Erythrocyte Sedimentation Rate, C-Reactive Protein, or Rheumatoid Factor Are Normal at Presentation in 35%–45% of Patients with Rheumatoid Arthritis Seen Between 1980 and 2004: Analyses from Finland and the United States

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ABSTRACT. ***Objective.*** To analyze erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF) tests in 2 databases of consecutive patients with rheumatoid arthritis (RA) over 25 years between 1980 and 2004, in Finland and the USA.

Methods. Databases of 1892 patients of 7 rheumatologists in Jyväskylä, Finland, and 478 of one author in Nashville, TN, USA, seen in usual care, were reviewed for the first recorded ESR and CRP, and all RF tests.

Results. Median ESR at presentation was 30 mm/h at both sites. Mean ESR was 36 mm/h in Jyväskylä and 35 mm/h in Nashville. ESR was < 28 mm/h in 45% and 47% of patients at the 2 sites, respectively. CRP was normal in 44% and 58%, and all RF tests were negative in 38% and 37%, respectively. Both ESR and CRP were normal in 33% and 42% of patients, and all 3 tests were normal in 15% and 14% of patients in whom they were assessed. All 3 tests were abnormal in only 28% in Jyväskylä and 23% in Nashville.

Conclusion. A majority of patients with RA seen between 1980 and 2004 had abnormal ESR, CRP, or RF. However, more than 37% of patients had ESR < 28 mm/h, normal CRP, or all negative RF tests. Similarities of laboratory test data at 2 sites on different continents with different duration of disease suggest generalizability of the findings. Normal ESR, CRP, and RF are seen in a substantial proportion of patients with RA at this time. (First Release May 1 2009; J Rheumatol 2009;36:1387–90; doi:10.3899/jrheum.080770)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
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An elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and/or positive rheumatoid factor (RF) test support a diagnosis of rheumatoid arthritis (RA). ESR ≥ 28 mm/h and/or abnormal CRP are frequent inclusion criteria for RA clinical trials[1]. American College of Rheumatology (ACR) remission criteria for RA include ESR < 20 mm/h for men and < 30 mm/h for women[2].

One report published in 1994 indicated that about 40% of patients with RA had a normal ESR[3]. This report has not been confirmed to date at other sites. Databases of consecutive patients with RA seen from 1980 to 2004, 1892 in Jyväskylä, Finland, and 478 in Nashville, TN, USA, include ESR, as well as CRP at first visit, and all RF tests, as analyzed in this report.

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MATERIALS AND METHODS

Patients. A database has been maintained of all patients with RA seen between 1980 and 2004 at Jyväskylä Central Hospital[4], and patients seen by one rheumatologist (TP) at Vanderbilt University in Nashville[5]. All patients had a diagnosis of RA made by a rheumatologist; more than 90% met formal criteria for classification of RA[6]. Patients in Nashville signed consent for results to be included in a database at Vanderbilt University. The study was approved by appropriate ethics committees.

Statistical analyses. The first recorded ESR was analyzed according to mean and median levels with interquartile ranges; < or ≥ 28 mm/h, an inclusion criterion for most clinical trials[1]; < 30 mm/h in women or < 20 mm/h in men — i.e., the values for ACR remission criteria[2]; ≤ 20 mm/h in women and ≤ 10 mm/h in men — i.e., more stringent "normal" values; and mean and median levels in 5-year periods, 1980-1984, 1985-1989, 1990-1994, 1995-1999, and 2000-2004. The first recorded CRP was analyzed similarly, including those with levels < 10 mg/l, the upper limit of normal at both sites. RF was recorded as positive or negative at any time,

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titers over the first decade of observation, and then as international units, so RF concentrations were not analyzed.

RESULTS

Patients. The cohorts appeared typical for RA: mean age 55 and 54 years, 67% and 70% female, and 62% and 63% positive for RF (Table 3) in Jyväskylä and Nashville, respectively. Patients differed in duration of disease, 72% < 1 year in Jyväskylä versus 24% < 1 year in Nashville, reflecting different medical systems. No significant association of duration of disease was seen with level of ESR, CRP, or RF at either site, and no significant differences in age and duration of disease were seen between patients who had available data or missing data for any test at either site.

ESR results. The median ESR was 30 mm/h at both sites, 30 and 30 mm/h in women and 31 and 27 mm/h in men, respectively (Table 1). The first recorded ESR was < 28 mm/h in 45% and 47% of patients, respectively (Table 1). ESR was < 30 mm/h in women or < 20 mm/h in men (a remission criterion) in 43% and 45% of patients in the 2 cohorts, respectively (Table 1).

ESR was < 30 mm/h in 49% and 48% of women, and < 20 mm/h in 32% and 37% of men, respectively. ESR ≤ 20 mm/h in women and ≤ 10 mm/h in men, a more stringent definition of "normal," was seen in 25% of Jyväskylä patients and 30% of Nashville patients. Median presenting ESR values at the 2 sites were 35 mm/h and 32 mm/h in 1980–1984, 31 and 31 in 1985–1989, 33 and 31 in 1990–1994, 29 and 26 in 1995–1999, and 28 and 25 in 2000–2004 (p = 0.004 in Jyväskylä, p = 0.01 in Nashville; Table 2).

CRP results. The median presenting CRP was 12 mg/l in 1749 patients in Jyväskylä and 6 mg/l in 175 patients in Nashville (Table 1). A normal CRP of < 10 mg/l was seen in 44% of patients in Jyväskylä and 58% in Nashville (Table 1). The lower CRP level and higher proportion of normal CRP values in Nashville may reflect that CRP was performed only since 1995, and Nashville patients seen more recently have better clinical status than in earlier years[7]. Among patients with available data, 33% and 42% had neither ESR ≥ 28 mm/h nor CRP ≥ 10 mg/l at the 2 sites (Table 3).

