The Predictive Value of Rheumatoid Factor Isotypes, Anti-Cyclic Citrullinated Peptide Antibodies, and Antineutrophil Cytoplasmic Antibodies for Mortality in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the significance of rheumatoid factor (RF) and its isotypes (IgA RF, IgG RF, and IgM RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and antineutrophil cytoplasmic antibodies (ANCA) in predicting mortality in patients with rheumatoid arthritis (RA).

Methods. The study population comprised 604 patients with RA participating in a cross-sectional study in 1987. Presence of RF (n = 604), RF isotypes (n = 206), anti-CCP (n = 184), and ANCA (n = 200) were determined in these patients from available baseline sera. Vital status was assessed in 1999 and multivariate Cox regression analysis used to compare mortality in RA patients with or without different antibodies.

Results. Of the 604 patients with RA, 55% were positive for RF, 66% for anti-CCP, and 14.5% for perinuclear ANCA. Twelve patients (19%) with RF were anti-CCP-negative and 34 (40%) without RF were anti-CCP-positive. Of the total 604 patients, 160 had died by 1999. Positive RF and high IgA and IgM RF levels predicted increased mortality, while positive anti-CCP or ANCA did not. However, high anti-CCP levels were related to an increased mortality risk.

Conclusion. Patients with RA with positive RF, especially IgA and IgM isotypes, carry a risk of dying earlier than patients without these serological findings. (J Rheumatol 2005;32:2089-94)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES
ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES MORTALITY RHEUMATOID FACTOR

The diagnosis of rheumatoid arthritis (RA) depends primarily on clinical manifestations of the disease. Up to 80% of patients with RA are rheumatoid factor (RF) seropositive[1], but these antibodies are also present in relatively high percentages in other autoimmune diseases and infections and even in healthy persons, particularly elderly individuals[2,3].

Since the discovery of RF, more specific autoantibodies have been found in the sera of patients with RA. However, many have been either less sensitive or technically inconvenient for routine use. Antibodies against cyclic citrullinated peptide (anti-CCP) were first reported in 1998[4] and were found to have very high specificity[5]. Commercial test kits were soon available and after few years' development of the CCP antigen, test sensitivity rose to a high level. Anti-CCP can be detected at an early stage, even before onset of clinical symptoms of RA[6].

Among serological markers, RF has been recognized as an important predictor of more severe disease, including extraarticular manifestations or bone erosion[7-9] and increased mortality[7,10-14]. Anti-CCP and antineutrophil cytoplasmic antibodies (ANCA) have been reported to be associated with disease severity and bone erosions[8,9,15-18]. This is the first study to evaluate anti-CCP and ANCA with respect to mortality in patients with RA.

MATERIALS AND METHODS

Study population. In 1987 in the city of Tampere (170,511 inhabitants in that year, 3.5% of the population of Finland) 1051 persons (834 women, 217 men) had confirmed definite or classic RA[19] according to diagnostic criteria of the 1958 American Rheumatism Association[20]. In 1988, 604 of these patients (470 women, 134 men) participated in a study of renal and urinary tract diseases in patients with RA, where general state of health, renal and urinary tract diseases, treatments, and severity of RA (using for example the Health Assessment Questionnaire, HAQ) were carefully recorded and RF determined[19]. At the time of the original study the mean age of 604 RA patients was 59 ± 13 years and the mean duration of RA 15 ± 10 years.

Altogether, 103 RA patients had clinical signs or symptoms of renal dis-

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ease in the original study in 1988[19]. Paired controls (matched for age, sex, and duration of RA) were selected for this nephropathy group from the remaining RA patients with normal serum creatinine and urinalysis[19]. RF isotypes (IgA, IgG, and IgM), anti-CCP, and ANCA in patients in the nephropathy group and their paired controls were determined from baseline serum stored at –20°C[18,19]. Serum was available for RF isotype analyses in 206 cases, for anti-CCP in 184, and for ANCA in 200. The study protocol was approved by the Ethics Committee of Tampere University Hospital.

