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Do Elevated Inflammatory Markers Associate With Infection in Revision Shoulder Arthroplasty?

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Abstract

Background: Serologic erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurements, which have been successfully utilized in the lower extremity, are thought to lack adequate sensitivity in the diagnosis of infection after shoulder arthroplasty. The purpose of this study is to determine the diagnostic performance of preoperative white blood cell (WBC) count, ESR, and CRP in the diagnosis of infection in the setting of revision shoulder arthroplasty with the gold standard of infection being defined as a later diagnosis of infection.

Patients and methods: A national insurance database between the years of 2007 and 2015 (PearlDiver, Warsaw, IN) was queried for those patients who underwent revision shoulder arthroplasty using a combination of procedural (common procedural terminology codes 23472 and 23474) and diagnostic codes (International Classification of Diseases [ICD]-9 code 81.97 and equivalent ICD-10 codes). This database contains demographics, laboratory data, and complication data to allow identification of patients with an infection within 1 year postoperatively.

Results: The database contained 1392 patients who met criteria. Among these, the best diagnostic performance was with a combined test which was positive if CRP, ESR, or WBC was positive with a sensitivity of 7% to 42%, a specificity of 92%, a positive predictive value of 8% to 45%, a negative predictive value of 91%, and an accuracy of 84% to 85%. On multivariate analyses, predictors included an abnormal ESR (odds ratio 2.4, $P = .05$) and male gender (3.8, $< .001$).

Conclusions: Those patients with an abnormal preoperative ESR have significantly increased odds of a subsequent infection following revision shoulder arthroplasty. ESR, CRP, and WBC in combination are specific but insensitive.

Level of Evidence: Diagnostic, Level III

Keywords

Periprosthetic sepsis, periprosthetic infection, erythrocyte sedimentation rate, C-reactive protein, shoulder arthroplasty, shoulder replacement

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Introduction

Periprosthetic joint infection (PJI) after shoulder arthroplasty can be devastating.[1] This complication occurs infrequently after shoulder arthroplasty in 0% to 4% of cases.[1,2] The diagnosis of infection in the setting of a painful shoulder arthroplasty is challenging.[1,3–6] Sensitivities for C-reactive protein (CRP) for infection in the setting of a painful shoulder arthroplasty have been reported to range from 0% to 46%,[7–14] while sensitivities for erythrocyte sedimentation rate (ESR) have been reported to range from 5% to 80%,[7–14] both of which are substantially lower than those reported for total knee arthroplasty and total hip arthroplasty in a similar scenario.[11,15,16] The disappointing diagnostic performance of CRP and ESR for shoulder PJI has led

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to significant interest in other more expensive and less readily available synovial markers such as interleukin (IL)-6, alpha defensin, and other markers, which have had mixed success.[8,14,17–19] Prior literature has been challenged by the lack of a universal agreement on ''gold standard'' as to what constitutes a clinically meaningful *Propionibacterium acnes* infection. Some studies have used the criteria developed by the musculoskeletal infection society[20]; however, these criteria use elevated ESR and CRP as minor criteria. Others have attempted to define a pathologic *P. acnes* culture based upon the number of positive cultures,[21] the length of incubation time to culture growth,[22] or a combination of factors—although the latter also utilizes ESR and CRP as minor criteria.[8] Certainly if less strict criteria are used for the diagnosis of infection, the diagnostic performance of ESR and CRP may be underestimated by prior literature.

We thus proposed to answer the following questions: 1) What is the diagnostic performance of preoperative white blood cell (WBC) count, ESR, and CRP in the diagnosis of infection in the setting of revision shoulder arthroplasty with the gold standard of infection being a later diagnosis of infection? 2) What are the predictors for subsequent infection after revision shoulder arthroplasty?

