

Incidence of Severe Outcome in Rheumatoid Arthritis During 20 Years

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ABSTRACT. Objective. Information from successive inception cohorts is needed to reveal changes in the endpoint severity of rheumatoid arthritis (RA). We assessed joint destruction and disability 8–20 years after the onset of RA to estimate the number of patients with severe disease at the endpoint.

Methods. Radiographs of the hands and feet were taken at onset and at 1, 3, 8, 15, and 20 years from entry among 103 patients with recent onset (< 6 mo) seropositive RA. The Larsen score of 0–100 of 20 joints of hands and feet, the Health Assessment Questionnaire (HAQ) index, and the number of large joint arthroplasties were used to assess severity. The cumulative number of patients with amyloidosis was recorded.

Results. The median progression of small joint destruction was 2–3% yearly. At the endpoint 36% of the patients had Larsen score 50–100 and 23% scored 67–100. The endpoint HAQ index was 2–3 in 16% of the 81 patients investigated. The number of large joint arthroplasties was 29 in 16 patients. A high Larsen score or HAQ was registered in 30 (29%) patients. The incidence of amyloidosis was 13.6%; at the end of the 20 year followup 9 of the 14 patients with amyloidosis had died.

Conclusion. Our prospective 20 year RA study is the first epidemiological survey in which 20 year severity in RA has been determined by 4 clinical measures; these data will serve as a basis for discussion of methods and comparison with other cohorts in the future. (J Rheumatol 2002; 29:688–92)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
HEALTH ASSESSMENT QUESTIONNAIRE

RADIOGRAPHS

OUTCOME
SEVERITY

In rheumatoid factor (RF) positive rheumatoid arthritis (RA) chronicity is seen most typically as persisting inflammatory synovitis, which results in joint damage best observed on conventional radiographs. Longterm studies have shown that inflammation was only partly controlled, and thus joint damage increased annually by 1.8% of the possible maximum damage measured using the Larsen score¹. After 5 years, joint destruction rather than joint pain and inflammation results in disability, mostly expressed by the patient-perceived Health Assessment Questionnaire (HAQ) index. The average annual increase in HAQ scores has been estimated at about 1%¹. Although there is individual variation in the progression, it irrevocably causes severe outcome in a considerable proportion of patients.

We have reported the mean progression of radiographic destruction of hands and feet during the first 20 years in 103 patients with RA², and more recently that 26% of the erosive cases ended in radiographic remission, when no progressive destruction could be detected³. Without remission severe disease may result; however, to our knowledge no generally accepted definition of severity, except death, exists. As a

basis for such discussion, findings from our inception cohort allow measurement of the 20 year incidence of severe joint damage, high Health Assessment Questionnaire results, and amyloidosis.

MATERIALS AND METHODS

During the period 1973–75 a total of 117 patients with recent (≤ 6 months) rheumatoid factor (RF) positive RA were studied at the Rheumatism Foundation Hospital in Heinola, Finland. The selection criteria, data collection strategy, and patient details have been described^{2,4,5}. Followup examinations were carried out at onset and at 1, 3, 8, 15, and 20 years from entry. At the 8 year followup in 1982, 103 patients had seropositive RA (70 women, 33 men), and they formed the final group of this study⁴. One patient refused radiographs at the 8 year checkup. The disease was erosive in 102 patients. Erosions were not a criterion for inclusion in this series. A total of 83 patients attended the 15 year followup, and 68 patients the 20 year followup during the year 1995–96, while 28 others had died and 7 could not attend because of severe disease other than RA. The age at onset ranged from 17 to 70 years, mean 45.0 (SD 13.2).

Use of disease modifying antirheumatic drugs (DMARD), prednisolone, and their combinations was registered at each checkup.

Radiographs of the hands and feet were taken in the dorsovolvar projection. The Larsen score was used⁶ to evaluate radiographs during the period 1982–97 (evaluation by author KK). The radiographs to be interpreted were compared with standard series on a scale of 0 to 5. Joints with only soft tissue swelling or osteoporosis were assigned a Larsen grade of 0, joints with pre-erosive changes or marked joint space narrowing a grade of 1⁷, and after reconstructive surgery a grade of 5. Grades for the 1st to 5th metacarpophalangeal and 2nd to 5th metatarsophalangeal joints and wrists (20 joints) were summed to form a Larsen score of 0–100 to demonstrate severity. The progression rate was calculated in relation to the remaining score. The formula used to calculate the relative progression was

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Submitted January 15, 2001; revision accepted October 23, 2001.

the score of the designated year minus the score of the previous year, divided by the total score minus the score of the previous year, i.e., the score change per amount of score available to change per year⁸.

