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Diagnosis of Infection in the Early Postoperative Period After Total Hip Arthroplasty

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Abstract

Background Diagnosis of periprosthetic joint infection (PJI) can be difficult in the early postoperative period after total hip arthroplasty (THA) because normal cues from the physical examination often are unreliable, and serological markers commonly used for diagnosis are elevated from the recent surgery.

Questions/purposes The purposes of this study were to determine the optimal cutoff values for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid white blood cell (WBC) count, and differential for diagnosing PJI in the early postoperative period after primary THA.

Methods We reviewed 6033 consecutive primary THAs and identified 73 patients (1.2%) who underwent reoperation for any reason within the first 6 weeks postoperatively. Thirty-six of these patients were infected according to modified Musculoskeletal Infection Society criteria. Mean values for the diagnostic tests were compared between groups and receiver operating characteristic curves generated along with an area under the curve (AUC) to determine test performance and optimal cutoff values to diagnose infection.

Results The best test for the diagnosis of PJI was the synovial fluid WBC count (AUC = 98%; optimal cutoff value 12,800 cells/μL) followed by the CRP (AUC = 93%; optimal cutoff value 93 mg/L), and synovial fluid differential (AUC = 91%; optimal cutoff value 89% PMN). The mean ESR (infected = 69 mm/hr, not infected = 46 mm/hr), CRP (infected = 192 mg/L, not infected = 30 mg/L), synovial fluid WBC count (infected = 84,954 cells/μL, not infected = 2391 cells/μL), and differential (infected = 91% polymorphonuclear cells [PMN], not infected = 63% PMN) all were significantly higher in the infected group.

Conclusions Optimal cutoff values for the diagnosis of PJI in the acute postoperative period were higher than those traditionally used for the diagnosis of chronic PJI. The serum CRP is an excellent screening test, whereas the synovial fluid WBC count is more specific.

Level of Evidence Level III, diagnostic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution approved the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

THA is one of the most successful operations in orthopaedic surgery with outstanding long-term outcomes in terms of reduction of pain and restoration of function [16]. Despite the overall success of THA, deep periprosthetic joint infection (PJI) remains one of the most devastating complications [3, 5, 7, 14, 17]. Although PJI is a relatively rare event, having a reported incidence of 0.5% to 2% [1, 10, 12], deep infection accounts for roughly 15% of all revision THAs in the United States [6].

The diagnosis of PJI in the early postoperative period is particularly difficult, because normal periincisional swelling and erythema can resemble the typical appearance of PJI [2]. Furthermore, otherwise useful laboratory tests traditionally used in the evaluation of PJI such as the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [20] normally are elevated in the early postoperative period [4, 15]. Finally, the synovial fluid white blood cell (WBC) count and percentage of polymorphonuclear cells (%PMN), which have been shown to be among the best tests for the diagnosis of PJI, have also been shown in one study to be elevated in the early postoperative period after TKA [2], likely secondary to postoperative hemarthrosis and physiologic postoperative inflammation [2, 9, 13, 18, 21]. Specifically, Bedair et al. [2] established diagnostic guidelines for diagnosing a PJI after TKA in the early postoperative period (within 6 weeks of surgery) and showed that the optimal cutoffs for CRP (95 mg/L) and synovial WBC count (10,700 cells/μL to optimize sensitivity and 27,800 cells/μL to optimize specificity) and differential (89%) are substantially higher than previously published cutoffs for a chronic prosthetic joint infection after TKA [11, 13, 18, 24]. However, no similar work has outlined diagnostic parameters for PJI in the early postoperative period after THA.

Thus, the purposes of our study were to determine (1) whether the synovial fluid WBC count with differential and serum CRP and/or ESR was different between infected and noninfected hips in the first 6 weeks postoperatively; (2) the optimal cutoff values of each of these markers that maximized sensitivity and specificity in diagnosing a PJI in the early postoperative period after THA; and (3) whether any combination of these tests improves diagnostic performance.

