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When Total Joint Arthroplasty After Septic Arthritis Can Be Safely Performed

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Background: Patients undergoing total joint arthroplasty (TJA) following septic arthritis are at higher risk for developing periprosthetic joint infection (PJI). Minimal literature is available to guide surgeons on the optimal timing of TJA after completing treatment for prior native joint septic arthritis. This multicenter study aimed to determine the optimal timing of TJA after prior septic arthritis and to examine the role of preoperative serology in predicting patients at risk for developing PJI.

Methods: A total of 207 TJAs were performed after prior septic arthritis from 2000 to 2017 at 5 institutions. Laboratory values, prior treatment, time from the initial infection, and other variables were recorded. Bivariate analyses were performed to identify the association between the time from septic arthritis to TJA and the risk of developing subsequent PJI. A subanalysis was performed between patients who underwent TJA in 1 setting (n = 97) compared with those who underwent 2-stage arthroplasties (n = 110). Receiver operating characteristic (ROC) curve analysis was performed for serum markers prior to TJA in predicting the risk of a subsequent PJI.

Results: The overall PJI rate was 12.1%. Increasing time from septic arthritis treatment to TJA was not associated with a reduction of PJI, whether considering time as a continuous or categorical variable, for both surgical treatment cohorts (all p > 0.05). Although the ROC curve analysis found that the optimal threshold for timing of TJA from the initial treatment was 5.9 months, there was no difference in the PJI rate when the overall cohort was dichotomized by this threshold and when stratified by 1-stage compared with 2-stage TJA. There was no significant difference in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level prior to conversion TJA between patients who subsequently developed PJI and those who did not.

Conclusions: Serum markers have limited value in predicting subsequent PJI in patients who undergo TJA after prior septic arthritis. There was no optimal interim period between septic arthritis treatment and subsequent TJA; thus, delaying a surgical procedure does not appear to reduce the risk of PJI.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

Native joint septic arthritis can lead to severe destruction of articular cartilage and development of accelerated arthritis¹. The infection can also result in bone destruction and soft-tissue contractures that further complicate this morbid condition. Although arthroplasty for septic arthritis results in pain relief and improved function for patients, complications including aseptic loosening¹ and subsequent periprosthetic joint infection (PJI)²⁻⁴ are common.

Several studies have demonstrated that native joint septic arthritis is a strong predisposing risk factor for the development

of PJI^{2,5}, perhaps the most devastating complication following TJA^{6,7}. In a meta-analysis of 1,300 TJAs performed on joints with prior septic arthritis, the reported PJI rate was found to be 5.96% (95% confidence interval [CI], 4.24% to 7.94%), which is much higher than the reported PJI rate of primary TJA for osteoarthritis (approximately 1%)^{8,9}. Because of the increased risk of complications, surgeons often are faced with a dilemma when treating these patients. There are relevant questions facing the orthopaedic community with clinical implications that relate to the staging of the arthroplasty after treatment of septic arthritis

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TABLE I Patient Demographic Characteristics				
	Total (N = 207)	PJI Group (N = 25)	Non-PJI Group (N = 182)	P Value
Age* (yr)	55.5 ± 14.4	56.7 ± 12.2	55.3 ± 14.7	0.837
Male sex†	103 (49.8%)	19 (76.0%)	84 (46.2%)	0.025
BMI* (kg/m ²)	27.0 ± 5.9	27.7 ± 5.0	26.9 ± 6.0	0.284
White race†	43 (20.8%)	8 (32.0%)	35 (19.2%)	0.186
Knee†	97 (46.9%)	13 (52.0%)	84 (46.2%)	0.583
Etiology of septic arthritis†				
Intra-articular injection	39 (18.8%)	1 (4.0%)	38 (20.9%)	0.089
Postoperative	82 (39.6%)	15 (60.0%)	67 (36.8%)	0.073
Hematogenous	28 (13.5%)	3 (12.0%)	25 (13.7%)	0.085
Others or unknown	58 (28.0%)	6 (24.0%)	52 (28.6%)	0.689
ASA class ≥3†	76 (36.7%)	12 (48.0%)	64 (35.2%)	0.357
Smoking habit†	28 (13.5%)	4 (16.0%)	24 (13.2%)	0.518
Alcohol abuse†	38 (18.4%)	3 (12.0%)	35 (19.2%)	0.583
Drug abuse†	16 (7.7%)	3 (12.0%)	13 (7.1%)	0.412
Diabetes†	31 (15.0%)	10 (40.0%)	21 (11.5%)	<0.001
Rheumatoid arthritis†	11 (5.3%)	1 (4.0%)	10 (5.5%)	1.000

*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

and whether any diagnostic tests can be used to predict who will develop subsequent PJI.