The HAQ index was used to evaluate disability⁹. These scores were available only at the 15 and 20 year checkups, and endpoint disability was studied in 81 of the 83 patients.

At the 15 year checkup a subcutaneous biopsy was taken in all patients to assess the presence of AA amyloidosis¹⁰. At the 20 year checkup amyloidosis was sought only if the patient had proteinuria or high serum creatinine. At the end of followup the numbers of arthroplasties performed on hip, knee, shoulder, and elbow joints were recorded.

Analysis of the cumulative proportion of endpoint Larsen scores was carried out according to the life table method. Mann-Whitney test was used to compare patients with and without amyloidosis.

RESULTS

Treatment. At onset the patients were treated with gold sodium thiomalate (GSTM), prednisolone and GSTM, or chloroquine, as shown in Table 1. After the 8 year followup in 1982 the variability was greater; e.g., sulfasalazine and methotrexate were introduced.

Severity. The median progression in destruction of 20 peripheral joints (Larsen score 0–100) was regularly 2–3% yearly during the 20 years, when the ceiling effect was eliminated, as shown in Figure 1. The results of this progression, the endpoint Larsen scores of 0–100, are shown in Figure 2. Only 2 patients had the maximum score of 100. The grade of destruction was $\geq 2/3$ or 67% of the maximum in 24 (23%) patients, as illustrated in Figure 2. The numbers of patients in other endpoint categories are shown in Table 2. The severe disease appeared slowly in patients, and the life table (Figure 3) reveals how 50% and 66% of the maximum destruction of 20 peripheral joints had occurred after 8 years. Correspondingly, the endpoint HAQ of 81 patients

(Figure 4) indicates that 13 (16%) patients had the poorest outcome, HAQ 2–3, and 49 (60%) had the best, HAQ 0–0.9.

Arthroplasties. At the end of followup 16 patients had 29 large joint replacements: one in 10 patients, 2 in 2 patients, 3 in 3 patients, and 6 in one patient. Arthroplasties were performed on 15 hips, 10 knees, 2 shoulders, and 2 elbows. The mean Larsen score of 59.2 (SD 30.7) in patients with arthroplasties was significantly higher ($p = 0.015$) than the 39.2 (SD 25.4) in those without. Correspondingly, the HAQ score of 1.7 (SD 0.77) was also higher ($p = 0.001$) than the 0.78 (SD 0.72) in nonoperated patients.

Amyloidosis. At the 20 year checkup, cumulatively, 14 of the initial 103 patients had developed secondary amyloidosis (13.6%), and 9 (64.3%) of the 14 had died. The 89 patients without amyloidosis had a mean endpoint Larsen score of 40 (median 35), whereas the 14 cases with amyloidosis had a mean Larsen score of 57.1 (median 54). The difference is significant ($p = 0.026$). The mean Larsen score was 39.5 in the 28 patients out of 103 who died, and of these, Larsen score was 50.2 in 9 patients with amyloidosis and 34.4 in the 19 without amyloidosis.

Effect of severity measurements. If the definition of severe disease is a Larsen score of 67–100 or HAQ 2–3 or 3 large joint arthroplasties, the 20 year incidence of severe RA was 29% (30/103). There were 6 patients with HAQ 2–3 (mean 2.25), who had Larsen scores of 0–47 (mean 22.8). Two of them had one large joint replacement, and one patient had 3. The 3 other patients with 3–6 arthroplasties had Larsen scores of 76–100. Thus, 3 arthroplasties did not add to the figure of 29%, and HAQ contributed only by 6%. Only 2 patients with 3 and 6 arthroplasties fulfilled all the 3 severity

Table 1. Treatment of 103 patients with RA during 20 years.

