Quantitative Target Values of Predictors of Mortality in Rheumatoid Arthritis as Possible Goals for Therapeutic Interventions: an Alternative Approach to Remission or ACR20 Responses?

THEODORE PINCUS and TUULIKKI SOKKA

ABSTRACT. Predictors of longterm mortality in rheumatoid arthritis (RA) include patient questionnaire measures, grip strength, walk time, physician and patient assessment of global status, joint examination abnormalities, erythrocyte sedimentation rate (ESR), and morning stiffness. In the rheumatology literature, these measures have been analyzed primarily according to mean values in groups or regression analyses, which are valuable to recognize that mortality in RA is predicted by more severe disease, but do not provide the clinician with specific goals of therapy. Goals for therapeutic intervention are often expressed either as complete remission or as statistically significant differences versus a placebo, as in a 20% or even 50% response of a measure such as the American College of Rheumatology Core Data Set. Remission may be too stringent, while statistically significant efficacy of a drug compared to placebo may not necessarily indicate effectiveness to control longterm damage. An alternative approach might be to identify possible target values for therapeutic efficacy that markers of a poor prognosis be "near normal" rather than necessarily at normal or remission levels, as has been explored in management of hypertension and diabetes. However, it remains uncertain whether the goal of therapy should be a "near normal" or entirely normal values for a clinical marker. Better control of quantitative markers that predict early mortality could provide a valuable approach to improving outcomes in RA. (J Rheumatol 2001;28:1723–34)

Key Indexing Terms:
MORTALITY RHEUMATOID ARTHRITIS PREDICTORS
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Increased mortality rates have been documented in most series of patients with rheumatoid arthritis (RA) reported from rheumatology clinical settings over the last two decades[1-41], with standard mortality ratios of 1.2 to 2.3:1. In general, standard mortality rates in RA have not changed substantially over the years[38], although even the most recent reports reflect therapeutic approaches of at least one decade earlier. Many types of quantitative measures, including demographic measures such as age, sex, and socioeconomic status, quantitative joint counts[42,43], radiographic scores[44-49], laboratory measures of inflammation, physical measures of functional status[50], as well as patient questionnaires[51,52], have been documented to predict increased risk for premature mortality[1,8,19]. These reports have shown that RA is a severe progressive disease[6,19,53], and that significantly higher mortality rates over the next 5–20 years are predicted by poor clinical status, rather than as a random event in RA, or as a result of drug toxicities, which is quite unusual[54]. However, application of these data in clinical trials and clinical care as target values for therapeutic interventions has not been developed extensively in RA, as in other chronic diseases such as hypertension and diabetes.

In modern management of hypertension and diabetes, it has been suggested that "target values" have been published such as a blood pressure of 140/90 in hypertension[55] or maintaining a hemoglobin A_{1C} level of 7.0% in diabetes[56], which are not "normal" but "near normal" goals of therapy. Pursuit of "near normal" target values may involve lower doses of drugs or fewer drugs than may be required to achieve complete remission[57], thus reducing risks of drug therapy while providing a prognosis that may be as good as the "normal" values[58,59]. However, this matter remains under study, as it has been suggested that only fully normal values are desirable[60].

The goal of treatment to improve markers of premature mortality in RA toward "near normal" target values might provide a compromise between two approaches to assess therapeutic efficacy, criteria for statistically significant differences between a drug versus placebo[61], or criteria for a clinical remission[57]. Statistical comparisons between effi-

From the Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; and Jyvaskyla Central Hospital, Department of Medicine, Jyvaskyla, Finland.

T. Pincus, MD, Vanderbilt University School of Medicine; T. Sokka, MD, Jyvaskyla Central Hospital.

Address reprint requests to Dr. T. Pincus, Vanderbilt University School of Medicine, Division of Rheumatology and Immunology, 203 Oxford House, Box 5, 1313 21st Avenue South, Nashville, TN 37232-4500.

cacy of a drug versus placebo according to an individual measure or the Core Data Set for clinical trials[62-65] may present too modest a goal with currently available disease modifying antirheumatic drugs and biologic therapies such as methotrexate, cyclosporine[66,67], leflunomide[68-71], etanercept[72], and infliximab[73]. By contrast, "remission criteria"[57] appear overly stringent for use in clinical trials and clinical care, as remission is unusual[74], even with new DMARD.

Predictive markers for higher or lower mortality rates in individual patients have been described in the rheumatology literature largely in terms of mean values, odds ratios, or regressions. These data characterize the severity of RA in groups of patients, but do not provide the clinician with "target goals" for an individual patient analogous to reduction of an elevated blood pressure or cholesterol in cardiovascular disease.