Patients and Methods

A retrospective analysis of prospectively collected data was performed using a commercially available full claims database collected by the U.S. insurer Humana. Humana patient data from January 1, 2007 to December 31, 2015 were reviewed using PearlDiver Technologies research software (PearlDiver, Warsaw, IN). This database represents over 20 million patients nationally across the United States and its territories. Data housed in PearlDiver include patient demographics, laboratory data, diagnoses, procedures, hospitalization details, and so forth. Patients are deidentified using an assigned encrypted patient identification number, allowing for longitudinal research.

Internal Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9/10-CM) procedural and diagnosis codes and Current Procedural Terminology (CPT) Codes were used to identify patients who met study criteria. The following codes were used to query revision shoulder arthroplasty patients: CPT-23473, CPT-23474, ICD-9-81.97, and its ICD-10 equivalents. We specifically focused upon revision arthroplasty instead of primary arthroplasty, as revision arthroplasties are those patients who are evaluated for infection preoperatively.

To obtain laboratory data for revision shoulder arthroplasty patients, Logical Observation Identifiers Names and Codes codes were used for ESR, CRP, and WBC tests. ESR, CRP, and WBC were divided into normal and abnormal values using cutoffs of 25 mm/hour, 10 mg/L, and 11,000 cells/mL. These were specifically developed to be conservative estimates as compared to prior literature.[7–14] These were all preoperative tests. Postoperative test results were not included as they do not address our research questions. Patients were considered to have a postoperative infection if they were diagnosed with a wound infection within 6 months postoperatively or a deep infection within 1 year of surgery. These diagnoses were queried using ICD-9 and their equivalent ICD-10 codes. As this is a database study, wound infection and deep infection are defined based upon the use of these specific codes. These definitions thus may vary from patient to patient and with reporting within the database. This database also contains the Charleson Comorbidity Index, which is a standardized score to quantify medical comorbidities.[23,24]

Statistical analysis included descriptive statistics and multivariate logistic regression. Multivariate logistic regression analyses were used to assess the effect of various predictors on the odds of postoperative infection. The model developed was analyzed with the Hosmer and Lemeshow goodness-of-fit (GOF) test and a Psuedo R^2. A P value of less than .05 was considered statistically significant. Using these data, sensitivity and specificity of CRP, ESR, and WBC for wound infection within 6 months or deep infection within 1 year were also calculated. We also calculated the sensitivities and specificities of combination tests—ie, if both CRP and ESR are abnormal, if both ESR and WBC are abnormal, and so forth. Of note, to preserve patient confidentiality, this data source does not provide exact numbers of patients when there are fewer than 11 per group and thus the sensitivities provided are estimates in some cases. However, logistic regression analysis and odds ratio (OR) calculations do use the exact numbers.

Results

Between 2007 and 2015, a total of 1392 patients underwent a revision shoulder arthroplasty procedure (Table 1). An overwhelming number of patients (94.7%) were between the ages of 50 and 84 with a slight majority being female (58.3%). Of those 1392 patients, 33 developed a wound infection within 6 months of surgery (2.4%) and 37 were diagnosed with a deep infection within 1 year postoperatively (2.7%). Preoperative ESR, CRP, and WBC laboratory data were abnormal for 31.5%, 18.8%, and 3.3% of revision shoulder arthroplasty patients, respectively. Sensitivities and specificities of CRP, ESR, WBC, and the combination tests are listed in Table 2.Combination tests had slightly improved specificity without substantial compromise in sensitivity.

When looking at both wound infections and deep infections combined, there were several significant predictors (Table 3). An abnormal ESR (OR 2.418, P value=.05, 95% confidence interval, CI, [1.388, 4.212]) and male gender (OR 3.763, $P<.001$, 95% CI [2.757, 5.135]) were significant predictors of patients sustaining a deep infection within 1 year. However, a Hosmer and Lemeshow GOF test showed poor model fit, $P=.0005$ and Psuedo $R^2=0.045$, suggesting that only 5% of the variance in subsequent infection risk can be predicted based upon laboratory values, gender, and comorbidities.