Patients and Methods

After institutional review board approval, we retrospectively reviewed prospectively collected data on a consecutive series of 6033 primary THAs performed by three fellowship-trained orthopaedic surgeons from January 2002 to October 2012. Of these 6033 THAs, 122 hips (2%) were found to have undergone a reoperation within the first 6 weeks postoperatively. Within this cohort, intraoperative or preoperative synovial fluid WBC count with %PMNs, preoperative ESR and CRP values, and synovial fluid culture results including organisms and sensitivities were evaluated.

Forty-nine patients were excluded for the following reasons: no ESR, CRP, or synovial fluid WBC count with differential performed (29); oral or intravenous antibiotics administered after primary THA and before revision THA within 2 weeks before laboratory test draw (16); reoperation performed on the same day of the index surgery (three); and reoperation performed at an outside hospital with no records available for review (one). Neither the use of prophylactic antibiotics before the revision surgery [23] nor inflammatory arthropathy [8] was considered an exclusion criteria. Thus, 73 hips (73 patients) were used for our analysis. Thirty-six of the 73 hips were diagnosed with PJI based on modified criteria of Parvizi et al. [20]; specifically, serologic values and synovial fluid WBC count with differential were not used to establish the diagnosis. The most commonly identified organism from cultures taken from within the joint was *Staphylococcus aureus* (Table 1). Reoperations for the remaining 37 hips included 19 for an early periprosthetic fracture or subsidence of a cementless femoral component, 12 for a superficial wound revision (confirmed with negative deep cultures), and six for instability. The mean age at time of surgery was 60 ± 12 years old (range, 29–89 years), and there were 34 women (47%) and 39 men (53%). The mean time from the index procedure to reoperation was 23 ± 10 days (range, 5–42 days).

Statistical Analysis

Normally distributed univariate data were analyzed using t-tests. Diagnostic variables were evaluated using logistic regression models for the prediction of infection.

Table 1. Organisms cultured in periprosthetic joint infections

Organism	Number of patients
Staphylococcus aureus	27
Methicillin-sensitive	7
Methicillin-sensitive	20
Group B Streptococcus	3
Staphylococcus lugdunensis	2
Klebsiella pneumoniae	1
Proponibacterium acnes	1
Multiple organisms	2

Youden's J statistic was used to determine sets of optimal cutoff values with clinically acceptable levels of sensitivity and specificity informing final judgment. The fit and clinical applicability of the predictive logistic models were evaluated using receiver operating characteristic (ROC) curves and associated area under the curve (AUC) measures. Combinations of diagnostic variables were included simultaneously in the models to evaluate any incremental use. All analysis was performed using SAS® Version 9.1.3 software (SAS Institute Inc, Cary, NC, USA).

Results

Compared with the noninfected group, the mean preoperative serum ESR and CRP values as well as the synovial fluid WBC count and %PMNs were all significantly higher in the infected group (Table 2).

ROC curves (Fig. 1A–D) revealed that the synovial fluid WBC count (AUC = 98%; optimal cutoff value 12,800 cells/μL) was the best test for diagnosis of acute infection after primary THA followed by the CRP (AUC = 93%; optimal cutoff value 93 mg/L), synovial fluid differential (AUC = 91%; optimal cutoff value 89% PMN), and ESR (AUC = 73%; optimal cutoff value 44 mm/hr). The sensitivity for the synovial fluid WBC and serum CRP was 89% and 88%, respectively, with the specificity for both tests being 100%; these two tests maximize sensitivity while maintaining perfect specificity.

Optimal cutoff values and testing performance are summarized (Table 3).

Diagnostic performance did not improve by combining the results of these tests.

Table 2. Mean values of diagnostic measures between infected and not infected hips

Diagnostic measure	Infected	Not Infected	p value
ESR	69 ± 30	46 ± 23	0.016*
(mm/hr)	(6–140)	(8–80)	
CRP	192 ± 109	30 ± 20	< 0.0001*
(mg/L)	(5–395)	(5–68.7)	
Synovial WBC	84,954 ± 108,948	2391 ± 2640	< 0.001*
(cells/μL)	(1400–455,322)	(260–12,680)	
%PMN	91 ± 7	63 ± 23	< 0.0001*
	(64–99)	(19–96)	

Values are expressed as mean ± SD with range in parentheses; error inflation was controlled using the stepdown Bonferroni method; * significantly different at the 0.05 level with the stepdown Bonferroni correction method; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; Synovial WBC = synovial fluid WBC count; %PMN = percentage polymorphonuclear cells.

