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Mortality and its predictors in patients with rheumatoid arthritis: a Danish population-based inception cohort study

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Objectives: To investigate mortality and its predictors in a retrospectively defined population-based rheumatoid arthritis (RA) inception cohort

Method: We included patients ascertained with incident RA from a region in the southern part of Denmark from 1995 to 2002. All patients fulfilled the 1987 American College of Rheumatology criteria for RA. The patients were followed from RA classification until death, emigration, or end of follow-up on 31 December 2013. We used personal record linkage with national public registers to obtain information on education, employment, cohabitation, comorbidity, and vital status.

Results: The cohort comprised 509 patients, of whom 200 (39%) died during 6079 person-years. The most frequent underlying causes of death were cardiovascular disease (34%), neoplasms (26%), and respiratory disease (12%). In rheumatoid factor (RF)-positive males, the standardized mortality ratio (95% confidence interval) from all causes was 1.47 (1.15–1.88), from cardiovascular disease 1.63 (1.09–2.46), from respiratory disease 2.03 (1.06–3.90), and from neoplasms 2.26 (1.02–5.03) in the age group < 70 years, and 2.45 (1.23–4.90) in the age group > 79 years. On applying Cox models after multiple imputations by chained equations, we found that RF modified the effect of age. Employment status, comorbidity, and gender were independent baseline predictors of subsequent mortality.

Conclusion: In this cohort, significant excess mortality was confined to RF-positive males. The effect of age was modified by RF, and employment status and comorbidity were independent predictors of mortality.

Rheumatoid arthritis (RA) is an autoimmune, inflammatory disease of unknown origin that often leads to disability (1). In cross-sectional studies of patients with established disease there is ample evidence that RA is associated with excess mortality (2). Studies of inception cohorts detect events from early on in the disease course (3), but excess mortality is less pronounced and data stem from few unique cohorts (2).

In patients with RA, rheumatoid factor (RF) has often been associated with mortality risk (2). In a large series of patients, the occurrence of RF did not increase with age but males were more often seropositive than females (4). Socioeconomic position (SEP) refers to socially derived, economic factors that influence the positions that an individual holds within society. SEP can influence health outcomes (5), but in RA inception cohorts only age and gender have been explored systematically as predictors of mortality risk (2). Although the occurrence of RF does not increase with age, the importance of RF in terms of mortality risk may perhaps change with age or gender in patients with RA.

In the general population, there is an inverse relationship between educational level and overall mortality risk (6, 7). Employment status has been associated with excess mortality, and being unemployed (8, 9) or outside the labour market increases mortality risk (9, 10), even in younger males (11). In Denmark, about 23% of the general population above 50 years of age live alone and cohabitation status has previously been associated with mortality (12).

Comorbid conditions may be independent predictors of mortality in RA (13–16), but in the medical literature there is no agreement on how to measure comorbidity. Several comorbidity indices have been developed and the choice of instrument may be influenced by the availability of data, the population under investigation, and the particular aim of a study (17).

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Previously, we have reported the incidence of RA in a region in the southern part of Denmark where the estimated ascertainment probability was at least 87% (18). The main objectives of the present study were to examine mortality and its predictors in a retrospectively defined, Danish RA inception cohort. At baseline, we included education, employment, cohabitation status, and comorbidity as potential predictors for subsequent mortality. Moreover, we looked for potential effect modification between RF and age and RF and gender.

Method

Patients and setting

The present cohort included patients with incident RA ascertained at a rheumatology hospital serving as a referral centre for patients with rheumatic diseases from the County of South Jutland, a region in the southern part of Denmark with a population of about 200 000 over the age of 15 years (19). In brief, medical records from 1995 to 2002 were scrutinized in 2004 to retrospectively identify patients who cumulatively fulfilled the list or tree format of the 1987 American College of Rheumatology criteria for RA (20). Patients were included if they were classified as having RA for the first time in the study period, if they were older than 15 years, and if they were residing in the county at the time the criteria were fulfilled. All patients were identified by the unique personal identification number, which is assigned to all Danish citizens by the Danish Civil Registration System (DCRS) (21). Using this approach, the incidence rate was 31/100 000 person-years in females and males combined, which was close to contemporary estimates from surrounding countries (19).

