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Association of Mortality With Disease Severity in Rheumatoid Arthritis, Independent of Comorbidity

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Objective. **To measure the extent to which mortality in rheumatoid arthritis (RA) is associated with disease severity, independent of the presence of coexistent diseases (comorbidity).**

Methods. **We measured disease severity and comorbidity among RA patients attending scheduled appointments at a rheumatology clinic. We used the Duke Severity of Illness Checklist (DUSOI), a clinical judgment-based measure of the severity of disease. We disaggregated the DUSOI into an RA component (RADUSOI), which we used to measure RA disease severity, together with a physician-rated 10-point global RA severity assessment. We measured comorbidity using the non-RA component of the DUSOI (COMDUSOI) and using the Charlson Comorbidity Index. Patients were contacted periodically for up to 6 years, during which we recorded deaths. We estimated the effect of disease severity and comorbidity on mortality using Kaplan-Meier survival curves, Cox proportional hazards models, and logistic regression with receiver operating characteristics (ROC) curve analysis.**

Results. **The sample comprised 779 patients. Followup ranged from 0.1 year to 6.3 years (mean 2.52 years), for an observation period of 2,315 patient-years. Seventy-five patients died (9.6%), for a total mortality of 3.2 per 100 patient-years (95% confidence interval 2.6–4.1). Both disease severity and comorbidity displayed significant bivariate associations with mortality. In multivariate Cox models adjusted for age, sex, and disease duration, the RADUSOI and global RA severity scores were associated with mortality independent of either the COMDUSOI or Charlson Comorbidity scores. The area under the ROC curve for a logistic model on mortality increased from 0.79 with age, sex, and disease duration included, to 0.84 after adding RA severity and comorbidity ($P \leq 0.005$ for the increase in ROC area).**

Conclusion. **RA disease severity is significantly associated with mortality regardless of the presence of comorbid disease. Combined with each patient's age, sex, and disease duration, information on RA severity and comorbidity allows an accurate prediction of mortality among patients with RA.**

Rheumatoid arthritis (RA) is associated with an increased risk of dying. This risk is elevated when RA is severe, as defined by the presence of advanced joint damage, functional limitations, disability, extraarticular disease, and rheumatoid factor positivity (1–8). Because RA is a joint-centered disease that, in most patients, does not affect the viscera, its increased mortality engenders questions about the cause of death. In fact, patients with RA die from a wide variety of illnesses (2,6,9). Their burden of coexistent diseases, or comorbidity, is also higher than expected as compared with people of the same age and sex without RA (10). Comorbidity has a negative influence on the physical and psychosocial condition of RA patients (11), and may be a major factor explaining the disease's high death rate (12). Although both disease severity and comorbidity have recognized associations with mortality in RA, their independent contribution to the death risk among RA patients has received less attention.

In the present analysis, we carefully measured disease severity and comorbidity in a sample of RA

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patients. We hypothesized that mortality would be associated with disease severity in RA, independent of comorbidity.

PATIENTS AND METHODS

Patients. Between January 1996 and April 2000, we recruited consecutive patients who met the classification criteria for RA (13). In addition to having RA, patients had to be older than 18 years of age. No other inclusion or exclusion criteria were applied.

Settings. We recruited patients from 6 outpatient rheumatology clinics in San Antonio, Texas: 1) an Army medical center, 2) an Air Force medical center, 3) a private, university-based clinic, 4) a community-based, 7-rheumatologist private practice, 5) a county-funded clinic, and 6) a Veterans Administration clinic.

Data collection procedures. Our study was approved by the institutional review board of each recruitment center. After obtaining the patients' written, informed consent, we conducted a comprehensive clinical evaluation and reviewed the available medical records. All evaluations were conducted by a physician or research nurse, with the assistance of a research associate, all of whom were trained in the correct assessment of the study variables. The evaluation's content is described below.

Sociodemographics. We ascertained each patient's age, sex, race/ethnicity, and years of formal education by self-report, as described previously (14).

Comorbidity measurements. *Duke Severity of Illness Checklist (DUSOI).* A physician scored the DUSOI, an instrument based on clinical judgment that reflects the extent of a patient's illness (15). To score the DUSOI, the physician compiled a list of the patient's health problems that were active at the time of the evaluation. Then, the physician assigned a value to 4 dimensions of each health problem. The 4 dimensions were as follows: symptoms, complications, prognosis, and treatability. Each dimension was graded on a 5-level scale, ranging from 0 to 4. Each level had specific definitions (for example, in the case of treatability, a score of 0 = no treatment needed, 1 = need for treatment questionable, 2 = treatment needed, with good response expected, 3 = treatment needed, but response questionable, and 4 = treatment needed, but expected response poor). The 4 ratings for each problem were then summed, divided by 16, and multiplied by 100, to obtain a severity score for the health problem, which could range from 0 for the lowest severity to 100 for the highest severity.