Predictive markers for mortality in RA or any chronic disease may be classified in 3 categories: (A) "demographic" variables such as age, sex, education level; (B) disease variables that are "non-modifiable" through direct medical care for RA, such as duration of disease, comorbidities, and extraarticular disease; (C) disease variables that are "modifiable" through direct medical care for RA, such as functional disability, swollen joint count, and erythrocyte sedimentation rate (ESR). A change of a modifiable marker from an unfavorable to a favorable value might provide a reasonable target for a therapeutic intervention, such as is seen in management of hypertension and diabetes. Longterm observational studies could be performed to determine whether favorable changes to a target value for a prognostic variable are associated with improvement in longterm survival, or whether complete remission might be optimal.

In this report we review predictive markers that were significant or not significant in all of 31 studies of mortality in RA that included a marker for higher mortality rates[1-41]. We present in greater detail 3 cohorts of patients with RA studied at Vanderbilt University over 5–15 years[19-21,33,34,50], in which results appear consistent with most reports in the rheumatology literature, including one study over 5 years that included most measures found in available publications. We then review reports that suggest possible target values for therapeutic interventions in RA that are relatively accessible in usual clinical care.

31 REPORTS IDENTIFYING RISK FACTORS FOR MORTALITY IN RA

Thirty-one cohorts that include a marker to predict mortality in RA are summarized for "demographic" and "non-modifiable" (Table 1) and "modifiable" predictive variables (Table 2). Three demographic variables (Table 1) were statistically significant predictors in more than two-thirds of reports in which they were available, age in 25 of 26 studies[1-11,17-20,26-28,30,31,33,34,36,37,39,40,75-81], male sex in 12 of 18 studies[3,7-10,16,26,27,29-31,37,78,79], and formal education level in 4 of 6 studies (Table 3). "Non-modifiable" disease variables that were statistically significant predictors in more than two-thirds of the reports in which they were available included comorbidities in 7 of 8 studies[19-21,26,30,31,34,38,79] and extraarticular disease in 5 of 7 studies[2,7,26,28,32], while duration of disease was significant in 7 of 12 studies[3,17,18,26,27,29,34,78] in which it was available (Table 3).

Among potentially ?modifiable? variables (Tables 2 and 3), statistically significant predictors of mortality in RA in more than two-thirds of the reports in which they were available included patient questionnaire measures in all of 9 studies[19-21,27,29,30,33,34,36,39,78], physician global assessment of status in all of 9 studies[2,4,13,16,17,26,31,34,78], physical measures of functional status such as grip strength and walk time in 4 of 5 studies, patient global assessment of status in 3 of 4 studies[29,30,34], and patient psychological distress in all of 3 studies[33,34,39] (Table 3). Variables that were statistically significant predictors in 50-67% of reported studies included joint count in 5 of 8 studies[2,19-21,26,34,78] and ESR in 4 of 8 studies[2,17,34,78]. Variables reported to be significant in fewer than 50% of studies included pain score in one of 3 studies[78] and rheumatoid factor in 4 of 13 studies[16-18,38,78]. Radiographic scores were significant predictors in 2 of 7 studies with the largest numbers of patients[26,78], while the radiograph was not a significant predictor in 5 studies with smaller numbers [13,20,31,34,36,82].

Despite extensive differences in these cohorts in size, location, year studied, duration of observation, and others, some general conclusions can be drawn concerning the predictors of mortality in RA (Tables 3 and 4). Statistically significant predictors of mortality included patient questionnaire responses, patient psychological distress, and physician assessment of global status in 100% of reports in which these measures were available, age in 96%, comorbidities in 88%, physical measures of functional status such as grip strength and walk time in 80%, patient global status in 75%, extraarticular disease in 72%, male sex in 67%, formal education level in 67%, joint count in 63%, ESR in 50%, duration of disease in 58%, pain score in 33%, rheumatoid factor in 31%, and radiograph in 28% of studies in which these measures were available. Taken together, these studies indicate that people with more severe RA, assessed according to a spectrum of measures, are more likely to die over the next 5–20 years, although characterizing severity quantitatively. To analyze in greater detail which measures might be most effective predictors of survival or mortality, we present analyses of mortality in RA in 3 cohorts of patients studied at Vanderbilt University since 1973.

PREDICTORS OF PREMATURE MORTALITY IN 3 COHORTS.

Three cohorts of patients with RA have been studied at Vanderbilt University over the last 27 years (Table 5): (A) 75 patients from Nashville with a baseline evaluation in

Table 1. Mortality in RA: predictive variables that are non-modifiable in medical care.