Therapy	Year of Followup					
	On admission, N = 103 N (%)	1, N = 103 N (%)	3, N = 103 N (%)	8, N = 103 N (%)	15, N = 83 N (%)	20, N = 68 N (%)
Drugs						
Hydroxychloroquine	37 (36)	43 (42)	40 (39)	26 (25)	8 (10)	9 (13)
Gold sodium thiomalate	58 (56)	46 (45)	39 (38)	25 (24)	13 (16)	11 (16)
Penicillamine	2 (2)	2 (2)	3 (3)	7 (7)	5 (6)	3 (4)
Azathioprine	0 (0)	0 (0)	0 (0)	1 (1)	3 (4)	3 (4)
Auranofin	0 (0)	0 (0)	0 (0)	0 (0)	4 (5)	8 (12)
Sulfasalazine	0 (0)	0 (0)	0 (0)	0 (0)	8 (10)	13 (19)
Methotrexate	0 (0)	0 (0)	0 (0)	0 (0)	3 (4)	8 (12)
Podophyllotoxin	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Prednisolone	27 (26)	34 (33)	34 (33)	39 (38)	28 (34)	26 (38)
Strategy						
No drugs	10 (10)	12 (12)	19 (18)	32 (31)	29 (35)	17 (25)
Single therapy	62 (60)	56 (54)	47 (46)	30 (29)	25 (30)	22 (32)
Single therapy with prednisolone	25 (24)	29 (28)	27 (26)	25 (24)	18 (22)	16 (24)
Prednisolone alone	1 (1)	3 (3)	6 (6)	14 (14)	10 (12)	4 (6)
Combination therapy	4 (4)	1 (1)	3 (3)	2 (2)	1 (1)	3 (4)
Combination therapy with prednisolone	1 (1)	2 (2)	1 (1)	0 (0)	0 (0)	6 (9)

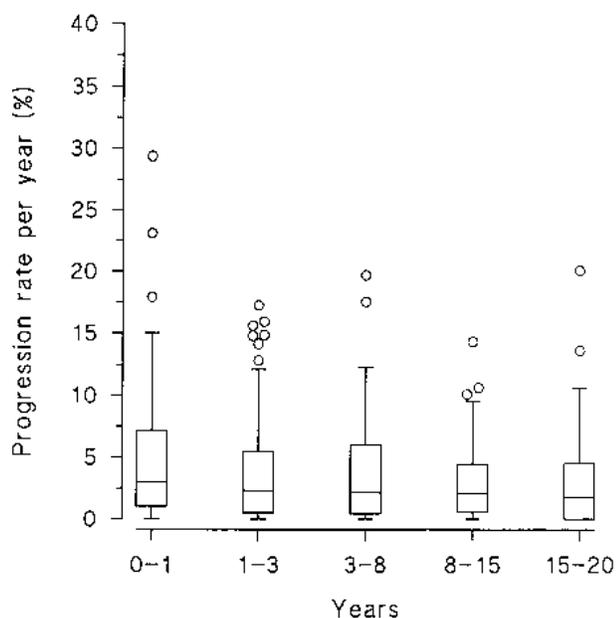


Figure 1. Progression rate of the Larsen score (0–100) in relation to the duration of RA.

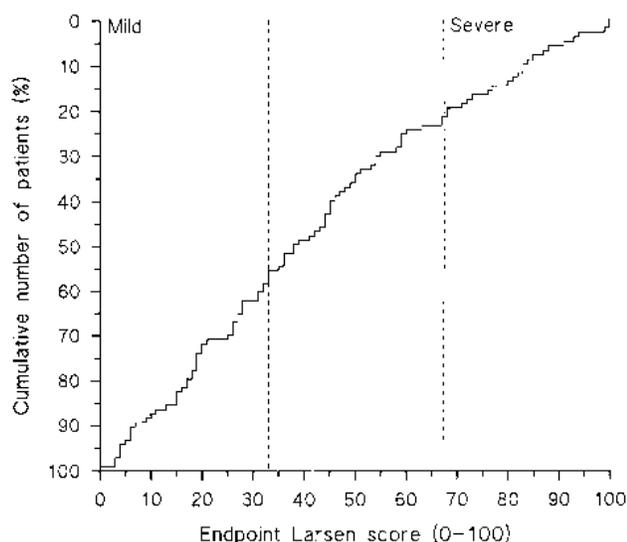


Figure 2. The endpoint Larsen scores (0–100) in 20 peripheral joints during 20 years in 103 patients with RA shown as cumulative frequency histogram. Broken lines divide the Larsen scores into tertiles.

requirements: the Larsen score was 76–100 and the HAQ was 2–2.6. The Venn diagram in Figure 5 shows the degree of overlap between the severity measures studied in 81 patients with 3 indicators available.

DISCUSSION

It is commonly accepted that patients with arthritis who are constantly RF negative have better prognosis than those who are positive¹¹. One reason for this is that the negatives may have hidden spondyloarthritis. To avoid heterogeneity, we studied only RF positive patients and excluded even from them 10 mild atypical cases⁴. These decisions presumably worsened the outcome of our patients compared with that in other series.

