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ORIGINAL ARTICLE

Association of Somatic Comorbidities and Comorbid Depression With Mortality in Patients With Rheumatoid Arthritis: A 14-Year Prospective Cohort Study

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Objective. **Patients with rheumatoid arthritis (RA) have a significantly increased risk of mortality compared with the general population. One of the most important predictors for mortality is somatic comorbidity. Moreover, studies have demonstrated that comorbid depression is associated with mortality. Which specific comorbidities are associated with mortality is less investigated. The purpose of this study was to investigate the association of a wide range of comorbidities with mortality in patients with RA.**

Methods. **Longitudinal data over a 14-year period were collected from 882 patients with RA. Data were assessed with questionnaires. The mortality status was obtained from the Statistics Netherlands for the period 1996–2011 for 99% of the patients. Somatic comorbidity was assessed in 1997, 1998, 1999, and 2008 and measured by a national population-based questionnaire including 20 chronic diseases. Comorbid depression was assessed in 1997, 1998, and 1999 and measured with the Center for Epidemiologic Studies Depression Scale. Cox regression was used to study the relationship between comorbidity and mortality.**

Results. **At baseline, 72% of the patients were women. The mean ± SD age was 59.3 ± 14.8 years, and the median (interquartile range) disease duration was 5.0 (2.0–14.0) years. A total of 345 patients died during the study period. Comorbidities that were associated with mortality were circulatory conditions (hazard ratio [HR] 1.60 [95% confidence interval (95% CI) 1.15–2.22]), respiratory conditions (HR 1.43 [95% CI 1.09–1.89]), cancer (HR 2.00 [95% CI 1.28–3.12]), and depression (HR 1.35 [95% CI 1.06–1.72]).**

Conclusion. **Comorbid circulatory conditions, respiratory conditions, cancer, and depression are associated with mortality among patients with RA. Careful monitoring of these comorbidities during the course of the disease and adequate referral may improve health outcomes and chances of surviving.**

INTRODUCTION

Patients with rheumatoid arthritis (RA) have a significantly increased risk of mortality (1–3) in comparison with the general population. Although the management of RA improved in the last decades, the survival in patients with RA has not improved to the same degree as that of the general population (4,5). Analyses of trends in RA mortality over time revealed 3 lines of evidence: systemic inflammation in RA may promote comorbidity, patients with RA have more serious comorbid conditions, and patients with RA may not receive optimal care for their comorbidities (6). A review about mortality in RA showed that comorbidities are one of the most significant predictors for mortality (7).

Which specific comorbid conditions are associated with mortality has been less investigated. Some studies evalu-

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Significance & Innovations

- This study investigated a wide range of comorbidities and which comorbid conditions are associated with mortality.
- Circulatory conditions, respiratory conditions, cancer, and depression were associated with mortality, even after adjusting for age, sex, socioeconomic status, disease duration, disease activity, and other comorbidities.
- A remarkable outcome was the association of depression with mortality.
- Raising the awareness of the importance of the comorbidities could contribute to optimizing care and ultimately reduce mortality in patients with rheumatoid arthritis.

ated a limited number of comorbid conditions (8,9). However, studying a wide range of comorbid conditions is needed to obtain a more comprehensive view and to provide clinically useful tools for optimizing care. One study investigated the association of a wide range of comorbid conditions with mortality (10) and found cancer and dementia as most highly associated with mortality. However, that study was conducted more than a decade ago.

The most important causes of death among patients with RA are cardiovascular diseases, respiratory diseases, digestive diseases, hematologic diseases, infectious diseases, and malignancies (11). However, the causes of death do not have to correspond with the preexisting comorbid conditions that are longitudinally associated with mortality. Preexisting comorbidities are a possible target of disease management.

A few studies found that comorbid depression was associated with mortality. One study found comorbid depression to be a predictor for all-cause mortality (12). Another study among veterans with RA also found depression to be a predictor for myocardial infarction (13). Depressed patients with RA were 40% more likely to have a myocardial infarction than nondepressed patients in that study.

The aim of this study was therefore to investigate a wide range of comorbidities, including comorbid depression, and which conditions are associated with mortality. Evaluating the relative contribution of specific comorbidities will provide valuable information for clinical practice and the management of patients with RA.

PATIENTS AND METHODS

Study design and population. In 1997, our research group started a longitudinal study on comorbidity and health outcomes in patients with RA (14). A sample of 1,251 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam, which included the patients from 7 allied outpatient clinics. For inclusion in the study, patients had to fulfill the following eligibility criteria: a diagnosis of RA according to the American College of Rheumatology criteria for RA (15), ages ≥16 years, adequate knowledge of the Dutch language, and at least 1 visit to a rheumatologist in the previous 2 years.