Subsequently, the patient's health problems were ranked according to the severity score, and entered into a formula that assigns full weight to the highest-ranking problem, followed by progressively diminishing weight for lower-ranking health problems. The formula can be represented as follows:

$$\mathrm{DUSOI} = \mathrm{Dx}_{\max} + \frac{100 - \mathrm{Dx}_{\max}}{100} \times \sum \frac{1}{2^{n-1}} \mathrm{Dx}_n$$

where $\mathrm{Dx}_{\max}$ indicates the highest ranking health problem and Dx_n is each subsequent health problem, with n representing the problem's severity ranking. The physicians responsible for grading comorbidity on the DUSOI scale were trained according to a standardized protocol. All of the problems listed and their severity ratings were reviewed by a second physician and, often, a third physician, and any disagreements were discussed before assigning a final value.

To assess the interrater reliability of the DUSOI according to these calculations, we used the records of 27 consecutively selected patients who had been evaluated by one of the study's physicians. This physician did not know these records would be used to test reliability. Three subsequent physicians, after receiving training about the DUSOI and its scoring, independently reviewed the 27 records without discussing their reviews with any other person. To test intrarater reliability, the first physician repeated the scoring of 12 randomly selected records after a 1-week interval.

Because of our interest in separating the contributions of RA from those of comorbid conditions, and because RA was among the top health problems in many of the patients in our sample, we applied the above-described formula to each patient's health problems after excluding the ratings for RA. We refer to this RA-free scale as the Comorbidity DUSOI (COMDUSOI).

Charlson Index. The second comorbidity scale that we used was the Charlson Comorbidity Index (16). This index records the presence or absence of 18 health problems, each one weighted for severity according to predefined values. The following health problems receive a weight of 1 in the index: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease without hemiplegia, dementia, chronic pulmonary disease, connective tissue disease (including RA), peptic ulcer disease, mild liver disease, and diabetes mellitus without end-organ damage. The following health problems receive a weight of 2: hemiplegia, moderate or severe renal disease, diabetes with end-organ damage, malignant neoplasms, leukemia, and lymphoma. Moderate or severe liver disease receives a score of 3. Metastatic solid tumor and the acquired immunodeficiency syndrome receive a score of 6. The final score is provided by the sum of the weights of each patient's health problems. The examining physician used a validated self-report questionnaire to interview the patients about the presence or absence of the predefined health problems (17). The physician then reviewed available medical records to verify the problems reported by the patient. If discrepancies between the medical record and the self-reported responses arose, the case was discussed among 3 or 4 physicians in order to decide on the final score. We tested the interrater reliability of the Charlson Index by having 2 physicians independently score the index in 20 consecutive patients, without discussing the score with any other person.

Disease severity measures. *DUSOI score for severity of RA (RADUSOI).* Using the approach outlined above for the DUSOI, the examining physician rated each patient's RA symptoms, complications due to RA, disease prognosis, and treatability of the disease on a 0–4 scale. The sum of these 4 ratings was divided by 16 and then multiplied by 100, to obtain the RADUSOI. To assess the concurrent validity of the RADUSOI as an RA disease severity measure, we compared it against simultaneously measured criterion standards, as described below.

RA global disease severity scale. At the time of the baseline evaluation, the examiner rated the severity of RA on

Table 1. Baseline characteristics of the rheumatoid arthritis (RA) study sample, according to vital status at followup

Individual characteristic	Vital status at followup*		*P*
	Living (n = 704)	Dead (n = 75)	
Sociodemographic variables			
Age, mean ± SD years	54 ± 13	67 ± 9	≤0.001
Men, n (%)	195 (28)	34 (45)	0.001
Years of education, mean ± SD	11 ± 4	9 ± 4	≤0.001
Race/ethnic background, n (%)			0.5
Hispanic	391 (56)	43 (57)	
White	243 (35)	29 (39)	
African American	50 (7)	3 (4)	
Asian	14 (2)	0 (0)	
Other ethnic group	6 (1)	0 (0)	
Clinical features			
Years with RA, mean ± SD	11 ± 10	16 ± 13	≤0.001
Tender joint count, mean ± SD	15 ± 13	17 ± 14	0.1
Swollen joint count, mean ± SD	8 ± 7	7 ± 7	0.3
Deformed joint count, mean ± SD	9 ± 10	18 ± 14	≤0.001
Subcutaneous nodules, n (%)	206 (29)	27 (36)	0.2
Rheumatoid factor positive, n (%)	620 (88)	64 (85)	0.7
Functional status and disability level			
Steinbrocker functional class, n (%)			≤0.001
Class I	160 (23)	3 (4)	
Class II	359 (51)	27 (36)	
Class III	161 (23)	29 (39)	
Class IV	24 (3)	16 (21)	
Modified Health Assessment Questionnaire, mean ± SD score	1.8 ± 0.7	2.3 ± 0.9	≤0.001
Comorbidity instruments			
COMDUSOI, mean ± SD†	46 ± 22	66 ± 19	≤0.001
Charlson Comorbidity Index, n (%)			≤0.001
1	419 (60)	22 (29)	
2	169 (24)	29 (39)	
≥3	116 (17)	24 (32)	
RA disease severity instruments			
RADUSOI, mean ± SD‡	48 ± 13	57 ± 16	≤0.001
Global disease severity, mean ± SD score	2.8 ± 2.1	4.8 ± 2.9	≤0.001

* Censoring date was April 30, 2002.
† COMDUSOI = Duke Severity of Illness Checklist (DUSOI) score for non-RA comorbid disease burden.
‡ RADUSOI = RA severity score derived from the DUSOI instrument (see text for details).

a graded scale, ranging from 0 to 10 and anchored by the categories "Mildest disease" and "Most severe disease." Examiners were instructed to consider each RA patient's global disease condition to assign this score, not just the inflammatory status of the joints. In our study, the Spearman-Brown reliability coefficient was 0.88 for this variable.

