Serological markers can lead to false negative diagnoses of periprosthetic infections following total knee arthroplasty

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Abstract Periprosthetic infections following total knee arthroplasty (TKA) are diagnostically challenging. We evaluated the sensitivity and specificity of ESR and CRP, false negative rates, whether false negative rates differed between early post-operative and late infections, and the predictive ability of ESR and CRP to differentiate infected patients. Between 2000 and 2007, a prospectively collected database was reviewed to identify patients with suspected periprosthetic infections, and who had ESR and CRP laboratory values. One hundred and thirteen patients were identified. False negative rates were calculated. Finally, receiver operating characteristic curves were used to determine the predictive ability of ESR and CRP to differentiate infected from non-infected patients. CRP had a sensitivity of 95% and specificity of 20%. ESR had a sensitivity of 91% and a specificity of 33%. The false negative rate was 9.2% for ESR, 5.3% for CRP, and 11.1% for combined ESR and CRP. False negative rates were higher for early post-operative infections. Although ESR and CRP can be excellent adjunctive diagnostic tools, we emphasise that because some patients may not mount a sufficient immune response, the entire clinical picture must

be evaluated, and periprosthetic infection should not be ruled out on the basis of ESR and CRP results alone.

Introduction

Periprosthetic infections following total knee arthroplasty are a challenge to diagnose and treat. The infection rate after primary total knee arthroplasty is reported to be between 1% and 2% [1, 2]. It can often be difficult to distinguish at the time of initial clinical presentation whether a patient might be suffering from an aseptic failure, or if the patient has a periprosthetic infection of their total knee arthroplasty. While various laboratory tests have been used to predict periprosthetic infection prior to operative intervention, no single test offers an absolute screening tool to differentiate between the two patient populations (aseptic, septic) [1, 3–13]. Many authors report using erythrocyte sedimentation rate (ESR), with a cutoff of 30 mg/h, and C-reactive protein (CRP), with a cutoff value of 10 mg/L, as serological markers of inflammation that can be used as differentiation tools for the diagnosis of periprosthetic infection [3, 8, 11–14].

However, there is much controversy in the literature regarding the appropriate use of these tests and their interpretation, as there are wide ranges of reported sensitivities and specificities with regard to the diagnosis of periprosthetic infections after total knee arthroplasty [15, 16]. One of the main concerns at the senior author's institution is the ability of the tests to pre-operatively diagnose infections in various patients with subsequently diagnosed periprosthetic infections after total knee arthroplasty who might not have mounted a strong immune response to the infection, and consequently have normal serological levels of these disease markers. In addition, because these tests are based on

Ethical board review This study has received a waiver from an appropriate ethics committee. All patients gave their informed consent before inclusion in this study.

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continuous data, patients might have false negative test results if their laboratory values are slightly lower than the accepted cutoff values, when in fact the patient does have a periprosthetic infection.

The purpose of this study was to assess the usefulness of preoperative serological markers (ESR and CRP) by answering the following four questions: (1) What is the sensitivity and specificity of each test independently of one another, and of the tests in combination for the diagnosis of periprosthetic infections after total knee arthroplasty? (2) In what percentage of patients would the diagnosis of infection have been missed if ESR and CRP were used alone to diagnose periprosthetic infection (false negative test results)? (3) Is there a difference in false negative rates if broken down by early postoperative infections and late infections? and (4) What is the predictive ability of ESR and CRP to differentiate between the populations of infected and non-infected patients (as defined by receiver operating characteristic curves)?

Patients and methods

A prospectively collected database of all patients who underwent revision total knee arthroplasty between 2000 and 2007 at the senior author's institution was reviewed to identify patients who had clinical and radiographic suspicion of periprosthetic infections following total knee arthroplasty, and who underwent diagnostic testing with ESR and CRP laboratory values. One hundred and forty-nine of these knees had an operation for suspected periprosthetic infection. Of these knees, 113 had serological tests (ESR, CRP) performed at the time of initial presentation and treatment. The other 36 knees did not have these serological tests because they already had strong evidence of a positive deeply infected knee arthroplasty by multiple criteria as outlined below. Demographic data collected for these patients included age, gender, body mass index, and type of infection (post-operative, chronic, acute haematogenous), which are listed in Table 1. Approval for this study was obtained from the institution's Institutional Review Board.