Study	Inclusion, Place	Followup, yrs	No. of Patients	Baseline Mean Age	Baseline Mean Disease Duration	SMR	Demographic Variables: Older Age	Demographic Variables: Lower Education Level	Demographic Variables: Sex (M)	Disease Variables: Duration of Disease	Disease Variables: Extraarticular Disease	Disease Variables: Comorbidity
Cobb, 1953[1]	1940s Massachusetts, USA	10	583	NA	NA	129	+	NA	NA	NA	NA	NA
Duthie, 1964[2]	1948–51 UK	9	307	NA	NA	214	+	NA	NA	NA	+	NA
Uddin, 1970[3]	1954–66 Canada	up to 10	475	NA	NA	129	+	NA	+	+	NA	NA
Jacoby, 1973[4] Rasker, 1981[5] Reilly, 1990[6]	1957–63 UK	up to 25	100	51	< 1	140	+	NA	NS	NA	NA	NA
Gordon, 1973[7]	1965–66 Canada	5	127	55	12	NA	+	NA	+	NA	+	NA
Isomaki, 1975[8] Koota, 1977[9] Mutru, 1985[10]	1959–68 Finland	3,5,10	1000	NA	NA	173	+	NA	+	NA	NA	NA
Monson, 1976[11]	1930–60 Boston, USA	up to 42	1035	NA	NA	185	+	NA	NA	NA	NA	NA
Fleming, 1978[12] Corbett, 1993[13]	1966-71, UK	up to 15	102	51	< 1	NA	NA	NA	NA	NA	NS	NA
Linos, 1980[14]	1950–74 Minnesota, USA	up to 25	521	NA	NA	116	NA	NA	NA	NA	NA	NA
Lewis, 1980[15]	1966–76 UK	11	311	NA	NA	113	NA	NA	NA	NA	NA	NA
Allebeck, 1981[16]	1965–67 Sweden	11	239	NA	NA	192M, 118F	NA	NA	+	NA	NA	NA
Scott, 1983, 1987[17,18]	1964–66 UK	up to 20	112	NA	NA	NA	+	NA	NA	+	NA	NA
Pincus, 1984, 1987, 1994[19–21]	1973 Tennessee, USA	9,15	75	55	11	162	+	+	NS	NS	NA	+ (heart disease)
Vandenbroucke,	1954–57 NL	up to 25	209	54	8	NA	NA	NA	NA	NA	NA	NA1984[22]
Prior, 1984[23] Symmons, 1986, 1998[24,25]	1964-78, UK	up to 22	448	NA	NA	270	+	NA	NA	NA	NA	NA
Mitchell, 1986[26]	1966–74 Canada	12	805	52	10	151	+	NA	+	+	+ (nodules)	+ (protein-uria)
Wolfe, 1988[27]	1981 Kansas, USA	3	400	55	10	NA	+	NA	+	+	NA	NA
Erhardt, 1989[28]	1976–79 UK	8	107	59	7	NA	+	NA	NA	NA	+	NA
Leigh & Fries, 1991[29]	1978 USA	8	263	55	13	NA	+	NS	+	+	NA	NS
Kazis, 1990[30]	1978–81 Boston, USA	5	279	NA	9	NA	+	NS	+	NA	NA	+
Jacobsson, 1993[31]	1965–89 Arizona, USA	up to 24	172	NA	NA	128	+	NA	+	NS	NS	+ (protein-uria)
Wolfe, 1994[78]	1973–1990, 4 centers, USA	up to 16	3501	53	9	226	+	+	+	+	+ (nodules)	NA
Callahan, 1996[33]	1985, 15 centers USA	5	1416	57	12	154	+	+	NS	NS	NA	NA
Callahan, 1997[34]	1984–86 Tennessee, USA	5	210	57	10	161	+	+	NA	+	NA	+
Wallberg-Jonsson, 1997[79]	1979 Sweden	15	606	55	13	157	+	NA	+	NA	NA	+ (former CVE)
Soderlin, 1998[36]	1989–91 Finland	5	103	59	16	NA	+	NA	NS	NS	NA	NA
Lindqvist, 1999[37]	1985–89 Sweden	up to 13	183	51	< 2	87	+	NA	+	NA	NA	NA
Gabriel, 1999[38]	1965, 1975, 1985 Minnesota, USA	10	670	63	NA	138	+	NA	NS	NA	NA	+
Maiden, 1999[39]	1984–85, UK	12	200	57	7	NA	+	NA	NA	NA	NA	NA
Sokka, 1999[40]	1983–89, Finland	up to 14	135	50	< 2	128	+	NA	NA	NA	NA	NA
Krause, 2000[41]	1980–87, Germany	up to 15	256	58	9	147 to 556	NS	NA	NS	NS	NA	NA

ESR: Erythrocyte sedimentation rate; CS: cross sectional; SMR: standardized mortality ratio; LO: longitudinal; +: significant association; NS: not significant; NA: not available; CVE: cardiovascular event.

Table 2. Mortality in RA: predictive variables that are modifiable in medical care.