There are minimal literature and unclear metrics to guide surgeons on when elective arthroplasty should be performed in patients with prior septic arthritis^{3,5}. Furthermore, the majority of studies are frequently of a small sample size given the very low incidence of septic arthritis in the population^{2,3,10-12}. Due to the aforementioned limitations, only case reports and low-powered studies frequently exist, resulting in inconclusive outcomes³. The primary purpose of this multicenter study was to determine the

optimal timing of TJA after prior native joint septic arthritis. In addition, the secondary objective of this study is to examine the role of preoperative serological markers in predicting subsequent PJI after TJA.

Materials and Methods

After institutional review board approval was obtained, a multicenter, retrospective study was performed; it included all patients from 5 institutions who underwent total joint (hip or knee) arthroplasty from 2000 to 2017 following prior native joint

TABLE II Treatment Failure Rate Stratified by Time from the Treatment of Septic Arthritis to TJA						
Time from Treatment to TJA	2-Stage Exchange			1 Stage After Irrigation and Debridement		
	PJI Rate*	HR†	P Value	PJI Rate*	HR†	P Value
Continuous variable						
Per 1-month increase	—	0.99 (0.95 to 1.04)	0.775	—	1.00 (0.98 to 1.01)	0.870
Categorical variable						
<3 months	12.5% (4 of 32)	Reference		20% (2 of 10)	Reference	
3 to <6 months	17.0% (8 of 47)	1.43 (0.43 to 4.73)	0.563	10.5% (2 of 19)	0.79 (0.07 to 8.70)	0.845
6 to <12 months	10.5% (2 of 19)	0.85 (0.16 to 4.64)	0.850	5.3% (1 of 19)	0.40 (0.03 to 6.46)	0.521
12 to <24 months	10.0% (1 of 10)	0.95 (0.11 to 8.54)	0.967	8.3% (2 of 24)	0.57 (0.05 to 6.29)	0.646

*The values are given as the percentage, with the number of patients in parentheses; these values did not include patients who had follow-up of ≥24 months. †The values are given as the hazard ratio (HR), with the 95% CI in parentheses.