Data were collected in 1997, 1998, 1999, 2002, and 2008 by means of self-administered questionnaires (16). The questionnaires comprised questions about sociodemographic characteristics (age, sex, marital status, educational level, and employment status), clinical characteristics (including comorbidity), health characteristics, and the use of health care services. Information on disease duration was retrieved from the patients' medical records, and disease activity was assessed during clinical examination at baseline. All participants provided written informed consent. The study was approved by the Reade/Slotervaart Institutional Review Board.

Measurements. *Mortality.* All patients who participated in the study at baseline were linked to the mortality records during the period 1996–2011 from the Register of the Statistics Netherlands (17). For patients who could not be linked to these records, data were obtained from the outpatient clinic register.

Comorbidity. Somatic comorbidity was assessed in 1997, 1998, 1999, and 2008. Somatic comorbidity was measured with a list adapted from the Health Interview Survey of the Statistics Netherlands (18), a validated list amenable to self-reporting (19). This list covers 20 chronic conditions that are relatively prevalent in The Netherlands. Respondents were asked to indicate whether they had had any of the conditions in the previous 12 months. The following 8 categories of chronic somatic comorbidity were created based on the body systems involved: circulatory conditions (myocardial infarction or other serious heart disorders, stroke), respiratory conditions (asthma or chronic bronchitis), digestive conditions (disorders of the stomach, disorders of the liver, disorders of the gall bladder, or serious disorder of the intestines longer than 3 months), genitourinary conditions (disorders of the kidneys, kidney stones, or inflammation of the bladder), neurologic conditions (migraine, dizziness with falling, or epilepsy), musculoskeletal conditions (herniated disc or chronic back pain), endocrine, metabolic and nutritional conditions (diabetes mellitus or disorders of the thyroid gland), cancer, and an additional category (hypertension, infection of the nasal cavity or frontal sinus, or skin conditions). This classification was in accordance with previous research also using the list about somatic comorbidity from the Health Interview Survey of the Statistics Netherlands (20).

Comorbid depression was assessed in 1997, 1998, and 1999. Comorbid depression was assessed with the Center for Epidemiologic Studies Depression Scale (CES-D) (21). The CES-D is a short self-administered scale designed to measure depressive symptomatology in the general population. The CES-D consists of 20 items and has a range of 0–60, with higher scores indicating more depressive symptomatology. Scores of ≥16 suggest presence of depression.

Table 1. Description of rheumatoid arthritis (RA) study population at baseline (n = 882)*

Characteristics	Values
Sex	
Men	248 (28.1)
Women	634 (71.9)
Age, mean ± SD years	59.3 ± 14.8
Disease duration, median (IQR) years	5.0 (2.0–14.0)
Disease activity (DAS28), mean ± SD	3.6 ± 1.3
Physical functioning (HAQ), mean ± SD	1.14 ± 0.80
Comorbid conditions, categories	
Circulatory	49 (5.6)
Respiratory	117 (13.3)
Digestive	84 (9.5)
Genitourinary	43 (4.9)
Neurologic	91 (10.3)
Musculoskeletal, other than RA	121 (13.7)
Endocrine, metabolic and nutritional	82 (9.3)
Cancer	18 (2.0)
Other	274 (31.1)
Depression	251 (28.5)

* Values are the number (%) unless indicated otherwise. IQR = interquartile range; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire.

Control variables. The control variables included age, sex, socioeconomic status (SES), disease duration, and disease activity. SES was indicated by educational level. We divided SES into 3 categories: low SES, indicating patients with no education or education at the primary school level, medium SES, indicating patients with education at the secondary school level, and high SES, indicating patients with a college or university level education. Disease activity was assessed by means of the Disease Activity Score in 28 joints (DAS28), separately scoring swelling and tenderness of 28 joints (and without using the visual analog scale for general health assessment) (22).

Statistical analysis. Participants with complete and incomplete followup were compared for statistically significant differences in baseline variables with chi-square tests and *t*-tests. To study the relationship between comorbidity and survival among patients with RA, we performed a Cox regression analysis. The variable "comorbidity" was added to all models as a time-varying covariate linking the comorbidity to time. This linking means that the last measured comorbid condition was applied. We first performed univariate analyses for each category of comorbidity, adjusted for age and sex. Secondly, we performed a multivariate analysis with all categories of comorbidity in the model. Depression was added to the model as a dichotomous variable (CES-D score <16 versus CES-D score ≥ 16). All models were adjusted for age, sex, SES, disease duration, and disease activity. In order to investigate whether the level of depression is associated with mortality risk, a multivariate analysis with the same model was performed. In this additional multivariate analysis, depression was added to the model as a continuous variable (continuous CES-D score). The hazard ratio (HR) resulting from the Cox regression analysis should be interpreted as the proportional change in the risk of mortality associated with the comorbidity at issue. All analyses were carried out using SPSS software, version 14.0. Results were considered statistically significant when P values were less than 0.05.

