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Cause and age at death in a prospective study of 100 patients with rheumatoid arthritis

J. J. RASKER* AND J. A. COSH

From the Royal National Hospital for Rheumatic Diseases, Bath

SUMMARY A series of 100 patients with rheumatoid arthritis (RA), first seen in the early months of their disease, have now been followed up for 18 years, and 43 have died. Rheumatoid disease directly caused death in 9, and the disease or its treatment contributed to death in 7. These 16 patients were younger at onset and younger at death than the 27 in whom death was unrelated to RA. Of clinical features noted 1 year after the onset of RA a worse ARA grading and a worse functional capacity were already evident in those 16 patients. Conversely, the 57 still surviving had a better ARA grading and a better functional capacity after 1 year than those who died. The survivors were also significantly younger than the rest at the onset of RA. The death rate throughout the follow-up period was higher in the patients graded as 'classical' than those graded as 'definite' RA after 1 year of disease.

The degree to which rheumatoid arthritis (RA) influences life expectancy and the causes of death is the subject of a number of reports. Some[1–6] indicate that patients with RA have a reduced life expectancy as a result of the disease. Others,[7 8] analysing the causes of death, distinguish between deaths attributable in some way to RA and deaths unrelated to it. Thus, Eulderink[7] found that among 111 deaths approximately 1 in 5 were related to the arthritis and 1 in 8 to its treatment. Similarly, Constable *et al.*[8] found among 100 deaths proportions of 1 in 6 and 1 in 4 respectively.

All of these reports, however, are open to bias in that they are based on patients admitted to hospital with established disease. They may therefore be dealing with selected patients suffering from relatively complicated forms of RA.

The present study is based on a series of 100 patients with RA seen initially by J.A.C. within a year of the onset of their disease, and followed up now for 18 years. Forty-three of the 100 have now died.

We here review the causes of their deaths and the degree to which rheumatoid disease caused or contributed to death. We have also reviewed clinical and laboratory data recorded 1 year after the onset of arthritis to see what idications they might give of the eventual cause and date of death.

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*Present address: Ziekenhuis Ziekenzorg, Enschede, The Netherlands.

Correspondence to Dr J. A. Cosh, Royal National Hospital for Rheumatic Diseases, Bath.

Patients and methods

All of the patients had, by definition, either definite or classical RA by the ARA criteria within 1 year of onset. They formed a consecutive series, without selection, in that all patients who were referred to J.A.C. and who met the above criteria for RA of recent onset were accepted into the series. There were 36 men and 64 women, of ages ranging from 18 to 81 years at onset (mean 50·6), and the average duration of RA when first seen was 3·7 months.[9 10] Contact has been maintained with all 57 surviving patients, and the cause of death is known in the 43 who have died.

Information on each patient's condition 1 year after the onset of RA was available for analysis as follows: clinical details of the arthritis, number of affected joints (joint score), the presence of nodules, grading of disease by ARA criteria,[11] functional capacity.[12] Laboratory investigations included haemoglobin ESR (Westergren), and Rose-Waaler titre. Further details of the 100 patients, the onset of their arthritis, and their state 11 years after onset are given elsewhere.[9] After 11 years 17 patients had died, and in 5 of these it was considered that RA had caused or contributed to death.

A review was made of the surviving patients in 1979 when the average duration of arthritis was 18 years. Information about those who had died was brought up to date. The cause and circumstances of death were known in all 43. Many were seen personally in their final illnesses and 16 had necropsies. Information was available on the remaining deaths through hospital records or through general practitioners in the case of those who died at home.

The deaths were classified into 3 groups: deaths directly due to RA and its systemic complications ('attributable'), deaths due to other causes, but with RA or its treatment as a contributory factor ('contributory'), and deaths from causes unrelated to RA ('unrelated'). A fourth group consisted of the 57 survivors.

Results

CAUSE OF DEATH

The three groups and the causes of death are summarised in the first three Tables.