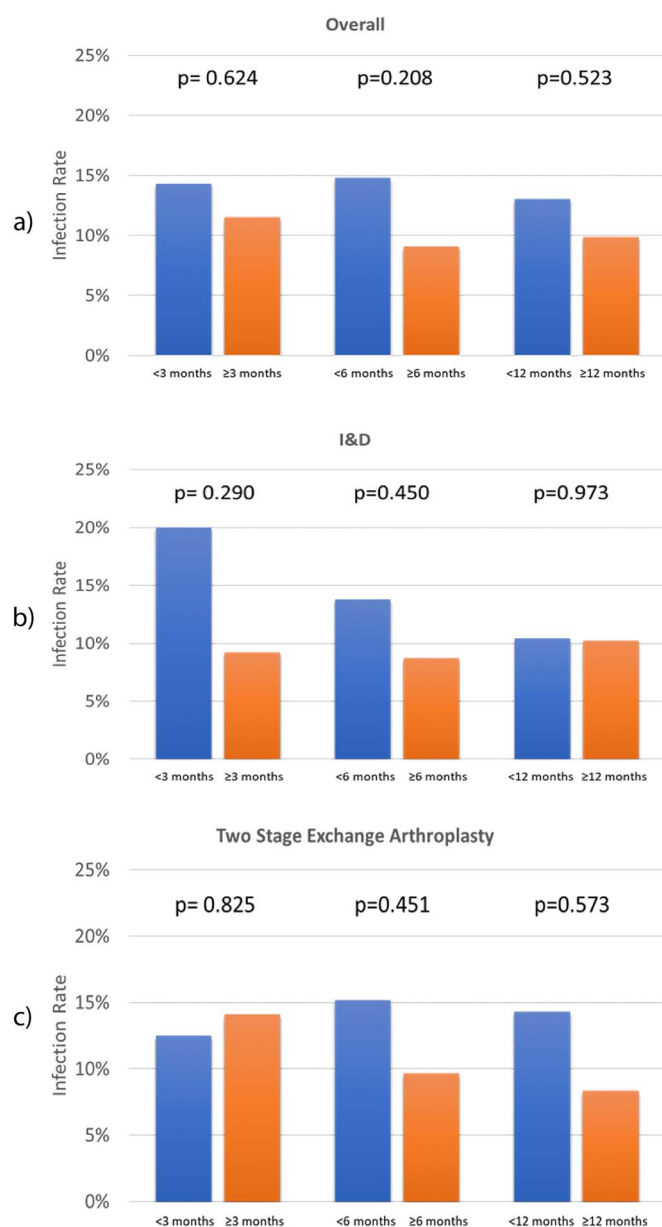


Fig. 1
PJI rate based on the time from the definitive septic arthritis surgical procedure to a conversion TJA based on the surgical treatment: overall (Fig. 1-A), 1 stage after irrigation and debridement (I&D) (Fig. 1-B), and 2-stage exchange (Fig. 1-C).

septic arthritis. Patients with osteomyelitis and patients without the minimum follow-up of at least 1 year were excluded. Patients with prior septic arthritis were identified on the basis of codes from the International Classification of Diseases, Ninth Revision and Tenth Revision (ICD-9 and ICD-10) and a query of the electronic medical record for the words “septic arthritis” and “native septic arthritis.” A manual review of the operative notes and medical record was then performed to confirm that arthroplasty was performed following prior septic arthritis of the same joint. The following pertinent variables were also

obtained: age, sex, body mass index (BMI), race, prior treatment, joint involvement, etiology of native joint septic arthritis, time from the last surgical procedure for a native septic joint to conversion TJA, the serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level at the time of conversion TJA, American Society of Anesthesiologists (ASA) class, smoking habit, alcohol abuse, drug abuse, history of diabetes, and rheumatoid arthritis. The final cohort consisted of 207 cases (110 hips and 97 knees) that included 97 patients who underwent 1-stage TJA and 110 patients who had resection and insertion of a spacer followed by the definitive TJA (the 2-stage group).

Surgical Technique

The surgical management of septic arthritis included irrigation and debridement through both open methods (63.9%) and arthroscopic methods (36.1%). Patients undergoing arthroplasty as a 2-stage procedure received an antibiotic-loaded cement spacer after resection of the bone and debridement of the native joint. The decision to perform TJA in 1 setting compared with 2 stages was based on surgeon preference, which may have factored in the host and the organism in making this decision. Patients undergoing 2-stage TJA received 4 to 8 weeks of systemic antibiotics based on a consultation with our infectious disease consultant.

The decision and timing of when to undergo the second-stage reimplantation after the initial spacer insertion were based on the surgeon’s discretion, given that there are no clear guidelines to that effect. There was some variability in the duration of an antibiotic holiday period and whether an aspiration was performed or serological markers were obtained prior to TJA. Routine intraoperative culture samples were again obtained in all patients during the TJA.

Primary Outcome

The primary treatment outcome of the study was the development of PJI following the subsequent TJA. The diagnosis of PJI was based on the Musculoskeletal Infection Society (MSIS) criteria for infection¹³.

Statistical Analysis

Demographic characteristics were compared between patients with and without the development of PJI using the independent t test, the Mann-Whitney test for continuous variables, and the chi-square test or the Fisher exact test for categorical variables.

Bivariate analysis was performed to determine the potential effect of the time duration from definitive treatment of native joint septic arthritis to TJA on PJI rates. In addition, receiver operating characteristic (ROC) curve analysis was performed to investigate the association between the time from septic arthritis treatment to TJA and the risk of future treatment failure from PJI. The area under the curve (AUC) was calculated and the optimal time cutoff was determined to maximize sensitivity and specificity. The cohort was dichotomized on the basis of that cutoff and the association with treatment failure was examined using

TABLE III Comparisons of ESR and CRP Levels Prior to TJA Between the PJI and Non-PJI Groups