Baseline data

Medical records. From medical records we collected the date of birth, gender, date of RA classification, date of symptom onset, swollen joint count (0–40 joints), immunoglobulin M (IgM) RF (IE/mL), erythrocyte sedimentation rate (ESR, mm/h), and erosions on radiographs of the hands or feet. If the date of symptom onset was mentioned in the records, we used that date. If only the month of onset was described, the date was set to the 15th of the month. If only the year was described, the date was set to 1 July. The presence of RF in serum was analysed using an enzyme-linked immunosorbent assay (22) with a cut-off at 8 IE/mL. Radiographs of hands and feet taken at the time of classification were registered as erosive, if described so in the records by a radiologist.

Registers

Statistics Denmark. Information on the highest attained educational level was provided by the Population's Education Register (23) and was categorized into short (primary school), medium (secondary school or vocational education), and higher education (longer educational programmes). From the Register-based Labour Force Statistics (24), data on employment status were categorized into employed and unemployed (including being unemployed and outside the labour market). Since education and employment status are associated with income (5), we did not record data on personal income. Cohabitation status was defined as living alone or with a partner, irrespective of marital status.

Danish National Patient Register (DNPR). The DNPR includes data on diagnoses at discharge from Danish hospitals since 1977 and outpatient clinics since 1995 (25). To define the presence of comorbidity at baseline, we used the 19 conditions of the Charlson Comorbidity Index (CCI) without weights (26). Originally, the CCI was evaluated in inpatients, but it has gained widespread use and has also been applied in outpatients with RA (27). As described by Thygesen et al (28), we counted the corresponding, first listed diagnosis at discharge with codes according to the 10th version of the International Classification of Diseases (ICD-10). In DNPR, the first listed diagnosis reflects accurately the main clinical condition of a hospital contact.

Causes of death. The vital status of the patients was followed through the DCRS from the date of RA classification until death, emigration, or the end of follow-up on 31 December 2013. In patients who died during follow-up, ICD-10 codes for the underlying causes of death were collected from the Danish Register of Causes of Death (DRCD) (29).

Statistics

Age- and gender-specific mortality rates from Statistics Denmark were used to calculate standardized mortality ratios (SMRs) from 1995 to 2013. For all hypothesis testing, the level of significance was 0.05. The association of variables at baseline with subsequent mortality by all causes of death was explored using Cox models. For multivariate analyses we used a stepwise, backwards deletion procedure with successive elimination of variables according to the Wald test. We hypothesized that the treatment paradigm of RA had changed from 1995 to 2002 and, to adjust for the impact of improvements in treatment on mortality risk, we added a proxy variable for two periods of classification (1995–1998 and 1999–2002). Potential effect modification was explored between RF and age and between RF and gender.

To minimize the risk of bias and loss of precision due to missing data, the Cox analyses were performed in data sets generated by multiple imputations by chained equations under the assumption that data were missing at random. Following White et al (30), the number of imputations was set in accordance with the fraction of

cases with at least one missing observation. The assumption of proportional hazards was examined by log–log plots and inspection of Schoenfeld residuals. Data were analysed using Stata, version 14 (StataCorp, College Station, TX, USA).

Ethics

The study was approved by the Danish Health and Medicines Authority (reg. no. 3-3013-1130/1) and the Danish Data Protection Agency (reg. no. 2015-41-4125).

Results

In total, 509 patients were included in the study. The median follow-up time was 13 years, yielding 6079 person-years. During follow-up, there were 200 deaths [110 among 344 females (32%) and 90 among 165 males (55%)]. For individual variables at baseline, observations were missing for 0–12% (Table 1) and observations were missing for at least one variable in 146 patients (29%). In total, 115 comorbid conditions were identified in 95 patients (19%) (Supplementary Table S1).

Table 1. Baseline variables and missing observations.

Baseline variable		Missing observations
Gender		0 (0)
Female	344 (68)	
Male	165 (32)	
Age at classification (years)	63 (53–71)	0 (0)
Rheumatoid factor		2 (0)
Positive	378 (75)	
Negative	129 (25)	
Erosions on radiographs		29 (5)
Yes	108 (23)	
No	372 (78)	
Erythrocyte sedimentation rate (mm/h)	30 (16–48)	59 (12)
Swollen joint count	5 (2–10)	49 (9)
Symptom duration (months)	8 (4–19)	35 (7)
Comorbid conditions, n		0 (0)
0	414 (81)	
1	78 (15)	
2	14 (3)	
3	3 (1)	
Employment status		53 (10)
Employed	165 (36)	
Unemployed	291 (64)	
Cohabitation status		0 (0)
Alone	125 (25)	
With partner	384 (75)	
Highest attained educational level		32 (6)
Short	274 (57)	
Medium	155 (33)	
Long	48 (10)	
Period		0 (0)
1995–1998	226 (44)	
1999–2002	283 (56)	

Data are shown as numbers (%) for categorical variables and missing observations, and median (interquartile range) for continuous variables. Comorbid conditions are as defined by the Charlson Comorbidity Index.