At presentation, the senior authors evaluated them for periprosthetic infection based on clinical and radiographic findings. Radiographic findings of osteitis, osteomyelitis, or early, progressive osteolysis within two years of primary total knee arthroplasty are considered suspicious for infection. Clinical symptoms suggestive of periprosthetic infection after total knee arthroplasty include the following: a clinical history of swelling, redness, or drainage at the surgical site, and persistent, unexplained, and unrelieved pain.

The definitive diagnosis of infection after total knee arthroplasty was determined by using the Leone and

Table 1 Primary diagnoses and demographic variables of the 113 patients who had erythrocyte sedimentation rate and Westergren C-reactive protein studies performed

Demographic data	Number of knees
Gender	
Male	61 (58)
Female	52 (51)
Infection diagnosis	
Post-operative	21
Chronic	68
Acute hematogenous	16
Not infected	8
Mean age in years (range)	61 (28–89)
Mean body mass index (range)	32.3 (17.0–54.7)

Hanssen criteria for determining infection in patients with total knee arthroplasty [10]. According to their diagnostic algorithm, one of the following four criteria were required for the diagnosis of periprosthetic infection: (1) two or more positive cultures with the same organism, (2) histological evidence of acute inflammatory response seen on intraoperative frozen section, (3) gross purulence, or (4) a draining sinus tract that communicates with the joint space. Additionally, a diagnosis of periprosthetic infection was made if greater than ten polymorphonucleocytes (PMNs) were observed on at least one intraoperative frozen histological section. Only deep incisional and joint space infections were considered periprosthetic infections; patients with haematomata or wound dehiscence that did not progress to affect the joint space were not included in this study.

To answer the first question posed in this study to determine sensitivities and specificities for ESR and CRP, the values of 10 mg/L for CRP, and 30 mm/h for ESR, were taken as cut off values. For any values greater than these, the test was considered positive for infection, and for any values less than these the test was considered negative. Sensitivities were calculated for four different combinations of tests: CRP alone, ESR alone, positive findings in ESR or CRP, positive findings in both ESR and CRP.

The second question concerned false negative rates. False negative rates were calculated to determine what percentage of patients would have been missed had these tests been used to screen for periprosthetic infection. Additionally, the above diagnostic criteria used to answer question one (CRP alone, ESR alone, CRP or ESR, CRP and ESR) were also used to stratify the results for false negative rates.

The third question again addressed false negative rates, but stratified the results by infection type. For patients with false negatives serological tests, pre-operative aspiration results were reviewed. Aspiration was not routinely performed

Table 2 Sensitivities and specificities for erythrocyte sedimentation rate and C-reactive protein as diagnostic tests for periprosthetic joint infection in total knee arthroplasty

Test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	False neg overall (%)	False neg post-op (%)	False neg chronic (%)
ESR	91 (83–95)	33 (12–65)	9.2	17	4.8
CRP	95 (88–98)	20 (6–50)	5.3	11	3.2
ESR or CRP	95 (89–98)	38 (14–69)	4.8	11	3.2
ESR and CRP	95 (87–97)	29 (10–59)	11.1	20	15.8

ESR erythrocyte sedimentation rate, CRP C-reactive protein, CI confidence interval, Neg negative, Post-op post-operative

if the patient met other criteria for infection; it was only performed pre-operatively if further verification was required or other diagnostic tests or clinical signs (i.e. Leone and Hanssen criteria, as described above) were equivocal. Leukocyte values for positive aspirations range between 1,100 and 3,000 white blood cells/mL [17, 18]. For the purposes of this study, aspirations were considered positive if they were greater than 3,000 white blood cells/mL. If they were between 1,100 and 3,000 cells/mL then aspirations were considered equivocal for infection. The patient population was stratified into two groups: early post-operative infections, defined as symptomatic presentation within six weeks of primary knee arthroplasty, and late infections, defined as any infection that symptomatically presented at a time later than six weeks from the initial total knee arthroplasty. Additionally, seven of the 237 knees treated for presumed aseptic failures were found to be infected at the time of surgery, and were considered latent infections, but none presented acutely and were considered late infections.