Discussion

Diagnosis of PJI can be difficult and the challenges of diagnosis are magnified in the early postoperative period (within the first 6 weeks). The typical evaluation for PJI includes a serum ESR and CRP followed by aspiration of the joint and measurement of the synovial fluid WBC count and differential [19]. These tests have been shown to be useful in the early postoperative period after TKA [2], albeit at optimal cutoff values higher than those used to diagnose chronic PJI; no similar work, however, is available to assist with the diagnosis of early PJI after THA. We thus sought to determine the use and optimal cutoff values of these commonly used tests in the first 6 postoperative weeks after primary THA.

Our study has several limitations. First, this is a retrospective study with all the inherent limitations of such a study design; in particular, there may be some selection bias, because several potential subjects were excluded because there was no record of the serum ESR, CRP, or synovial fluid WBC and/or differential. Nevertheless, we believe that not having these data points did not significantly affect our ability to identify clinically useful diagnostic tools for PJI in the early postoperative period after THA, because these findings are similar to previously reported values after TKA [2]. Furthermore, PJI in the first 6 weeks after surgery is rare (0.60% incidence in this series), which makes prospectively studying it difficult. Furthermore, every effort was made to identify all reoperations in this series and confirm all laboratory values. Second, our patient population was from one orthopaedic practice, which raises the question of whether the results here are generalizable to other practices or practice settings. However, all of the senior authors are high-volume surgeons at a high-volume center that is well experienced with managing complications, including PJI, after total joint arthroplasty. Furthermore, the multisurgeon design may help diminish any such individual practice bias. Our patient population may all have been biased toward PJI, because we did not sample all patients who received an aspiration or other diagnostic workup for PJI, but rather only those who underwent reoperation within the first 6 weeks when the diagnosis could be confirmed using both deep cultures and histopathologic examination of periprosthetic tissues. Furthermore, it is important to recognize that all of these values are a continuum that realistically changes over time with higher values closer to the time of surgery that gradually decrease. Finally, although picking a specific cutoff value is clinically useful, it is an oversimplification and all of these values must be interpreted in light of the clinical situation.

Only one prior study of which we are aware has examined the use of the synovial fluid WBC cell count and