Our followup commenced in 1973, when GSTM and (hydroxy) chloroquine were the only DMARD used. GSTM treatment was often discontinued because of side effects, which would appear to be the reason for the high number of destructive joints seen at the 8 year followup (Figure 3). After that followup in 1982, treatment of RA in Finland became more extensive, as illustrated in Table 1, and it will thus be possible in the future to compare whether combination therapy or more aggressive therapy will end in better longterm results in RF positive patients¹².

The severity of RA is the reason for its high economic impact on society. Even at the 3 year checkup in this study, RA had the poorest outcome compared with nonspecific, HLA-B27 related or psoriatic arthritis. The measurements were joint score, function score, number of eroded joints, erythrocyte sedimentation rate, and working ability¹³. The cumulative rate of work disability reached 80% during 20 years in our cohort¹⁴. However, Larsen scores did not explain this rate of retirement¹⁴.

In classic studies, some 10% of RA patients have been confined to a chair or bed 10–15 years after onset of disease^{15,16}. The prospective Droitwich study¹⁷, although the patients did not form an inception cohort, established that by 20 years most patients (54%) were either dead (35%) or severely disabled (19%). At that time the mean Larsen score for hands and wrists was 51% of the maximum¹⁷. To make comparison of longterm studies possible, even those completed in different decades, we recommend the simplest measurement, the Larsen score of 0–100 in general use, as it accounts for the peripheral joints, where rheumatoid destruction is greatest^{18,19}. We suggest that if 2/3 of maximum destruction takes place during followup, the patient's disease is severe, as it was in 23% of our series (Figure 2). It may be argued that with this score only a few

Table 2. Endpoint distribution of 103 patients with RA according to Larsen score of 0–100 during 20 years.

	Larsen Score						
	0–24	25–49	50–74	75–100	0–33	34–66	67–100
No. of patients (%)	30 (29)	36 (35)	20 (19)	17 (17)	46 (45)	33 (32)	24 (23)

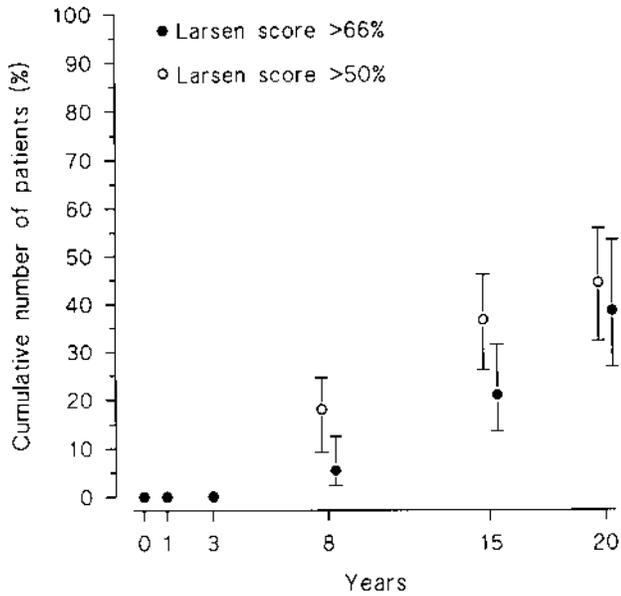


Figure 3. Cumulative percentages of patients (with 95% CI) with Larsen score over 50% and 66% of the maximum Larsen score calculated by the life table method during 20 years.

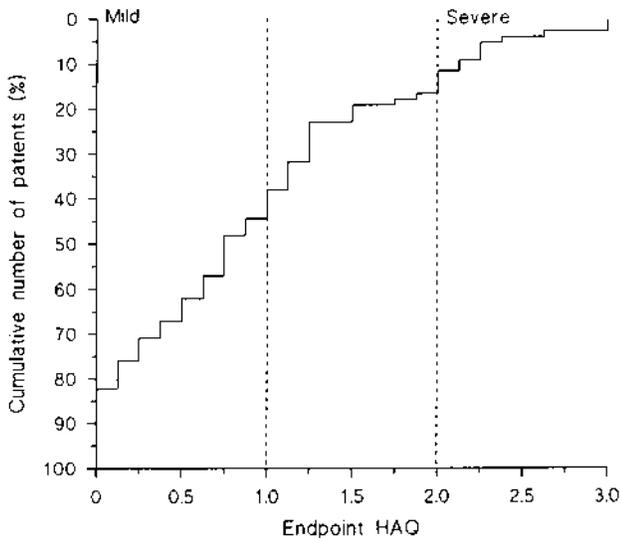


Figure 4. The cumulative frequency histogram shows the endpoint HAQ scores of 81 patients with RA during 20 years.