Musculoskeletal examination. A physician or research nurse, both of whom were trained in joint examination techniques, assessed 48 joints in each patient for the presence or absence of tenderness or pain on motion, swelling, or deformity (18). For the joint examinations, the Spearman-Brown reliability coefficients were 0.94 for tenderness/pain on motion, 0.90 for swelling, and 0.98 for deformity.

Additional clinical details. We defined disease duration as the period spanning from the time of diagnosis of RA, as reported by the patients. The physical examination also noted the presence or absence of subcutaneous nodules. The rheumatoid factor status and the erythrocyte sedimentation rate were obtained on the day of evaluation or within the previous 3 months. Current use of prednisone and disease-modifying antirheumatic drugs was obtained by medical record review, which was supplemented by patient self-report.

Steinbrocker functional class. The Steinbrocker functional classification (19) was assigned by the physician or a research nurse who was trained in physical function assessment. The Steinbrocker functional classification is used to rate the extent of physical disability on a 4-level scale. The scale ranges from class I ("complete functional capacity with ability to carry out all usual duties without handicaps") to class IV ("largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care"). Spearman-Brown reliability of the Steinbrocker classification in our study was 0.84.

Modified Health Assessment Questionnaire (M-HAQ). Each patient completed the 8-item M-HAQ (20), which asks respondents to rate the amount of difficulty in performing 8

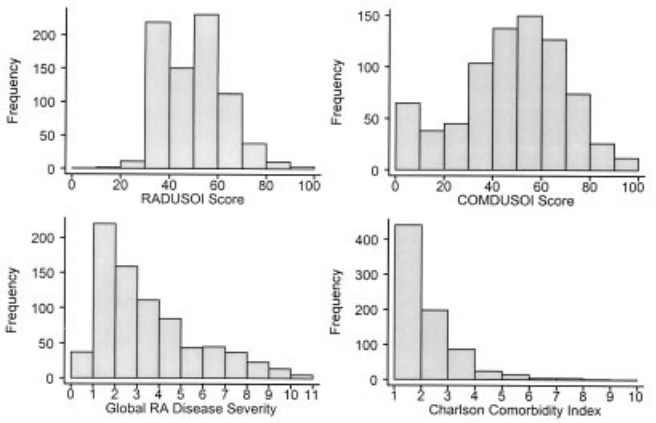

Figure 1. Frequency distribution of the rheumatoid arthritis (RA) Duke Severity of Illness Checklist (RADUSOI), the RA physician-rated global severity measure, the non-RA Comorbidity DUSOI (COMDUSOI), and the Charlson Comorbidity Index scores among patients with RA (see Patients and Methods for detailed descriptions of each measure).

activities of daily living. Response options for the degree of difficulty included "none," "some," and "much difficulty," as well as "unable" to perform these activities, and responses were expressed on a scale of 1–4 in ascending order of difficulty ratings. In our population, reliability of the M-HAQ was 0.97 (21).

Survival followup. Starting in 1997, patients have been contacted annually for followup assessments. The censoring date for the present analysis was April 30, 2002. We have learned of deaths through family members, friends, neighbors, or other physicians, or through public databases on deaths. All have been confirmed by death certificate.

Statistical analysis. We calculated the mortality rate and its 95% confidence interval (95% CI) using a person-years approach. We used Student's *t*-test and chi-square to test for baseline differences between patients who survived and those who died. We compared the RADUSOI and the global RA disease severity scale with concurrently measured criterion standards using Spearman's rank order correlation coefficient. We used the Kaplan-Meier method to estimate survival differences between subjects grouped according to RA severity and comorbidity (22). We tested differences in the survival functions between groups using the log-rank method. We used multivariable Cox proportional hazards models to estimate the influence of the RA disease severity and comorbidity measures on survival, adjusting for covariates (23). We included age, sex, and disease duration in all models, because these 3 variables may be associated with survival in RA (24). To assess the performance of the RA severity and comorbidity scales as predictors of death within the 6-year followup period, we compared the area under the receiver operating characteristics (ROC) curve of the logistic models that included age, sex, disease duration, comorbidity, and RA severity as predictors (25). We used the Spearman-Brown coefficient to assess reliability (26). All analyses were conducted using a desktop personal computer with the Stata statistical software package, version 7.0 (College Station, TX).

RESULTS

We enrolled 779 patients. Their baseline characteristics, according to vital status as of April 30, 2002, are shown in Table 1. The followup time period ranged from 0.1 year to 6.3 years (mean 2.52 years), for a total period of observation of 2,315 person-years. During this time, 75 patients died (9.6%), for a mortality rate of 3.2 per 100 patient-years (95% CI 2.6–4.1).

