Discordance between erythrocyte sedimentation rate and C-reactive protein measurements: clinical significance

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ABSTRACT

Objective. *C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are common measures of systemic inflammation. Our goal was to identify clinical factors associated with CRP/ESR discordance.*

Methods. *We identified patients with ESR and CRP results at our academic hospital over six months. We matched individuals with discordant results (one measure in highest tertile, other in lowest), by age and sex to those with non-discordant results, and reviewed medical records for laboratory and clinical factors. We employed analysis of variance (ANOVA) and Chi squared tests to compare these variables in discordant and non-discordant subjects. We used conditional logistic regression to estimate the relative risk of CRP/ESR discordance associated with each variable.*

Results. *2069 patients had CRP and ESR measured on the same day; 87 had discordant results, 55 (2.6%) with elevated ESR/low CRP, 32 (1.5%) with elevated CRP/ low ESR. Underlying infection was associated with > 14 fold risk of elevated ESR/low CRP discordance (p < 0.001). Renal insufficiency was associated with increased risk of elevated ESR/low CRP discordance, (p = 0.003). RA patients were slightly less likely to have elevated ESR/low CRP, (p = 0.008, NS after Bonferroni correction). Low serum albumin was associated with both kinds discordance.*

Conclusions. *Infection, renal insufficiency, and low albumin were associated with having elevated ESR/low CRP; low albumin predicted elevated CRP/low ESR and elevated ESR/low CRP discordance. RA patients were less likely to have elevated ESR/depressed CRP. ESR as a measure inflammation in systemic rheumatic disease may be limited in settings of infection, renal insufficiency, and low albumin.*

Introduction

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) are the two most common laboratory measurements of systemic inflammation in clinical practice. These two tests are used for the diagnosis and monitoring of a variety of conditions, in particular rheumatic diseases and infections. Often viewed as interchangeable, the two measures rely on different pathophysiologic mechanisms. The ESR measurement is a simple measurement of the velocity (in mm/hr) of sedimentation of erythrocytes in anticoagulated freshly drawn blood in a standardized vertical tube. Inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and IL-1 stimulate the liver to produce acute phase reactant proteins (fibrinogen, immunoglobulins, hapto-globin, CRP and others). These proteins, in particular fibrinogen and immunoglobulins, increase the dielectric constant in the blood, allowing erythrocytes to form rouleaux and increasing the velocity of their descent in the tube (1). The ESR is thus an indirect measure of systemic inflammation which has been criticized as being neither sensitive nor specific, but is nonetheless widely used (2). The CRP, on the other hand, is a highly conserved pentameric peptide produced in the liver in response to inflammatory cytokines. It was discovered in 1930 in the sera of patients with pneumonia (3) and plays a role in the recognition and elimination of foreign pathogens and cellular debris.

There has been debate as to the accuracy and sensitivity of the ESR and CRP in conditions such as rheumatoid arthritis (RA) (4-10), SLE (11-14), ankylosing spondylitis(AS) (15, 16), and polymyalgia rheumatica/ giant cell arteritis (PMR/GCA) (17). A variety of systemic conditions, such as age, sex, anemia, and pregnancy may influence CRP and ESR measurements (15, 18-20). In patients with RA, in particular, it has been suggested that the discordance between the two measures may be due to the sensitivity of the ESR to inflammatory responses with a longer time course than the rise in CRP of the acute phase response (5). Decreased responsiveness of CRP to non-infectious inflammation in SLE has been reported, despite elevations of TNF-α and IL-1 during active disease (14). The goal of this case-control study was to investigate those frustrating situations for clinicians in which the ESR

and CRP values are discordant, and to attempt shed light on the circumstances that lead to discordant results in these markers of systemic inflammation.