Study	No. of Patients	Functions	Joint Count	Radiographic Stage	ESR	RF+	Functional Status Questionnaire	Pain Scores	Patient Global Status	Physician Global Status	Psychological Status
Cobb, 1953[1]	583	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Duthie, 1964[2]	307	NA	+	NA	+	NA	NA	NA	NA	+ (Steinbrocker)	NA
Uddin, 1970[3]	475	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Jacoby, 1973[4]	100	NA	NS	NA	NS	NS	NA	NA	NA	+ (Steinbrocker)	NA
Rasker, 1981[5]											
Reilly, 1990[6]											
Gordon, 1973[7]	127	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Isomaki, 1975[8]	1000	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Koota, 1977[9]											
Mutru, 1985[10]											
Monson, 1976[11]	1035	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fleming, 1976[12]	102	NA	NA	NS	NA	NS	NA	NA	NA	+ (Steinbrocker)	NA
Corbett, 1993[13]											
Linos, 1980[14]	521	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lewis, 1980[15]	311	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Allebeck, 1981[16]	239	NA	NA	NA	NA	+	NA	NA	NA	+ (Steinbrocker)	NA
Scott, 1983, 1987[17,18]	112	NA	NA	NA	+	+	NA	NA	NA	+ (5 functional classes)	NA
Pincus, 1984, 1987, 1994[19–21]	75	+ (button, walk)	+	NS	NA	NA	+ (long)	NA	NA	NA	NA
Vandenbroucke, 1984[22]	209	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Prior, 1984[23]	448	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Symmons, 1986, 1998[24,25]											
Mitchell, 1986[26]	805	+ (grip strength)	+	+	NS	NS	NA	NS	NA	+ (ARA functional class)	NA
Wolfe, 1988[27]	400	NA	NA	NA	NA	NA	+ (HAQ)	NA	NA	NA	NA
Erhardt, 1989[28]	107	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Leigh & Fries, 1991[29]	263	NA	NA	NA	NA	NA	+ (HAQ)	NA	+	NA	NA
Kazis, 1990[30]	279	NA	NA	NA	NA	NA	+ (AIMS)	NA	+ (AIMS general health)	NA	NA
Jacobsson, 1993[31]	102	NA	NA	NS	NA	NS	NA	NA	NA	+ (Steinbrocker)	NA
Wolfe, 1994[78]	3501	NA	+	+	+	+	+ (HAQ)	+	NA	+ (Steinbrocker)	NA
Callahan, 1996[33]	1416	NA	NA	NA	NA	NA	+ (HAQ)	NA	NA	NA	+ (helplessness)
Callahan, 1997[34]	210	+ (button grip, walk)	+	NS	+	NS	+ (MHAQ)	NS	+	+ (ACR functional class)	+ (helplessness)
Wallberg-Jonsson, 1997[79]	606	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA
Soderlin, 1998[36]	103	+ (Keitel)	NS	NS	NS	NS	+ (HAQ)	NA	NA	NA	NA
Lidqvist, 1999[37]	183	NA	NA	NA	NA	NS	NA	NA	NA	NA	NA
Gabriel, 1999[38]	670	NA	NA	NA	NA	+	NA	NA	NA	NA	NA
Maiden, 1999[39]	200	NA	NA	NA	NA	NA	+ (HAQ)	NA	NA	NA	+ (social deprivation)
Sokka, 1999[40]	135	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Krause, 2000[41]	256	NS	NS	NA	NS	NS	NA	NA	NS	NA	NA

ESR: Erythrocyte sedimentation rate; CS: cross sectional; LO: longitudinal; +: significant association; NS: not significant; NA: not available; ACR: American College of Rheumatology.

1973 and review after 9 years in 1982 and after 15 years in 1988[21]; (B) 210 patients from Nashville with baseline evaluations in 1985 and review after 5 years in 1990[34]; and (C) 1416 patients from 15 rheumatology private practice settings in 8 US cities, with baseline evaluations in 1985 and review after 5 years in 1990[33].

COHORT A — 75 PATIENTS WITH BASELINE IN 1973

The 75 patients in Cohort A had an extensive baseline evaluation in 1973[19,20,50], and reviews in 1982[19,20,83] and 1988[21]. The standardized mortality ratios were 1.86 at 5 years, 1.92 at 10 years, and 1.62 at 15 years[21]. Attributed causes of

Table 3. Predictive markers for mortality in RA in 31 published cohorts.

	Statistically Significant	Differences but not Statistically Significant	Not Available	Significant When Available, %	No. of Studies in which Variable is Reported
Demographic variables					
Age	25	1	5	96	26
Formal education level	4	2	25	67	6
Male sex	12	6	13	67	18
Disease variables not modifiable through therapy for RA					
Extraarticular disease	5	2	24	72	7
Comorbidity	7	1	23	88	8
Duration of disease	7	5	19	58	12
Disease variables modifiable through therapy for RA					
Joint count	5	3	23	63	8
Radiograph	2	5	24	28	7
ESR	4	4	23	50	8
RF positivity	4	9	18	31	13
Patient questionnaire — measures of functional status	9	0	22	100	9
Pain score	1	2	28	33	3
Patient assessment of global status	3	1	27	75	4
Physician assessment of global status	9	0	22	100	9
Psychological status	3	0	28	100	3
Physicial measures of functional status	4	1	26	80	5

Table 4. Variables associated with mortality in 31 studies of mortality in RA. Number of studies in which variable significant/total number of studies.

