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# Outcome After 40 Years with Rheumatoid Arthritis: A Prospective Study of Function, Disease Activity, and Mortality

NICOLA J. MINAUR, RICHARD K. JACOBY, JOHN A. COSH, GORDON TAYLOR, and JOHANNES J. RASKER

**ABSTRACT.** In an inception cohort of 100 patients with rheumatoid arthritis (RA) we studied course and outcome after 40 years, regarding function, disease activity, cause and age of death, and prognostic factors. Function, joint count, erythrocyte sedimentation rate (ESR), hemoglobin (Hb), rheumatoid factor (RF), and the number of orthopedic operations were measured in 100 consecutive referrals between 1957 and 1963 with either definite or classical RA at one year after onset of symptoms. Subjects have been followed for a mean of 40 years, or until death. In May 1999, 84 subjects had died. Of the 16 survivors, 8 (50%) were severely disabled from RA while 5 (31%) had normal function. The mean joint score had gradually increased over 40 years. Death was directly attributable to RA in 13, while RA or its treatment contributed to death in 11 subjects. In the other 60 deceased subjects, cardiovascular causes accounted for 28 deaths (33% of total deaths). Features at one year that were associated with mortality up to 40 years after onset by regression analysis were: older age ( $p < 0.0001$ ), lower Hb ( $p = 0.0461$ ), and worse function ( $p < 0.0001$ ). The standardized mortality ratio of the cohort at 40 years was 2.13 (confidence interval 1.26–3.60), and median survival was reduced by 10 years for men and 11 years for women compared to the general population. In conclusion, RA is a progressive disease impairing function up to 40 years after onset, with shortened life span. The leading cause of death was cardiovascular disease. (J Rheumatol 2004;31 Suppl 69:3–8)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS      PROSPECTIVE STUDY      MORTALITY      FUNCTION

Rheumatoid arthritis (RA) is a common, chronic inflammatory joint disease. The course varies, but there is often persistent joint inflammation, despite treatment with disease modifying antirheumatic drugs (DMARD). There have been many reports of increased mortality in association with RA<sup>1–5</sup>.

We studied the outcome of RA in 100 patients prospectively from within a year of onset for a mean of 40 years. This series has been reported at 11 years<sup>6</sup>, 15 years<sup>7</sup>, 18 years<sup>8</sup>, 20 years<sup>9</sup>, and 25 years<sup>10</sup> after disease onset, and included the first report of an association of poor function in RA with mortality<sup>8</sup>.

The association of radiographic damage of metacarpophalangeal (MCP) joints and carpal bones as well as mutilans deformity with both degree of damage and subluxation in the cervical spine as well as duration of corticosteroid treatment in this cohort was reported after 15 years<sup>11</sup>. We now report the findings after 40 years.

## MATERIALS AND METHODS

The cohort consisted of consecutive referrals from a population of 82,000 to a single consultant (JAC) at the Royal National Hospital for Rheumatic Diseases, Bath, UK, between 1957 and 1963. All subjects of this outpatient, clinic-based study lived within 25 km of Bath. The mean duration of arthritic symptoms prior to first hospital visit was 4 (standard deviation, SD, 3) months. Subjects were examined within a year of symptom onset, and all fulfilled the 1958 American Rheumatism Association (ARA, American College of Rheumatology) definition of definite or classical RA<sup>12</sup> at one year after onset of symptoms.

Detailed records were made one year after onset of symptoms. The following data were collected at 1, 11, 15, 18, 25, and 40 years: Steinbrocker functional grade<sup>13</sup>, hemoglobin (Hb), rheumatoid factor (RF), Westergren erythrocyte sedimentation rate (ESR, mm/h), diagnosis according to 1958 ARA diagnostic criteria<sup>12</sup>, total clinical joint score (see below), and information on medication and orthopedic surgery. A review was also conducted at 20 years, but joint score and ESR were not recorded<sup>9</sup>.

Briefly, Steinbrocker functional capacity activity grading was as follows: grade 1, fit for all activities; grade 2, moderately restricted; grade 3, markedly restricted; grade 4, confined to bed or chair<sup>6,13</sup>.

