Efficacy of Erythrocyte Sedimentation Rate and C-Reactive Protein Level in Determining Periprosthetic Hip Infections

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Abstract

The diagnosis of periprosthetic hip infections is often challenging. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level blood laboratory tests are commonly used to aid in the diagnosis.

We studied the sensitivity, specificity, and false-negative rates of ESR and CRP level in a prospective group of patients who underwent revision total hip arthroplasty between 2000 and 2008. Seventy-seven patients with periprosthetic hip infections and ESR and CRP data were identified. Chi-square analysis was performed to determine the significance of false-negatives, compared with sex, body mass index, primary diagnosis, infection type, and immunity status.

ESR had 89% sensitivity and 69% specificity. CRP level had 93% sensitivity and 40% specificity. The false-negative rate was 10.8% for ESR and 7% for CRP level. The false-negative rate for ESR and CRP level combined (with either result positive) was 3%. All false-negatives in the combined group were immunocompromised. Chi-square analysis did not find a significant correlation between false-negatives and any other variables.

ESR and CRP level are useful in the diagnosis of periprosthetic hip infections. Ordering these tests concurrently reduces the chance of false-negative results.

Infection after total hip arthroplasty (THA) is often a diagnostic challenge. Recent large studies have found a 1% to 2% incidence of post-THA infection in the United States.[1-4] In addition, the recurrence rate has been reported to be as high as 10%.[5,6] A recent study found that more than 100,000 Medicare patients undergo THA per year.[7] With so many of these procedures being performed, many revision arthroplasties are also required because of infection. Furthermore, the sequelae of this complication can be devastating and they are often managed with antibiotic therapy for several months, extended hospital stays, and additional surgical procedures.[8] Patients often present with nonspecific signs of insidious hip pain or lucencies on radiographic examination. Serologic markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, are commonly used in the diagnosis of these infections.[3,9-16] However, as no single test has been shown to accurately diagnose periprosthetic infections, these serologic markers are often used in conjunction with the constellation of other signs, symptoms, and tests.[17]

There is controversy regarding the efficacy and accuracy of using only serologic markers to diagnose periprosthetic infection of the hip. The sensitivity and specificity of these commonly used tests vary widely. Many authors have responded with recommendations to combine these serologic tests with synovial fluid cultures, interleukin 6 levels, or intraoperative frozen sections to predict infection.[16,18-25] At the senior author's (MAM) institution, many patients who underwent revision had false-negative ESR and CRP values, which were later confirmed for infection. It is suspected that some patients may not have been able to mount a strong enough inflammatory response, resulting in normal serologic marker data. Furthermore, as ESR and CRP cutoff values are based on continuous data, there is a chance that a weakly positive marker may be read as normal.

We conducted a study to determine the efficacy of ESR and CRP level in diagnosing known periprosthetic hip infections. We examined the sensitivity and specificity of these tests for predicting infection. In addition, we examined the false-negative rates of each test and compared them with other variables, including sex, body mass index (BMI), infection type, and immune status. A combination of ESR and CRP test results was examined to see what the sensitivity, specificity, and false-negative rate were when either variable tested positive. We tested the validity of the values for ESR and CRP level to determine the predictive ability and

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Table I. Demographics of Infected Patients

Mean Age, y (range)	61 (19-89)
Sex	
Men	32
Women	45
Mean Body Mass Index (range)	28.6 (17.1-56.1)
Infection Type	
Acute (<4 wk)	21
Hematogenous	6
Chronic (late)	50
Immunocompromised	
Yes	41
No	36

Table II. Organisms Cultured in Infected Total Hip Arthroplasties

Organism	Patients n	(N = 77) %
Methicillin-resistant *Staphylococcus aureus*	33	42.9
Coagulase-negative *S aureus*	9	11.7
Methicillin-sensitive *S aureus*	6	7.8
Enterococcus (group D)	5	6.5
Pseudomonas aeruginosa	4	5.2
Streptococcus viridans	3	3.9
Enterobacter cloacae	3	3.9
Corynebacterium species	2	2.6
Morganella morganii	1	1.3
Proteus mirabilis	1	1.3
Klebsiella pneumoniae	1	1.3
Vancomycin-resistant *Enterococcus*	1	1.3
No Growth	8	10.4

optimal cutoffs for diagnosing infection while minimizing false-negative results in our cohort.