Type of Variable	Reported Significant in		
	> 67%	50–67%	< 50%
Demographic variables			
Age	25/26	—	—
Formal education level	4/6	—	—
Male sex	12/18	—	—
Disease variables not modifiable through therapy for RA			
Extraarticular disease	5/7	—	—
Comorbidity	7/8	—	—
Duration of disease	—	7/12	—
Disease variables modifiable through therapy for RA			
Joint count	—	5/8	—
Radiograph	—	—	2/7
ESR	—	4/8	—
RF positivity	—	—	4/13
Patient questionnaire — measures of functional status	9/9	—	—
Pain score	—	—	1/3
Patient assessment of global status	3/4	—	—
Physician assessment of global status	9/9	—	—
Psychological status	3/3	—	—
Physical measures of functional status	4/5	—	—

death were superficially similar to deaths in the general United States population. Cardiovascular disease was listed as the cause of death in 44% of the patients, similar to published series of patients with RA[16,84-86].

Mortality over 15 years was significantly higher in patients who were older, had fewer years of formal education, male sex, more involved joints, comorbid cardiovascular disease, higher walking time, higher button test values, lower grip strength, greater functional disability according to a patient activities of daily living (ADL) questionnaire, and higher scores according to a 3 item disease adjustment scale. In Cox proportional hazards models, ADL scores and

formal education level remained significant and independent predictors of mortality when age and duration of disease were included in models[21].

Relative risks for mortality over 5, 10, and 15 years were computed according to values above and below the median values for each available variable (Table 6). In unadjusted analyses, most variables other than duration of disease and morning stiffness identified significantly greater risk of mortality at 5, 10, and 15 years. In general, higher risks remained significant when adjusted for age, duration of disease, sex, and formal education level.

COHORT B — 210 PATIENTS WITH BASELINE IN 1985

Cohort B[34] included 210 consecutive patients with RA who had a baseline assessment in 1985, in whom quantitative measures not available in Cohort A were obtained, including joint count and radiographic, laboratory, and questionnaire measures. Five years after baseline, 206 of the 210 patients were accounted for. Survival of patients in the poorest prognostic categories was in the range of 70%, in contrast to 50% in Cohort A, suggesting possible improved survival from 1982 to 1990.

Measures that differed significantly at baseline in patients who would survive or die over the next 5 years included age, formal education, duration of disease, number of comorbidities, joint limited motion, as well as grip strength, walk time, and button time, similar to results in Cohort A (Table 7). In addition, ESR, American Rheumatism Association (ARA) Functional Class, modified Health Assessment Questionnaire (MHAQ) scores for functional status, global status, and helplessness were significant predictors of 5 year mortality[34]. Measures that did not differ significantly between the 2 groups included joint swelling, tenderness, deformity or pain on motion, radiographic scores, rheumatoid factor status or titer, and patient questionnaire scores for dissatisfaction and pain (Table 6).

Table 6. Adjusted* relative risk of death in 75 patients with RA over 5–15 years. From Pincus, *et al*, 1994[21].

	5 Years	15 Years
Demographic variables		
Age (≥ 58 yrs)	3.5:1	2.8:1
Sex (male)	2.3:1	1.6:1
Formal education level (≤ 11 yrs)	2.1:1	2.2:1
Disease variables		
Duration of disease (≥ 10 yrs)	0.7:1	1.5:1
Joint count (≥ 18/42 joints)	3.7:1	3.0:1
Morning stiffness (≥ 60 min)	1.4:1	1.1:1
Cardiovascular disease (present)	3.2:1	1.2:1
Functional status variables		
Patient questionnaire (≤ 91.5% "with ease")	6.6:1	2.9:1
Modified walking time (≥ 20 s)	6.5:1	1.9:1
Button test (≥ 60 s)	5.3:1	2.3:1
Grip strength (≤ 82 mm Hg)	8.4:1	3.2:1

*Adjusted for age, duration, sex, and education.

In Cox regressions, age, comorbidities, MHAQ scores, and other measures of functional status were significant predictors of 5 year mortality[34]. In survivors, most measures of damage, including joint deformity, walk time, and radiographic scores, indicated disease progression. However, measures of activity were generally somewhat improved, including joint swelling, joint tenderness, pain scores, and rheumatoid factor titer, or essentially unchanged, including joint pain on motion, ESR, and MHAQ scores. Therefore, it appears that measures of inflammatory activity were stable and sometimes improved, while measures of damage indicated progression in the same patients over 5 years[34]. These data, and similar observations by others[53,87-89], suggest that measures of inflammatory activity may underestimate severe longterm outcomes in RA, and longterm studies should include measures of damage to assess effectiveness of therapies.

Table 5. Cohorts of patients with RA studied at Vanderbilt University.

