FACTORS PREDICTING DEATH, SURVIVAL AND FUNCTIONAL OUTCOME IN A PROSPECTIVE STUDY OF EARLY RHEUMATOID DISEASE OVER FIFTEEN YEARS

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SUMMARY

Sixty-four survivors from a prospective study of early rheumatoid disease were assessed again at a mean of 15.2 years from presentation and their status compared with 29 patients who had died. Eleven of the dead and only two of the survivors had been treated with steroids. There was a small increase in mortality due to the disease itself but only one death was directly caused by it.

As might be expected, those who died were older. In the first year of disease, they had lower haemoglobin levels, a lower body mass, higher sedimentation rates and higher levels of blood urea. One-fifth at entry to the study and two-fifths by the time of death, had poor functional capacity.

Of 64 survivors, six had poor functional capacity at entry and nine after 15 years. Discriminant analysis was performed to identify the most powerful combination of early features predicting a poor functional outcome. A combination including early erosive change, seropositivity, poor grip strength and cervical subluxation predicted the outcome correctly in 73% of survivors.

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Almost 60% of survivors remained with or improved to normal function at 15 years suggesting that morbidity is not as bad as has been suggested in the past.

KEY WORDS: Early rheumatoid arthritis, Prospective study, Functional outcome.

A PROSPECTIVE study of early rheumatoid disease was initiated in 1966 in order to study the long-term outcome and to identify any factors indicating a poor prognosis so that more aggressive management and life-style modification might be instituted at an early stage.

We now present some of the early factors which forecast outcome of disease in those who survived and in those who died.

MATERIAL AND METHODS

One hundred and thirty-three patients presenting with early RA between 1966 and 1971 were originally invited to enter a prospective study. Thirty-one patients were excluded, five because of wrong diagnosis, two because the notes were lost and 24 who attended so irregularly that their inclusion was not worthwhile.

This study is therefore based on 102 patients who were followed up until 1984 or until death. All had disease of less than a year's duration at entry. The design of the study and the results after an initial follow-up at a mean of 4.5 yr were reported in 1976 [1-3].

We included patients who fulfilled the ARA criteria [4] for Possible and Probable disease, expecting that a proportion of them would develop Definite or Classical disease. Sixty-nine patients had Definite or Classical disease at entry and 18 of the other 33 developed criteria fulfilling these grades at some time during follow-up.

The status of all 102 patients was ascertained in 1984. Twenty-nine patients had died, 38 were still attending the research clinic and a further 26 who no longer attended were examined by one of us (S.D.) either at the hospital or in their own homes. Five patients declined to take part and the remaining four, none of whom were registered as having died, could not be traced. These nine (two male, seven female) are the 'defaulters'.

A standard clinical examination including laboratory tests and X-rays of hands, feet and cervical spine was performed in the 64 survivors. Functional outcome was assessed using the Steinbrocker grading [5] and the Stanford Health Assessment Questionnaire [6] was administered to 60 of the survivors.

Statistical analysis

Data were analysed as previously described [7] using the Statistical Package for the Social Sciences. Contingency tables for categorical variables were analysed by the χ² test to obtain uncorrected P values. The Spearman ranked correlation coefficient (r) was used to assess the non-Gaussian variables. Discriminant analysis was used to identify the most powerful combination of features in the prediction of outcome groups.

RESULTS

The demographic data of all 102 patients are shown in Table I. The mean ages at presentation were as follows: 46.5 yr (range 19–70 yr) for the 64 survivors, 60.3 yr (range 43–74 yr) for the 29 who died and 50.5 yr
TABLE I
DEMOGRAPHIC DATA

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Survivors</th>
<th>Dead</th>
<th>Defaulters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 102</td>
<td>n = 64</td>
<td>n = 29</td>
<td>n = 9</td>
</tr>
<tr>
<td>Mean age at presentation (yr)</td>
<td>50.5</td>
<td>46.5</td>
<td>60</td>
<td>47.4</td>
</tr>
<tr>
<td>Mean follow-up (yr)</td>
<td>12</td>
<td>16</td>
<td>4.8</td>
<td>7.1</td>
</tr>
<tr>
<td>% male</td>
<td>43</td>
<td>39</td>
<td>59</td>
<td>22</td>
</tr>
<tr>
<td>% female</td>
<td>57</td>
<td>61</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1:1.3</td>
<td>1:1.6</td>
<td>1:0.7</td>
<td>1:1.35</td>
</tr>
</tbody>
</table>

(M:F 44:58)

(range 19–74 yr) for the whole group. The mean age at death was 57.4 yr in men and 72.6 yr in women.