Materials and methods
Subject identification and medical record review
The medical record numbers of all patients who had blood drawn for either CRP or ESR assays as outpatients at our academic hospital between January 1, 2004 and June 30, 2004, were downloaded from the hospital database. We then established tertiles of CRP and ESR values (based on sex and age given that CRP and ESR are influenced by these factors (21)). All patients who had had *both* CRP and ESR measurements performed *on the same day* as outpatients during these six months were selected and, applying the tertile cutoffs from the larger group above, those with discordant values were identified (CRP measurements in the highest tertile and ESR measurements in the lowest tertile *or* ESR measurements in the highest tertile and CRP measurements in the lowest tertile). We used the risk set method (22) to control for confounding by sex and age. Each case was matched to up to 5 non-discordant subjects by sex and age (± 2 years). Two cases with elevated ESR and low CRP had no matched control and were dropped from the final analysis.

The medical records of identified subjects with both discordant and non-discordant CRP and ESR results were reviewed in detail for known and suspected past and current medical conditions, in particular the current presence of rheumatic disease, connective tissue disease, vasculitis, anemia, diabetes, malignancy, infection. We also sought the results of laboratory measurements, including complete blood counts, aspartate aminotransferase, creatinine, and serum albumin levels, and titers of antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and antibodies to double-stranded DNA and extractable nuclear antigens, if available, as close in time as possible to the date of ESR and CRP measurement, at most within three months of that blood draw.

Table I. Demographics from larger dataset (n = 2069).

	Elevated CRP/ Depressed ESR	Elevated ESR/ Depressed CRP	All possible controls	p^*
N	32	55	1982	
Mean age, years (SD)	50.1 (13.9)	55.5 (19.0)	52.6 (16.4)	0.31
Female n (%)	28 (88)	42 (76)	1380 (70)	0.05

$^*p$-value for age from ANOVA test and p-value for sex from Chi-Square test (across all three groups).

CRP and ESR measurements
CRP and ESR determinations were performed in the hospital clinical laboratory. High-sensitivity CRP assays were performed using a standard assay (23) and ESR measurement was done by the Ves-Matic 20 Westergren method (24).

Statistical analyses
We established tertiles for CRP and ESR values and selected cases and controls using the risk set method (22). We employed analysis of variance (ANOVA) and Chi squared tests to evaluate the age and sex distributions for subjects with discordant values (as defined above) compared to subjects with non-discordant values. We used conditional logistic regression to estimate the adjusted relative risk of being discordant for CRP and ESR results for each of the clinical variables. Separate models were used for factors associated with elevated CRP/depressed ESR and for factors associated with elevated ESR/ depressed CRP. We used a Bonferroni correction to control for the multiple comparisons in this analysis. (A p-value of less than $\alpha = 0.05/16 = 0.003$ was considered significant.) Database management was performed in Microsoft Excel, ACCESS and all statistical analyses were performed in SAS v9.1 (SAS Institute, Cary, North Carolina). Hospital Institutional Review Board approval was obtained for this study.

Results
Eight thousand, nine hundred and nine patients had CRP measured and 5924 patients had ESR measured as outpatients during the six-month time period examined. These values were used to establish tertile cutoffs. During this time, 2069 patients had *both* CRP and ESR drawn on the same day. Of these, 70 women and 17 men had discordant CRP and ESR values; 32 had elevated CRP and low ESR, and 55 had low CRP and elevated ESR. Compared to all those who had non-discordant CRP and ESR values, there was no significant difference among the cases in mean age, and although there were more women among the cases than among all possible controls, this difference was not statistically significant (Table I). In pairwise comparisons (not shown), we found a significantly larger proportion of females in the elevated CRP/low ESR group as compared to the controls ($p = 0.03$); however, there was no statistically significant difference in age or sex between the elevated ESR/low CRP group and the controls ($p = 0.37$).

The results of conditional logistic regression models controlling for age and sex, are shown in Table II. In analyses comparing those with elevated ESR and depressed CRP to their sex and age-matched controls, two significant associations were found. Having an underlying infection was associated with a greater than 14 times increased risk of having an elevated ESR and depressed CRP ($p < 0.001$). For each increase in serum creatinine level of 1 mg/dl, the risk of having discordantly elevated ESR and depressed CRP increased by 5.5 ($p = 0.003$). A suggestive, but not statistically significant, inverse association between having a diagnosis of RA and having a discordantly elevated ESR with depressed CRP was also seen: patients with RA were 63% less likely to have this pattern of discordance compared to patients with other diagnoses ($p = 0.008$) Low albumin was associated with discordance between ESR and CRP results in both directions: for each one g/dL decrease in serum albumin level, an 20% increase in the odds of being discordant with elevated ESR and depressed CRP ($p = 0.004$) and a 13% increase in the odds of being discordant

Table II. Results of conditional logistic regression controlling for age and sex.