The joint score used at each review was the number of joints clinically affected with a maximum possible score of 23<sup>6</sup>. The following joints were scored individually: wrist (maximum score 2), elbow (2), shoulder (2), neck (1), temporomandibular joint (2), hip (2), knee (2), tibiotalar ankle

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joint (2), and subtalar or midfoot joint (2). The proximal interphalangeal, MCP, and metatarsophalangeal joints in each extremity were regarded as one unit (each comprising 5 joints, maximum score for each unit 1) (score 6).

The local research ethics committee granted approval for the 1999 review. The 16 survivors were traced and 15 agreed to attend an interview and examination. One patient agreed to be interviewed by telephone. Four patients who were unable to travel to hospital were seen at home. Radiographs were not taken.

Cause of death was taken as recorded on death certificates, obtained from the Registrar of Deaths, Bath, UK, from hospital and general practitioner records. The number of post mortems in this series was 20 (24% of those who died). In only 12 cases (14%) was RA mentioned on the death certificate, confirming that death certificates are not a reliable way of identifying RA subjects<sup>14</sup>. The standardized mortality ratio (SMR) compares the death rates in the RA population and in the population as a whole<sup>15</sup>. SMR were calculated using age and sex-appropriate death rates for the Bath area, provided by the Office for National Statistics, London, UK. Calculations were conditional on the subjects being alive in 1960. Statistical analysis was by Cox regression analysis of baseline features to explore associations with mortality.

RF was measured in different ways (Rose-Waaler, ELISA) over the course of the study and was converted to a score as follows: 0 (negative 1/8–1/16, 0–40 IU/ml); 1 (weakly positive 1/32–1/64, 41–100 IU/ml); 2 (moderately positive 1/128–1/256, 101–250 IU/ml); and 3 (strongly positive 1/518–1/2048, > 250 IU/ml) RF titers.

Hb was converted when necessary from percentages to g/dl (100% Hb converts to 14.8 g/dl).

## RESULTS

*The survivors.* Clinical characteristics of survivors at each review are shown in Table 1. The 16 survivors in 1999 had developed RA between 36 and 42 (mean 39.7, SD 1.7) years before and were aged 54 to 90 years. The male to female ratio had been 1:1.8 initially but changed to 1:4.3 by 40 years, when only 3 of the 16 survivors were men.

During the first year of disease, one patient was RF negative and remained so during 40 years. Fifteen out of 16 had been RF positive, but only 3 of 12 tested remained positive 40 years later. There were signs of previous (joint deformities) or current (synovitis) inflammation due to RA in all patients, and the mean joint count had increased to 14 over the course of the study.

Mean Hb had increased slightly, and mean ESR had fallen slightly over the 40 years. Rheumatoid nodules were present in 7 out of 15 patients seen in person. In 1999, only 3 of the 16 were currently taking DMARD: azathioprine (n = 2) and sulfasalazine (1), but 14 had been taking DMARD at some time in the past. Only 2 (12.5%) had never taken DMARD or corticosteroids. Of the 16 survivors, only 6 were still attending a rheumatology clinic.

There had been a total of 34 orthopedic operations due to RA in 9 out of 16 survivors. One patient had undergone 10 operations: 4 large joint replacements and 6 other orthopedic operations.

*Functional change over 40 years.* The Steinbrocker functional grade of survivors at each review is shown in Table 2. Although only 11% of subjects were in the worst functional grades (3 and 4) at 1 year, by 40 years, 8 (50%) subjects were severely disabled due to RA (grade 3 or 4). The mean functional grade increased with time.

*The outcome of the 100.* We determined the “terminal” functional grade of each subject (the grade that was recorded at the last review before death). In 47 subjects (56%) the grade prior to death was 3 or 4. The time before death of the last review was a mean of 41 (SD 30) months (median 42, range 1–121).

*Orthopedic surgery.* The majority of subjects did not undergo orthopedic surgery during the 40 years of followup. Large joint replacement surgery (hip, knee, elbow, and ankle) was carried out in 21 subjects, who had between 1 and 5 joint replacements each. The total number of joints replaced was 42. In addition, 39 subjects had orthopedic surgery other than large joint replacement (such as synovectomy, tendon repair, and MCP joint replacement). There were 100 such operations, with individuals undergoing between 1 and 6 such operations. Joint replacement tended to be done later in the disease than other surgery: the median time to the first large joint replacement was 17 years, and 9 years to other orthopedic surgery.