'Attributable' deaths. In Table 1 are listed the 9 patients whose deaths were directly attributable to rheumatoid disease. Three, cases 5, 7, and 8, died from renal failure due to amyloid disease, confirmed at necropsy and attributed to the rheumatoid disease. Two, cases 4 and 9, died from rheumatoid heart disease (one of them postoperatively), which was confirmed at necropsy. Four had vasculitis with infarctions and other lesions as a result, but only 1 had a necropsy, case 2. Case 1, for whom necropsy was refused, suffered peripheral vasculitic lesions, malignant hypertension, renal failure, and died with a probable mesenteric occlusion. Case 3, for whom necropsy was refused, had severe vasculitis, and gangrenous lesions of feet. Case 6, with rapidly progressive seropositive RA had vasculitis with mononeuritis and polyneuritis, and while suffering from this developed total heart block. No pacemaker service was then available (1961), and he died at home some months later in a Stokes-Adams attack. Although necropsy confirmation was lacking, heart block was attributed to rheumatoid heart disease in view of the current activity of the vasculitis rather than to degenerative disease of the conducting tissue.

'Contributory' deaths. Table 2 shows the 7 patients in whom rheumatoid disease or its treatment contributed to death without being its primary cause. In 6 of these drug therapy was considered to be a contributory factor. Patient 2 died of reticulosarcoma within a year of starting azathioprine therapy.[14 15] Patients 3 to 7 were receiving corticosteroids, and this contributed to the infection which brought about their deaths. Patient 1 died of septicaemia after hip arthroplasty; diabetes was a contributory factor as well as the RA for which operation was performed. Necropsies were performed in 4 of the 7.

'Unrelated' deaths. Table 3 summarises the causes

Table 1 *'Attributable' deaths: 9 deaths attributable to rheumatoid disease*

Patient	*Sex*	*Age at onset of RA (years)*	*Cause of death*	*Age at death (years)*	*Duration of RA (years)*
1	M	30	Vasculitis Malignant hypertension Renal failure	35	5
2	M	35	Vasculitis Sepsis pneumonia	49	14
3	M	48	Vasculitis Gangrene	59	11
4	F	52	Constrictive pericarditis Postop. death	60	8
5	M	58	Amyloid Renal failure	74	16
6	M	59	Vasculitis Heart block	62	3
7	F	60	Amyloid Renal failure	69	9
8	F	60	Amyloid Renal failure	67	7
9	F	61	Rheumatoid heart disease	69	8
Mean		51·4		60·4	9·0

Ages are given by completed calendar year in this and subsequent tables. Necropsies were performed in 6 of the 9 (not in cases 1, 3, and 6). Patients 4 and 9 have been reported in detail elsewhere, where they are shown as cases 8 and 10 respectively.[13]

Table 2 *'Contributory' deaths: 7 deaths to which rheumatoid disease or its treatment contributed*

Patient	*Sex*	*Age at onset of RA (years)*	*Cause of death*	*Age at death (Years)*	*Duration of RA (years)*
1	F	32	Hip surgery Diabetes Septicaemia	45	13
2	M	47	Reticulosarcoma Azathioprine	61	14
3	F	57	Diverticulitis Peritonitis Steroid therapy	64	7
4	F	68	Septic arthritis Septicaemia Steroid therapy	69	1
5	F	54	Immobilised Pyelonephritis, renal failure, steroid therapy	71	17
6	F	63	Stroke, septicaemia Steroid therapy	78	15
7	F	69	Bronchopneumonia Osteoporosis Steroid therapy	88	19
Mean		55·7		68·0	12·3

Necropsies were performed in cases 1–4.

Table 3 *'Unrelated' deaths: 27 deaths from causes unrelated to RA*

Cause of death	*Number of patients*
Cardiac infarct	11
Congestive heart failure	3
Cerebrovascular accident	4
Carcinoma	4
Cor pulmonale, Myasthenia	1
Cerebral atherosclerosis	4
Sex	M 13 : F 14
Age at onset RA (mean and range)	61·0 yr (25–81)
Age at death	71·9 yr (38–89)
Duration of RA	10·9 yr (1–21)

Necropsies were performed in 6 of the 27.

of death in the 27 patients whose deaths were unrelated to rheumatoid disease. If the circumstances of the patients' terminal illness were not known to the authors, the patients' general practitioners were consulted; in none of these patients was it considered that RA had contributed to death. Cardiac infarction, in 11 cases, was the commonest single cause. Necropsies were performed in 6 of the 27.