Table 2. Underlying cause of death.

Cause	ICD-10 code	
Cardiovascular	I00–I99	68 (34)
Neoplasms	C00–D48	52 (26)
Pulmonary	J00–J99	23 (12)
Skin, bone, connective tissue	L00–M99	10 (5)
Gastrointestinal	K00–K93	8 (4)
Metabolic	E00–E90	8 (4)
Infectious	A00–B99	5 (3)
Other*	Other codes	26 (13)
Total		200 (100)

Data are shown as numbers (%).
*One patient, for whom there were no data in the Danish Register of Causes of Death, was included in 'other'.
ICD-10, 10th version of the International Classification of Diseases.

Causes of death

The underlying causes of death in eight groups, in accordance with ICD-10 codes, are shown in Table 2. RF was not available in two male patients and one of the patients died subsequently from respiratory disease (RD). There were no data in the DRCD for one male patient, and the cause of death was thus registered as 'other'. The most frequent causes of death were cardiovascular disease (CVD) (34%), neoplasms (26%), and RD (12%). There were no significant differences in the underlying causes of death according to gender [χ^2-test = 12.2, 7 degrees of freedom (df), p = 0.092] or RF status in females (χ^2-test = 6.4, 7 df, p = 0.498) or in males (χ^2-test = 10.0, 7 df, p = 0.187).

Standardized mortality ratio

SMRs were calculated for all causes of death, and death from CVD, neoplasms, and RD (Table 3). In male patients, the SMR was significantly increased from CVD, and in RF-positive male patients from all causes of death, CVD, and RD, and from neoplasms in specific age groups.

Cox analysis

After transformation of symptom duration on a logarithmic (log (log)) scale, the assumption of proportional hazards was fulfilled for all variables. In univariate Cox models, gender, number of comorbid conditions, employment status, ESR, swollen joint count, and highest attained educational level were associated with

Table 3. Standardized mortality ratio (SMR) from all causes and the three most frequent specific causes of death.

	All causes			Cardiovascular disease			Neoplasms			Respiratory disease		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Females	110	115	0.96 (0.79–1.15)	31	37	0.83 (0.59–1.18)	27	29	0.93 (0.64–1.35)	12	12	0.98 (0.56–1.72)
RF												
Positive	87	85	1.03 (0.83–1.27)	24	27	0.89 (0.59–1.32)	20	22	0.91 (0.59–1.43)	10	9	1.11 (0.60–2.06)
Negative	23	30	0.76 (0.51–1.15)	7	10	0.69 (0.33–1.44)	7	7	0.96 (0.46–2.01)	2	3	0.61 (0.15–2.45)
Age, RF-positive (years)												
< 70	14	16	0.90 (0.54–1.52)	0	2	0.00 (NA)	7	6	1.20 (0.57–2.52)	2	1	1.67 (0.42–6.70)
70–79	28	28	1.02 (0.70–1.48)	8	8	1.02 (0.51–2.04)	5	10	0.52 (0.22–1.26)	5	4	1.42 (0.59–3.40)
> 79	45	42	1.08 (0.81–1.45)	16	17	0.94 (0.57–1.53)	8	6	1.26 (0.63–2.51)	3	4	0.70 (0.23–2.17)
Males	90	77	1.16 (0.95–1.43)	37	27	1.40 (1.01–1.93)	25	21	1.19 (0.80–1.76)	11	8	1.31 (0.73–2.37)
RF												
Positive	63	43	1.47 (1.15–1.88)	23	14	1.63 (1.09–2.46)	19	12	1.56 (0.99–2.44)	9	4	2.03 (1.06–3.90)
Negative	26	34	0.76 (0.52–1.11)	14	12	1.14 (0.67–1.92)	6	9	0.69 (0.31–1.53)	1	4	0.25 (0.04–1.81)
Age, RF-positive (years)												
< 70	11	9	1.25 (0.69–2.25)	3	2	1.65 (0.53–5.13)	6	3	2.26 (1.02–5.03)	1	0	2.21 (0.31–15.67)
70–79	25	19	1.35 (0.92–2.00)	9	6	1.47 (0.76–2.82)	5	6	0.80 (0.33–1.92)	6	2	3.00 (1.35–6.67)
> 79	27	16	1.72 (1.19–2.52)	11	6	1.79 (0.99–3.23)	8	3	2.45 (1.23–4.90)	2	2	1.01 (0.25–4.04)