Forty-four men and 58 women originally entered the study, a sex ratio of 1:1.3. In the 29 (17 men and 12 women) who died, the ratio was 1.4:1 whilst for the survivors (25 men, 39 women), the ratio was 1:1.6.

No attempt was made to assess formal education levels but all 102 patients were seen by a social worker who assessed their socio-economic class according to the Registrar General’s classification [8] where Class I is Professional; II, Intermediate; III, Skilled; IV, Semi-skilled and V, Unskilled. Data are missing for seven patients. Of 95 where data are available, seven patients were in Class I; 23 in II; 51 in III; 12 in IV and two in V.

FEATURES OF DISEASE IN THOSE WHO DIED AND THE SURVIVORS

Table II shows some of the features of disease in the two groups. Though more of the dead had nodules, the difference is not significant. The numbers of patients with peripheral erosions, cervical subluxation and sero-positive disease are similar in the dead and in the survivors. Whilst 20% of those who were to die and 9% of survivors were already in Functional Grade (FG) III and IV at presentation, 45% of the dead had developed this degree of disability at the last clinic visit prior to death compared with 14% of survivors in 1984.

Eleven (39%) of the 29 patients who died had been treated at some time with oral steroid drugs compared with two (3%) of the 64 survivors and two of the nine defaulters. All 15 thus treated had Definite or Classical disease when treatment was initiated. Three patients were started on steroid treatment before they attended the research clinic, 10 received steroids at some time during the first 2 yr of disease and the other two later after 5 and 8 yr respectively. Steroid treatment once started was stopped in only two survivors. Indications for steroid treatment were severe disease (nine patients), immunoblastic lymphoma (one), respiratory disease (one) and rheumatoid lung (one). The reason for using steroids in the remaining three patients is not clear.

Details of orthopaedic procedures were not routinely entered on the research proformata until 1984 and the hospital notes of six patients who died are missing so our information is not complete.

Twelve of 64 survivors (19%) had 28 operations between them (eight knee replacements, four hip replacements, two elbow replacements, two amputations for peripheral vascular disease, one neck fusion, one finger joint replacement, two knee synovectomies, two carpal tunnel decompressions, two forefoot arthroplasties, two Keller’s procedures and two removals of elbow nodules). Only one survivor improved from Functional Grade (FG) II to I after a series of five replacement operations, seven did not change their FG and one, whose knee replacement became infected, deteriorated. Two survivors refused forefoot arthroplasty and stayed in the same grade. A third survivor refused wrist arthrodesis but her FG improved from II to I when her wrist became ankylosed.

Six sets of hospital notes concerning the 29 patients who died are lost. Four of the other 23 had six operations (one knee replacement, one hip, one pantalar fusion, one knee arthrodesis, one Benjamin osteotomy and one forefoot reconstruction) between them. Three stayed in the same FG and one improved after two procedures. One patient refused bilateral knee replacements and her FG deteriorated from II to IV.

Of 34 operations in toto, four were soft tissue pro-

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**TABLE II**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Dead (n = 29)</th>
<th>Alive (n = 64)</th>
<th>X²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules</td>
<td>12 (41)</td>
<td>20 (31)</td>
<td></td>
<td>N.S.</td>
</tr>
<tr>
<td>Peripheral erosions</td>
<td>25 (86)</td>
<td>50 (78)</td>
<td>0.36</td>
<td>N.S.</td>
</tr>
<tr>
<td>Cervical subluxation</td>
<td>5 (18)</td>
<td>12 (19)</td>
<td></td>
<td>N.S.</td>
</tr>
<tr>
<td>Scat ≤16 (first visit)</td>
<td>17 (59)</td>
<td>25 (39)</td>
<td>2.34</td>
<td>N.S.</td>
</tr>
<tr>
<td>Functional Grade III/IV:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First visit</td>
<td>6 (21)</td>
<td>6 (9)</td>
<td>0.00</td>
<td>N.S.</td>
</tr>
<tr>
<td>Last visit</td>
<td>13 (45)</td>
<td>9 (14)</td>
<td>0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>Second line drugs</td>
<td>9 (32)</td>
<td>35 (55)</td>
<td>3.58</td>
<td>0.058</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>11 (39)</td>
<td>2 (3)</td>
<td>17.32</td>
<td>0.00003</td>
</tr>
</tbody>
</table>
cedures and were performed during the first 4 yr of disease, a further six (two arthrodeses, two Keller's and two removals of nodules) were performed in years 5 to 8 and the others were performed after 8 yr of disease. Thirteen of 16 patients undergoing surgery had Classical or Definite disease at presentation and two others developed these criteria at a later stage.