Survivors. The 57 survivors are now of mean age 57 years (range 35–89). There are 40 women and 17 men (F : M=2·4 : 1).

AGE OF ONSET

Comparisons of the age at onset of RA in the 4 groups are shown in Table 4. As the first 2 groups are small in number they have been combined for statistical purposes.

It is seen that patients dying of causes unrelated to RA had a significantly later age of onset than those dying directly, or in part, as a result of RA (61·0 years compared with 53·3). Conversely the survivors had a significantly earlier age of onset than the other groups (44·9 years compared with 53·3 and 61·0).

AGE AT DEATH

Comparisons of the age at death in the three groups is also shown in Table 4. The age at death from unrelated causes, 71·9 years, is significantly higher than that for the attributable deaths (60·4) or for attributable and contributory deaths combined (63·7).

RELATIONSHIP WITH FEATURES OF THE EARLY STAGES OF RA

We now turned to the data available on individual patients 1 year after the onset of their arthritis to see what differences could be found at that early stage between patients in the three groups, and the survivors.

Sex differences. Overall, there were relatively more deaths among men (19/36 or 53%) than among women (24/64 or 37·5%). This difference did not reach statistical significance, either overall or within individual groups. However, as a result of the higher proportion of deaths in men the sex ratio of the survivors is now more predominantly female (2·4 : 1) than it was in the original 100 patients (1·8 : 1).

In the group with 'unrelated' deaths, the ARA grading at one year was worse for women than for men, but this did not reach statistical significance.

ARA grading. The American Rheumatism Association (ARA) grading after one year of arthritis is shown in Table 5 for the different groups. In all,

Table 5 *ARA grading at 1 year after onset*

Group	*No.*	*Definite*	*Classical*	*Significance*	
Attributable	9	1	8		
Contributory	7	1	6		
Combined	16	2	14	χ^2 4·16 P<0·05	χ^2 8·58 P<0·01
Unrelated	27	13	14		
Survivors	57	33	24		
Totals	100	48	52		

Table 4 *Age at onset, age at death, and duration of RA with comparisons*

Group	*No.*	*Age at onset, mean in years±SD*	*Age at death, mean in years±SD*	*Duration of RA, mean in years±SD*
Attributable	9	51·4±11·6	60·4±12·0 *	9·0±3·9
Contributory	7	55·7±13·1	68·0±13·6	12·3±5·7
Combined	16	* 53·3±12·0	* 63·7±12·7	10·4±4·8
Unrelated	27	* 61·0±10·4 **	* 71·9±10·9 *	10·9±4·7
Total dead	43	58·3	69·0	10·7
Survivors	57	* 44·9 **	Age now 63·4	18·5
Total	100	50·6		

*Significantly different, P<0·05; **P<0·001.

48 patients had the grading of 'definite' RA after 1 year, and 52 'classical'. By definition the series did not include any patients with the grade of 'probable' RA at that stage. The 'attributable' and 'contributory' groups combined are seen to have had a worse grading than the rest, and they compared particularly badly with the survivors. The 57 survivors thus had significantly fewer criteria of RA in the early stages than did the 16 patients whose rheumatoid disease caused or contributed to death.

Functional capacity. The functional capacity after 1 year of arthritis is shown in Table 6 for patients in the different groups. Again, the 'attributable' and 'contributory' groups combined were significantly worse than the others, and this was mainly due to the poor status of the patients in the 'attributable' group.

Other features. No significant differences could be found between the 4 groups in respect of haemoglobin, ESR, or Rose-Waaler titre after 1 year of disease. Nor was any difference seen in body weight, joint score, or the incidence of nodules.

