Erythrocyte sedimentation rate and C-reactive protein levels are poorly correlated with clinical measures of disease activity in rheumatoid arthritis, systemic lupus erythematosus and osteoarthritis patients

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Abstract

Objective

To determine the patterns and correlation of elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels with outcome measures in rheumatoid arthritis (RA), and compare it to systemic lupus erythematosus (SLE) and osteoarthritis (OA) patients.

Methods

Brooklyn Outcomes Arthritis Registry Database (BOARD) was analyzed to determine both first visit and mean values of ESR and CRP, along with disease activity measures in each patient. Data were analyzed with descriptive statistics and correlations.

Results

Among all patients half of all (n=377) ESR results were elevated. In RA patients the proportions of having both ESR and CRP elevated, both within normal levels, and only one elevated and the other normal were similar. For all diagnosis, both ESR and CRP have weak positive correlations with disease activity measures measured at first visits. ESR and CRP have a modest positive correlation with each other across all three disease groups.

Conclusion

In this cohort of RA, SLE and OA patients, ESR and CRP values were modestly correlated with each other and they were weakly correlated with disease activity measures. These data suggest that another look at the role of ESR and CRP as markers of inflammation in RA patients seen in routine care may be in order.

Key words

Erythrocyte sedimentation rate, C-reactive protein, rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis.

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Introduction

Different measures are used for evaluating disease activity in rheumatoid arthritis (RA). Laboratory tests such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been an integral part of the clinicians repertoire for many years, used as markers of inflammation, although there is still no clear consensus on when to use one, the other, or both. CRP has recently become the more preferred serological marker for evaluating acute disease activity (1-4). In addition disease activity score (DAS) and its derivatives use ESR or CRP as part of their score and as such they have found increased use and discussion regarding their role in disease activity assessment. Because of the way these indices are calculated, ESR and CRP may play a disproportionately significant role in the overall score (5). An additional problem is that up to 40% of RA patients at presentation have normal ESR or CRP (6), which makes it hard to use these measures in close to half of active, treatment requiring RA patients.

The quantitative usefulness of ESR versus CRP has been evaluated in many studies with no clear consensus (1-4, 7-13). ESR and/or CRP are part of the American College of Rheumatology (ACR) core data set for measuring disease activity in RA and have been used in clinical trials as the main laboratory marker of disease activity in RA (14). Our aim was to determine ESR and CRP values in our RA, SLE and OA patients to see how well they correlated with measures of disease activity and determine if there was a difference among these different diagnoses.

Material and methods

Patients seen in a private practice by YY complete a multidimensional health assessment questionnaire (MDHAQ), available in English and Spanish, at each visit. This self-report questionnaire includes a 10-item functional capacity scale, pain, fatigue, and global assessments on 10 cm visual analog scales (VAS), psychological distress (PSHAQ), and duration of morning stiffness (AM). We included all patients which were monitored in the Brooklyn Outcomes of Arthritis Registry Database (BOARD) (15) from January 1, 2002 to December 1, 2007 with a diagnosis of RA, SLE and OA. All ESR and CRP results were extracted. ESR and/or CRP values done within a plus or minus 2-week period of the visit were included and tagged to the visit for comparative purposes. All first visit observations, all observations, and the average of each patient's total observations were studied for analytical purposes.

CRP was measured by immunoturbidimetry or nepholometry with a CRP≥0.5 mg/dL considered abnormal and ESR was measured using the Westergren method with>25 mm/h was considered as abnormal. More relevant clinical elevations were also examined, being defined as any measure which was twice the elevated cutpoint. Each laboratory reading was compared on an individual basis as a mean for each patient and on a collective group basis. The total positive CRP (≥0.5) was compared to the total CRP (≥0.5 plus <0.5) for each cohort. The combination of elevated and normal ESR to CRP was also analyzed for each group. ESR/CRP from each visit was correlated with the other disease outcome measures for RA, SLE and OA patients. We chose SLE as the inflammatory disease control and OA as the non-inflammatory disease control to compare with the RA cohort.

Almost all parameters (except age and age of onset of disease) are distributed non-normally. Correlations between ESR and CRP to functional status, pain VAS, fatigue VAS, global VAS patient, and global VAS physician were completed using Spearman's rank correlation. The conventional statistical significance criterion of alpha = 0.05 was used. Statistical analysis was completed using Stata v9.2 (College Station, TX).

Results

A total of 377 patients were available for analysis, with 79 SLE, 188 RA and 110 OA patients. Table I shows the demographics and the disease activity scores of each cohort separately and also for all the patients combined.