IgA, IgG, and IgM RF determinations by enzyme immunoassays. RF was determined by quantitative immunoturbidic assay (FS-RF, positive if ≥ 30 U/ml) and by Waaler-Rose test (WaRo, positive if ≥ 64). A patient was considered RF-positive if a positive result was obtained in any assay used. RF isotype specificity (IgA, IgG, IgM) was determined by enzyme immunoassay (EIA)[21,22] using swine IgG as antigen source.

Anti-CCP antibody determination by EIA. Second-generation ELISA kits for detection of IgG anti-CCP antibodies were purchased from Euro-Diagnostica (Immunoscan RA, Mark 2, Malmo, Sweden). The assay was performed according to manufacturer's instructions. Quantitative antibody levels (in arbitrary units, U) were obtained from the standard curve defined by the manufacturer. Results were considered positive when the antibody level exceeded 25 U. Sera with absorbances over the highest standard (1600 U) were diluted and reanalyzed.

ANCA determinations by indirect immunofluorescence. Indirect immunofluorescence employing ethanol and formalin-fixed human granulocytes was used to detect ANCA[23]. Different staining patterns of ANCA, i.e., cytoplasmic ANCA (cANCA) and perinuclear ANCA (pANCA), were identified. Positive sera were titrated to endpoint. Dilutions of 1:20, 1:50, 1:100, 1:200, 1:500, 1:1000, 1:2000, and 1:4000 were used for titration and titers ≥ 50 were considered positive. In all pANCA-positive patients, antinuclear antibodies (ANA) were also determined on cryostat sections of rat liver and kidney. If positive for ANA, the patient was considered to be pANCA-positive only if the pANCA titer was more than 2 dilution factors higher than that of ANA[24].

Evaluation of mortality. Information on vital status on August 31, 1999, and time of death was evaluated from data of the Official Statistics of Finland as described[25,26].

Statistical analysis. SPSS software version 11.5 was used for statistical analysis. Risk of death was estimated by using Cox proportional hazard survival analysis with followup time (from the original study to death) as response variable, and is expressed as hazard ratio (HR) with 95% confidence intervals (CI). The multivariate model quantifies the predictive value of each variable in the model when all variables are analyzed together. We used the forward selection method performed in a stepwise manner. The multivariate model included age and disease duration at study entry, sex, and different serum antibodies (RF isotypes, anti-CCP, and ANCA) as independent variables. Subgroups of RA patients with and without antibodies were compared using Student's t test, Kruskal-Wallis test (for continuous variables), and the chi-square test (for categorical variables). P values less than 0.05 were considered significant. Kaplan-Meier curves were generated for the patients with or without antibodies comparing survival for each year of followup.

RESULTS

Baseline descriptive data in the original study. Baseline data on patients with RA with and without antibodies studied are presented in Table 1. The sex ratio of patients with different antibodies did not differ from those without, but patients with RF and anti-CCP were older. More severe RA was associated with positive RF, anti-CCP, and pANCA. Patients without anti-CCP determination (n = 22) did not differ from those with the determination (data not shown). Occurrence of other diseases such as diabetes, hypertension, coronary disease, and heart failure was similar in every patient group (data not shown).

Altogether, 330 (55%) patients with RA were positive for RF using WaRo or FS-RF analyses (Table 1). EIA analyses showed IgA RF in 97 (48%), IgG RF in 60 (29%), and IgM RF in 123 (60%) patients. The proportion of RF-positive patients was 59% if all 5 determinations were taken into account. Altogether, 122 (66%) had anti-CCP antibodies; 34 (40%) of the RF-negative patients were anti-CCP-positive and 12 (19%) of RF-positive patients were anti-CCP-negative. One hundred thirty-four (73%) patients had RF and/or anti-CCP antibodies and 50 (27%) were negative for these antibodies. We found pANCA in 29 (15%) and atypical cANCA in 2 (1%) (Table 1).

Mortality and RF, anti-CCP, and pANCA. Out of the 604 patients with RA, 160 (26%) had died by 1999. The mean age at death was 75.9 ± 9.6 years. Survival probability curves in RA patients with or without different antibodies are presented in Figure 1.