The fourth question addressed the predictive ability of ESR and CRP serological tests to accurately differentiate between two unique populations: one that has a periprosthetic infection after total knee arthroplasty, and a population of patients that are aseptic [6, 19]. Receiver operating characteristic (ROC) curves were used for this. ROC curves plot the sensitivity versus one minus the specificity of a given test for a set of continuous data. The continuous data is used to attempt to detect a difference between two populations having overlapping normal distributions. The ROC curve compares predictive ability using different cut-off values of a test to determine the optimal cut-off point where the most patients with the disease have a positive test, while limiting the false negative rate. The area under the curve is frequently used as a measure of how useful the test is. The closer the line is to the upper left hand corner of the graph (all true positives, with no false positives), the closer the test is to an ideal discriminator between the two groups. In this ideal situation, the area under the curve (AUC) is equal to 1; an AUC of 0.5 or less indicates decreasing usefulness in differentiating between the two groups.

Statistical methods

Using the above-defined cut-off values, ESR and CRP values were compared versus a confirmed diagnosis of infection, to determine sensitivity and specificity. An Excel spreadsheet (Microsoft Corp., Redmond, Washington) was used for statistical analyses and the Wilson score method was used to calculate 95% confidence intervals. Additionally, receiver operating characteristic curves were generated using JMP® Statistical Discovery Software (SAS Institute, Inc., Cary, North Carolina).

Results

For the overall group, the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were found to have high sensitivities and low specificities. CRP had a sensitivity of 95% (95% confidence interval, 88–98%) and a specificity of 20% (95% confidence interval, 6–50%).

Fig. 1 Receiver operator characteristic (ROC) curve for erythrocyte sedimentation rate in diagnosing periprosthetic infection in total knee arthroplasty

Fig. 2 Receiver operator characteristic (ROC) curve for C-reactive protein in diagnosing periprosthetic infection in total knee arthroplasty

Similarly, calculations on measured ESR values gave a sensitivity of 91% (95% confidence interval, 83–95%) and a specificity of 33% (95% confidence interval, 12–65%). For a positive ESR or CRP test, the sensitivity was found to be 95% (95% confidence interval, 89–98%) and the specificity was found to be 38% (95% confidence interval, 14–69%). For positive ESR and CRP tests, the sensitivity was calculated to be 89% (95% confidence interval, 81–93%) and the specificity was found to be 29% (90% confidence interval, 10–59%). All results are summarised in Table 2.

There were 14 positively infected patients who had false negative serological tests. The overall false negative rate was found to be 9.2% for ESR and 5.3% for CRP. When the patient was considered infected if either of the tests (ESR or CRP) were positive, the false negative rate was 4.8%, and when the patient was considered infected if both ESR and CRP were greater than their cut-off values the false negative rate was 11.1%. All false negative rates are summarised in Table 2. Additionally, on reviewing aspiration results for these infected patients who had false positive results, seven of the patients had pre-operative aspirations performed. Of these seven, only two had results that were above the white blood cell threshold defined for a definitive infection.

Table 4 Reported sensitivities and specificities for ESR and CRP as a diagnostic tool for infected total knee arthroplasty

ESR erythrocyte sedimentation rate, CRP C-reactive protein

Authors	Year	ESR		CRP	
		Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Bare et al. [4]	2006	63	55	60	63
Austin et al. [3]	2008	91	72	94	74
Johnson et al. (this study)	2009	91	33	95	20

Table 3 Receiver operator characteristic curve values

Test	Cutoff value	AUC
ESR	30 mm/h	0.781
CRP	10 mg/L	0.794

ESR erythrocyte sedimentation rate, CRP C-reactive protein, AUC area under the curve

False negative rates were also calculated when broken down by infection type. Patients with early post-operative infections had higher false negative rates for CRP and ESR (11% and 17%, respectively), when compared to the CRP and ESR levels obtained from patients who presented with late infections (3.2% and 4.8%, respectively). The *p*-value between the two groups for CRP was found to be 0.23, and for ESR it was 0.13.

Figures 1 and 2 show receiver operating characteristic (ROC) curves for ESR and CRP, respectively. The area under the curves was calculated to be 0.781 for the ESR ROC curve and 0.794 for the CRP ROC curve. These results are shown in Table 3.