The inter- and intrarater reliability of the patient-averaged DUSOI was 0.87 and 0.90, respectively. For the total Charlson Comorbidity Index score, the inter-rater reliability was 0.94. These reliability estimates may reflect a lower bound because, in our study, all comorbidity scores underwent a second level of review by one or more physicians who discussed the case prior to the final score. Graphs depicting the frequency distribution of the RA severity and comorbidity scores among the 779 patients are shown in Figure 1. The Spearman's correlation between the 2 RA severity scales, the RADUSOI and the RA global severity rating, was 0.55 ($P \leq 0.0001$), while the correlation between the 2 comorbidity scales, the COMDUSOI and the Charlson Index, was 0.45 ($P \leq 0.0001$). The correlations between the comorbidity scales and RA disease severity scales were modest, with r values ≤ 0.23 in the 4 pairwise comparisons between both comorbidity scales and both RA severity scales.

The 2 RA disease severity scales correlated, to a similar extent, with the other concurrently ascertained

Table 2. Correlation between RA disease severity measures and criterion standards*

Criterion	Disease severity measure	
	RADUSOI	Global RA severity
Age	0.20	0.26
Disease duration	0.30	0.33
Tender joint count	0.23	0.19
Swollen joint count	0.19	0.18
Deformed joint count	0.55	0.67
Erythrocyte sedimentation rate†	0.17	0.23
Steinbrocker functional classification	0.44	0.68
Modified Health Assessment Questionnaire score	0.34	0.38
COMDUSOI‡	0.23	0.18
Charlson Index‡	0.07§	0.21

* Values shown are Spearman's rank order correlation coefficients. All coefficients are significant at $P \leq 0.0005$, unless noted otherwise. See Table 1 for definitions.
† Data were available on 719 patients.
‡ COMDUSOI versus Charlson Index correlation 0.45 ($P \leq 0.0001$).
§ $P = 0.054$.

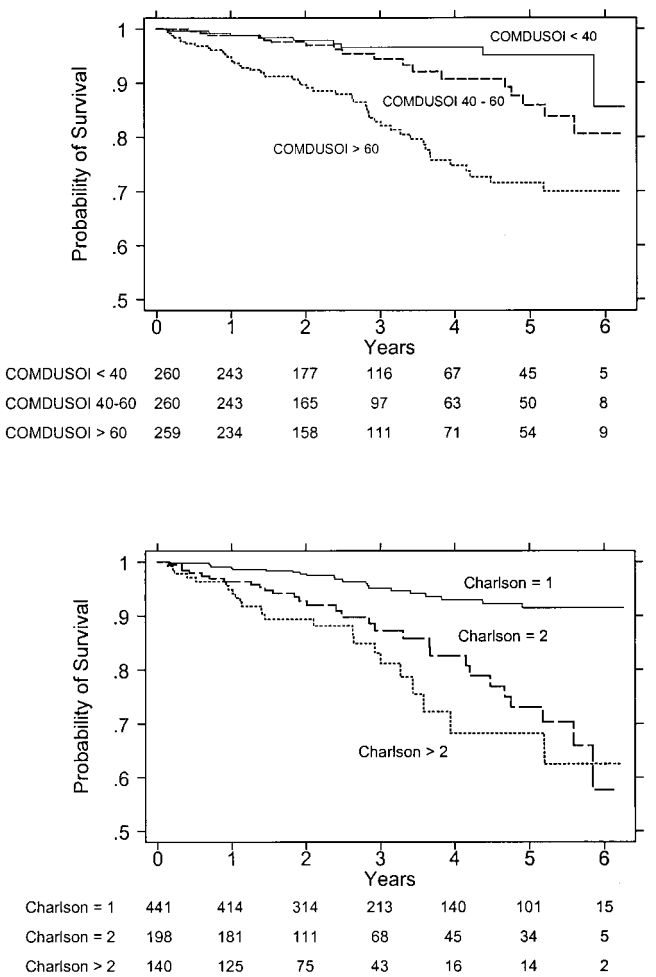

Figure 2. Estimated survival curves for each comorbidity scale, using the Kaplan-Meier technique. **Top,** Survival in relation to the COMDUSOI categories. The difference in survival probability between the 3 categories was significant (log-rank χ^2 [with 2 degrees of freedom] = 29.24, $P \leq 0.0001$). **Bottom,** Survival in relation to the Charlson Comorbidity Index categories. Patients with a Charlson score of 1 had RA only, without other comorbidities scored on this scale (log-rank χ^2 [with 2 degrees of freedom] = 33.18, $P \leq 0.0001$). Values next to the categories are the number of patients in each category in each year of followup. See Figure 1 for definitions.

variables that reflect the intensity of disease activity or the extent of joint damage (Table 2). The correlation was strongest with the measurements of joint damage and physical disability. Nevertheless, both RA severity scales also correlated modestly, but significantly, with the measures of disease activity. The presence of subcutaneous nodules, a marker of severe disease, was also associated with significantly higher scores on both RA severity scales (mean ± SD RADUSOI score 54 ± 13 among patients with nodules versus 47 ± 13 among those without nodules [$P \leq 0.0001$]; mean ± SD global RA severity score 3.9 ± 2.6 among patients with nodules versus 2.6 ± 2.0 among those without nodules [$P \leq 0.0001$]).