Ninety per cent of the dead but only 45% of survivors had Definite or Classical disease by the time of their last clinic visit.

**PATIENTS WHO DIED**

By 4.5 yr of follow-up [2], 10 patients had died at a mean age of 65.2 yr. By 15.2 yr, another 19 with a mean age of 69.7 yr had died. The mean age at death for all 29 patients is 68.2 yr. Of those who died, 17 (59%) were male. The mean age at presentation for those who died was 60.3 yr in both sexes.

Ten patients (eight male) died from ischaemic heart disease and one of them also had fibrosing alveolitis. Seven, two of whom had insulin-dependent diabetes, died from bronchopneumonia. Six died from neoplastic disease (two lung carcinomas, one carcinoma of rectum, one of prostate, one of breast and another from immunoblastic lymphoma). One patient committed suicide, one died of cor pulmonale and one of respiratory failure. Two patients died from cerebrovascular disease. The only patient where death was due to rheumatoid disease, died from rheumatoid heart disease; her case is reported elsewhere [9]. In only seven of 29 Death Certificates was RA mentioned.

The mortality experience of the cohort was compared with population-expected rates (Fig. 1). The horizontal axis in Fig. 1 shows the year of follow-up. The vertical axis shows the ratio of the observed survival and that of the survival to be expected if the patients had experienced the same age, sex and calendar year specific mortality as the general population of England and Wales. In other words, had the patients' survival been identical to that of the general population, the ratio would be 100%.

There is only a small increased mortality in the rheumatoid patients. This relatively reduced survival increases with time; that is to say, with increasing duration of disease, the excess mortality itself increases.

**FUNCTIONAL ASSESSMENT OF SURVIVORS**

Final Functional Grades for the 64 survivors are shown in Table III. Features of their disease are shown in Table IV. The age at disease presentation is similar in all four FGs.

By 1984, nine survivors were in FG III or IV. All nine had erosive disease and four had nodules. Four of the six who had originally presented already in FG III or IV, had developed cervical subluxation.

The small number (only three) of men in FG III or IV by 1984 reflects the high mortality in men; 10 of the 12 who had reached grades III or IV had died by 1984. Twelve (41%) of the 29 patients who died were in FG III or IV at their last clinic attendance.

When changes between FG at presentation and at the last assessment in 1984 were analysed, 15 survivors (23%) had improved, 37 (58%) were the same and 12 (19%) had deteriorated. Thirty-eight survivors (59%) either improved to FG I or began in that grade and stayed there.

Four of 20 survivors (20%) in socio-economic Classes I and II had deteriorated functionally and eight of 42 (19%) in Classes III, IV and V.

Sixty of 64 survivors completed the Stanford Health Assessment Questionnaire (HAQ). Despite the small number, there is a good correlation coefficient of 0.77 between HAQ and FG. Sixty survivors had a mean of HAQ of 0.95. Of 42 survivors who had presented with Classical or Definite disease, the 24 women had a mean HAQ of 1.2 at 15 yr compared with 1.05 for men.
ANALYSIS AND PREDICTION OF FINAL FUNCTIONAL GRADES

We have previously reported [7] that a high RF, low haemoglobin and a high platelet count at presentation are the most powerful predictors for the development of erosive change at 3 yr from presentation; the same features with the addition of poor grip strength and high joint score were identified as predictors of the severity of erosive change at 10 years [10].

As far as predicting the final functional outcome is concerned, no single variable nor even a combination of variables at the time of presentation was successful. If variables are averaged over the first 2 yr of disease however, discriminant analysis can pick out features which in combination predict the final functional grade (FGI, FGII or FG III/IV). This analysis is shown in Fig. 2 and identifies the final FG correctly in 73% of the survivors; the length of each black line signifies the relative importance of each variable.

The development of erosive change during the first 2 yr of disease is the most powerful single predictive feature for a poor functional outcome but is strengthened in a stepwise manner by poor (less than 150 mmHg) grip strength, seropositivity, the presence of cervical subluxation, a high body mass, a high score and so on. The relative weight for feature is reflected by the size of the change in Rao’s V which measures the differences between group means.