Altogether, 104 (32%) of the RF-positive and 56 (21%) of the RF-negative patients had died by the time of evaluation of vital status in 1999 (Figure 1a; p = 0.003). In univariate Cox regression analysis positive RF predicted increased mortality in the total RA population (Table 2). The same was also observed in a multivariate model including age, sex, disease duration, nephropathy data, and RF as independent variables (Table 2). The risk ratio (hazard ratio, HR) varied slightly depending on the definition of RF positivity used (HR 1.32–1.80, Table 2). If HAQ or subcutaneous nodules were added to the model, positive RF did not predict increased mortality. Nor did positive RF predict mortality if the model included only RA patients with anti-CCP antibody determination (n = 184). In that cohort high FS-WaRo titer (HR 1.001, p = 0.018), but neither positivity of RF isotypes nor their levels, predicted increased mortality.

By 1999, 38 (39%) IgA RF-positive and 36 (33%) IgA RF-negative patients (p = 0.445), 26 (43%) IgG RF-positive and 48 (33%) IgG RF-negative (p = 0.131), 50 (40%) IgM RF-positive and 24 (30%) IgM RF-negative patients (p = 0.171) had died. High IgA RF and IgM RF levels predicted increased mortality in the multivariate model including age, sex, disease duration, and RF status as independent variables (HR = 1.003, p = 0.003 for IgA RF; HR = 1.002, p = 0.006 for IgM RF; Table 2), whereas a high level of IgG RF did not. If HAQ or subcutaneous nodules were added to the model, the IgA RF level still predicted increased mortality (HR 1.003, p = 0.05), but IgM RF did not.

Fifty (41%) of the anti-CCP-positive and 19 (31%) anti-CCP-negative RA patients had died by 1999 (Figure 1b; p = 0.171). Positive anti-CCP (≥ 25 U) did not predict mortality (Table 2). However, high levels of anti-CCP (over median value of population ≥ 174 U) predicted increased mortal-

Table 1. Characteristics of RA patients with or without different antibodies in the original study in 1988. Results are expressed as medians unless otherwise defined. Comparison between patients with and without different antibodies was made using Student's t test, Mann-Whitney test (for continuous variables) and the chi-square test (for categorical variables). P values less than 0.05 were considered significant. RF was considered positive if quantitative immunoturbidic assay was ≥ 30 U/ml or Waaler-Rose-test titers ≥ 64.

	RF (n = 604)			Anti-CCP (n = 184)			pANCA (n = 198)		
	Pos n = 330	Neg n = 274	p	Pos n = 122	Neg n = 62	p	Pos n = 29	Neg n = 169	p
Age, yrs	59.7	57.3	0.021	63.9	58.7	0.005	59.9	62.3	0.301
Male, %	24	20	0.161	26	26	0.915	14	28	0.111
Disease duration, yrs	14.2	14.7	0.594	15.7	16.3	0.715	19.3	15.4	0.054
ESR, mm/h	33	25	< 0.001	36.8	30.27	0.083	46	32	0.002
Hb, g/l	128	130	< 0.001	126	130	0.065	122	129	0.018
HAQ, 1–3	0.71	0.43	< 0.001	0.88	0.54	0.001	1.11	0.68	0.003
Subcutaneous nodules, %	46	30	< 0.001	45	22	0.005	52	39	0.179
Nephropathy, %	17.3	16.7	0.673	52.5	54.8	0.943	72	45	0.005
Positive RF, %				72*	19*	0.001	59*	56*	0.809
Positive anti-CCP, %	88*	40*	< 0.001				66*	56*	0.105

RF: Rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; pANCA: perinuclear antineutrophil cytoplasmic antibodies; HAQ: Health Assessment Questionnaire; ESR: erythrocyte sedimentation rate; Hb: hemoglobin. * Percentages were calculated only for patients with both antibody determinations.

ity in the univariate model (HR = 1.68, p = 0.034; Table 2). In the age, sex, and disease duration adjusted multivariate model, the tendency was the same (HR = 1.60, p = 0.057; Table 2). If HAQ or subcutaneous nodules were added into the model, high anti-CCP level did not predict mortality. A total of 53 (40%) patients with RF and/or anti-CCP antibodies and 16 (32%) patients without these antibodies had died by 1999. Mortality was not significantly different in these groups (Figure 1c; p = 0.347) and positivity for RF and/or anti-CCP did not predict mortality in the univariate or multivariate model (Table 2).