Both comorbidity scales and RA severity scales displayed strong bivariate associations with the probability of survival, and these associations were statistically significant. Figure 2 plots the survival function according to comorbidity categories, and similarly, Figure 3 plots the survival function according to disease severity.

We used multivariate Cox regression to explore

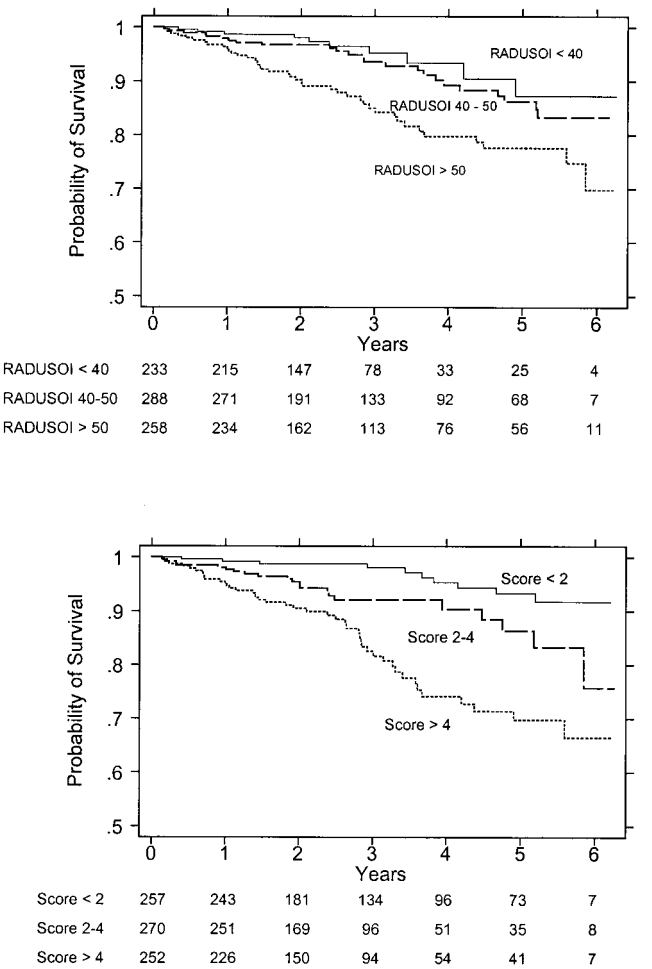

Figure 3. Estimated survival curves for each RA severity scale, using the Kaplan-Meier technique. **Top,** Survival according to the RADUSOI categories. The difference in survival probability between the 3 categories was significant (log-rank χ^2 [with 2 degrees of freedom] = 15.03, $P \leq 0.0001$). **Bottom,** Survival according to the RA global severity scale (log-rank χ^2 [with 2 degrees of freedom] = 33.5, $P \leq 0.0001$). Values next to the categories are the number of patients in each category in each year of followup. See Figure 1 for definitions.

Table 3. Independent association of RA disease severity and comorbidity with mortality*

Variable	Risk of death			
	Model 1	Model 2	Model 3	Model 4
Severity scale				
RADUSOI (range 6–93)	1.02 (1.00–1.04)†	1.03 (1.02–1.05)‡	–	–
Global severity (range 0–10)	–	–	1.20 (1.10–1.31)‡	1.29 (1.18–1.41)‡
Comorbidity scale				
COMDUSOI (range 0–98)	1.04 (1.02–1.05)‡	–	1.03 (1.02–1.05)‡	–
Charlson Index (range 1–9)	–	1.34 (1.15–1.56)‡	–	1.32 (1.13–1.54)
Likelihood ratio chi-square§	126.7	109.5	137.3	124.4

* Except where otherwise indicated, values are the hazard ratio (95% confidence interval), adjusted for age, sex, and disease duration. Hazard ratios are the proportional change in the risk of death associated with a 1-unit change in the independent variable. Models 1–4 are Cox logistic regression analyses in which only one comorbidity and one disease severity scale was included in each. See Table 1 for definitions.
† $P \leq 0.05$.
‡ $P \leq 0.001$.
§ For comparison, the chi-square value for the model that included only age, sex, and disease duration was 86.8.

the independent influences of RA severity and comorbidity on survival. We tested 4 models, each of which included one comorbidity scale and one disease severity scale. Our objective with this approach was to show that the effect of severity and comorbidity on mortality did not depend on the type of measurement scale. We included age, sex, and disease duration as covariates in these models to control for the possibility of confounding by these potentially important mortality predictors. We found significant independent associations with mortality for both of the disease severity scales and both of the comorbidity scales. The age-, sex-, and disease duration–adjusted hazard ratios for each comorbidity and severity measure are provided in Table 3. These hazard ratios should be interpreted as the proportional change in the risk of death associated with a 1-unit change in the independent variable. Thus, a hazard ratio of 1.03 associated with the COMDUSOI represents a 3% increase in the risk of death per unit increase in that scale, which ranged from 0 to 98 in our study. In the case of the Charlson Index, which in the present study ranged from 1 to 9, each unit increase was associated with an even larger increase in the hazard ratio for death, because Charlson units represent a greater proportion of the scale's range.

