition to baseline HAQ quartile affecting the probability of mortality in each interval, experiencing a decline in function as measured by average change in HAQ score is associated with a lower probability of surviving in each year of followup (Figure 3). Accordingly, after 10 years about

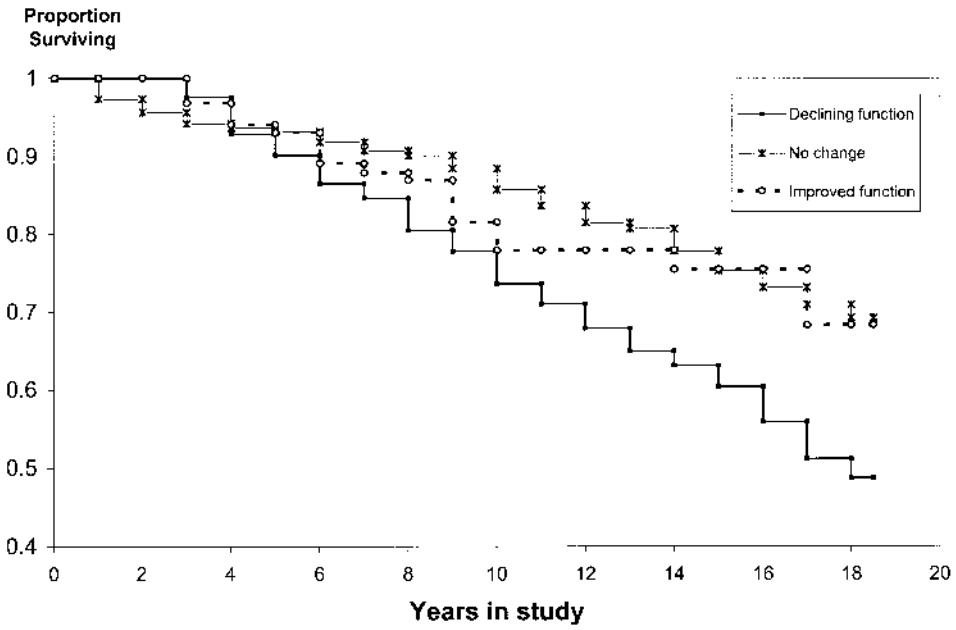

Figure 3. Survival rate among UCSF RA Panel members, by annualized change in HAQ score.

Table 2. Cox proportional hazard models of the annual risk of death, 1983-2000, UCSF RA Panel

Predictor Variable	Proportional Hazard Models				
	Baseline HAQ HR (95% CI)	Add HAQ Change HR (95% CI)	Add Demographic Characteristics HR (95% CI)	Add Other Health Measure HR (95% CI)	Add Other Health Change HR (95% CI)
Baseline HAQ, per 0.25 point	1.17 (1.12, 1.22)	1.22 (1.17, 1.28)	1.18 (1.13, 1.23)	1.15 (1.09, 1.22)	1.15 (1.09, 1.22)
Change in HAQ, per 0.03 point[a]		1.17 (1.14, 1.21)	1.12 (1.08, 1.17)	1.12 (1.08, 1.16)	1.12 (1.08, 1.17)
Age, per 5 yrs			1.42 (1.33, 1.52)	1.42 (1.33, 1.52)	1.42 (1.32, 1.51)
Male			2.48 (1.87, 3.29)	2.38 (1.79, 3.16)	2.43 (1.83, 3.24)
White			1.17 (0.80, 1.73)	1.23 (0.83, 1.82)	1.24 (0.84, 1.82)
Household size			1.01 (0.92, 1.11)	1.01 (0.92, 1.12)	1.02 (0.93, 1.12)
Education, yrs			0.97 (0.94, 1.01)	0.97 (0.94, 1.01)	0.98 (0.94, 1.02)
Married (vs. never married)			0.59 (0.34, 1.02)	0.58 (0.33, 1.00)	0.57 (0.33, 0.99)
Widowed/divorced/separated (vs never married)			0.75 (0.43, 1.32)	0.73 (0.42, 1.28)	0.73 (0.42, 1.29)
Duration of RA, yrs				1.00 (0.99, 1.01)	1.00 (0.99, 1.01)
In fair or poor health				1.28 (0.98, 1.68)	1.43 (1.06, 1.92)
Count of swollen joints				1.00 (0.95, 1.05)	0.98 (0.93, 1.04)
Pain rating				1.00 (0.99, 1.00)	1.00 (0.99, 1.01)
Comorbidity, no. of conditions				1.28 (1.10, 1.49)	1.24 (1.06, 1.45)
DMARD, no. of medications				0.99 (0.82, 1.18)	0.96 (0.80, 1.17)
Declining health status					0.81 (0.58, 1.15)
Change in swollen joint count[a]					1.26 (0.93, 1.71)
Change in pain rating[a]					1.00 (0.97, 1.03)
Increased no. of comorbid conditions					0.81 (0.62, 1.05)
Increased no. of DMARD					0.82 (0.57, 1.18)
Model chi-square, DF[b]	56, 1†	73, 1†	206, 7†	14, 6*	7, 5†

* $p < 0.05$; † $p < 0.01$.

[a] Total change, averaged over number of years in study. [b] Model chi-square comparing each successive model to the one immediately preceding. First model is compared to an intercept-only model.

29% of those experiencing declining function had died, compared to about 16 and 22% of those who had reported no change or improvement in function, respectively. By 15 years, 44% of those experiencing declining function had died, but only 27 and 24% of those reporting no change or improvement in function, respectively. By 18 years, 51% of those reporting declining function had died, whereas only 31 and 32% of those reporting no change or improvement in function, respectively. Clearly, avoiding the experience of declining function lowers the probability of death over the 18 years of followup. Using the log-rank test, we compared mortality risks by dyads of strata defined by whether average change in HAQ represented improvement, no change, or worsened functional status. Those who reported improved function did not differ from those reporting no change in function, but those reporting declining function had a significantly elevated risk of dying compared to those with no change in function or those whose function improved (data not shown).