	Cohort A	Cohort B	Cohort C
No. of patients	75	210	1416
Baseline year	1973	1985	1985
Review year	1982[19,20,50] 1988[21]	1990[34]	1990[33]
No. (%) at review	75 (100)	206 (98)	1384 (98)
Advantages	First cohort with extensive demographic and functional status measures, including questionnaire and physical measures	Includes complete quantitative joint count, radiographic score, laboratory data	Patients of 15 rheumatologists in 8 US cities. Extensive patient questionnaire data
Disadvantages	No quantitative joint count per ARA Glossary, radiographic scores, or laboratory data	Systematic reviews available only every 5 years	Does not include physical examination, radiographic, and laboratory data

COHORT C — 1416 PATIENTS WITH BASELINE IN 1985

Cohort C[33] included 1416 patients diagnosed as having RA by 15 rheumatologists in private practice rheumatology settings in 11 cities in 6 states and Washington, DC: Menlo Park, Palo Alto, and Santa Cruz, California; Vero Beach and Palm Beach, Florida; Boise, Idaho; Minneapolis, Minnesota; Philadelphia, Pennsylvania; Memphis and Nashville, Tennessee; and Washington, DC. These patients completed mailed self-report questionnaires at the beginning of 1985 and semiannually or annually thereafter[90].

Five years after baseline, 982 persons (69.3%) returned a questionnaire, 174 (12.3%) were deceased, 228 (16.1%) responded to telephone questions about their status, and 32 (2.3%) were lost to followup. Thus vital status at 5 years was available for 1384 patients, 97.7% of the original cohort. No significant differences were seen in baseline demographic or clinical status variables between patients who were accounted for after 5 years and those who were lost to followup.

Over the 5 year period, 174 patients (12.6%) died, versus expected mortality of 120 (8.7%)[91]; the standardized mortality ratio was 1.54, similar to other published series monitored by rheumatologists[20,26,92,93]. Age, formal education level, MHAQ scores, and helplessness scores were associated significantly with 5 year mortality, as in previous studies[94-102], while disease duration, income, marital status, occupation, race, sex, and therapy were not associated significantly with mortality.

In a Cox proportional hazards regression model, formal education level, age, MHAQ ADL score, and sex were significant in prediction of 5 year mortality. In Cox models that included helplessness scale scores, formal education level was no longer significant[33], suggesting that helplessness may mediate associations between low formal education level and premature mortality.

POSSIBLE TARGET VALUES FOR QUANTITATIVE CLINICAL MEASURES AS GOALS FOR THERAPEUTIC INTERVENTIONS

Reports of identifiable target values that are relatively accessible to the clinician are presented in Table 8. Most of the target values have involved joint counts and measures of functional status, including patient questionnaires and global and physical measures. Mitchell[26] reported that more than 85% of patients with ARA Functional Class I, fewer than 14 active joints, or grip strength > 200 mm Hg survived over the next 10 years, compared to fewer than 77% of patients with ARA Functional Class I and II or grip strength < 200 mm Hg. Pincus, *et al*[20,21] (Cohort A from Vanderbilt University) reported that more than 83% of patients with joint counts of less than 20 of 42 involved joints, patient questionnaire scores greater than 80% of ADL performed "with ease," modified walking time < 10 seconds, button

Table 7. Mean baseline values of measures of activity and damage as possible predictors of mortality 5 years later in Cohort B of 210 patients monitored in Nashville 1985–90. From Callahan, *et al,* 1997[34].

Measure	Total	Alive	Dead	p
Age (yrs)	51.0	55.1	65.5	< 0.001
Comorbidities (No.)	1.27	1.14	1.52	< 0.001
Patient global status (1–4)		2.2	2.6	< 0.001
Walk time (s)		10.8	16.8	< 0.001
Button test (s)	68.5	62.6	96.2	< 0.001
ESR (mm/h)	36.3	33.7	48.3	0.004
MHAQ—ADL (1–4)	2.04	1.98	2.32	0.005
Helplessness score (1–4)	2.43	2.41	2.55	0.007
Grip strength (mm Hg)	101.8	108.7	86.4	0.026
Joint limited motion (42 joints)	9.2	8.2	13.3	0.006
Formal education (yrs)	10.6	10.8	9.4	0.031
Duration of disease (yrs)	9.7	9.1	12.7	0.033
Joint count—total (42 joints)	13.4	12.8	15.9	0.041
Dissatisfaction—ADL (1–4)	2.22	2.21	2.51	0.051
Radiographic erosion (1–4)	1.46	1.40	1.75	0.058
Joint pain on motion (42 joints)	8.9	8.4	11.1	0.091
Joint deformity (42 joints)	8.1	7.6	10.5	0.106
Pain—ADL (1–4)	2.42	2.38	2.60	0.128
Joint swelling (42 joints)	15.0	14.5	17.0	0.157
Radiograph—total (1–4.33)	1.23	1.20	1.36	0.198
Joint tenderness (42 joints)	15.9	15.6	17.4	0.382
Radiographic malalignment (1–4)	0.21	0.20	0.28	0.343
Radiographic joint space narrowing (1–5)	2.19	2.16	2.31	0.474
Pain—VAS (1–4)	5.37	5.40	5.19	0.677