Table 1. Characteristics of the surviving subjects at each review.

|   | Duration of RA, yrs |                |                |                |                |                |                      |
|---|---------------------|----------------|----------------|----------------|----------------|----------------|----------------------|
|   | 1                   | 11             | 15             | 18             | 20             | 25             | 40                   |
| No. of subjects alive, M:F                        | 100 36:64           | 83 29:54       | 65 19:45       | 57 17:40       | 54 16:38       | 37 8:29        | 16 3:13              |
| Age at onset, yrs, mean (SD, range)               | 50 (14, 17–81)      | 49 (15, 17–81) | 47 (13, 17–81) | 45 (13, 17–73) | 44 (13, 17–73) | 41 (12, 17–67) | 34 (11, 17–53)       |
| Mean months to presentation (SD)                  | 4 (3)               | 4 (3)          | 4 (3)          | 4 (3)          | 4 (3)          | 4 (3)          | 4 (3)                |
| Rheumatoid factor, no. positive, score 2 or 3 (%) | 81 (81)             | 44 (53)        | 17 (27)        | 25 (44)        | 16 (31)        | 15 (41)        | n = 13<br>3 (23)     |
| ARA status: classical, definite, probable, not RA | 51, 5, 0, 0         | 38, 2, 5, 1    | 31, 26, 0, 6   | 31, 1, 13, 0   | 32, 9, 8, 4    | 12, 9, 7, 7    | n = 15<br>2, 8, 4, 1 |
| Joint count, mean (SD)                            | 4.5 (2.4)           | 7.5 (5.2)      | 10.3 (5.9)     | 12.7 (7.5)     | NA             | 12.5 (7.3)     | 13.9 (7.1)           |
| Hb, g/dl, mean (SD)                               | 12.3 (1.7)          | 13.4 (1.6)     | 13.2 (1.9)     | 13.1 (1.9)     | 12.9 (1.9)     | 12.3 (1.8)     | 13.4 (1.5)           |
| ESR, mm/h, mean (SD)                              | 48.8 (29.5)         | 25.2 (19.1)    | 37.0 (28)      | 37.2 (30.7)    | NA             | 42.3 (32.3)    | 32.8 (26.8)          |

RA: rheumatoid arthritis; Hb: hemoglobin; ESR: erythrocyte sedimentation rate; SD: standard deviation; NA: not available (joint score was not measured at 20 yrs, and plasma viscosity rather than ESR was measured).

Table 2. Steinbrocker functional capacity of survivors at each review.

|                            | Year of Review |             |             |             |             |             |             |
|----------------------------|----------------|-------------|-------------|-------------|-------------|-------------|-------------|
|                            | 1              | 11          | 15          | 18          | 20          | 25          | 40          |
| No. of survivors           | 100            | 83          | 65          | 57          | 54          | 35          | 16          |
| No. assessed in person (%) | 98 (98)        | 81 (98)     | 65 (100)    | 55 (96)     | 54 (100)    | 33 (94)     | 15 (94)     |
| Grade 1, n (%)             | 58 (59)        | 31 (38)     | 9 (14)      | 17 (31)     | 13 (24)     | 12 (36)     | 5 (33)      |
| Grade 2, n (%)             | 29 (30)        | 25 (31)     | 23 (35)     | 16 (29)     | 17 (31)     | 14 (42)     | 3 (20)      |
| Grade 3, n (%)             | 7 (7)          | 17 (21)     | 25 (38)     | 22 (40)     | 20 (37)     | 6 (18)      | 5 (33)      |
| Grade 4, n (%)             | 4 (4)          | 9 (11)      | 8 (12)      | 1 (2)       | 4 (7)       | 3 (9)       | 3 (20)      |
| Mean functional grade (SD) | 1.59 (0.83)    | 2.06 (1.02) | 2.49 (0.89) | 2.14 (0.88) | 2.28 (0.92) | 2.00 (0.94) | 2.38 (1.15) |

SD: standard deviation. Percentages are rounded up or down, so totals are not always 100%.