Rheumatoid factor results. A positive RF was seen in 62% and 63% of patients at the 2 sites (Table 1). Overall, 15% and 14% of patients at the 2 sites had normal ESR and CRP, as well as negative RF tests, while 28% and 23% had abnormal results in all 3 tests (data not shown).

Table 1. Demographic and clinical status measures at presentation of patients with RA during 1980-2004 in 1892 patients in Jyväskylä, Finland, and 738 patients in Nashville, TN, USA.

Feature	Jyväskylä N = 1892	No. Patients Tested	Nashville N = 738	No. Patients Tested
Demographic measures				
Age, yrs, mean (SD)	55 (16)	1892	54 (14)	738
No. females, %	67	1892	70	738
Race Caucasian, %	100	1892	86	736
Clinical measures				
Duration of disease < 1 yr, %	72	1778	24	729
Duration of disease, median (IQR)	6 (3, 12) months	1778	3.3 (0.9, 11) years	729
Functional disability score on HAQ/MHAQ (0–3)	0.88 (0.38, 1.38)	1083	0.87 (0.38, 1.25)	730
Rheumatoid factor, % positive	62	1874	63	292
Hemoglobin, g/l	131 (122, 140)	1853	133 (122, 142)	437
ESR, mm/h				
Median (IQR): all patients	30 (16, 49)	1892	30 (15, 45)	478
Median (IQR): women	30 (17, 50)	1267	30 (15, 47)	341
Median (IQR): men	31 (16, 49)	625	27 (12, 43)	137
ESR < 28 mm/h, %	45	1892	47	478
< 30 mm/h for women; < 20 for men				
All patients, %	43	1892	45	478
Women, %	49	1267	48	341
Men, %	32	625	37	137
≤ 20 mm/h for women; ≤ 10 for men				
All patients, %	25	1892	30	143
Women, %	31	1267	33	341
Men, %	14	625	21	137
C-reactive protein, mg/l				
Median (IQR)	12 (3, 34)	1749	6 (3, 20)	175
C-reactive protein < 10 mg/l, %	44	1749	58	175

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; IQR: interquartile range; MHAQ: Multidimensional Health Assessment Questionnaire.

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Table 2. Mean and median ESR and CRP Jyväskylä and Nashville in 5-year periods 1980-2004.

	Jyväskylä			Nashville		
	Median	Mean	No. of Patients	Median	Mean	No. of Patients
ESR, mm/h						
1980-1984	35	40	219	32	39	108
1985-1989	31	36	305	31	35	123
1990-1994	33	39	363	31	37	90
1996-2000	29	29	508	26	31	73
2000-2004	28	34	497	28	28	84
Total	30	36	1892	30	35	478
CRP, mg/l						
1980-1984	21	31	142	NA	NA	0
1985-1989	14	5	280	NA	NA	0
1990-1994	15	27	343	7	21	23
1996-2000	9	22	494	6	17	68
2000-2004	11	24	480	6	18	77
Total	12	25	1749	6	18	168

Table 3. Number (%) at presentation of patients with RA with ESR < or ≥ 28 mm/h in Jyväskylä and in Nashville compared to CRP < or ≥ 10. N = 1744 patients in Jyväskylä; N = 170 patients in Nashville. Data in parentheses are percentages.

	Jyväskylä		
	ESR		Total
CRP	≥ 28 mm/h	< 28 mm/h	
≥ 10 mg/l	775 (44)	202 (12)	977 (56)
< 10 mg/l	199 (11)	568 (33)	767 (44)
Total	974 (56)	770 (44)	1744 (100)
	Nashville		
	ESR		Total
CRP	≥ 28 mm/h	< 28 mm/h	
≥ 10 mg/l	48 (28)	22 (13)	70 (41)
< 10 mg/l	29 (17)	71 (42)	100 (59)
Total	77 (45)	93 (55)	170 (100)

DISCUSSION

These results confirm similar analyses reported in 1994 concerning ESR[3], extended to CRP and RF with similar results. Laboratory test findings were similar in 2 cohorts with extensive differences in duration of disease and possible prior treatment in Nashville, and were also similar to data reported from Wichita, KS, USA[3], suggesting generalizability. ESR and CRP were generally concordant, but were discordant in 11%–17% of patients, again with similar findings at the 2 sites.

Several limitations are seen in these studies. First, there were missing values in some patients, particularly in Nashville; however, no selection criteria were used to determine which patients would or would not be assessed for any test, and patients with available or missing test data were similar in age and duration of disease. Second, only cross-sectional data at presentation are analyzed for ESR and CRP, and higher levels may have been seen at other times, although the ESR does change substantially in a large fraction of patients[8]. Third, Finland and the USA are advanced rheumatology settings, in which ESR levels may be lower than in other countries[9]. Fourth, more sensitive tests for CRP might have led to increased proportions with abnormal values; however, these studies sought to simulate "real-world" conditions for treating rheumatologists.

The details of whether a normal ESR, CRP, or RF result may be seen even in 30%, 40%, or 50% of patients with RA appear less important than recognition that many individuals have normal test results. It is likely that the proportion of patients with normal laboratory tests may be an underestimate, resulting from "spectrum bias"[10], as patients with normal laboratory tests may be less likely to be referred to rheumatology treatment centers for possible RA or inflammatory arthritis than those with abnormal tests. In the

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cohorts studied, fewer than 1 in 3 patients had abnormal values for all 3 tests, and at least 1 in 6 had normal values for all 3 tests.

In conclusion, ESR, CRP, and RF test results are abnormal in a majority of patients with RA, and these data may remain helpful in clinical management of certain patients. However, a substantial proportion of patients have normal test results.

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