Table 2 summarizes the results of the Cox proportional hazards regression analysis. Consistent with the findings from the foregoing analysis, the baseline HAQ score had a significant and substantial effect on mortality; each 0.25 increase in the HAQ score was associated with a hazard ratio of 1.17 (first column of Table 2). And, even after taking the initial HAQ score into account, each small increment of 0.03 in the average change in HAQ score was associated with a hazard ratio of 1.17 (second column of the table). Taking demographic characteristics into account (third column of Table 2) reduces the magnitude of the hazard ratio for the baseline HAQ and average change in HAQ only slightly, from 1.22 to 1.18 in the former case and from 1.17 to 1.12 in the latter. Adding health characteristics to the models had little effect on the hazard ratios associated with baseline and average change in HAQ scores (columns 4 and 5, Table 2).

Among the demographic characteristics, each increment of 5 years of age was associated with an elevated hazard ratio for mortality in all the models, as was male sex. In addition, being married had a protective effect for mortality, although it was only statistically significant in the final model. In the models that included measures of health status and health change, each additional comorbid condition increased the hazard rate for mortality. In the final model, none of the measures of change in health status had a significant association with risk of death, with the exception of the HAQ score change variable noted above.

We also estimated a model that included an interaction term for the measures of baseline HAQ and average change in HAQ, in order to assess if the effect of the change in HAQ score was dependent on the level of one's initial HAQ measurement. The interaction term in this model was not significant, indicating that change in HAQ affected mortality similarly across quartiles of HAQ score; this last model was not included in Table 2.

Using 1990 as a basis of comparison, the UCSF RA Panel members had a standardized mortality ratio of 1.32 relative to the US population with similar age and sex characteristics, indicative of a higher mortality rate. Using 1990 as a basis of comparison, the SMR for men and women in the UCSF RA Panel were 1.37 and 1.33, respectively. Using 1985 or 1995 as alternative bases for comparison, the SMR for the UCSF RA Panel members were 1.25 and 1.37, respectively, not substantially different from the 1.32 figure using 1990 as the basis of comparison.

DISCUSSION

In the traditional view, RA is a severe disease, albeit one with impact principally limited to the quality of life, not its quantity[26]. That view no doubt shifts attention of granting agencies and the public away from the condition, since diseases with a principal effect on mortality are often seen as more worthy of funding. However, the traditional view has been altered by a series of studies that show that, in fact, mortality among persons with RA is substantially elevated, as noted in comprehensive reviews[1,5,11,26]. The near unanimity of the finding that mortality among persons with RA is elevated is all the more striking given the heterogeneity in the sampling frames (incidence vs prevalence and clinical vs population based cohorts), demographic characteristics and national origin of the populations studied, and duration of followup.

Our study adds to the literature on mortality among persons with RA but differs from prior studies because of a combination of 3 factors: the large sample size (1269), longterm followup (as long as 18 yrs), and prospective and serial measurement of functional status via the HAQ score. The overall results are broadly consistent with most of the studies in the literature in finding elevated mortality rates for persons with RA, although the SMR of 1.32 we report is on the low end of SMR derived from other prevalence cohort studies[11].

The large sample size of this study allows us to make reliable estimates of the effect of the initial HAQ score and the average change in HAQ score on mortality. We found that both the initial HAQ and the average change in HAQ score have a profound effect on mortality rates. With respect to the former, by the eighteenth year of followup, 29% of those in the first (best) quartile of function had died, versus 33, 34, and 54% of those in the second through fourth (worst) quartiles of function. Similarly, by 18 years, 51% of those reporting declining function had died, whereas only 31 and 32% of those reporting no change or improvement in function, respectively, had.

The Cox proportional hazard regression analyses indicate that the initial level of HAQ score and extent of change in HAQ score independently affect mortality risk. Further, the

effect of the average change in HAQ on mortality does not differ among quartiles of initial HAQ score, suggesting that sparing additional loss of functional capacity reduces mortality risk throughout the spectrum of initial functional status, in turn suggesting that the provision of an intervention that preserves functional status is appropriate regardless of the initial severity of functional status.

The magnitude of the effect of initial HAQ score and the average change in HAQ score on mortality risk was not reduced substantially when demographic and health characteristics (including change in health characteristics over time) were taken into account. Thus, it would appear that almost all of the effect of poor functional status and declining functional status is due to these functional status measures, not to such characteristics of the persons with poor function as demographics and poor general health status. Nevertheless, several characteristics other than functional status were associated with higher mortality, including advanced age, male sex, reporting fair or poor health status, and having a greater number of comorbid conditions. On the other hand, being married (compared to never having been married) reduced mortality risk. The finding that male sex and older age elevate mortality risk is consistent with some, but not all studies[1,5].

Although our study does document that both beginning with good function and avoiding loss of function will reduce mortality risk, and although there is short term evidence from clinical trials that several remittive agents reduce loss of function, the observational nature of our study prevents us from concluding that the use of effective agents accounts for the reduced mortality. This is because effective agents may have been given in a non-random fashion to those predestined to have a lower (or, for that matter, higher) mortality rate. Accordingly, the time may be propitious to implement trials of sufficiently long duration to establish that the use of select therapeutic agents accounts for both the preservation of function and the subsequent reduced mortality risk. In the interim, with the advantage of a large sample size, longterm followup, and prospective and serial measurement of function, we have observed that both initial functional status and subsequent change in functional status are profound markers of mortality risk among the persons with RA in our study.

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