Methods

Data were prospectively collected for all patients who underwent revision THA between September 2000 and August 2008 at the Rubin Institute for Advanced Orthopaedics, Sinai Hospital, Baltimore, Maryland. All revisions were followed for a minimum of 1 year to determine the development of a subsequent infection. Infection was determined to be the reason for revision in 108 cases, 77 of which underwent diagnostic testing with ESR and CRP level. Patients who did not undergo serologic testing had other definitive signs or symptoms of infection (draining sinus, etc), which are described later. Additional demographic data collected included age, sex, BMI, infection type, and presence or absence of concomitant immunocompromising disease. Organisms were also cultured from patients' hips. Institutional review board approval was obtained for this study.

Two of the authors (MAM, RED) evaluated all THA patients who presented with hip pain. Clinical symptoms suggestive of post-THA infection included erythema, swelling, and drainage at the surgical site. Patients with persistent pain unexplained by any other etiology were suspected to have an infection as well. Radiographic evidence of loosening or progressive osteolysis within the first 2 years after surgery was also considered a strong sign of possible infection.

Patients were diagnosed with infection on the basis of 1 of 3 criteria: (1) strong clinical evidence of infection, such as fever and hip pain associated with gross purulence or a draining sinus tract communicating with the hip joint space; (2) positive microbial culture by either joint aspiration or intraoperative sample;[3] and (3) histologic evidence of a mean of more than 5 polymorphonuclear cells on frozen sections from synovial surface biopsy.[26] Not all tests were performed on each patient. Patients with strongly positive ESR and CRP values with radiolucency were not deemed infected unless they fulfilled 1 of the 3 listed criteria. Infection was based on the overall clinical and intraoperative findings.

Table III. Serologic False-Negative Rates in Immunocompromised Patients

	n	% ESR	% CRP	% ESR or CRP
Immunocompetent	43	7.5	5.1	0
Immunocompromised	34	15.2	9.7	6.7
All	77	10.8	7	3

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

To determine the sensitivity and specificity of ESR in predicting periprosthetic infection, we used a preset cutoff of 30 mm/h. ESR of more than 30 mm/h was considered positive for infection, and ESR of 30 mm/h or less was considered negative.[9] Similarly, for CRP values we used a cutoff of 10 mg/L. CRP of more than 10 mg/L was considered positive for infection, and CRP of 10 mg/L or less was considered negative.[9,11,27,28] Sensitivity and specificity were calculated for ESR and CRP alone, then for a positive result in ESR and CRP in both tests, and last for a positive result in either ESR or CRP.

False-negative rates were calculated for the patients who had known periprosthetic hip infections and whose ESR and CRP test results were normal (not elevated). The percentage of false-negatives was first derived from individual test results for normal ESR and CRP. Next, false-negative results were determined by combining the ESR and CRP laboratory results for each infected patient. The false-negative rate was found for patients who had negative test results for both ESR and CRP (neither test result was elevated). False-negative rates were then repeated with the patient being considered infected if either one, or both, laboratory values tested normal. Chi-square tests were calculated to determine the significance of the false-negative rates of the serologic tests compared with sex, BMI, primary diagnosis at time of primary THA, infection type, and immune status.