The above combination of factors was also tested in a separate sample of another 43 patients whose mean age, sex ratio and disease severity are similar to those of the 64 survivors but who joined the study after 1971. In this group, the final FG was correctly predicted in 67% of patients.

Features present in the first 2 yr of disease which are particularly predictive for FG III and IV are moderate to severe erosive change [10], an average grip strength of less than 150 mmHg, a high body mass index, joint score (the number of joints with active synovitis) of more than 12 and a mean FG of II or worse.

DISCUSSION

Age and sex incidence

Jacoby et al. required at least Definite disease for entry to the Bath study [11]; other than that, the Middlesex patients are demographically similar. In the Bath study, the mean age at presentation was 50.6 yr compared with 50.4 yr in the current study. In those

![Development of erosions](Image)

Fig. 2.—Discriminant analysis. Combination of clinical and laboratory features present in the first 2 yr of follow-up in stepwise manner in order to predict final functional grade into three groups (I, II, or III/IV) in those who survive for 15 yr. *Chronic persistent disease rather than relapsing/remitting.
surviving 15 yr, the mean ages at presentation were 46.7 yr in Bath [12] and 46.4 yr in the current study.

Though a near equal sex incidence was found in the very early disease subgroup of the Bath study [11], in patients presenting to Otten and Boerma [13] and also to Caruso et al. [14], most other studies of early disease such as those by Van der Heijde [15] and Eberhardt et al. [16], report a sex incidence of 1:1.6 in early disease. The sex ratio of our 102 patients is 1:1.3 but if we had included the 24 patients (19 women) who were excluded from the study because of erratic attendance, the sex incidence would become 1:1.6. We do not know why these 24 patients attended irregularly, nor can we explain why the sex incidence of another cohort of 109 patients (data are yet to be analysed) who joined the study between 1972 and 1988 should be 1:2.4.

By 15 yr, the sex ratio has become 1:1.6 in the Middlesex survivors and 1:2.4 in those at Bath [17]. In both studies, this is because comparatively more men have died. The changing ratio becomes even more obvious by 25 yr of follow-up in the Bath study when the ratio changes to 1:3.6 [18].

Features of disease

Only one of the 29 patients who died did not fulfil the criteria for Definite or Classical disease at some time during follow-up. Nine (36%) of the 25 patients presenting with Classical and 13 of 44 patients (30%) presenting with Definite disease died. The Bath study [17, 18] and the studies by Mitchell et al. [19] and Erhardt et al. [20] show higher mortality in Classical than in Definite disease.

Prior et al. [21] found that 50% of patients who died during an 11-yr follow-up had been treated with steroids whilst Allebeck et al. [22] showed an almost twofold increase in mortality amongst steroid-treated patients. Of the 15 Middlesex patients who received steroids, only four, two of them defaulters, were alive at 15 yr.

It was, and still is the policy at the Middlesex to use systemic corticosteroid treatment sparingly, for fear of long-term adverse effects.

Only 15% of the Middlesex patients (19% of survivors) underwent surgery whereas in Bath, 29 of 65 (45%) of survivors had undergone surgery by 15 yr. This difference cannot be explained by the absence of information in six patients who had died nor is it explained by less severe disease for all but one of the 16 Middlesex patients operated upon either presented with or developed Classical or Definite disease.

Though the mean age at presentation was higher in the patients who died than in the survivors, survivors whether they presented before or after the age of 60 had fewer features of disease as shown by the ARA criteria.

Fifty-eight per cent of the Bath patients [23] and 41.4% of the Middlesex patients presenting with Classical or Definite disease had reached FG III or IV by the time of their last visit to the research clinic before death.

We conclude that compared with survivors, those who died had more severe disease, were more often treated with steroids and became more disabled during the course of their illness.

Causes of death

Ten of 29 (34%) patients died from ischaemic heart disease. This figure compares with the 26% reported by Koota et al. [24] and by Mutru et al. [25], 26% in the Bath study [12], 34% in that reported by Uddin et al. [26] and 33% by Lewis et al. [27].

Six (21%) patients died from neoplastic disease. Pincus [28] calculating the mean cumulative total of deaths from 13 different studies comprising 2262 deaths in RA found 14.1% (range 7-28%) deaths from neoplasia.