We also estimated the diagnostic accuracy of these baseline measurements as predictors of death during the observation period. We modeled death as a logistic function of age, sex, disease duration, and the comorbidity and severity scores. We then estimated the predicted probability of death for each person, based on each of the models tested, and calculated the area under the ROC curve for the prediction. Models including both a severity and a comorbidity variable had significantly greater area under the ROC curve ($P \leq 0.005$ for the increase in ROC area) than did a model that included only age, sex, and disease duration. This is shown graphically in Figure 4.

Because of the possibility that our inclusion of deaths that occurred within 1 year of recruitment in these analyses could overestimate the influence of comorbidity and disease severity, we repeated all of the analyses after excluding the 19 patients who died within 1 year. All of our findings remained essentially unchanged following this exclusion, without loss of significance of comorbidity or disease severity as death predictors in RA.

DISCUSSION

Mortality in this RA sample was associated with disease severity in a manner that was independent of the burden of coexistent disease. This finding is important because it further situates RA as a systemic illness with pathophysiologic consequences that transcend the joint. Markers of disease severity were among the first factors that were recognized to increase the risk of death among RA patients (1,3,4,11). However, early studies of survival in RA did not include formal measures of coexistent disease, leaving open the possibility of confounding by this variable. This omission may, in part, explain why the high mortality risk in this disease is underrecognized outside of rheumatology, since it is not intuitively apparent why a disease that targets joints should also increase the risk of death.

More recently, a study in which comorbidity was measured carefully demonstrated that RA is indeed accompanied by a greater presence of coexistent illness, as compared with the observations in age- and sex-matched subjects without RA (10,12). This confirmed

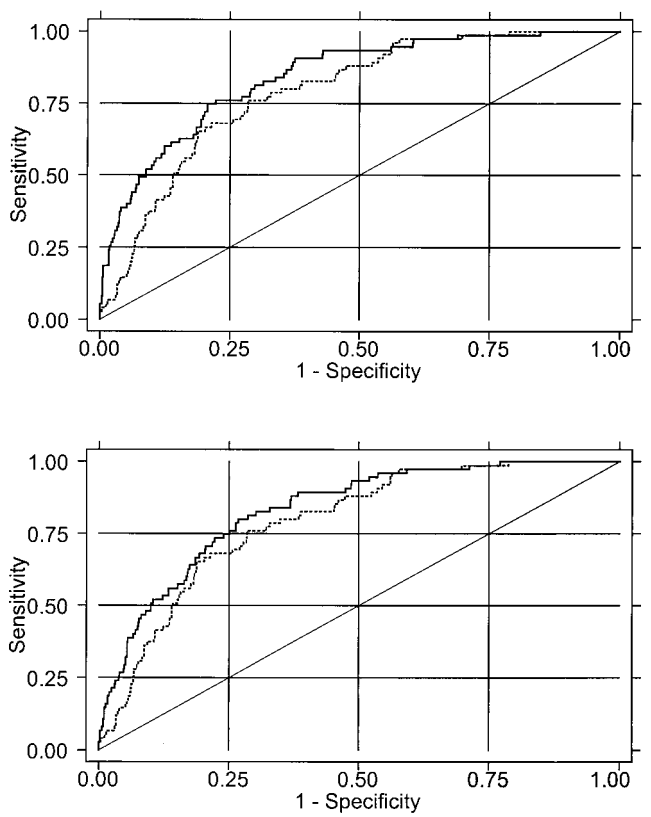

Figure 4. Receiver operating characteristics (ROC) curves of logistic models, using age + sex + disease duration alone as mortality predictors (broken jagged line in **Top** and **Bottom**) (area under the ROC curve 0.79, 95% confidence interval [95% CI] 0.75–0.84) versus age + sex + disease duration + disease severity + comorbidity. **Top,** Solid jagged line represents age + sex + disease duration + COMDUSOI + RADUSOI (area under the ROC curve 0.84, 95% CI 0.80–0.89). **Bottom,** Solid jagged line represents age + sex + disease duration + RA global severity + Charlson Comorbidity Index (area under the ROC curve 0.83, 95% CI 0.79–0.87). See Figure 1 for other definitions.

that, as in other diseases, comorbidity in RA has a strong negative influence on survival (10,12). The contribution of our study has been to provide an estimate of the independent effect of both disease severity and comorbidity on RA survival.

We used 2 validated scales to measure comorbidity. The Charlson Comorbidity Index is a checklist of 18 conditions, each weighted by the mortality risk conferred to hospitalized people (16). This widely used index is simple and does not require the investigator to judge the severity of each condition, which makes it convenient and facilitates its implementation for research. However, the Charlson Index is not sensitive to variation in severity within a given condition, and it limits investigators to 18 conditions. The DUSOI complements the Charlson Index by providing an open-ended way to classify a condition's severity. This allows the clinician-investigator to record and severity-score any health problem. In our study, both the DUSOI and the Charlson Index had excellent reliability.