Twelve (41%) of the pANCA-positive and 64 (38%) of the pANCA-negative RA patients had died by 1999 (Figure 1d; p = 0.720). Neither positivity for pANCA nor high ANCA titers predicted mortality in the univariate or multivariate model (Table 2).

DISCUSSION

Our objective was to analyze whether RF, anti-CCP, and ANCA have an association with mortality as they have with severe disease. All 5 RF detection methods were evaluated either alone or in combination, and this is the first study to assess the predictive value of anti-CCP and ANCA in respect to mortality in patients with RA.

In previous studies, positive RF has predicted increased mortality[10-14], but the risk related to positive RF has varied considerably (OR 1.93–11.9)[12,13]. High levels of RF have also been reported to be associated with increasing mortality risk[10,11]. However, only IgM RF and not other RF isotypes have usually been measured[11-13]. In our study, positive RF (WaRo or FS-RF positive) predicted increased mortality when all patients with RA were included in the statistical analyses. The same result was obtained when any one of the 5 RF methods was taken into account. The risk of death varied from 1.32 to 1.80 depending on the definition of RF positivity used, slightly lower than in previous studies[12,13]. However, in a smaller subgroup (only patients with anti-CCP antibody determination) high FS-WaRo titers but not RF isotypes predicted increased mortality. If the HAQ or RA nodules were added to the multivariate model, positive RF did not predict increased mortality. This might be due to HAQ and positive RF being highly correlated variables and in fact measuring the same aspect: disease severity. Both IgA RF and IgM RF levels predicted increased mortality in the multivariate model including age, sex, and disease duration. Even if HAQ or subcutaneous nodules were added in the model, IgA RF level still predicted increased mortality.

The proportion of RF-positive patients in the original study was 55% (59% if all tests were taken into account), which was lower than generally regarded. The total RA population (n = 604) was population-based, which might partly explain this discrepancy. On the other hand, 70% of RA patients with nephropathy and 69% of RA patients without nephropathy (paired controls) were RF positive. So patients with RF isotypes, anti-CCP, and pANCA determinations were more likely to be RF-positive and the proportion was similar to earlier reports. The cutoff level of FS-RF (≥ 30 IU/ml) was higher than generally used. If the cutoff value for FS-RF was ≥ 15 IU/ml or ≥ 20 IU/ml, the proportion of RF positive patients rose to 67% or 64%, respectively.

B cell activation and production of RF is an indicator of severe disease in RA[27]. RF has an immune complex processing capacity to activate the complement cascade contributing to target organ involvement[28]. High RF levels have been associated with subcutaneous nodules[29] and extraarticular manifestations such as rheumatoid vasculitis[30], which have themselves been reported to correlate with increased mortality in RA[31]. Although the difference in prognosis