The independent variables used in the χ^2 analysis are

Table IV. ESR and CRP Compared With Other Variables

Variable	ESR Positive	ESR Negative	ESR *P*	CRP Positive	CRP Negative	CRP P	ESR or CRP Positive	ESR or CRP Negative	ESR or CRP *P*
Sex			.704			.378			.508
Men	25	4		30	1		28	0	
Women	41	4		36	4		38	2	
Body Mass Index			.930			.675			.747
< 25.5	27	3		27	2		26	1	
25.51-30	15	2		14	2		15	1	
30.1-35.5	10	2		10	1		11	0	
> 35.5	10	1		11	0		10	0	
Primary Diagnosis			.969			.930			.469
Osteoarthritis	35	3		33	3		34	1	
Osteonecrosis	5	1		5	1		5	1	
Trauma	10	1		10	0		10	0	
Hip dysplasia	5	1		5	0		5	0	
Rheumatoid arthritis	9	1		8	1		9	0	
Osteomyelitis	1	0		1	0		1	0	
Slipped capital femoral epiphysis	0	0		1	0		0	0	
Ankylosing spondylitis	0	0		1	0		0	0	
Infection Type			.178			.611			.100
Acute	19	2		19	1		20	0	
Hematogenous	4	2		5	1		5	1	
Late	43	4		42	3		41	1	
Immunocompromised			.454			.647			.191
Yes	28	5		28	3		28	2	
No	38	3		38	2		38	0	

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

defined here. BMI was stratified into normal weight (<25.5 kg/m^2), overweight (25.5-30.5 kg/m^2), obese class I (30.5-35.5 kg/m^2), and obese class II (>35.5 kg/m^2), as described by the World Health Organization.[29] Infection, as defined by Segawa and colleagues,[30] was classified into 1 of 3 types: (1) acute (<4 weeks after surgery); (2) hematogenous (confirmed identical cultured organism from an infection in a different part of the body that subsequently caused a periprosthetic hip infection); and (3) late or chronic (>4 weeks after surgery). Immunocompromised status was defined as presence of diabetes mellitus, human immunodeficiency virus, or cancer on or off chemotherapy; chronic daily use of corticosteroids for any reason; or presence of another immunocompromising disease. Patients who did not meet any of these criteria were classified as immunocompetent.

Data Evaluation

Data were obtained from patient charts and entered into a spreadsheet in SPSS Statistics 17.0.1 (SPSS, Chicago, Illinois). ESR of more than 30 mm/h was considered a positive for infection, and CRP of more than 10 mg/L was considered a positive for infection. Sensitivity, specificity, and positive and negative predictive values were then calculated for each of these tests with 95% confidence intervals (CIs) using a Wilson score method. Similarly, these values were calculated for combined ESR and CRP values that were negative for one test or positive for both tests.

False-negative rates were then calculated and compared. Chi-square analysis was used to compare the false-negative rate of ESR and CRP values with respect to sex, BMI, primary diagnosis, infection type, immunity status, and presence of inflammatory disease. The Fisher exact test was used to compare the differences in proportions of binomial variables to determine significance. In cases with multiple categories, Pearson χ^2 was used. $P<.05$ was used to determine significance.

We sought to confirm the validity of the serologic marker levels for ESR and CRP to determine if there are cutoffs that may be more sensitive without a sacrifice of test specificity. This was done with receiver operating characteristic (ROC) curves. ROC curves were constructed for all patients. Area under the curve, which measures the overall accuracy of the test, was determined to confirm validity. The previously established cutoff values were then compared with the observed data points on the ROC curve to determine if there are more optimal cutoffs for ESR and CRP to maximize sensitivity and specificity for diagnosing periprosthetic hip infections.

Results

Patient demographics are listed in Table I and Table II summarizes which organisms were cultured from the patients' hips. For all patients who underwent revision THA for infection, a positive ESR was found to have 89% sensitivity (95% CI, 80%-94%) and 69% specificity (95% CI, 51%-83%) in identifying infection. A positive CRP had 93% sensitivity (95% CI, 85%-97%) and 40%

Table V. Literature Review of Sensitivity and Specificity of ESR and CRP in Periprosthetic Hip Infection

Study	Infected Hips	Erythrocyte Sedimentation Rate, % (CI)				C-Reactive Protein, % (CI)			
		Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Berbari et al[32]	1270[a]	74 (71-77)	72 (63-79)	—	—	64 (52-74)	92 (77-97)	—	—
Chevillotte et al[16]	20	50 (25-75)	69 (59-78)	21	89	83 (59-96)	56 (45-67)	29	94
Ghanem et al[12]	127	94 (89-98)	70 (65-75)	55.5	96.9	91 (85-95)	77 (72-81)	60.5	95.6
Müller et al[13]	50	—	—	—	—	95	62	88	80
Schinsky et al[14]	55	97 (93-100)	39 (31-47)	42	96	94 (87-100)	71 (64-79)	59	96
Shukla et al[15]	87	78	69	23	4	67	55	15	7
Spangehl et al[3]	35	82 (65-93)	85 (78-91)	58	95	96 (78-100)	92 (85-96)	74	99
Present study	77	89 (80-94)	69 (51-83)	88	71	93 (85-97)	40 (23-59)	81	67