RESULTS

Response. Of the eligible patients, 882 (76%) returned the questionnaire in 1997 (16). Of these patients, 755 (crude response 85%, net response [the response in patients not deceased] 87%) returned the questionnaire in 1998, 683 (crude response 77%, net response 81%) in 1999, 529 (crude response 60%, net response 71%) in 2002, and 370 (crude response 42%, net response 62%) in 2008. Patients with incomplete followup were older, had longer disease duration, higher baseline DAS28 scores, and lower baseline physical functioning, and more often had circulatory problems, respiratory conditions, and cancer, compared with patients with complete followup.

Of the 1,251 patients who were selected at baseline, 1,237 (99%) could be linked to the Municipal Register at Statistics Netherlands, with 5 patients deceased according to the outpatient clinic register. For 9 patients, no information about mortality could be obtained. Of the 882 patients who responded at baseline, 876 could be linked to the Municipal Register at Statistics Netherlands, 4 patients were found in the register of the outpatient clinic, and 2 patients were excluded from the analyses because no mortality data were available. The number of patients who died during the study period was 345.

Study population. Baseline patient characteristics are summarized in Table 1. Of all patients at baseline, 72% were women, the mean ± SD age was 59.3 ± 14.8 years, and the median (interquartile range) disease duration was 5.0 (2.0–14.0) years.

Association of specific comorbidities and mortality. Table 2 shows the results of the Cox regression analyses investigating which comorbid conditions are associated with mortality. Univariate analyses showed that circulatory conditions, respiratory conditions, digestive conditions, cancer, and depression were associated with mortality ($P < 0.05$). In the multivariate model, circulatory conditions, respiratory conditions, cancer, and depression were associated with mortality. Using the continuous CES-D score resulted in an increased risk of mortality of 2% with each point of increase on the CES-D score (HR 1.02, $P = 0.007$). Diagnostics of collinearity between the categories of comorbidity showed that collinearity was not an issue.

DISCUSSION

Data from this large prospective cohort study showed that circulatory conditions, respiratory conditions, cancer, and depression were associated with mortality. This finding provides valuable information for clinicians, because they could possibly treat these comorbidities.

Table 2. Association of specific comorbidities and mortality in patients with rheumatoid arthritis (RA) (n = 882)*

	Univariate analysis†			Multivariate analysis‡		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Circulatory conditions	1.67	(1.23–2.26)	0.001	1.60	(1.15–2.22)	0.006
Respiratory conditions	1.51	(1.17–1.95)	0.002	1.43	(1.09–1.89)	0.011
Digestive conditions	1.59	(1.10–2.30)	0.015	1.46	(0.99–2.15)	0.058
Genitourinary conditions	1.02	(0.68–1.54)	0.921	0.89	(0.59–1.36)	0.595
Neurologic conditions	0.95	(0.70–1.28)	0.725	0.77	(0.56–1.07)	0.123
Musculoskeletal conditions other than RA	0.96	(0.72–1.27)	0.774	0.93	(0.69–1.25)	0.618
Endocrine, metabolic, and nutritional conditions	1.13	(0.82–1.55)	0.451	1.00	(0.71–1.40)	0.986
Cancer	2.20	(1.43–3.40)	<0.001	2.00	(1.28–3.12)	0.002
Other conditions	0.95	(0.76–1.18)	0.616	0.81	(0.64–1.03)	0.081
Depression	1.47	(1.18–1.83)	0.001	1.35	(1.06–1.72)	0.016

* HR = hazard ratio; 95% CI = 95% confidence interval.
† Outcome of Cox regression analyses, with comorbidity as time-varying covariate, and adjusted for age and sex.
‡ Outcome of Cox regression analyses, with comorbidity as time-varying covariate, and adjusted for age, sex, socioeconomic status, disease duration, disease activity, and all other comorbidities.

The association of somatic comorbidity with mortality has been previously described in the literature (7). However, in these studies, comorbidity is usually measured with a dichotomous score (23), a sum score (24), or an index score (25), while clinical practice asks for simply recording the presence or absence of a specific comorbid condition (26). To our knowledge only 1 other study investigated the association of a wide range of comorbidities with mortality (10) and found partly the same associated comorbidities. However, in that study, data collection of the inception cohort took place between 1955 and 1994, while in our study data collection started in 1997 and included patients with RA with a median disease duration of 5 years. Our cohort was likely treated with modern medication for RA and possibly also for comorbidities.