O, observed number of deaths; E, expected number of deaths; CI, confidence interval; RF, rheumatoid factor; NA, not applicable.

Table 4. Baseline predictors of mortality in Cox models after multiple imputations by chained equations.

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Female	1		1	
Male	1.98 (1.50–2.61)	0.000	1.73 (1.29–2.33)	0.000
RF#age*				
RF negative	1.11 (1.09–1.13)	0.000	1.10 (1.08–1.12)	0.000
RF positive	1.12 (1.10–1.14)	0.000	1.11 (1.09–1.13)	0.000
Comorbid conditions				
0	1		1	
1	2.34 (1.68–3.25)	0.000	1.64 (1.17–2.29)	0.004
2	4.61 (2.55–8.33)	0.000	3.32 (1.80–6.12)	0.000
3	12.22 (3.82–39.07)	0.000	5.48 (1.67–17.94)	0.005
Employment status				
Employed	1		1	
Unemployed	7.06 (4.32–11.53)	0.000	1.86 (1.04–3.35)	0.037
Log (log (symptom duration))†	0.82 (0.61–1.10)	0.191		
Erythrocyte sedimentation rate	1.01 (1.01–1.02)	0.000		
Swollen joint count	1.02 (1.00–1.04)	0.041		
Erosive on radiographs				
No	1			
Yes	1.21 (0.87–1.68)	0.254		
Cohabitation status				
With partner	1			
Alone	1.34 (0.98–1.82)	0.068		
Highest attained educational level				
Long	1			
Medium	1.37 (0.69–2.73)	0.368		
Short	2.60 (1.36–5.00)	0.004		
Inclusion period				
1999–2002	1			
1995–1998	0.96 (0.72–1.29)	0.784		

HR, hazard ratio; CI, confidence interval; p, p-value for Wald test; RF, rheumatoid factor.
*Term for effect modification of RF and age. †Logarithmic transformation of logarithm to symptom duration. Comorbid conditions are as defined by the Charlson Comorbidity Index.

subsequent mortality (Table 4). On a multiplicative scale, the effect of age was modified by RF and vice versa. The effect of gender was not modified by RF. In a multivariate model, gender, age modified by RF, number of comorbid conditions, and employment status were significantly associated with mortality. ESR was not significantly associated with mortality ($p = 0.066$, Wald test) and was eliminated from the model. In a multivariate model including gender, age modified by RF, number of comorbid conditions, employment status, and ESR, the interaction between age and RF was still present ($p = 0.000$ and $p = 0.000$, Wald test). In a multivariate analysis in the subgroup of patients of working age (18–64 years), employment status was also significantly associated with mortality (data not shown).

Discussion

In the present study, we found significant excess mortality in RF-positive males from all causes of death, CVD, and RD, and from neoplasms in specific age groups. At baseline, the effect of age was modified by RF, and employment status and comorbidity were independent predictors of subsequent mortality.

Our results underline that a stratified analysis may help to identify the subgroup of RA patients at risk of excess mortality. In early RA, smoking status is associated with mortality from all causes, CVD, and lung cancer (31) but, unfortunately, we did not know the smoking status of our patients. In an independent study from the same population from where our patients originated, a higher proportion of males than females were smokers (32). In the present study, we cannot rule out that the association between gender, RF, and mortality was caused by unmeasured confounding. In the Norfolk Arthritis Register (NOAR), excess mortality was found in RF-positive females from CVD and in males from all causes and RD (31). The distribution of smokers within or between the cohorts could perhaps have helped to explain the different mortality pattern between our study and the NOAR study (31). Our patients were older, follow-up was longer, and the proportion of RF-positive patients was higher than in the NOAR study. These factors could have increased the power to detect excess mortality in our rather small group of males. In two separate reports from Rochester, Minnesota, USA, mortality was increased in RF-positive patients from CVD and RD (33) and in males from all causes of death (15).