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NPV, negative predictive value, PPV, positive predictive value.
[a]Study included infected hips and infected knees.

specificity (95% CI, 23%-59%). Positive ESR and CRP values had 84% sensitivity (95% CI, 73%-91%) and 77% specificity (95% CI, 57%-90%). A positive ESR or CRP value had 97% sensitivity (95% CI, 90%-99%) and 23% specificity (95% CI, 10%-43%).

The false-negative rates for ESR and CRP were 10.8% and 7%, respectively. When patients who underwent both tests were stratified as infected if either one or both tests were positive, the false-negative rate decreased to 3%. When stratified for immune status, the false-negative rates dropped to 7.5% for ESR and 5.1% for CRP in immunocompetent patients (Table III). In addition, when ESR and CRP values were combined, there were no false-negative results in the immunocompetent patients, whereas the immunocompromised patients had a false-negative rate of 6.7% (P = .191). There were no statistically significant correlations between patients with false-negative results to sex, BMI, primary diagnosis at time of primary THA, infection type, or immune status (Table IV).

The ROC curves had cutoff values similar to those reported in the literature (Figure). The area under the curve was 0.769 for ESR (95% CI, 0.650-0.889) and 0.721 for CRP (95% CI, 0.588-0.854). ESR of 32.5 mm/h was determined to maximize the sensitivity and specificity of the test, which was similar to the cutoff reported in the literature of 30 mm/h (specificity of 69% and sensitivity 89%). Similarly, CRP of 9.79 mg/L maximized sensitivity and specificity. At the literature value of 10 mg/L for CRP, sensitivity decreased from 97% to 94% on the curve. Specificity was unchanged between the 2 values. CRP of 11.1 mg/L increased test specificity by 5%. However, this also decreased test sensitivity to 93%.

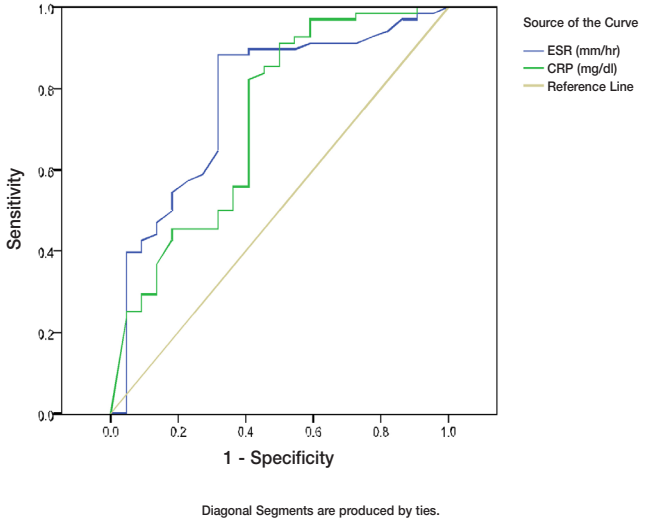

Figure. Receiver operating characteristic curve for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level.

Discussion

Distinguishing periprosthetic infection from aseptic loosening is often difficult in patients whose only presenting symptom is hip pain. ESR and CRP level have been useful markers for making this distinction, but false-negative results in patients with minimal hip pain can have disastrous long-term consequences if proper treatment is not instituted in a timely manner. The present study found high sensitivity for ESR and CRP values in their ability to identify post-THA periprosthetic infections. One concern was that some patients might not mount an immune response strong enough to produce serologic results indicative of infection. There was an association between immunocompromised patients and higher false-negative serologic test results for ESR and CRP (Table III). Most notably, the false-negative rate for the tests combined was 6.7% in immunocompromised patients. This study also showed ESR and CRP to be moderately good tests for diagnosing periprosthetic infection based on ROC curves with ideal cutoffs similar to what has been reported in the literature. Overall in this study, there was no significant statistical correlation involving age, sex, BMI, primary diagnosis at time of THA, infection type, or immunocompromised status.