In this study patients with incomplete followup were older, had longer disease duration, higher baseline DAS28 scores, and lower baseline physical functioning. This finding implies that more severe patients dropped out of the study, often the patients with more severe comorbidities. Therefore, the relationship between the specific comorbidities and mortality might be stronger than this study suggests.

A remarkable result was the association of comorbid depression with mortality. In the multivariate analysis, depression was added to the model as a dichotomous score, which implies that depression was identified by the CES-D cutoff of $\geq$16. Using the continuous score of the CES-D, in the additional multivariate analysis, resulted in an even higher risk for mortality, with 2% increased risk with each point of increase for depression on the CES-D. This result means that a patient with the maximum score in our cohort of 41 has an increased risk of mortality of $1.02 \times 41 = 2.25$, compared with a patient with the minimum score of zero. This finding emphasizes even more the importance of depression in patients with RA. In this cohort, the duration of depression, or being depressed at more than one time point, did not result in an increased mortality risk (data not shown).

A study by Ang et al (12) found comorbid depression to be an independent risk factor for mortality in RA. Little is known about the mechanisms that account for the association between comorbid depression and mortality. Depression may increase the risk of mortality through several factors (27). However, this relationship is complex.

The major strengths of our study were its longitudinal design, its long-term followup period, the large patient sample, the relatively high response rate during the followup period, and the mortality data that could be obtained for almost all patients. Another strength of the study is that not only were baseline comorbidity scores used to determine the association with mortality, but that comorbidity was measured at 4 time points during the 14-year followup period. In the statistical model, the comorbidity was updated over time. A few study limitations have to be considered. In our study, information about comorbidity was self-reported and patients were asked whether they had had a comorbid condition in the past 12 months, which may have led to underestimation of comorbidity. For example, patients who had a myocardial infarction 5 years previously and were taking medication for the condition could consider themselves as not having cardiovascular comorbidity. However, the list that was used has been validated (19).

Depression was measured with a self-reported questionnaire. Studies investigating prevalence of depression in RA populations show that the prevalence of depression is higher when measured with self-reported measurement instruments than when diagnosed by psychiatric interview (28). The depression measured should therefore be interpreted as a possible depression (21). To our knowledge, the association between depression measured by interview and mortality has never been investigated in patients with RA. Future research should establish whether measuring depression by diagnostic interview changes the association between depression and mortality in patients with RA.

In addition, self-reported somatic comorbidity was recorded at 4 time points of measurement, while comorbid depression was measured at 3 time points. This difference could have led to less accurate measurement of comorbid

depression compared to somatic comorbidity. However, an additional analysis, with 3 time points of measurement for somatic comorbidity, did not result in different conclusions with respect to the relationship between comorbidities and mortality (data not shown).

This study was initially designed to study health outcomes in patients with RA. Therefore, potential clinical confounders such as body mass index, cholesterol, and blood pressure were not collected, which could have resulted in an overestimation of the risk of depression.

Our results highlight the importance of specific comorbidities, in relation to mortality, for daily clinical practice. We do not have information with respect to the adequacy of the treatment that participants received for their comorbidities. However, patients with RA are possibly better treated for their arthritis than for their comorbid conditions (29,30). For example, underdiagnosis of depression by general practitioners occurs frequently among patients having chronic somatic diseases (20). We recommend that clinicians place greater emphasis on comorbid conditions in patients with RA. How to implement such a recommendation in daily clinical practice will depend on the structure of the health care system at hand. In The Netherlands, this recommendation could necessitate an important role for rheumatologists, in signaling and underlining the importance of their comorbid conditions to the patient, and for the general practitioner in monitoring, referring, and coordinating care. Assessing comorbidity and adequate disease management for comorbidity are crucial parts of the clinical evaluation and treatment of patients with RA. Clinical practice guidelines should incorporate clinically relevant comorbidities to optimize care and ultimately reduce mortality.

Comorbid circulatory conditions, respiratory conditions, cancer, and depression are associated with mortality among patients with RA. Careful monitoring of these comorbidities and adequate referral may improve health outcomes and chances of surviving.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Ms van den Hoek had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Van den Hoek, Boshuizen, Roorda, Tijhuis, Dekker, van den Bos.

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Analysis and interpretation of data. Van den Hoek, Boshuizen, Roorda, Tijhuis, Nurmohamed, Dekker, van den Bos.

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