Correlation of ESR and CRP with each disease activity measure in the entire cohort is shown in Table II. Even

Table I. Summary of the clinical measures on 377 patients by diagnosis.

	Systemic lupus		Rheumatoid arthritis		Osteoarthritis		Total	
Variable	Median	IQR	Median	IQR	Median	IQR	Median	IQR
No.	79		188		110		377	
Age (years)	42.51	23.95	53.93	17.18	60.62	17.18	54.05	19.90
Duration (years)	0.07	0.55	0.15	1.10	0.12	1.03	0.12	1.02
No. Female (%)	73	(94.8%)	155	(82.5%)	87	(80.6%)	315	(84.5%)
Education (years)	15.00	5.00	12.00	4.00	12.50	4.00	12.00	4.00
ESR	31.91	31.00	24.07	30.00	14.83	20.00	23.00	29.67
CRP	0.35	0.70	0.47	0.98	0.35	0.80	0.43	0.81
Function	0.55	0.80	1.67	2.67	0.50	0.70	0.83	1.50
Psych	2.20	3.89	2.20	2.78	2.20	3.30	2.20	3.30
Pain	4.43	5.00	4.89	3.88	5.12	4.00	4.90	4.09
Fatigue	4.80	5.56	4.23	4.28	5.00	5.00	4.58	4.50
Global	4.68	4.72	4.39	3.43	4.56	3.90	4.50	3.85
Morning Stiff (min)	30.00	58.17	20.00	54.50	13.13	25.00	17.50	54.33
MD Global	1.30	1.40	1.69	1.60	1.33	1.17	1.50	1.43
Swollen 28	–	–	1.00	2.83	–	–	–	–
Tender 28	–	–	3.00	5.5	–	–	–	–
Encounters (n)	4	6	3	3	1	1	2	4

IQR: Interquartile (25th-75th) range.

Table II. Spearman correlations of clinical measures with ESR and CRP on 377 patients.

	ESR		CRP	
	Spearman's *r*	*p*-value	Spearman's *r*	*p*-value
CRP	0.457	<0.0001	1	
Function	0.200	0.0001	0.275	<0.0001
Psych	-0.047	0.3639	0.034	0.5108
Pain	0.098	0.0586	0.204	0.0001
Fatigue	0.050	0.3363	0.144	0.0052
Global	0.102	0.0485	0.207	0.0001
AM Stiff (min)	0.062	0.2539	0.124	0.0218
MD Global	0.140	0.0077	0.212	<0.0001

though some of the variables (function, patient and physician global assessment for ESR and pain, fatigue, morning stiffness, patient and physician global assessment, and swollen and tender joint counts for CRP) were statistically significantly correlated, levels of correlation were weak for all measures. (r<0.35).

Table III shows the correlations by each diagnosis and similar trends are observed. We also analyzed the correlations when only the initial visits were taken into account (for the whole cohort, separate diagnosis data not shown) (Table IV). This was done to control for possible effect of treatment on ESR and CRP values but the results were similar, with weak levels of correlation (Table V).

For RA patients, some of the weakest correlations were seen between ESR and CRP and tender and swollen joint counts (Table III) which are usually taken as markers of active inflammation.

Among RA patients, 46% had an elevated CRP and a similar percentage had an elevated ESR. By contrast, SLE patients had a higher percentage of ESR abnormality than CRP (62% *vs.* 46%) and both values were lower for OA patients (Table VI).

When we examined the abnormal values for both ESR and CRP, for either ESR or CRP or, none, (Table VII A and B) RA patients were evenly distributed. When we analyzed clinically more relevant elevations where we took twice the upper limit of normal for ESR and CRP values, the numbers of patients with both ESR and CRP elevations decreased to about 10%, from 29% when any value above the normal limit was considered. The most consistent result was when both ESR and CRP were normal and the frequency of this was similar in all 3 diseases.

Discussion

Unlike previous studies that compared ESR and CRP in one disease, we chose to compare these inflammatory markers across three disease states, two considered inflammatory and one non-inflammatory. Our purpose of such an approach was to determine whether or not ESR and CRP were correlated with outcomes in RA when compared with an inflammatory and non-inflammatory disease control. In addition, we wanted to see if the occurrence of high or normal values of these inflammatory markers were any different among these 3 common rheumatologic conditions.

Our results suggest that ESR and CRP levels do not correlate strongly with other disease activity measures. There were several statistically significant correlations; however they are weak and clinically not meaningful. When we assessed the initial visit data, to account for some effect of treatment on the variables, same trends were seen. This would seem to limit the usefulness of ESR and CRP for use in treatment decision-making.