Of seven (24%) patients dying from bronchopneumonia, four were aged over 75 at death. Their relatively advanced age may explain why this rate is higher than that reported by Uddin et al. [26] and by Vandebroucke et al. [29] who found 14 and 11% respectively. Only one of these seven patients did not have Classical or Definite disease.

Functional assessment of survivors and defaulters

All seven defaulters who presented under the age of 60 began in FG I or II and continued in those grades until their last visit. Both defaulters who presented at over 60, began in FG I or II but one was in FG III at the last visit.

Callahan and Pincus [30] have shown a poorer clinical status in patients who had not completed high school studies. We did not assess educational level but the percentages (20 vs 19%) of those survivors in socioeconomic Classes I and II and in Classes III, IV and V who deteriorated functionally during follow-up are similar.

We found a correlation coefficient of 0.77 between HAQ scores and FG which is comparable to the figure of 0.65 reported by Sherrer et al. [31].

Table V shows the mean functional grades at presen-
tation and at 3, 11, and 15 yr for all 64 survivors and for the 42 who presented with Classical or Definite disease. Also given for comparison are the mean grades of the 65 Bath survivors [12].

Early on, the mean FG of the Middlesex and Bath survivors is similar but by 15 yr, that of the 42 Middlesex survivors who had presented with Classical or Definite disease is 1.9 compared with 2.5 for Bath [12].

Sherrr et al. [31] report greater disability in women whilst Deighton et al. [32] demonstrate that greater disability in women is due to more severe disease. The mean FG at entry to the Middlesex study is 1.6 for women and 1.7 for men; by 15 yr, the mean FG of those presenting with Classical or Definite disease is 2.1 for women and 1.6 for men. In the Bath study, the mean FG is 2.6 for women and 2.2 for men.

The explanation of poor functional outcome in other studies [31, 33–35] is at least partly due to longer disease duration at entry. Scott et al. [36] paint a gloomy picture of RA. All their 112 patients were treated with steroids and 20 yr after entry, 35% had died and only 19% of survivors were in FG I or II. At entry to their study, one-third had a disease duration of 5 yr or more and three-quarters were already in FG III or worse. Referral of only the more severely affected patients from other hospitals to Droitwich between 1964 and 1966 is probably a significant factor.

Like Ramos-Renus et al. [37], we are of the opinion that the long-term use of steroids in rheumatoid disease is associated with greater morbidity. As far as we know, the first authors to report a ‘rather worse’ functional capacity in patients treated with steroids were Rasker and Cosh [38]. At 15 yr, 33 survivors had received steroids and 29 had not. The mean FG of patients not treated with steroids was 2.2 and that of the steroid-treated patients was 2.7. It is with great respect that we suggest that the poorer functional outcome in the Bath survivors was because, overall, 47% of patients had received steroids [12]. The reason for the gloom shown by Scott et al. [36] may be not only because their patients had a long disease duration at entry to the study but that in addition, all their patients received steroid treatment.

Analysis and prediction of final functional grade

Outcome in our original study at 4.5 yr [2] was assessed on functional grading together with clinical features such as grip strength, duration of early morning stiffness and extent of joint disease. Indicators of a poor outcome were an initial high joint score, poor grip strength and poor functional capacity together with a high ESR and high titres of RF. Significant adverse prognostic features also included low body weight, the number of ARA criteria fulfilled, a blood urea of 6.5 mm or more and the presence of peripheral erosive damage. Anaemia was less significantly correlated with poor outcome at the 0.01 level.

The present study measures outcome only on the functional capacity of those surviving after a mean of 15 yr. We confirm a poor outcome with early features such as erosive change, poor grip strength and seropositivity. A new feature, that of cervical subluxation occurring within the first 2 yr of disease, now achieves prominence as a prognostic indicator of eventual poor outcome but anaemia, low body weight and raised ESR no longer appear. The reason for the disappearance is that most of the patients who presented with those features have now died.

CONCLUSION

We suggest that the relatively good functional outcome in our 64 survivors at 15 yr should give some cause for optimism and note that as long ago as 1957, Duthie and his colleagues [39] felt to conclude ‘it is likely that, in many patients, the disease runs a mild course giving rise to little disability’.

ACKNOWLEDGEMENTS

We thank our patients, those who have helped to assess them and the Arthritis and Rheumatism Council which gave financial support to the study in its early years.

REFERENCES