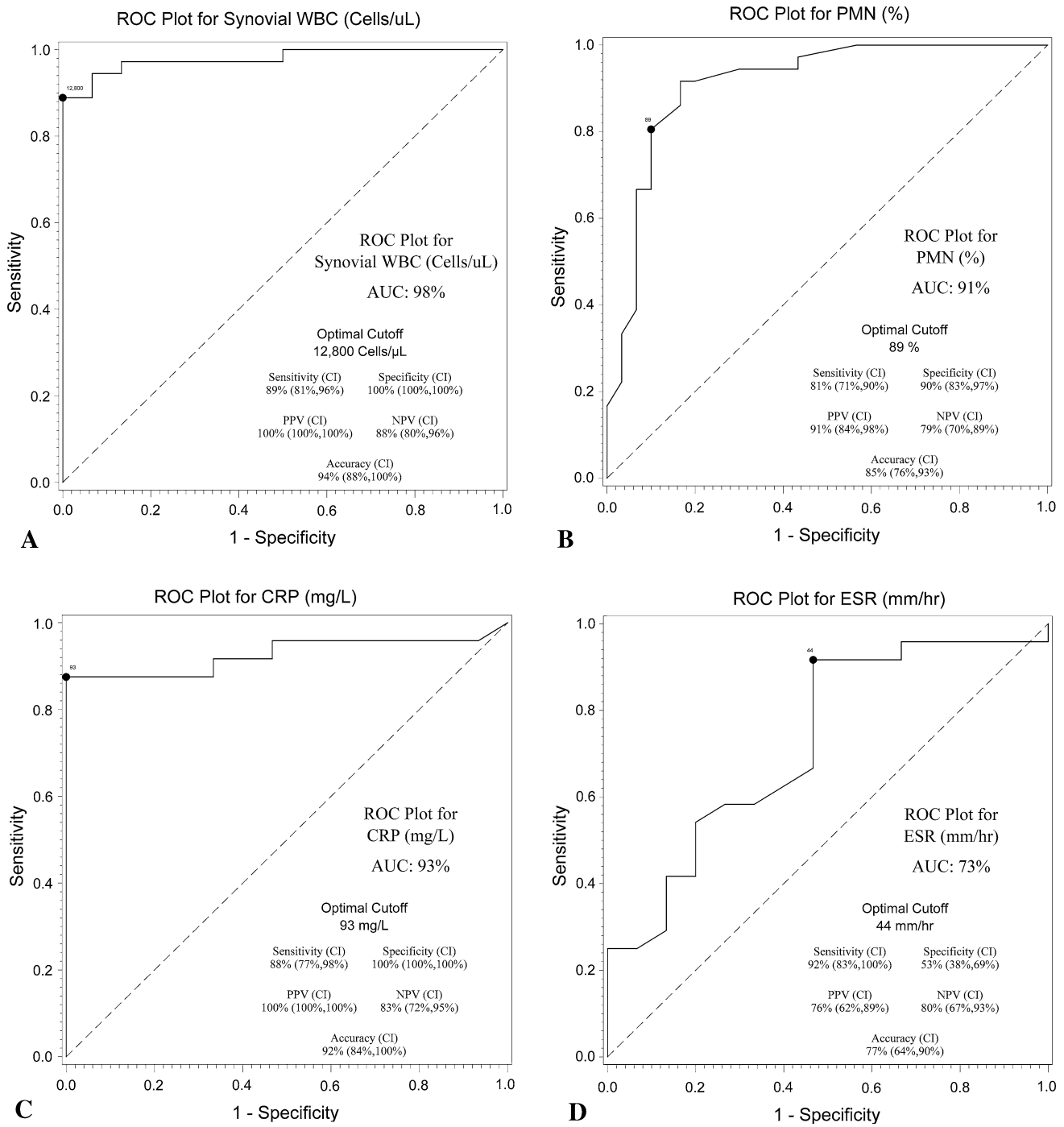

Fig. 1A–D (**A**) A ROC curve for the synovial WBC count is shown with an AUC of 98%. A cutoff value of 12,800 cells/µL demonstrates 89% sensitivity, 100% specificity, 100% PPV, 88% NPV, and 94% accuracy. (**B**) A ROC curve for %PMN is shown with an AUC of 91%. A cutoff value of 89% demonstrates 81% sensitivity, 90% specificity, 91% PPV, 79% NPV, and 85% accuracy. (**C**) A ROC curve for the serum CRP levels is shown with an AUC of 93%. A cutoff value of 93 mg/L demonstrates 88% sensitivity, 100% specificity, 100% PPV, 83% NPV, and 92% accuracy. (**D**) A ROC curve for the serum ESR is shown with an AUC of 73%. A cutoff value of 44 mm/hr demonstrates 92% sensitivity, 53% specificity, 76% PPV, 80% NPV, and 77% accuracy. PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval.

differential in the diagnosis of chronic PJI after a primary THA [21]. That series described 201 consecutive revision THAs and demonstrated that a synovial WBC count of greater than 4200 cells/µL and percentage of PMNs greater than 80% yielded sensitivities of 84% each and specificities of 93% and 82%, respectively, in diagnosing a PJI after a

Table 3. Optimal cutoff values and performance of diagnostic measures

Diagnostic measure	Optimal cutoff values	AUC	Sensitivity*	Specificity*	PPV*	NPV*	Accuracy*
ESR	44 mm/hr	73%	92% (83%–100%)	53% (38%–69%)	76% (62%–89%)	80% (67%–93%)	77% (64%–90%)
CRP	93 mg/L	93%	88% (77%–98%)	100% (100%–100%)	100% (100%–100%)	83% (72%–95%)	92% (84%–100%)
Synovial WBC	12,800 cells/μL	98%	89% (81%–96%)	100% (100%–100%)	100% (100%–100%)	88% (80%–96%)	94% (88%–100%)
%PMN	89%	91%	81% (71%–90%)	90% (83%–97%)	91% (84%–98%)	79% (70%–89%)	85% (76%–93%)

* Ninety-five percent confidence intervals in parentheses; AUC = area under the receiver operating characteristic curve; PPV = positive predictive value; NPV = negative predictive value; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; Synovial WBC = synovial fluid WBC count; %PMN = percentage polymorphonuclear cells.