	ESR Elevated/ CRP Depressed (n = 53 discordant/170 concordant)			ESR Depressed/CRP Elevated (n = 32 discordant/120 concordant)		
	n. cases discordant/ non-discordant	Hazard ratio	p^*	n. cases discordant/ non-discordant	Hazard ratio	p^*
Primary Diagnosis						
RA	11 / 77	0.37	< 0.01	11 / 48	0.85	0.68
SLE	9 / 20	1.53	0.34	5 / 17	1.05	0.92
Infection	11 / 2	14.19	< 0.001*	2 / 1	4.22	0.26
Gout/Pseudo-Gout	1 / 3	0.73	0.80	2 / 0	n/a	n/a
Polymyositis/ Dermatomyositis	2 / 2	2.50	0.45	0 / 2	n/a	n/a
Psoriatic Arthritis	1 / 10	0.46	0.48	1 / 6	0.83	0.86
Sjogren's	3 / 0	n/a	n/a	0 / 1	n/a	n/a
Mixed Connective Tissue Disease	1 / 2	2.5	0.45	2 / 2	4.41	0.14
Polymyalgia Rheumatica/Giant Cell Arteritis	4 / 23	0.33	0.09	0 / 8	n/a	n/a
Other Vasculitides*	2 / 1	3.70	0.32	1 / 3	1.28	0.84
Laboratory Values						
Albumin (per 1 g/dL)		0.20	< 0.001*		0.13	< 0.003*
Creatinine (per 1 mg/dL)		5.53	0.002*		1.44	0.28
White Blood Cell Count (per 1000 cells/µL)		0.88	0.07		1.10	0.12
Hematocrit (per 5%)		1.01	0.83		1.00	0.77
Platelets (per 10, 000 cells/µL)		0.96	0.03		0.97	0.10
Aspartate aminotransferase (AST, per 5 U/L)		1.31	0.02		1.08	0.23

*$p < 0.003$ significant after Bonferroni correction.
**Other vascultides includes Wegener's, Churg-Strauss, small vessel and hypersensitivity vasculitis.

with depressed ESR and elevated CRP were observed.

Discussion

Although ESR and CRP measurements reflect different aspects of systemic inflammation, generally they are either elevated or depressed at the same time. During a six month period, 4% of patients who had ESR and CRP performed on the same day in our academic hospital clinical laboratory had discordant results. This case-control study examined clinical factors potentially associated with this discordance. We have found that serum albumin and creatinine, and the presence of underlying infection or RA are associated with discordance between the ESR and CRP values in a clinical setting, with infection and increased creatinine increasing the risk of having a disproportionately elevated ESR, and RA lowering this risk. Having a low serum albumin is associated with a variety of systemic illnesses; we found that having normal serum albumin was "protective" against both kinds of discordance between markers of systemic inflammation. It is known that chronic renal failure elevates the ESR, probably via increased serum fibrinogen concen-

trations (25), and in our population, elevation in serum creatinine was associated with ESR/CRP discordance.
Among patients with RA, Wolfe has reported that ESR correlates better then CRP with measures of chronic inflammation, such as anemia, immunoglobulin elevations, as well as with rheumatoid factor. He has suggested that ESR may be a better measure of chronic inflammation in RA, while CRP more accurately reflects the acute phase response(5). Among our group of patients, those followed for RA had a slightly lower odds of having discordantly elevated ESR and depressed CRP compared to those with other diagnoses.
It has also been suggested that in SLE, unlike in RA and other disease states, the CRP is relatively unresponsive to SLE disease activity, and that elevations of the CRP thus are more likely to reflect active infection(11,12,14). Suh and colleagues reported no correlations between CRP levels and IL-2, IL-6, IL-10, IL-12 or IFN-γ levels in SLE or RA patients without infection, whereas there was a strong correlation between IL-6 levels and CRP in SLE in the presence of infection(14). We did not find that SLE was associated with an in-