Discussion

The diagnosis of PJI after shoulder arthroplasty is challenging. Serologic ESR and CRP measurements, which have been successfully utilized in the lower extremity are thought to lack adequate sensitivity.[7–14] The purpose of this study is to determine the diagnostic performance of preoperative WBC count, ESR, and CRP in the diagnosis of infection in the setting of revision shoulder arthroplasty with the gold standard of infection being defined as a later diagnosis of infection or need for irrigation and debridement. We found that those patients with an abnormal preoperative ESR and/or male gender have significantly increased odds of developing a subsequent infection after revision shoulder arthroplasty, suggesting that ESR does have prognostic value.

Our study has several limitations. As with all database studies, certainly data that would be available in a retrospective cohort study is not available, such as indication for revision, type of revision, whether the patient received postoperative antibiotics, whether the patient had inflammatory arthritis, the exact preoperative timing of the serologic studies, the exact timing of the postoperative irrigation and debridement, culture data, bacterial load, previous surgeries, perioperative details, revision details, and many other individual patient details. The use of subsequent infection as a marker for infection has limitations. Chronic indolent infections such as *P. acnes* that may present only as postoperative pain may also never under revision or irrigation and debridement and thus may be uncounted by our methodology. The latter issue could lead to an overestimation of the diagnostic accuracy of ESR. However, the authors suggest that, while imperfect, these criteria allow for surgeons to identify the outcome of greatest interest to the

Table 1. Patient Demographics.

Demographic	Patient count
Age	
15–44	<60
45–49	27
50–54	65
55–59	105
60–64	177
65–69	299
70–74	314
75–79	233
80–84	125
85–89	35
90 and over	25
Gender	
Female	811
Male	581
Shoulder arthro revisions	1392
Wound infection within 6 months	46
Deep infection within 1 year	50

Table 3. Logistic Regression Assessing the Influence of Independent Variables on Deep Infection Within 1 Year or Wound Infection Within 6 Months Postoperatively.

Independent variable	OR	95% CI	*P*
Abnormal ESR	2.095	1.170, 3.752	.050
Abnormal CRP	1.626	0.947, 2.792	1.000
Abnormal WBC	0.938	0.521, 1.687	1.000
Gender	3.763	2.757, 5.135	<.001
CCI	0.754	0.750, 0.758	1.000

CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; WBC, white blood cell.

Table 2. Sensitivity and Specificity for Each Preoperative Measure.

Variable	Abnormal CRP	Abnormal ESR	Abnormal WBC	CRP/ESR	WBC/CRP	WBC/ESR	CRP/ESR/WBC
Sensitivity	8%–45%	12%–45%	25%–69%	40%–50%	8%–45%	12%–45%	7%–42%
Specificity	83%	68%	21%–79%	72%–85%	91%	84%	92%
PPV	5%–33%	2%–18%	10%	8%–16%	10%–51%	5%–34%	8%–45%
NPV	89%	89%–93%	92%–94%	90%–99%	89%	90%–93%	91%
Accuracy	75%–77%	65%	74%–76%	68%–84%	82%–83%	79%–80%	84%–85%

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NPV, negative predictive value; PPV, positive predictive value; WBC, white blood cell.

patient in the later diagnosis of an infection. Because this particular database is linked to the insurance provider, if patients change insurance providers then they are no longer covered within the database. As a result, the length of follow-up for the included patients is essentially unknown. Certainly type II error is possible as some of our statistical comparison may be underpowered. However, this is the largest sample size available for this type of comparison to date because of the database design. As with all database studies, data entry errors or omissions are possible.