Discussion

Periprosthetic infections following total knee arthroplasty are a diagnostic challenge. ESR and CRP are commonly used serological markers that have often been used to try to differentiate between infected and aseptically failed total knee arthroplasties. The concern for the surgeon attempting to diagnose infection is the occasional patients who are unable to mount an adequate immune response in order to boost their laboratory values above these cut-off levels. The risk might be in concluding that a patient with low values is not infected. This prompted our investigation of ESR and CRP values for the diagnosis of infected total knee arthroplasty for suspected periprosthetic infection. We found that ESR and CRP had high sensitivities and low specificities, that there was an 11% false negative rate, that there were more false negative test results in early post-operative infections than late infections, and that CRP and ESR have a moderate ability to differentiate between infected and non-infected patient populations based on ROC curves.

There are several limitations of this study. First, this was an analysis of a prospectively collected database from patients who were operated upon at a single institution by only a few surgeons. In addition, because ESR and CRP are not routinely used at the senior author's institution for the diagnosis of periprosthetic knee infections, not every patient who underwent revision knee arthroplasty for suspected infection had these tests collected; many obviously infected patients did not get these tests. However, this does not negate the findings that certain patients do not mount a sufficient immune response to diagnose a periprosthetic infection, although inclusion of all patients prospectively may have slightly changed the percentages of these patients. If a prospective study is to be performed, the authors recommend that data should be collected from all patients undergoing revision total knee arthroplasties for any reason. Nevertheless, we believe that the information being presented further confirms the benefits and drawbacks of using these serological tests.

Table 4 summarises sensitivities and specificities for ESR and CRP as reported by various authors in the literature. The sensitivity of this study is consistent with prior sensitivities published by Austin et al. in which the reported sensitivity was the same as in our study for ESR (91%) and similar for CRP (94% compared to our finding of 95%) [3]. Austin et al. believed that because of its low cost and high sensitivity, ESR and CRP are good tests to rule out infection. While we agree with this conclusion, we also urge authors to use caution and clinical judgment when ruling out infection as 11% of our patients (and up to 20% of patients when considering acute post-operative infections alone) had false negative test results. Additionally, Della Valle et al. recently presented data that showed that a mean CRP level of 17.1 mg/L was observed in early post-operative infections after total knee arthroplasties undergoing revision. The mean CRP level in patients with early post-operative infections in our study was 31 mg/L. Based on those results, Della Valle et al. concluded that the optimal cut-off value for CRP results was 9.5 mg/L. Although this value is slightly different than the cut-off that we used for our study, there were no cases that would have had their diagnosis changed if we had analysed the data with a cut-off of 9.5 mg/L rather than 10 mg/L.

Bare et al. reported sensitivities of 63% and 60% for ESR and CRP, respectively, and they concluded that ESR and CRP should not be used for the sole diagnosis of periprosthetic infection [4]. These sensitivities are considerably lower than the sensitivities of our study. Their differences might be explained by a different definition of infection. Also, our specificities of 33% and 20% (ESR and CRP, respectively) are in contrast to those reported by both

Bare et al. and Austin et al [3, 4]. One of the main reasons for this difference may be that in our study, ESR and CRP are not routinely performed when there is low clinical suspicion of infection. Consequently, a negative test is more likely to be a false negative, generating a low ability of a negative test to disprove infection (specificity). This was confirmed by the findings in the patients with false negative serology who had aspirations performed. A majority of the aspirations were also equivocal, which is further evidence in support of an overall decreased immune response.

Based on our findings, and the experiences of the senior author, ESR and CRP can be excellent adjunctive diagnostic tools to aid in the diagnosis of periprosthetic infection following total knee arthroplasty. Although we found a relatively high sensitivity that was comparable to that previously reported in the literature, we do not believe that these tests alone should be used to rule out a diagnosis of periprosthetic infection due to the high false negative rates (as high as 20% if both CRP and ESR must be above the threshold to diagnose infection in acute postoperative infections). Some patients appear to be unable to mount a sufficient immune response to be above the threshold of cut-off values for a positive test result. We emphasise that the entire clinical picture must be taken into account and that periprosthetic infection should not be ruled out on the basis of ESR and CRP results alone.

Conflict of interest statement M.A.M. is a consultant for Stryker Orthopaedics and Wright Medical Technologies, and receives royalties from Stryker Orthopaedics. The remaining authors have no disclosures to make. No external funding was received specifically in support of this work.

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