Our study showed the proportions of patients of having both ESR and CRP

Table III. Spearman correlations of clinical measures with ESR and CRP on 377 patients by diagnosis.

		ESR		CRP	
		Spearman's *r*	*p*-value	Spearman's *r*	*p*-value
CRP	SLE	0.398	0.0003	–	–
	RA	0.452	<0.0001	–	–
	OA	0.530	<0.0001	–	–
Function	SLE	-0.028	0.8086	0.297	0.0080
	RA	0.315	<0.0001	0.251	0.0005
	OA	0.124	0.1954	0.236	0.0132
Psych	SLE	-0.188	0.0979	-0.089	0.4373
	RA	0.124	0.0911	0.137	0.0615
	OA	-0.168	0.0800	-0.031	0.7472
Pain	SLE	-0.027	0.8142	0.155	0.1737
	RA	0.212	0.0034	0.295	<0.0001
	OA	0.121	0.2070	0.100	0.2979
Fatigue	SLE	-0.100	0.3815	0.127	0.2637
	RA	0.167	0.0224	0.217	0.0028
	OA	-0.008	0.9386	0.057	0.5541
Global	SLE	0.068	0.5495	0.164	0.1478
	RA	0.173	0.0178	0.267	0.0002
	OA	0.075	0.4346	0.125	0.1930
AM Stiff (min)	SLE	0.046	0.6997	0.261	0.0270
	RA	0.082	0.2717	0.028	0.7050
	OA	-0.038	0.7224	0.149	0.1664
MD Global	SLE	0.039	0.7434	0.071	0.5510
	RA	0.158	0.0305	0.258	0.0004
	OA	0.236	0.0186	0.175	0.0827
Swollen 28	SLE	–		–	
	RA	0.030	0.6856	0.190	0.0089
	OA	–		–	
Tender 28	SLE	–		–	
	RA	0.100	0.1743	0.176	0.0157
	OA	–		–	

Table IV. Spearman correlations of first visit clinical measures with ESR and CRP on 377 patients.

	ESR		CRP	
	Spearman's *r*	*p*-value	Spearman's *r*	*p*-value
CRP	0.457	<0.0001	1	
Function	0.191	0.0002	0.240	<0.0001
Psych	0.000	0.9995	0.068	0.1894
Pain	0.138	0.0071	0.214	<0.0001
Fatigue	0.101	0.0518	0.189	0.0002
Global	0.145	0.0049	0.187	0.0003
AM Stiff (min)	0.125	0.026	0.182	0.0011
MD Global	0.164	0.0023	0.194	0.0003

elevated, both within normal limits, and only one elevated were similar in the RA cohort. One would expect more elevated markers of inflammation and closer ratios of ESR/CRP combinations between the two inflammatory groups as shown by other authors when studied in a single disease (4-7, 9-14, 16-24). Interestingly, this was not very different among SLE and OA patients either.

In our data it was more likely that ESR was more elevated in SLE patients and CRP was more elevated in RA patients. OA patients had the lowest values. However, the actual numbers were very close to each other and we are not sure about the clinical significance of these differences. Our study did not show a significant and convincing trend, contrary to other studies, regarding the use of CRP and ESR. Other studies have concluded that the more direct inflammatory marker CRP was a better marker for acute disease activity in RA than ESR (4, 11, 12), and has stronger association with disease activity in SLE (22). They concluded that it was partly due to the many influencing factors that effect ESR, but also the nature of CRP itself (3-6). Though, one must keep in mind suggestive evidence that CRP is associated with factors such as age, smoking, coronary artery disease, increased cholesterol and glucose levels (23, 25).

Limitations to our study include the cut off levels we used for elevated levels for both ESR and CRP. Some consider ESR>30 mm/hr as a better number for inclusion, therefore excluding some outliers (23). However the impact this may have on disease activity measures is small and again clinically not significant. In addition when we analyzed our data considering clinically elevated levels of ESR and CRP (taken as twice the upper limit of normal) we found similar results. Another shortcoming is that the assay used for measuring CRP may not be as sensitive or specific compared to high sensitivity CRP assays (21). Further, variables such as hematocrit, complement, albumin, and coexistent conditions were not considered in the statistical analysis. A further limitation that may have influenced our results is

Table V. Spearman correlations of first visit clinical measures with ESR and CRP on 377 patients by diagnosis.