test < 40 seconds, and grip strength for women > 100 mm Hg survived over the next 10 years, compared to 50% or fewer of patients with more than 30 involved joints, fewer than 80% activities performed "with ease," modified walking time > 30 seconds, or button test > 120 seconds. Scott, *et al*[18] found survival over the next 20 years was 80% in patients with baseline functional capacity of I or II on a scale of I–V, and 79% in patients with baseline ESR < 20, compared to 33% in patients with baseline functional status IV or V, and 57% if ESR was > 50. Corbett, *et al*[13] reported survival of 72% over the next 15 years in patients with functional grade I and II, compared to 50% in functional grade III and IV. Callahan, *et al* in 1996[33] (Cohort C from 15 rheumatology practices coordinated at Vanderbilt University) reported 95% five year survival in patients with baseline helplessness scores of 2 or less on a scale of 1–4, compared to 77% of patients with scores of 2.6 or more. Studies of a third cohort of 210 patients at Vanderbilt University (Cohort B)[34] indicated 5 year survival of 100% in patients who were classified at baseline as ARA Functional Class I, global status of 1, or walking time < 6 seconds, or MHAQ scores of 1 on a scale of 1–4. Survival was greater than 90% in patients with perceived helplessness score < 2, button time < 40 seconds, grip strength > 125 mm Hg, ESR < 20, and more than 80% if 8 or fewer involved joints, radiographic scores were less than 0.5 at baseline, on a scale of 0–4.33. By contrast, 5 year survival was 75% in patients with baseline global status of 4 or ESR > 60, 72% with radiographic scores greater than 2, and less than 70% in patients with ARA Functional Class IV, MHAQ scores greater than or equal to 3, perceived helplessness greater than 2.8, and button time > 120 seconds. The poorest 5 year survival of 40% was seen in patients who were unable to walk. Soderlin[36] found survival of 88% in patients with Functional Class I and II and less than 6 in the Keitel lower extremity functional status test, compared to 70% in patients with Functional Class III and IV and 65% in those with Keitel score greater than or equal to 13.

None of these studies included detailed data comparing an absolutely normal score with a "near normal" score. Nonetheless, an overview of the data indicates that in many analyses, patients with "near normal" values had a prognosis similar to those with normal values, although further rigorous analyses of this matter are required.

Table 8. Mortality in RA: favorable versus unfavorable values for predictive or associated variables that are modifiable in medical care.

Study	Years	No. of Patients	Variable	Favorable		Unfavorable	
				Value	Alive, %	Value	Alive, %
Mitchell, 1986[26]	12 (mean) 10 year data in table	805	ARA functional class	I	89	II-IV	76
			Number of active joints	< 14	85	≥ 14	77
			Grip strength	> 200	86	< 200	76
Pincus, 1987[20]	9	75	Joint count (42 joints)	< 20	90	≥ 30	44
Pincus, 1994[21]	15 10 year data in table	75					
			Long questionnaire (% "with ease)	≥ 80	83	< 80	12
			Modified walking time (s)	< 10	90	≥ 30	25
			Button test (s)	< 40	100	≥ 120	33
			Grip strength (mm Hg) (Females only)	> 100	100	≤ 100	70
Scott, 1987[18]	20	112	Functional capacity (I-V)	I-II	80	IV-V	33
			ESR	≤ 20	79	> 50	57
Corbett, 1993[13]	15	102	Functional grade (I-IV)	I-II	72	III-IV	50
Callahan, 1996[33]	5	1394	Helplessness score (1–4)	≤ 2.0	95	> 2.6	77
Callahan, 1997[34]	5	210	ACR functional class (I-IV)	I	100	IV	57
			MHAQ difficulty (1–4)	1.00	100	≥ 3	62
			Perceived helplessness (1–4)	≤ 2.00	90	> 2.80	62
			Global status (I-IV)	I	100	IV	75
			Walking time (s)	≤ 6	100	Unable to walk	40
			Button time (s)	≤ 40	95	> 120	65
			Grip strength (mm Hg)	> 125	92	< 68	80
			Joint count (0–70)	≤ 8	80	> 48	65
			ESR	< 20	92	≥ 60	75
			X-ray scores (0–4.33)	≤ 0.50	80	> 2.00	72
Soderlin, 1998[36]	5	103	Functional class (I-IV)	I-II	88	III-IV	70
			Keitel lower extremity function test (0–44)	0–6	86	≥ 13	65

ESR: Erythrocyte sedimentation rate; MHAQ: modified Health Assessment Questionnaire; HAQ: Health Assessment Questionnaire.