Cumulative death rate and ARA grading. One year after onset of RA there were 48 patients with the grading of 'definite' and 52 with the grading of 'classical' RA (Table 5). The cumulative death rates for patients in these 2 classes over the 18 or so years of follow-up are shown in Fig. 1. The worse death rate in the 'classical' patients became more manifest after the 10th year. The mortality now stands at 54% (28/52) for the 'classical' compared with 31% (15/48) for the 'definite' grade patients: a highly significant difference (P=0·01).

Patients in these 2 classes are comparable in their mean age of onset (51·25 years for the 'classical' and 49·9 for the 'definite'). However, Table 5 shows that the 'classical' grade patients had a high proportion of deaths related to RA (14/28), whereas 'definite' grade patients only had 2 out of 15.

Corticosteroid treatment. Forty-nine of the 100 patients were treated with corticosteroids in the early stages of their arthritis, and some of the survivors continue on a low dosage now. We compared the frequency of corticosteroid treatment in 4 groups.

Table 6 *Functional capacity 1 year after onset*

Group	*No.*	*1*	*2*	*3*	*4*	*Significance*	
Attributable	9	1	2	5	1		
Contributory	7	3	2	1	1		
Combined	16	4	4	6	2	$t=3\cdot24$, $P<\cdot01$	$t=5\cdot07$, $P<\cdot001$
Unrelated	27	14	11	2	0		
Survivors	57	39	15	3	0		
Totals	100	57	30	11	2		

Also the 'attributable' group differed significantly from 'unrelated' group and survivors (P 0·001).

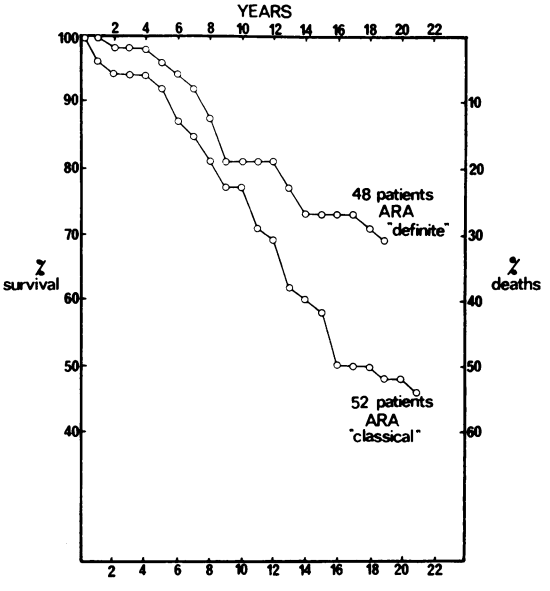

Fig. 1 *The cumulative death rate from all causes is shown during the follow-up period for the 2 grades of 'definite' and 'classical' RA. Grading was made after 1 year of arthritis. The 2 grades are nearly equal in number (48 'definite' and 52 'classical') and in age of onset (means of 49·9 and 51·25 years respectively), but the final figures for deaths are significantly different (P=0·01).*

Table 7 *The incidence of corticosteroid therapy*

Group	*No.*	*Corticosteroid therapy*		*Significance*	
		Yes	*No*		
Attributable and Contributory combined	16	15	1	χ^2 9·70, $P<\cdot01$	χ^2 12·21, $P<\cdot001$
Unrelated	27	11	16		
Survivors	57	23	34		

Table 7 shows that the 'attributable' and 'contributory' groups combined had a significantly higher incidence of corticosteroid treatment than the other groups. This is due to the former groups of patients having more serious disease and stronger indications for the use of corticosteroids.

We found no association between corticosteroid treatment and deaths from cardiovascular disease. Thus, in the 'unrelated' group strokes and cardiac infarcts caused death in 10 of the 11 patients given corticosteroids, and in 10 of the 16 patients not so treated; not a significant difference.