From 1955 to 2007, an increasing mortality gap was described between RA patients and the general population, driven by deaths from CVD and RD in RF-positive individuals (34). However, this trend has not been confirmed in more recent cohorts (35, 36). The most frequent underlying causes of death in our study were CVD, followed by neoplasms and RD. This contrasts with empirical data from the general Danish population in 2013, where 30% died from neoplasms, 25% from CVD, and 12% from RD (37). From 2012, the Danish population has been considered to be at low risk of fatal CVD (38). However, our data indirectly suggest that the decreasing trend is not yet expressed in Danish RA patients, who, in the future, could perhaps benefit from the implementation of updated recommendations for cardiovascular risk management (39).

In our study, employment status was an independent predictor of subsequent mortality in the entire cohort and in patients of working age. Owing to the relatively small size of our population, we defined unemployment as being unemployed or outside the labour market for other reasons. However, our results are in accord with various studies of the general population using different measures of mortality risk (8–11). The effect of unemployment upon the risk of illness can be attributed to several factors. Among them, models that emphasize the importance of loss of income, loss of time structure, social contact, status, identity, and sense of collective purpose for jobless people seem to have explanatory value (40). Individuals with longer education may more easily understand advice on healthy lifestyle, which may reduce the overall mortality risk compared with those with short education (6). In our study, educational level was only associated with mortality for patients with short education in the univariate analyses. In a large study from the general population, the association between educational level and mortality disappeared when lifestyle factors and quality of life were introduced in a multivariate analysis (7). In the study by Sokka et al (41), type of occupation and educational level were not predictors of mortality, but Young et al (13) found that categories of the Carstairs Deprivation Index were associated with subsequent mortality in patients with RA. We did not find an association between cohabitation status and mortality.

In our study, comorbidity was associated with mortality. A total of 19% of our patients had one or more comorbid conditions included in the CCI. This is similar to the results from a large RA inception cohort where the baseline prevalence of comorbid conditions as defined by the CCI was 18% (27). Our results confirm that the approach described by Thygesen et al (28) for identifying conditions of the CCI provides relevant prognostic information in patients with RA. Recently, a new comorbidity index was presented for patients with rheumatic diseases. This index was validated using ICD-9 data (42) but in Denmark, only ICD-10 data are available from administrative sources.

In our cohort, the association of age with subsequent mortality was modified by RF. This means that the impact of age on mortality risk, i.e. hazard ratio, at classification with RA was significantly higher in RF-positive than in RF-negative patients. The biological explanation for this finding is not clear. As reviewed by Tan and Smolen (43), RF may form immune complexes followed by a series of

immunological events that lead to inflammation. Indeed, RF-positive patients with RA have higher levels of pro-inflammatory cytokines than RF-negative patients (44). In this situation, the presence of RF could perhaps add to the systemic inflammatory burden of senescence, which has been associated with excess mortality risk in elderly populations without RA (45, 46). In our study, however, ESR was not associated with subsequent mortality in a multivariate model, and the effect modification of age and RF was still present after adjusting for ESR. In the Reykjavik study (47), the presence of RF in individuals without RA was associated with excess mortality from all causes and CVD but, as in our study, the association was not explained by ESR.

The major strengths of our study are that we were able to ensure complete follow-up and to gather additional information from well-described Danish registries using unique personal identification numbers. In inception cohorts, some patients of interest may not be referred to health facilities covering a population owing to either mild, self-limited disease or severe disease leading to early death. However, as discussed in a previous work by our group (18), we believe that in the present cohort the risk of left censorship was low. The main weakness of our study is that the RA cases were ascertained retrospectively. We could not retrieve all pertinent information, such as detailed smoking habits, from medical records. Furthermore, the patients were recruited before patient-reported measures of disability and disease activity, as well as a test for anti-citrullinated peptide antibodies, were introduced on a routine basis at the referral centre.

Conclusion

In this population-based RA inception cohort, we found significant excess mortality in RF-positive males. The effect of age was modified by RF, and employment status and the presence of comorbid conditions at baseline were independent predictors of subsequent mortality.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary Table S1. Comorbid conditions at baseline as defined by the Charlson comorbidity index, numbers (%)

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