DISCUSSION

These data indicate unequivocally that mortality in patients with RA is predicted by more severe disease 5–15 years earlier, and is not simply a random event in people with RA or secondary to drug toxicities. Myllykangas-Luosujärvi, *et al* found that among 1666 Finnish patients with RA who died in 1989, DMARD contributed to only 6 deaths (0.3%), while nonsteroidal antiinflammatory drugs contributed to 30 deaths (1.8%)[54]. Therefore, more severe disease was the primary basis for premature mortality over the subsequent 5–20 years. While mortality is not the primary outcome of interest in care of patients with RA, it is clearly an unequivocally undesirable outcome. Furthermore, predictors of mortality have also been predictors of work disability and functional declines[52,103], so that these markers would appear to provide useful targets for therapeutic interventions.

More than two-thirds of 31 studies that included potential predictors of mortality in RA were in agreement that age, comorbidities, patient questionnaire responses, physician global status, physical measures of functional status such as grip strength and walk time, patient global status, patient psychological distress, male sex, extraarticular disease, and formal education level are significant predictors of mortality in RA. Variables that were significant predictors of mortality in 50–67% of studies reported included joint count, ESR, and duration of disease. Variables reported to be significant in some studies, but fewer than half, included pain score, rheumatoid factor, and radiograph. In general, variables were more likely to be statistically significant in cohorts that were larger and had longer duration of observation and higher number of deaths, as might be expected.

The data from 31 studies of mortality in RA (Tables 1–4) are similar to those from a single cohort of patients studied at Vanderbilt University in which all variables are available (Table 6). Again, age, comorbidities, patient questionnaire responses, physical measures of functional status such as grip strength and walk time, patient psychological distress, and formal education level are more discriminatory predictors of mortality than joint count, ESR, and duration of disease. Again, the variables that were not significant predictors of mortality were pain score, rheumatoid factor, and radiograph.

It appears possible that further research might lead to recognition of target values associated with a favorable prognosis that might not necessarily be entirely normal or achieve "remission," but nonetheless leave the patient with as favorable a prognosis as a complete remission, with lower risks of aggressive therapy. Such target values have been described in hypertension[55] and diabetes[56], in which it is recognized that although lower blood pressure predicts better survival, at least some observers suggest that reduction of blood pressure may be dangerous below a certain point[58], although others do not agree[60]. Similar considerations exist in reduction of glucose and hemoglobin A_{1C} in management of diabetes[56].

It is important to recognize limitations of the approach of target values as presented to date. First, there have not been any systematic comparisons of which the authors are aware, including in their own research, to compare an absolute "normal" value with a "near normal" value in determining a longterm prognosis. An overview of data suggests it is possible that "near normal" values may be associated with as good a prognosis as "normal" values, but this remains to be documented definitively. Second, the observation of more favorable outcomes associated with certain values does not necessarily indicate that a change in unfavorable to a more favorable value would necessarily improve longterm outcomes, although this phenomenon has now been documented in one report[41]. Third, the degree of influence that therapy might have in an individual patient remains unknown, as longterm outcome reflects in part endogenous, genetically determined "natural history" of disease, which can vary from relatively indolent to very aggressive. Fourth, many clinicians, including rheumatologists, continue to regard data from a laboratory or other high technology source as more clinically important than data from patient questionnaires, and do not regard patient data as analogous to "objective" measures such as blood pressure, hemoglobin A_{1C}, glucose, serum cholesterol, etc. However, this situation appears to be changing as the value of patient questionnaires in clinical care becomes increasingly apparent[52].

A reasonable hypothesis in contemporary care of RA is that a change to a more favorable value, analogous to a near normal blood pressure or hemoglobin A_{1C}, might improve longterm outcomes. A serious conundrum for rheumatologists may be that markers for *overtreatment* in hypertension or diabetes such as hypotension or hypoglycemia, which tell a clinician that it might be appropriate to withdraw one or more drugs or reduce dosage of a drug, are not available in RA. Therefore, a goal for true remission in all patients might incur risks of possible DMARD toxicity in overtreatment of many patients. If longterm prognosis may be improved as much by achieving "near normal" target values of partial remission, improved outcomes with lesser risk may occur. Further research concerning target values in RA would appear of value to improve longterm outcomes.

Finally, the resources that have been available to document that improvements in disease measures in hypertension and diabetes were associated with improved outcomes will not be available for longterm studies of RA. Further, a longterm randomized trial involving placebo or weak DMARD is neither practical nor ethical[104], with information available concerning longterm morbidity and mortality of RA. There is a need to develop more effective simplified methodologies for large longterm observational studies, in order to document significant changes in the "natural history" without a control group. Rheumatologists might

establish databases to document longterm outcomes; simple patient questionnaires can provide sufficient data to accomplish this goal[52,103]. An effort to support development of longterm databases, which may document substantial changes in the natural history of RA, might be a goal of government funding organizations, foundations, professional societies, and pharmaceutical companies at this time.

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