Discussion

We consider that our analysis of the causes of death in RA represents the true state of affairs in that our 100 patients were first seen early in their disease, mainly as referrals to clinics, not necessarily admitted to hospital, and followed up for some 18 years. All, within a year of onset, met the criteria for 'definite' or 'classical' RA and were an otherwise unselected series. Other reported analyses are less truly representative in that they are based on patients already admitted to hospital with established RA[1 3 4] or include 'probable' RA patients[5 6] or are simply a review of deaths in hospital of patients having RA.[8]

Nevertheless, our results are little different from those of other reports; Table 8, comparing our series with 3 others, shows remarkable similarities. However, our patients had an older mean age of death, 69 years, compared with 63 in each of the other 3 series. Our patients also had an older mean age of onset, 50·6 years, compared with 45 years in Reah's patients.[3]

We noted a higher overall mortality in men than in women (53% and 37·5% respectively over 18 years). This is a general finding,[3–6] and here Reah's figures are very close to our own (54% and 39%), though occurring in the shorter period of 13 years. The long-term effect of this higher male mortality is to increase the female preponderance in patients with long-standing RA. In this way the female : male ratio in our patients rose from 1·8 : 1 in the 100 patients at onset to 2·4 : 1 in the survivors 18 years later.

We found that patients whose deaths were due to or related to RA had a younger age of onset and a younger age of death than those whose deaths were unrelated to RA. Certainly the former had more serious disease than the others as indicated by their worse ARA grading and worse functional capacity after 1 year of arthritis. Surprisingly, the more serious nature of their disease was not reflected in the figures for ESR, haemoglobin, or Rose-Waaler titre at that early stage.

As might be expected, the presence of additional criteria of disease in patients with 'classical' RA has a harmful long-term effect on prognosis and survival. This is well shown in the cumulative death rates charted in Fig. 1.

Those dying of causes unrelated to RA and the survivors had less serious arthritis, with better ARA grading and functional capacity at 1 year. An important difference between these 2 groups is in age of onset, namely, a mean of 61 years for the former against only 44·9 years for the latter.

Some reports reveal a high incidence of deaths from infection in RA.[1 5 6 16 17] We found this in our 'attributable' and 'contributory' groups among whom 8 of the 16 deaths were caused by infection. However, there were no deaths from infection in the 'unrelated' group, in whom cardiovascular causes predominated, so that the overall figure for infections was 8 in 43, or 19%, not an unduly high proportion.

An increased incidence of deaths from cardiac infarction is reported in some series.[4–6] Others[1 18] report the reverse, and speculate that regular aspirin dosage may protect rheumatoid patients by reducing platelet adhesiveness and lessening the formation of thrombus and atheroma. Our analysis shows a high incidence of cardiac infarction, namely 11 out of 43 (26%). We categorised all 11 as being unrelated to RA, as there is no proved connection between RA and coronary disease. Vasculitis plays no significant part here.[19]

It is generally accepted that RA causes some reduction in life expectancy. This is shown either by comparison with standard life tables[1 3 5] or by comparison with an equal number of matched controls, followed up for some years.[6] In the latter study the groups are large, consisting of 500 rheumatoid patients and 500 controls followed up for 5 years.

Our figures are too small for us to make accurate estimates of loss of life expectancy. However, reference to life tables suggests that the 'attributable' group had a loss of life expectancy of some 15 years, the 'contributory' group about 10 years, and the 'unrelated' group 5 years.

On this basis we suggest that the generally agreed reduction of life span in patients with RA is mainly

Table 8 *Cause and age of death in RA: comparison of 3 published series with our own*

Series	*No. of deaths*	*Mean age at death (years)*	*Deaths attributed to RA*	*Deaths to which RA contributed*	*Combined*	*Deaths unrelated to RA*
Reah: Harrogate 200 patients[3]	80	63	—	—	42·5%	57·5%
Eulderink *et al.* Leiden[7]	111	63	21%	13%	34%	66%
Constable *et al.*[8] Edinburgh and Birmingham Rasker and Cosh	100	63	16%	28%	44%	56%
Bath: 100 patients	43	69	21%	16%	37%	63%

attributable to a minority of patients, about one-third in number, who have relatively severe disease and die 10 or more years prematurely as a result. The majority of patients, having less severe disease, have a nearly normal life span, and die ultimately of unrelated causes.

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