Within our study, CRP had a sensitivity of 7% to 45% and a specificity of 83%, and ESR had a sensitivity of 11% to 45% and a specificity of 68%. These are within the range of the previously reported sensitivity and specificity of these tests, although these vary widely within the literature. In the setting of shoulder arthroplasty, Dennison et al.[7] reported a sensitivity for CRP of 30% and for ESR of 80%, Dodson et al.[25] reported a sensitivity for CRP of 91% and a sensitivity for ESR of 45%, Grosso et al.[8] reported a sensitivity for CRP of 46% and a sensitivity for ESR of 42%, Piper et al.[11] reported a sensitivity of 16% to 42% for CRP and 32% to 63% for ESR, Topolski et al.[13] reported a sensitivity for CRP of 25% and for ESR of 14%, and Villacis et al.[14] reported a sensitivity of 0% for CRP and of 47% for ESR. Several studies have demonstrated that mean ESR/CRP do not differ between groups considered infected or potentially infected and those that are normal.[12,14,22,26,27] This is also true for shoulder infections not in the setting of arthroplasty. In the setting of infection after open reduction and internal fixation of a proximal humerus fracture, Athwal et al.[28] reported a sensitivity of 50% for CRP and a sensitivity of 66% for ESR. In the setting of infection after a rotator cuff repair, Athwal et al.[29] reported a sensitivity of 13% for the WBC count, 50% for CRP, and 60% for ESR. When arthroscopic biopsy was used as a gold standard, the sensitivities of ESR and CRP were only 5% each.[9] In the setting of a prior arthroscopy, Millett et al.[10] found that sensitivities of ESR and CRP are 20%. Certainly these are dramatically lower than in total knee arthroplasty and total hip arthroplasty where a recent systematic review reported pooled sensitivities for WBC of 45%, ESR of 75%, and CRP of 88%,[15] which are even lower than those reported by some individual centers of up to 47% for WBC, 94% for CRP, and 100% for ESR.[16] Based upon these data, in a recent review, Hsu et al.[3] provided the recommendation that ESR and CRP lack adequate sensitivity to rule out infection with a grade of "B." We also studied combination tests, with the best accuracy being with the combined CRP/ESR/WBC test, which had a specificity of 92%, a negative predictive value of 91%, and an accuracy of 84% to 85%. Similar to previous studies, our results suggest that ESR and CRP being insensitive do have diagnostic value and should be obtained and evaluated preoperatively.

Within our data, only 5% of the variance in subsequent infection risk can be predicted based upon laboratory values, gender, and comorbidities. Certainly this would support investigating other factors that may explain the variation in infection risk. Several studies have found biopsy to be of diagnostic value.[21,30] Several studies have examined alpha defensin,[18] IL-6,[8,14,19] and other cytokines.[17] While these factors are promising, previous results have been mixed.[8,14,19] Several of these studies have demonstrated a poor correlation between ESR/CRP and these newly identified factors, which certainly suggest that these factors provide additional diagnostic information that may provide more predictive power.[18,19] Certainly more research is necessary to identify further infection risk predictors so that this risk can be mitigated and patients can be properly stratified.

Those patients with an abnormal preoperative ESR and/or male gender have significantly increased odds of developing a subsequent infection after revision shoulder arthroplasty. Similar to previous studies using culture results as the gold standard, these results suggest that laboratory tests do have value in the preoperative setting prior to revision arthroplasty.

Authors' Note

The work for this study was performed at Rush University Medical Center in Chicago, IL and at the University of Utah in Salt Lake City, UT.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Peter N Chalmers declares that he has no conflicts of interest in the authorship or publication of this contribution. Shelby Sumner declares that she has no conflicts of interest in the authorship or publication of this contribution. Robert Z Tashjian is a paid consultant for Cayenne Medical and Mitek; has stock in Conextions, INTRAFUSE, and KATOR; receives intellectual property royalties from IMASCAP, Shoulder Innovations, and Zimmer; receives publishing royalties from JBJS, and serves on the editorial board for the Journal of Orthopaedic Trauma. Anthony A Romeo serves on boards for the AOSSM, the ASES, Orthopedics, Orthopedics Today, SAFE, SLACK, and LWW; is a paid consultant for Arthrex; is a paid speaker for Arthrex; receives royalties from Arthrex and Saunders and SLACK; receives research support from Arthrex, DJO, Ossur, and Smith and Nephew; and receives other financial support from Arthrex, Saunders, and SLACK.

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