We extracted the component attributable to RA alone from the DUSOI, which we called the RADUSOI. We also recalculated the score excluding the RA values, which we called the COMDUSOI. Our purpose in doing these operations was 2-fold. First, we wanted to remove the substantial contribution of RA to the DUSOI score because it interfered with our goal of separating RA severity from comorbidity. In removing the RA contribution from the DUSOI, our second goal became a byproduct in that we were able to calculate the sum of the scores for symptoms, complications, prognosis, and treatability of RA to produce the RADUSOI, which thus provided a reasonable RA severity index. This was borne out by the good correlation of the RADUSOI with the deformed joint count, Steinbrocker functional class, and M-HAQ score (Table 2). The RA global severity assessment, scored on a 0–10 scale by the examining clinician, also correlated well with concurrent variables that reflected RA severity. All 4 of the scales used in our study were strongly linked to survival in bivariate analyses, even when only deaths that occurred $\geq$1 year after the beginning of the observation period were considered. Adjustment for the potential confounding effects of age, sex, and disease duration did not remove this association, which is an important observation, particularly given the likelihood of an association between age and comorbidity.

The predictive accuracy of a multivariate model such as that tested here is provided by the area under its ROC curve. Without any information about a patient, random choice would give an accuracy of 50% in predicting death, equal to a coin flip. We have shown that information on a patient's age, sex, and disease duration increases the predictive accuracy to 79%, and that adding comorbidity and disease severity further raises the accuracy to 84%. This compares favorably to the accuracy of frequently used diagnostic systems (27).

Our aim with these analyses was to test the independent effect of disease severity and comorbidity as determinants of mortality in RA. We thus employed what could be described as a purely biomedical model, in that it included only disease-related variables in the analysis. Although we documented a significant association between these variables and mortality, there are likely to be additional factors associated with mortality

in RA that we did not consider here. Examples of factors that would fit within a bio-psychosocial health paradigm, and which may also affect mortality in RA, include educational level, marital status, psychological limitations, and other psychosocial indicators (24). Exploring how these factors influence mortality after accounting for disease severity and comorbidity represents an interesting avenue for future research.

Some aspects of our study merit a cautionary note in interpretation. We recruited the patients in our sample from clinics where they had a scheduled appointment with a rheumatologist. Thus, our findings are most applicable to the type of patient with established RA who is usually seen in a rheumatologist's office for continuing care. The clinical facilities from which we recruited patients provided us with the full range of RA disease severity and comorbidity. This enabled us to test valid hypotheses about the influence of disease severity and comorbidity on mortality (28). However, it should be noted that the prevalence and distribution of comorbidity in our sample may differ from that of the total population of RA patients.

We recruited a significant proportion of our patients after their RA had been present for a number of years, which allowed us to study the full range of disease-induced damage. However, this may also have introduced bias by excluding patients who died or whose disease remitted before we began recruitment. Replicating our analysis in an inception cohort, however, would likely require a substantially larger sample and a longer followup period in order for comorbidity, disease-induced damage, and mortality to accrue to an extent sufficient to test our hypotheses.

Our findings have potential clinical implications. The observation that comorbidity is a major contributor to mortality in RA should serve to focus attention on other diseases that may affect RA patients. Although it is not a widespread practice, a significant proportion of rheumatologists fulfill a primary care role for RA patients (29). Many RA patients also look to the rheumatologist as their principal doctor, even when a primary care physician has been assigned to them. In light of our findings, rheumatologists should continue to keep a watchful eye on their patients' nonrheumatologic coexistent illnesses.

It is not clear how the severity of RA could lead to an increased mortality risk in a manner independent of comorbidity. Plausibly, severe RA can mask the recognition of comorbid conditions associated with mortality, and these may not be picked up by comorbidity instruments. Alternatively, severe RA can be associated with occurrence of conditions that cause sudden, unexpected death, which would also not appear in comorbidity scales. It is also possible that severe RA leads to a greater exposure to medications and their side effects. Neither of the comorbidity measurement scales we used provide for direct scoring of drug toxicity.

The high death risk associated with RA may also be a consequence of an excess allostatic load, or global adverse physiology caused by the presence of a chronic illness (30). Stress induced by RA or other persistent unfavorable conditions may lead to a maladaptive response by the neuroendocrine and other systems. This process, over time, is believed to increase the cumulative biologic risk to the cardiovascular and other systems (31). In-depth physiologic measurements are needed to capture this variable (32), and further study is needed to understand its possible role in explaining mortality and other outcomes in RA.

Finally, it is also possible that we overestimated the effect of comorbidity on mortality. Some of the comorbidities we encountered (for example, osteoporosis, diabetes mellitus) may be linked to RA and its treatment. We did not attempt to tie individual comorbidities to RA. It is likely that this would have resulted in a stronger association between RA severity and mortality than that observed in this study.