joints are considered. Unfortunately, the destruction in RA is not only peripheral. We have proved previously with these data that a Larsen score of 0–100 correlates significantly with the 15 year destruction of hips ($p = 0.015$), glenohumeral joints ($p < 0.001$), acromioclavicular joints ($p < 0.001$), and elbow joints ($p < 0.001$)^{20–23}. Recently Drossaers-Bakker, *et al* also observed that radiographic damage in hands and feet correlated significantly (0.76

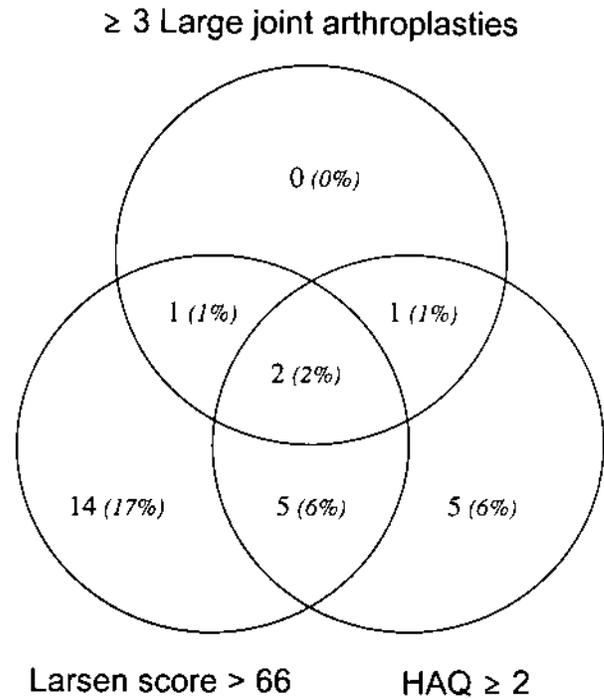


Figure 5. The degree of overlap between the endpoint severity indicators: 3 or more large joint arthroplasties, Larsen score (0–100) over 66, and HAQ score ≥ 2 ($n = 81$).

Spearman) with that in all large joints at 12 year followup of 105 female patients with RA²⁴. Peripheral joint destruction explained the amount of variance in the HAQ index almost as well as that of all joints: 59% and 61%, respectively.

The mean of the 0–100 Larsen score shown in Figure 2 was 44.5². In those 28 patients who died it was 39.5, probably because the progression of the disease halted. It seems to us that mortality was related to severe RA mainly in those patients who developed AA amyloidosis. We also found that mortality did not change the means of Larsen scores in patients followed for 8, 15, and 20 years with the current data². However, the small number of patients does not justify valid conclusions dealing with this issue.

Kageyama, *et al* have shown that patients with multiple arthroplasties have significantly poorer life prognosis than those with only one or 2 lower limb joint replacements²⁵. With this in mind we accepted 3 large joint arthroplasties as a marker of severe RA, but we found only 4 such cases during the 20 year followup, although peripheral joint destruction had been substantial. As some arthroplasties are indicated because of osteoarthritis — for example, our only nonerosive patient underwent one total hip arthroplasty — we consider that the number of arthroplasties is not the best definition of severity in adult onset rheumatoid disease. Based on the followup of a cohort of 1600 RA patients, Wolfe and Zwillich estimated that 25% of patients will undergo total joint arthroplasty within 23 years from disease

onset²⁶. In that population 57% were knee arthroplasties, whereas in patients we studied, hips were replaced most frequently during the 20 years (15 hips, 10 knees).

According to the HAQ index 16% of the 81 patients assessed had severe disease. The mean HAQ was 1.01 (95% CI 0.8–1.2) at the 20 year followup¹⁴, which is consistent with findings elsewhere^{27–29}. Leigh, *et al* surmised that after 20 years, comorbidity and senescence themselves can affect disability more rapidly than RA, which may also affect our 15–20 year disability³⁰. The age adjusted correlation coefficient between the HAQ index and the Larsen score was 0.46 at the 20 year checkup¹⁴.

The results of our 20 year prospective study indicate that the median progression of destruction in patients with RF positive RA is 2–3% yearly. This destruction causes severe disease in at least one-quarter of patients. The incidence of amyloidosis was 13.6% during 20 years. In 2001 it was 15.5%. Since onset, patients with amyloidosis also had clinically significantly more severe disease than the remainder¹⁰.

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