		ESR		CRP	
		Spearman's *r*	*p*-value	Spearman's *r*	*p*-value
CRP	SLE	0.478	<0.0001	.	
	RA	0.482	<0.0001	.	
	OA	0.458	<0.0001	.	
Function	SLE	0.040	0.7236	0.315	0.0048
	RA	0.290	0.0001	0.191	0.0088
	OA	0.154	0.1082	0.276	0.0035
Psych	SLE	-0.032	0.7773	0.025	0.8302
	RA	0.120	0.1020	0.127	0.0823
	OA	-0.143	0.1368	0.001	0.9942
Pain	SLE	0.100	0.3807	0.228	0.0436
	RA	0.197	0.0067	0.250	0.0005
	OA	0.230	0.0157	0.148	0.1228
Fatigue	SLE	0.017	0.8830	0.196	0.0831
	RA	0.148	0.0439	0.226	0.0020
	OA	0.064	0.5076	0.136	0.1617
Global	SLE	0.233	0.0384	0.254	0.0237
	RA	0.164	0.0243	0.202	0.0053
	OA	0.125	0.1932	0.107	0.2651
AM Stiff (min)	SLE	0.225	0.0673	0.312	0.0103
	RA	0.122	0.1146	0.094	0.2225
	OA	-0.020	0.8561	0.290	0.0082
MD Global	SLE	0.180	0.1482	0.127	0.3098
	RA	0.134	0.0693	0.202	0.0059
	OA	0.272	0.0080	0.212	0.0406
Swollen 28	SLE	.		.	
	RA	-0.017	0.8211	0.056	0.4487
	OA	.		.	
Tender 28	SLE	.		.	
	RA	0.060	0.4126	0.182	0.0122
	OA	.		.	

that we did not use a disease specific clinical tool such as the Systemic Lupus International Collaborating Clinics damage index or the Systemic Lupus Activity Measure as a clinical assessment tool in the inflammatory control group. However, MDHAQ has been shown to be useful in both SLE and OA (26, 27).

Significant numbers of physicians base clinical judgment on results of laboratory inflammation markers and less on patient derived measures. Patient measures have been shown to be very good predictors of disease course and are rarely normal in active disease (28, 29). Our results necessitate the questioning of the current use of the laboratory marker trend in the clinical assessment of RA patients, as well as the clinical use of ESR and CRP in everyday practice. We suggest that neither CRP nor ESR is better in the clinical setting to monitor inflammatory activity in the RA patient and that the role of and dependence on ESR and CRP as markers of inflammation in RA patients in everyday practice should be re-evaluated.

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Table VI. Abnormal and clinically elevated laboratory results in all recorded ESR and CRP by diagnosis.

		ESR				CRP			
		Abnormal		Elevated		Abnormal		Elevated	
	No.	no.	%	no.	%	no.	%	no.	%
Systemic lupus	381	236	61.94%	122	32.02%	175	45.93%	94	24.67%
Rheumatoid arthritis	748	343	45.86%	133	17.78%	344	45.99%	203	27.14%
Osteoarthritis	176	59	33.52%	22	12.50%	76	43.18%	45	25.57%
Total	1305	638	48.89%	277	21.23%	595	45.59%	342	26.21%

Table VII A. Combination of clinically elevated laboratory studies in all recorded ESR and CRP by diagnosis.

Clinically elevated	ESR - / CRP -		ESR + / CRP -		ESR - / CRP +		ESR + / CRP +		
	no.	%	no.	%	no.	%	no.	%	Total
Systemic lupus	219	57.48%	68	17.85%	40	10.50%	54	14.17%	381
Rheumatoid arthritis	485	64.84%	60	8.02%	130	17.38%	73	9.76%	748
Osteoarthritis	127	72.16%	4	2.27%	27	15.34%	18	10.23%	176
Total	831	63.68%	132	10.11%	197	15.10%	145	11.11%	1,305

Table VII B. Combination of abnormal laboratory studies in all recorded ESR and CRP by diagnosis.

Abnormal	ESR - / CRP -		ESR + / CRP -		ESR - / CRP +		ESR + / CRP +		
	no.	%	no.	%	no.	%	no.	%	Total
Systemic lupus	104	27.30%	102	26.77%	41	10.76%	134	35.17%	381
Rheumatoid arthritis	279	37.30%	125	16.71%	126	16.84%	218	29.14%	748
Osteoarthritis	85	48.30%	15	8.52%	32	18.18%	44	25.00%	176
Total	468	35.86%	242	18.54%	199	15.25%	396	30.34%	1,305

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