THA and that ESR greater than 30 mm/hr and CRP greater than 10 mg/L yielded sensitivities of 97% and 94%, respectively [21]. If these values had been applied to our patient population in the early postoperative period (first 6 weeks), PJI would have been falsely diagnosed, triggering inappropriate treatment in a large number of cases. For example, nearly one-third of the noninfected patients in our study had a synovial fluid %PMN > 80%, the traditional threshold for PJI.

Our results are more consistent with the work of Bedair et al., who studied 146 consecutive knees evaluated for infection from a somewhat larger cohort of 11,964 primary TKAs in the early postoperative period. They similarly found that the synovial WBC count was the most useful diagnostic tool for a PJI in the first 6 weeks after a primary TKA with an optimal cutoff value of 27,800 cells/μL yielding 84% sensitivity and 99% specificity; if 10,700 cells/μL was selected as the cutoff value, sensitivity was optimized over specificity with values of 95% and 91%, respectively [2]. In our group of consecutive THAs, we also found that the synovial WBC count is the most useful diagnostic tool for diagnosing an early postoperative PJI after THA, even in the midst of baseline-elevated inflammation, with an optimal cutoff of 12,800 cells/μL yielding 89% sensitivity and 100% specificity, which is similar to the 10,700 cells/μL cutoff recommended by Bedair et al. [2]. Postoperative hemarthrosis is common in the early postoperative period after a primary THA or TKA and could potentially confound the diagnostic accuracy of the synovial fluid WBC count. However, Bedair et al. found no difference in diagnostic performance when adjusting the synovial WBC count for the presence of hemarthrosis [2] and therefore, we deemed adjusting the synovial WBC count based on the number of red blood cells to be unnecessary. The percentage of PMN in our series was also found to be a very useful test (AUC = 91%) at an optimal cutoff point of 89%, which is interestingly the same value proposed by Bedair et al. [2]. Clinically, we use this as a secondary test when the synovial fluid WBC count is not clearly positive or negative.

Serologic tests are an integral part of the diagnosis of chronic PJI because they are easily obtained and inexpensive. We found that the serum CRP was likewise extremely useful, even in the early postoperative period, however, at a value much higher than that typically suggested for the diagnosis of chronic PJI; we identified an optimal cutoff of 93 mg/L compared with 10 mg/L as reported in the two studies that we are aware of that have evaluated the use of this test in the diagnosis of chronic PJI after THA [21, 22]. In practice, we use the CRP as a screening test and any patient with a value approaching this number (93 mg/L) is aspirated and a synovial fluid WBC count, differential, and cultures are obtained to further establish the appropriate diagnosis and management. A surprising finding was that ESR demonstrated some diagnostic use, contrary to the observation made by Bedair et al. [2], with an optimal threshold of 44 mm/hr. Given the outstanding performance of the synovial fluid WBC count, however, combining test results in and of itself did not improve the ability to confirm or refute the diagnosis, although this has been done in previous studies with varying success [2, 11, 21].

In summary, our study suggests that the commonly used tests for the diagnosis of chronic PJI are similarly useful in the early postoperative period (within the first 6 weeks), albeit at cutoff values that are quite different from those traditionally used. Furthermore, the application of standard cutoff values would falsely trigger treatment for PJI in many cases. In practice, we use the serum CRP (the least invasive test that maximizes sensitivity and specificity) as a screen for infection and perform an aspiration of the joint if the CRP approaches the optimal cutoff value of 93 mg/L or if the clinical suspicion for infection is high for other reasons such as sudden onset of fever, purulent drainage, sepsis, or immunocompromised state. The optimal cutoff value for the synovial fluid WBC count (the best test for diagnosis) is 12,800 cells/μL and is the single best

predictor of periprosthetic hip infection in the early postoperative period; the percentage of PMN is also useful at a threshold value of 89%. Although useful, these tests are not perfect, and when in doubt, the treating physician can still use synovial fluid cultures to assist with diagnosis so long as antibiotics have not been administered before aspiration of the joint, although relying completely on cultures may delay definitive treatment.

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