**Medication.** Corticosteroids were taken by 57 subjects for more than 1 year. The majority of subjects were treated with a DMARD during the study, although 20 subjects did not receive a DMARD. Only 8 subjects received no DMARD or corticosteroid. Thirty-seven subjects were treated with 1 DMARD only; 22 with 2 DMARD; 12 with 3; 7 with 4; 1 subject was treated with 5, and 1 with 6 DMARD. Combination treatment was not used. The most common DMARD used was hydroxychloroquine (used in 70 cases), then intramuscular gold (46), D-penicillamine (22), and azathioprine (11). Dosages were as advised at the time<sup>7</sup>. Methotrexate, sulfasalazine, and cyclophosphamide were used only rarely: in 4, 3 and 1 cases, respectively.

**Causes of death.** Of the original 100 subjects, 84 had died by 1999. Table 3 shows causes according to whether death was attributable to RA directly (n = 13), to RA or its treatment (n = 11), or was unrelated to RA (n = 60).

Cardiovascular disease accounted for 28 of the 60 deaths (33% of all deaths), and cerebrovascular disease for 11 (13% of all deaths). Rates of death were not increased due to malignancy, accident, or suicide.

**Standardized mortality ratio.** The SMR was calculated as 1.15 (95% confidence interval, CI, 1.04–1.27) at 11 years, 1.27 (95% CI 1.10–1.46) at 15 years, 1.42 (95% CI 1.17–1.73) at 20 years, 1.60 (95% CI 1.16–2.20) at 25 years, and 2.13 (95% CI 1.26–3.60) at 40 years. The mortality excess increased throughout the followup period. The survival curves for the cohort and the SMR of the general

population in the Bath area are shown in Figure 1, divided by sex. Male subjects died a median of 10 years, and the female subjects 11 years, earlier than expected.

**Associations with outcome in RA.** Categorical variables entered in the analysis were: sex, the highest first-year ESR (greater/less than 30 mm/h), the highest first-year RF score, corticosteroid use (> 1 year), and Steinbrocker functional grade at 1 year. Continuous variables entered were: Hb at 1 year, age at onset of RA, and joint score at 1 year.

Using Cox regression analysis of the 84 subjects who had died, significant associations with mortality were found for: age at onset (p < 0.001), Hb (p = 0.046), and Steinbrocker functional capacity at one year after onset of symptoms (p < 0.001). Male sex (p = 0.065), maximum RF during the first year (p = 0.901), and maximum ESR during the first year (p = 0.713) were not associated. Treatment with corticosteroids for at least 1 year was not predictive of mortality, but was positively correlated with both high ESR and worse functional grade at 1 year. Steroid use was not correlated with either male or female sex (correlation coefficient –0.049, p = 0.631) or rheumatoid factor levels (correlation coefficient 0.061, p = 0.545).

## DISCUSSION

We followed 100 cases of rheumatoid arthritis (RA) from diagnosis for 40 years, or until death. The study has many strengths, including measurement of function from the first

Table 3. Causes of death in 84 subjects by category.

|                           | n  | M:F   | Mean Age at Death, yrs (SD, range) | Mean Duration of RA at Death, yrs (SD, range) |
|---------------------------|----|-------|------------------------------------|---|
| Death attributable to RA* | 13 | 6:7   | 60 (12, 35–78)                     | 15 (10, 3–39)                                 |
| RA contributed to death** | 11 | 1:10  | 70 (12, 45–88)                     | 19 (9, 1–33)                                  |
| Death unrelated to RA***  | 60 | 26:33 | 76 (11, 38–99)                     | 20 (10, 2–40)                                 |

Causes of death were: \* rheumatoid vasculitis (n = 5), renal amyloid (n = 4), rheumatoid heart disease (n = 2), cervical myelopathy (n = 2). \*\* Immobilized by arthritis (n = 6), septicemia (n = 3), peritonitis (n = 1), amyloid (n = 1). \*\*\* Cardiovascular (n = 28), cerebrovascular (n = 11), malignancy (n = 10), respiratory (n = 8), perforated bowel (n = 1), renal failure (n = 1), old age (n = 1).