creased risk of discordantly depressed CRP and elevated ESR, however.
In our study, underlying infection was strongly associated with discordantly elevated ESR and depressed CRP levels. Most likely these differences are attributable to the fact that the infections in our cases were mainly chronic ones (osteomyelitis, infected prosthetic joints, and cellulitis). While the two measures are highly correlated, CRP in the circulation has a much more abrupt rise and shorter half-life. The ESR is primarily determined by plasma concentrations of fibrinogen, concentrations of which increase slowly after an inflammatory stimulus, reaching their peak in 7-10 days and, with removal of the stimulus, declining back to baseline over the same time course (26).
Analysis of the factors that cause one measure of systemic inflammation to be disproportionately high or low with respect has methodologic challenges. We attempted to control for the influence of age and sex, both of which are related to ESR and CRP, by stratifying by age and sex and choosing matched controls. In this case-control study, we did not have enough subjects with relatively rare conditions such as cry-

oglobulinemia or monoclonal gammopathy to be able to evaluate the effect of such disease states on CRP and ESR discordance, and may not have had enough patients with SLE, PMR and GCA, and other connective tissue diseases to detect less powerful associations. Our method of selecting cases and controls for this study, patients who had had both markers of inflammation measured on the same day, may have introduced a subtle bias if clinicians ordered both tests only in unclear or complicated clinical situations. More likely, however, certain clinicians routinely order both tests simultaneously for all of their patients. Additionally, we did not have simultaneously collected measures of RA or SLE disease activity (*e.g.*, disease activity score, DAS (27), or systemic lupus erythematosus activity measure, SLAM(28)) or medications in order to examine the effects of these factors on CRP/ESR levels and discordance, and our data concerning the influence of titers of antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, and antibodies to double-stranded DNA and extractable nuclear antigens was too sparse to allow analysis.

Which of the two measures is the more accurate measure of systemic inflammation is likely to be different for different disease states. Our results underscore that infection, serum albumin, and creatinine are associated with discordance between the two measures however. Our findings have implications for the monitoring of patients with RA and other systemic rheumatic diseases. In particular, while the ESR has been suggested to be a more valuable measure of disease activity in RA (5), it may be unduly influenced by elevations of serum creatinine, abnormalities of serum albumin level, and the presence of chronic infection, hindering its interpretation in these settings. Further studies involving larger cohorts of patients with RA and SLE are warranted to establish the differ-

ential utility of these two measures of systemic inflammation.

Acknowledgements

References
1. HOLLEY L, WOODLAND N, HUNG WT *et al.*: Influence of fibrinogen and haematocrit on erythrocyte sedimentation kinetics. *Biorheology* 1999; 36: 287-97.
2. SOX HC JR, LIANG MH: The erythrocyte sedimentation rate. Guidelines for rational use. *Ann Intern Med* 1986; 104; 515-23.
3. TILLET WS, FRANCIS T JR: Serologic reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *J Exp Med* 1930; 52; 561-71.
4. WALSH L, DAVIES P, MCCONKEY B: Relationship between erythrocyte sedimentation rate and serum C-reactive protein in rheumatoid arthritis. *Ann Rheum Dis* 1979; 38: 362-3.
5. WOLFE F: Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. *J Rheumatol* 1997; 24: 1477-85.
6. PAULUS HE, RAMOS B, WONG WK *et al.*: Equivalence of the acute phase reactants C-reactive protein, plasma viscosity, and Westergren erythrocyte sedimentation rate when used to calculate American College of Rheumatology 20% improvement criteria or the Disease Activity Score in patients with early rheumatoid arthritis. Western Consortium of Practicing Rheumatologists. *J Rheumatol* 1999; 26: 2324-31.
7. DESSEIN PH, JOFFE BI, STANWIX AE: High sensitivity C-reactive protein as a disease activity marker in rheumatoid arthritis. *J Rheumatol* 2004; 31; 1095-7.
8. PAULUS HE, BRAHN E: Is erythrocyte sedimentation rate the preferable measure of the acute phase response in rheumatoid arthritis? *J Rheumatol* 2004; 31: 838-40.
9. WARD MM: Relative sensitivity to change of the erythrocyte sedimentation rate and serum C-reactive protein concentration in rheumatoid arthritis. *J Rheumatol* 2004; 31: 884-95.
10. PINCUS T, SOKKA T: Complexities in the quantitative assessment of patients with rheumatic diseases in clinical trials and clinical care. *Clin Exp Rheumatol* 2005; 23 (Suppl. 39); S1-9.
11. PEPYS MB, LANHAM JG, DE BEER FC: C-reactive protein in SLE. *Clin Rheum Dis* 1982; 8: 91-103.
12. GABAY C, ROUX-LOMBARD P, DE MOERLOOSE P *et al.*: Absence of correlation between interleukin 6 and C-reactive protein blood levels in systemic lupus erythematosus compared with rheumatoid arthritis. *J Rheumatol* 1993; 20: 815-21.