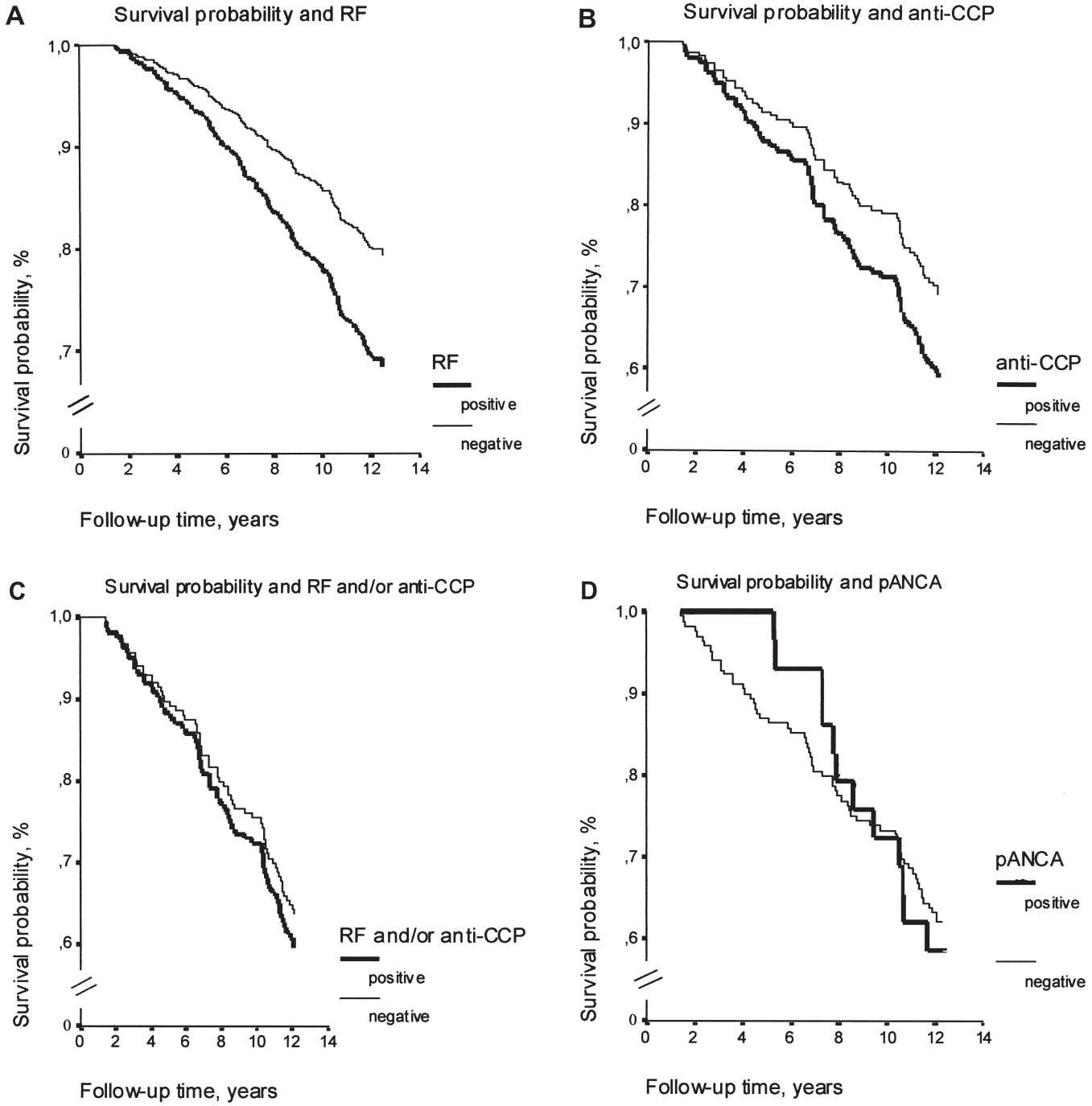

Figure 1. Kaplan-Meier plots for mortality according to the presence or absence of (A) rheumatoid factor (RF); (B) anti-citrullinated peptide antibodies (anti-CCP); (C) RF and/or anti-CCP; and (D) perinuclear antineutrophil cytoplasmic antibodies (pANCA).

between RF-positive and RF-negative RA patients is quite obvious, the role of RF is not clear.

In our cohort, 66% of patients had anti-CCP antibodies, a slightly higher occurrence than found in previous studies[6,9]. Nineteen percent of patients with RF were anti-CCP-negative and 40% without RF had anti-CCP. The proportion of RF-negative patients with anti-CCP is similar to that previously described[8,32,33]. Presence of anti-CCP did not predict mortality when a cutoff value of 25 U was used. However, high anti-CCP levels were associated with increased mortality risk. Patients with RF or anti-CCP antibodies appeared to be subject to higher mortality than those without these antibodies (40% vs 32%), but the difference was not statistically significant. This might be a consequence of the small size

Table 2. Immunological features as predictors of mortality in patients with RA. Results of the Cox univariate analyses and age, sex, and disease duration adjusted multivariate model when each immunological test was at a time in the model. Anti-CCP levels were divided in 2 categories by using median level of the population (174 U) as cutoff value. High anti-CCP level included mean values over 174 U.