We conclude that mortality in RA is independently associated with the severity of the disease and with the extent of the comorbid disease burden. Further studies are needed to understand the mechanisms whereby disease severity can lead to increased mortality in RA.

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REFERENCES

1. Pincus T, Callahan LF, Vaughn WK. Questionnaire, walking time and button test measures of functional capacity as predictive markers for mortality in rheumatoid arthritis. J Rheumatol 1987; 14:240–51.
2. Jacobsson LTH, Knowler WC, Pillemer S, Hanson RL, Pettit DJ, Nelson RG, et al. Rheumatoid arthritis and mortality: a longitudinal study in Pima Indians. Arthritis Rheum 1993;36:1045–53.
3. Chehata JC, Hassell AB, Clarke SA, Mattey DL, Jones MA, Jones PW, et al. Mortality in rheumatoid arthritis: relationship to single

and composite measures of disease activity. Rheumatology (Oxford) 2001;40:447–52.
4. Van Schaardenburg D, Hazes JM, de Boer A, Zwinderman AH, Meijers KA, Breedveld FC. Outcome of rheumatoid arthritis in relation to age and rheumatoid factor at diagnosis. J Rheumatol 1993;20:45–52.
5. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Occurrence of extraarticular disease manifestations is associated with excess mortality in a community based cohort of patients with rheumatoid arthritis. J Rheumatol 2002;29:62–7.
6. Cobb S, Anderson F, Bauer W. Length of life and cause of death in rheumatoid arthritis. N Engl J Med 1953;249:553–6.
7. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. Arthritis Rheum 1994;37:481–94.
8. Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period. Arthritis Rheum 2002;46:625–31.
9. Mitchell DM, Spitz PW, Young DY, Bloch DA, McShane DJ, Fries JF. Survival, prognosis, and causes of death in rheumatoid arthritis. Arthritis Rheum 1986;29:706–14.
10. Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. J Rheumatol 1999;26:2475–9.
11. Berkanovic E, Hurwicz M-L. Rheumatoid arthritis and comorbidity. J Rheumatol 1990;17:888–92.
12. Gabriel SE, Crowson CS, O'Fallon WM. A comparison of two comorbidity instruments in arthritis. J Clin Epidemiol 1999;52: 1137–42.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
14. Escalante A, del Rincón I, Mulrow CD. Symptoms of depression and psychological distress in Hispanics with rheumatoid arthritis. Arthritis Care Res 2000;13:156–67.
15. Parkerson GR Jr, Broadhead WE, Tse CK. The Duke Severity of Illness Checklist (DUSOI) for measurement of severity and comorbidity. J Clin Epidemiol 1993;46:379–93.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
17. Katz JN, Chang LC, Sangha O, Fossel AH, Bates DW. Can comorbidity be measured by questionnaire rather than medical record review? Med Care 1996;34:73–84.
18. Orces CH, del Rincón I, Abel MP, Escalante A. The number of deformed joints as a surrogate measure of damage in rheumatoid arthritis. Arthritis Care Res 2002;47:67–72.
19. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria for rheumatoid arthritis. JAMA 1949;140:659–66.
20. Pincus T, Summey JA, Soraci SAJ, Wallston KA, Hummon NP. Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum 1983;26:1346–53.
21. Escalante A, Galarza-Delgado D, Beardmore TD, Baethge BA, Esquivel-Valerio J, Marines AL, et al. Cross-cultural adaptation of a brief outcome questionnaire for Spanish-speaking arthritis patients. Arthritis Rheum 1996;39:93–100.
22. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
23. Cox DR. Regression models and life tables. J R Stat Society (Series B) 1972;34:187–220.
24. Callahan LF, Cordray DS, Wells G, Pincus T. Formal education and five-year mortality in rheumatoid arthritis: mediation by helplessness scale score. Arthritis Care Res 1996;9:463–72.
25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the area under two or more correlated receiver operating curves: a non-parametric approach. Biometrics 1988;44:837–45.
26. Winer BJ, Brown DR, Michels KM. Statistical principles in experimental design. 3rd ed. New York: McGraw-Hill; 1991.
27. Swets JA. Measuring the accuracy of diagnostic systems. Science 1988;240:1285–93.
28. Rothman K, Greenland S. Generalizability. In: Rothman K, Greenland S, editors. Precision and validity in epidemiologic studies. Philadelphia: Lippincott-Raven; 1998. p. 133–4.
29. Ward MM. Provision of primary care by office-based rheumatologists: results from the National Ambulatory Medical Care Surveys, 1991–1995. Arthritis Rheum 1999;42:409–14.
30. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. Price of adaptation: allostatic load and its consequences. MacArthur studies of successful aging. Arch Intern Med 1997;157:2259–68.
31. Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsivity and socioeconomic status: a mechanism for increased cardiovascular disease risk? Eur Heart J 2002;23: 1757–63.
32. Karlamangla AS, Singer BH, McEwen BS, Rowe JW, Seeman TE. Allostatic load as a predictor of functional decline: MacArthur studies of successful aging. J Clin Epidemiol 2002;55:696–710.