13. VILA LM, ALARCON GS, MCGWIN G JR *et al.*: Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXIX. Elevation of erythrocyte sedimentation rate is associated with disease activity and damage accrual. *J Rheumatol* 2005; 32: 2150-5.
14. SUH CH, CHUN HY, YE YM *et al.*: Unresponsiveness of C-reactive protein in the non-infectious inflammation of systemic lupus erythematosus is associated with interleukin 6. *Clin Immunol* 2006; 119: 291-6.
15. RUOF J, STUCKI G: Validity aspects of erythrocyte sedimentation rate and C-reactive protein in ankylosing spondylitis: a literature review. *J Rheumatol* 1999; 26: 966-70.
16. YILDIRIM K, ERDAL A, KARATAY S *et al.*: Relationship between some acute phase reactants and the Bath Ankylosing Spondylitis Disease Activity Index in patients with ankylosing spondylitis. *South Med J* 2004; 97: 350-3.
17. SALVARANI C, CANTINI F, BOIARDI L *et al.*: Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis. *Clin Exp Rheumatol* 2003; 21: (Suppl. 32); S23-8.
18. KANFER EJ, NICOL BA: Haemoglobin concentration and erythrocyte sedimentation rate in primary care patients. *J R Soc Med* 1997; 90: 16-8.
19. VAN DEN BROE NR, LETSKY EA: Pregnancy and the erythrocyte sedimentation rate. *Bjog* 2001; 108: 1164-7.
20. KUSHNER I, RZEWNICKI D, SAMOLS D: What does minor elevation of C-reactive protein signify? *Am J Med* 2006; 119: 166, e17-28.
21. CASWELL M, PIKE LA, BULL BS *et al.*: Effect of patient age on tests of the acute-phase response. *Arch Pathol Lab Med* 1993; 117: 906-10.
22. BRESLOW NE, DAY NE: Statistical methods in cancer research. IARC Workshop 25-27 May 1983. *IARC Sci Publ* 1987; 82: 1-406.
23. WHICHER JT, RITCHIE RF, JOHNSON AM *et al.*: New international reference preparation for proteins in human serum (RPPHS). *Clin Chem* 1994; 40: 934-8.
24. BEDELL SE, BUSH BT: Erythrocyte sedimentation rate. From folklore to facts. *Am J Med* 1985; 78 (6 Pt 1); 1001-9.
25. SHUSTERMAN N, KIMMEL PL, KIECHLE FL *et al.*: Factors influencing erythrocyte sedimentation in patients with chronic renal failure. *Arch Intern Med* 1985; 145: 1796-9.
26. VOLKANIS JE: Acute phase proteins in rheumatic disease. Arthritis and Allied Conditions. K. W.J. Philadelphia, Lippincott, Williams, and Wilkins 2001: 504-14.
27. VAN DER HEIJDE DM, VAN 'T HOF M, VAN RIEL PL *et al.*: Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993; 20: 579-81.
28. LIANG MH, SOCHER SA, ROBERTS WN *et al.*: Measurement of systemic lupus erythematosus activity in clinical research. *Arthritis Rheum* 1988; 31: 817-25.