A limitation of this study is that serologic test results were not performed on all patients who underwent revision THA. At Dr. Mont's institution, these tests are not commonly performed for patients in whom the likelihood of infection is high or already confirmed by other means, such as with a positive culture from aspiration

of a draining sinus. Similarly, some patients for whom the suspicion for infection was low and who underwent revision did not have a routine ESR or CRP level drawn. Other limitations of the study are its relatively small sample size and single-institution results. However, these limitations do not disprove that patients who undergo revision THA may not mount an immune response sufficient for diagnosing a periprosthetic infection and that this study further confirms the limitations of these tests in certain patients.

In Table V, the results of this study are summarized and compared with results reported in the literature. Sensitivity and specificity of ESR and CRP level have varied widely in the past and similarly in this study. In a study of 35 infected hip arthroplasties, Spangehl and colleagues[3] found the sensitivity of ESR and CRP to be 82% and 96%, respectively (95% CIs, 65%-93% and 78%-100%, respectively). When ESR and CRP levels were combined in their study, no infected patient had both serologic markers normal. They concluded that, though ESR and CRP are nonspecific inflammatory markers, after a careful history is obtained to rule out presence of other inflammatory causes, the combination of ESR and CRP is an excellent economic screening tool for excluding infection. In a similar study of 127 infected hip arthroplasties, Ghanem and colleagues[12] found 94% sensitivity for ESR (95% CI, 89%-98%) and 91% sensitivity for CRP (95% CI, 85%-95%). When they combined ESR and CRP values for either result being positive, sensitivity increased to 97.6%, and they concluded that the combination of ESR and CRP can be highly effective in reducing false-negative rates.

Few authors have reported ROC curves to determine ideal ESR and CRP cutoff values.[13,31] Ghanem and colleagues[12] examined use of ROC curves to determine ideal ESR and CRP cutoffs for maximizing sensitivity and specificity. They determined that ESR of 31.0 mm/h and CRP of 20.5 mg/L are ideal. In the present study, we found a similar ideal ESR cutoff, 32.5 mm/h, but a lower ideal CRP cutoff, 9.76 mg/L.

The present study found low specificity for CRP in diagnosing periprosthetic hip infections. This finding differs from that in other reports. A meta-analysis of serologic markers in 1270 periprosthetic hip and knee infections noted an overall specificity of 92% (95% CI, 77%-97%) for CRP,[32] compared with 40% (95% CI, 23%-59%) in the present study. In another study of 201 hips, 55 of which were infected, CRP had 71% specificity (95% CI, 64%-79%).[14] The low specificity in the present study might be partially explained by the previously mentioned fact that, at our institution, these serologic markers are not routinely drawn for patients unlikely to have a periprosthetic infection. In addition, our institution is a tertiary-care center for orthopedic joint problems—where many cases are complicated by other inflammatory conditions, such as rheumatoid arthritis and ankylosing spondylitis, which can elevate CRP levels and lead to low specificity. In this study, 47% of the noninfected patients with positive CRP values had an underlying disorder that causes an elevation in CRP level. A patient's past medical history should be reviewed before interpreting test results, as these inflammatory disorders, along with multiple other diseases (eg, chronic renal failure, lung cancer), can cause false elevations in CRP.

Used in combination, the serologic markers of ESR and CRP level constitute an excellent adjunct test for diagnosing periprosthetic hip infections. We found similar sensitivity of ESR (89%) and CRP (93%). However, the specificity of ESR (69%) and CRP (40%) found in this study was lower than what has been reported elsewhere. Physicians should be suspicious in cases in which patients present with hip pain and have normal serologic tests and an underlying immunocompromising disorder. The degree of suspicion for infection in these patients should be higher during surgery.

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