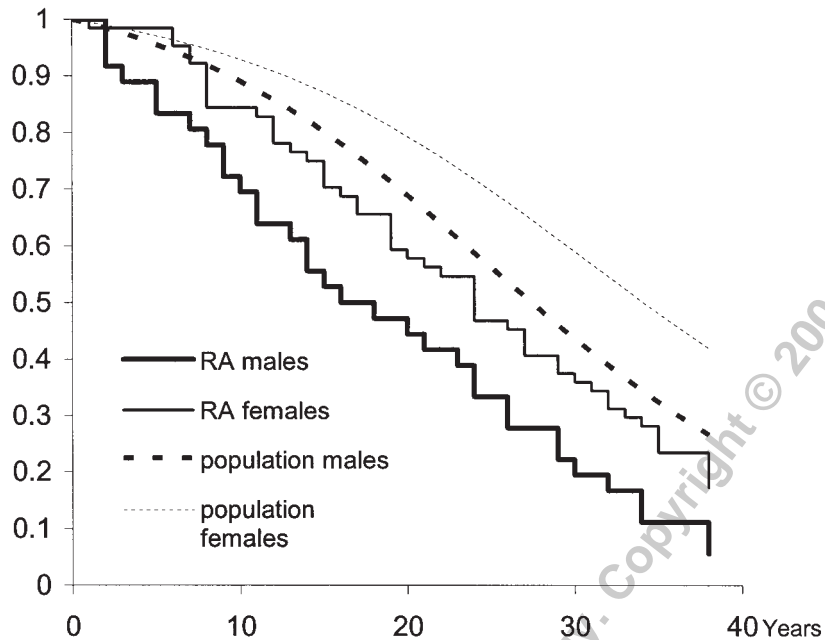


Figure 1. Survival curves for the subjects with rheumatoid arthritis and the general population in Bath over the period of the study, divided by sex.

year of disease, complete case ascertainment, and inclusion only of subjects with classical or definite RA.

We found survival was reduced by a median of 11 years for women and 10 years for men, with an overall SMR of 2.13 (95% CI 1.26–3.60) after 40 years. This is similar to results reported by others<sup>3,5,16</sup>. The SMR increased from 1.15 (95% CI 1.04–1.27) at 11 years to 2.13 (95% CI 1.26–3.60) at 40 years. Similarly, Wolfe and colleagues, who studied 3501 outpatients for up to 35 years, found a SMR of 2.26 and the SMR increased with duration of followup<sup>5</sup>. This emphasizes the importance of lengthy followup: the few studies that have not found increased mortality associated with RA have had a mean followup of 9.8 years<sup>17</sup> and 5.8 years<sup>18</sup>.

Previously, the increased mortality associated with RA was attributed to infections<sup>1</sup> and corticosteroid treatment<sup>19</sup>. Rarely does RA itself result in death<sup>5,8</sup>, although 13% of our series did die from direct effects of the disease process: vasculitis, renal amyloid, cervical myelopathy, and rheumatoid heart disease.

There is strong evidence for the role of inflammation in the atherosclerotic process<sup>20,21</sup>. Ischemic heart disease is now accepted as the leading cause of death in RA<sup>22,23</sup>; increased prevalence of atherosclerosis has been demonstrated in patients with RA<sup>24,25</sup>; and traditional cardiac risk factors cannot account for the excess of cardiovascular deaths observed in RA<sup>26,27</sup>. It has been proposed that endothelial dysfunction consequent on the immune dysfunction of RA (e.g., upregulated tumor necrosis factor- $\alpha$ )

underlies the accelerated atherosclerosis<sup>28</sup>. RA subjects have also been shown to have levels of antibodies against oxidized low density lipoprotein and other components of the lipid pathways higher than controls, which, together with activated endothelium, may lead to premature plaque formation<sup>29</sup>. Atherosclerotic diseases were dominant in our series, with 28 (33% of all deaths) and 11 deaths (13%) due to ischemic heart disease and stroke, respectively.

Functional status declined over time, so that after 40 years 50% of survivors were severely disabled (Steinbrocker grade 3 or 4), while only 31% were unimpaired (Steinbrocker grade 1). It is probable that function would have been even worse without the 34 operations performed in 9 of the 16 survivors.