		Univariate Model			Multivariate Model		
Variable	N	HR	95% CI	p	HR	95% CI	p
Age, yrs	604	1.09	1.07–1.11	0.001	1.09	1.04–1.09	0.001
Gender, male	604	2.29	1.63–3.20	0.001	2.19	1.56–3.07	0.001
Disease duration, yrs	604	0.96	0.94–0.98	0.001			
HAQ, 0–3	604	1.80	1.42–2.28	0.001	2.03	1.63–2.53	0.001
Subcutaneous nodules	604	1.53	1.09–2.15	0.013	2.04	1.49–2.79	0.001
RF (any of the 5 RF tests positive)	604	1.80	1.28–2.53	0.001	1.55	1.10–2.19	0.011
RF (WaRo and/or FS-RF positive)	604	1.64	1.18–2.27	0.002	1.49	1.07–2.06	0.017
RF WaRo	604	1.32	0.95–1.82	0.089	1.57	1.13–2.19	0.007
FS-RF	604	1.63	1.18–2.24	0.003	1.41	1.01–1.95	0.038
RF WaRo, titer	604	1.001	1.000–1.001	0.004	1.001	1.001–1.002	< 0.001
FS-RF, level	604	1.001	1.001–1.02	< 0.001	1.001	1.001–1.001	< 0.001
RF IgA, level	206	1.005	1.002–1.008	0.001	1.003	1.002–1.008	0.003
RF IgG, level	206	1.008	1.001–1.015	0.049			
RF IgM, level	206	1.002	1.000–1.003	0.024	1.002	1.001–1.003	0.006
Anti-CCP	184	1.44	0.85–2.44	0.176			
Anti-CCP, level	184	1.000	1.000–1.000	0.010	1.000	1.000–1.000	0.044
High anti-CCP level	184	1.68	1.04–2.72	0.034	1.60	0.98–2.68	0.057
RF and/or anti-CCP	184	1.51	0.84–2.71	0.126			
pANCA	200	1.05	0.56–1.95	0.868			
pANCA, titer	200	1.000	0.999–1.001	0.769			

HR: hazard ratio, relative multiplicative effect of variable on the hazard function corresponding to a 1-unit change in that variable only. 95% CI: 95% confidence interval; N = number of patients with antibody determination; HAQ: Health Assessment Questionnaire; RF: rheumatoid factor; WaRo: Waaler-Rose test positive if titer ≥ 64; FS-RF: quantitative immunoturbidic assay of RF positive if ≥ 30 U/ml; anti-CCP: anti-cyclic citrullinated peptide antibodies positive if > 25U; pANCA: perinuclear antineutrophil cytoplasmic antibodies positive if titer ≥ 50.

of these subgroups. Positive pANCA was found in 14.5% of patients, which is slightly lower than in other reports[34,35]. Neither ANCA positivity nor high ANCA titers were related to mortality in the univariate or multivariate model in this cohort, a circumstance for which we can offer no good explanation.

The limitation of this study is that the cohort was not population-based as was the original study of 604 patients. Part of the immunological determination was done in RA patients with nephropathy and their paired controls without nephropathy. In addition, the study population here consisted of RA patients with long disease duration. Although these factors might have a confounding effect, our results seem to indicate that patients with RA with high immunological activity appear to carry an increased risk of death. It would be desirable to measure this activity at disease onset and focus the most effective treatment on these patients. Moreover, it would also be beneficial to assess the predictive value of anti-CCP for mortality in RA patients from antibodies already determined in early RA.

In summary, the presence of RF, particularly high IgA RF and IgM RF levels, predicted increased mortality in patients with RA. Positive anti-CCP or ANCA were not associated with mortality risk, but high anti-CCP levels predicted increased mortality.

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