The functional scores at last review before death showed that 26% were wheelchair-bound or bedridden (Steinbrocker grade 4), while another 30% were severely dependent upon others (Steinbrocker grade 3). If subjects had been reviewed immediately prior to death, even more cases of severely disabled RA may have been recorded. Thus 56% of cases were severely disabled by the time of death, the same figure as found in this series after 20 year followup<sup>30</sup>. This finding contrasts with reports by some suggesting that in the majority of cases RA is a mild disease that “burns out” and leaves little disability<sup>17,18</sup>.

The joint score used here is a measure of joint damage, and the mean score increased over time in the survivors up to 40 years. Most radiographic joint scores plateau after some years and cannot measure further damage. Our find-

ings suggest that RA does not burn out in the majority of patients. The joint score compares well with the articular damage score, which includes a weighting of the joints<sup>31</sup>.

**Prognostic markers.** At 40 years, some baseline variables still had prognostic value in the survivors. Associations with all-cause mortality were found to be age at onset ( $p < 0.001$ ), Hb during the first year ( $p = 0.046$ ), and worse Steinbrocker functional grade (grade 3 or 4) at one year after onset of symptoms ( $p < 0.001$ ). As expected, older age is consistently identified as being associated with earlier death. Lower Hb is a surrogate marker for more severe rheumatoid disease. Poor function, whether expressed as a Steinbrocker functional grade or Health Assessment Questionnaire score<sup>32</sup>, is predictive of future disability and mortality<sup>7,8,33</sup>.

Maximum RF and maximum ESR, each during the first year, were not associated with mortality. Male sex was associated with higher mortality in this series at 15 years<sup>7</sup> and 25 years<sup>10</sup>, but just failed to reach significance at 40 years. These findings may be due to the small number of male subjects and of subjects overall who were alive at 40 years.

The fact that 80% of subjects received at least one DMARD, and only 8% were never treated with a DMARD or corticosteroids, reflects the entry criteria of classical or definite RA. In contrast, a Swedish study included 183 subjects with early RA (less than 24 months of symptoms) recruited in the 1980s, 38% of whom were never treated with a DMARD<sup>17</sup>. They found no increase in mortality associated with RA after a mean of 10 years, but many subjects did not develop radiographic erosions; these cases may not have fulfilled criteria for RA by the end of the first year, as was required for inclusion in our series.

The 100 subjects in our series were treated appropriately for the time, but today's therapy is very different, with widespread use of methotrexate, sulfasalazine and, more recently, anti-tumor necrosis factor- $\alpha$  agents. Despite this, there is still no cure for RA, which remains a cause of significant morbidity. It has been suggested that RA is becoming a milder disease<sup>34</sup>. However, Silman and co-authors recognized that milder cases of RA are being referred to rheumatologists, related to increased disease recognition and opportunity for referral. In our series, deaths due to rheumatoid complications such as amyloid and vasculitis occurred mainly in the early years. The reasons for the reduced incidence of these complications in later decades are unclear<sup>35</sup>. Evidence that mortality associated with RA is increasing despite newer treatment modalities comes from Gabriel, *et al*, who compared 3 Mayo Clinic RA cohorts from 1965, 1975, and 1985<sup>36</sup>. The mortality in the later cohorts was increased, while that in the normal population had improved. The same group have reported an SMR of 1.27 (95% CI 1.13 to 1.41) in a cohort of patients with RA followed for up to 40 years<sup>37</sup>. The subjects had developed RA between 1955 and 1994, and so some had the condition

for less than 10 years. This may explain why the SMR is lower than we found, as all our subjects developed RA during the same 12 month period and were followed for 40 years, or until death.

In contrast to the temporal trend of increased mortality discussed above<sup>36</sup>, there is some evidence that methotrexate may improve mortality due to RA<sup>38</sup>.

## CONCLUSION

We found that RA is associated with reduced life expectancy of a median of 10 years in men, and 11 years in women, and a standardized mortality ratio of 2.13 (95% CI 1.26–3.60) at 40 years. The majority of survivors at 40 years were severely disabled and still had joint inflammation. Patients with poor function early in the course of RA did particularly badly, suggesting more aggressive therapy should be targeted at this group. Benefits may be reduced mortality and morbidity due to atherosclerotic disease, and less orthopedic surgery for joint failure.

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