	PJI Group*	Non-PJI Group†	P Value
Total			
ESR‡ (mm/hr)	29.9 ± 23.8	22.8 ± 24.2	0.231
CRP‡ (mg/L)	8.7 ± 6.8	13.3 ± 41.4	0.659
ESR >30 mm/hr§	8 (42.1%)	37 (26.6%)	0.18
CRP >10 mg/L§	4 (25.0%)	27 (20.9%)	0.748
1 stage after irrigation and debridement			
ESR‡ (mm/hr)	41.8 ± 33.6	22.5 ± 22.3	0.06
CRP‡ (mg/L)	8.1 ± 3.7	19.9 ± 61.9	0.643
ESR >30 mm/hr§	3 (50.0%)	14 (25.0%)	0.333
CRP >10 mg/L§	1 (16.7%)	11 (20.8%)	1
2-stage exchange			
ESR‡ (mm/hr)	24.4 ± 16.6	23.0 ± 25.6	0.846
CRP‡ (mg/L)	9.1 ± 8.3	8.7 ± 14.5	0.932
ESR >30 mm/hr§	5 (38.5%)	23 (27.7%)	0.514
CRP >10 mg/L§	3 (30.0%)	16 (21.1%)	0.685

*In the PJI group, 19 patients had ESR prior to TJA and 16 patients had CRP prior to TJA. †In the non-PJI group, 139 patients had ESR prior to TJA and 129 patients had CRP prior to TJA. ‡The values are given as the mean and the standard deviation. §The values are given as the number of patients, with the percentage in parentheses.

the chi-square test. Furthermore, the diagnostic value of ESR and CRP in predicting PJI after TJA was assessed using ROC curves and AUC analyses. Prediction scores are typically considered acceptable if their AUC exceeds 0.7, with an AUC of 0.5 representing a test with no value (toss of a coin) and an AUC of 1.0 signifying a perfect test. The optimal threshold was determined using the Youden index. Significance was set at $p < 0.05$. All statistical analyses were performed with R statistical software (The R Foundation for Statistical Computing; <http://www.R-project.org>).

Results

Overall, 12.1% (25) of 207 patients with prior native joint septic arthritis developed PJI following conversion TJA with a mean follow-up (and standard deviation) of 4.8 ± 3.1 years. The demographic characteristics and other characteristics of the cohort are presented in Table I. Patients with diabetes ($p < 0.001$) and male sex ($p = 0.025$) were more likely to develop subsequent PJI after arthroplasty (Table I).

The influence of the interval between the treatment of septic arthritis to TJA on PJI rates was investigated. Patients who developed PJI after TJA had a mean interval of 13.7 ± 27.3 months, and patients who did not develop PJI had a mean interval of 21.0 ± 54.6 months ($p = 0.472$). In the bivariate analysis, increasing time from septic arthritis treatment to TJA, whether considered as a continuous or categorical variable, was not associated with a reduction in PJI for both surgical treatment cohorts (all $p > 0.05$) (Table II). Figure 1 demonstrates that delaying definitive arthroplasty to ≥ 1 year did not result in a significant reduction in the development of PJI for the overall cohort and when stratified by treatment procedure.

ROC curve analysis was performed to investigate the association between the time interval from septic arthritis treatment to TJA and the risk of future PJI; the AUC was 0.46 and the optimal time interval was 5.9 months. There was no significant difference in the PJI rates between patients who underwent a TJA < 5.9 months from the time of treatment (14.8%) and those patients who underwent a TJA at > 5.9 months (9.1%) ($p = 0.21$). Neither treatment group revealed a significant association between a time interval of 5.9 months to TJA and consequent PJI rates ($p = 0.45$ for the 1-stage cohort and $p = 0.45$ for the 2-stage cohort) (Fig. 1).

The comparisons of ESR and CRP levels between PJI and non-PJI groups are presented in Table III. There was no significant difference in ESR and CRP levels at the time of TJA between patients with and without development of PJI in the overall cohort and when stratified by surgical intervention treatment (all $p > 0.05$). ROC curves were generated to determine the capacity of serum ESR and CRP for predicting PJI after TJA (Fig. 2), with an AUC of 62.5% (95% CI, 49.7% to 75.3%) for ESR and 65.8% (95% CI, 53.8% to 77.9%) for CRP in the total cohort. Similar results were observed in the 1-stage cohort: 68.9% (95% CI, 45.5% to 92.3%) for ESR and 69.3% (95% CI, 55.4% to 83.3%) for CRP. The findings were also similar in the 2-stage cohort at 59.6% (95% CI, 44.4% to 74.9%) for ESR and 63.0% (95% CI, 45.1% to 81.0%) for CRP. Using the Youden index, the optimal threshold value was 8.5 mm/hr for ESR and 4.3 mg/L for CRP in the total cohort; however, both values are within the normal reference range.

Organism information is presented in Table IV. The organism at the initial native joint septic arthritis infection and

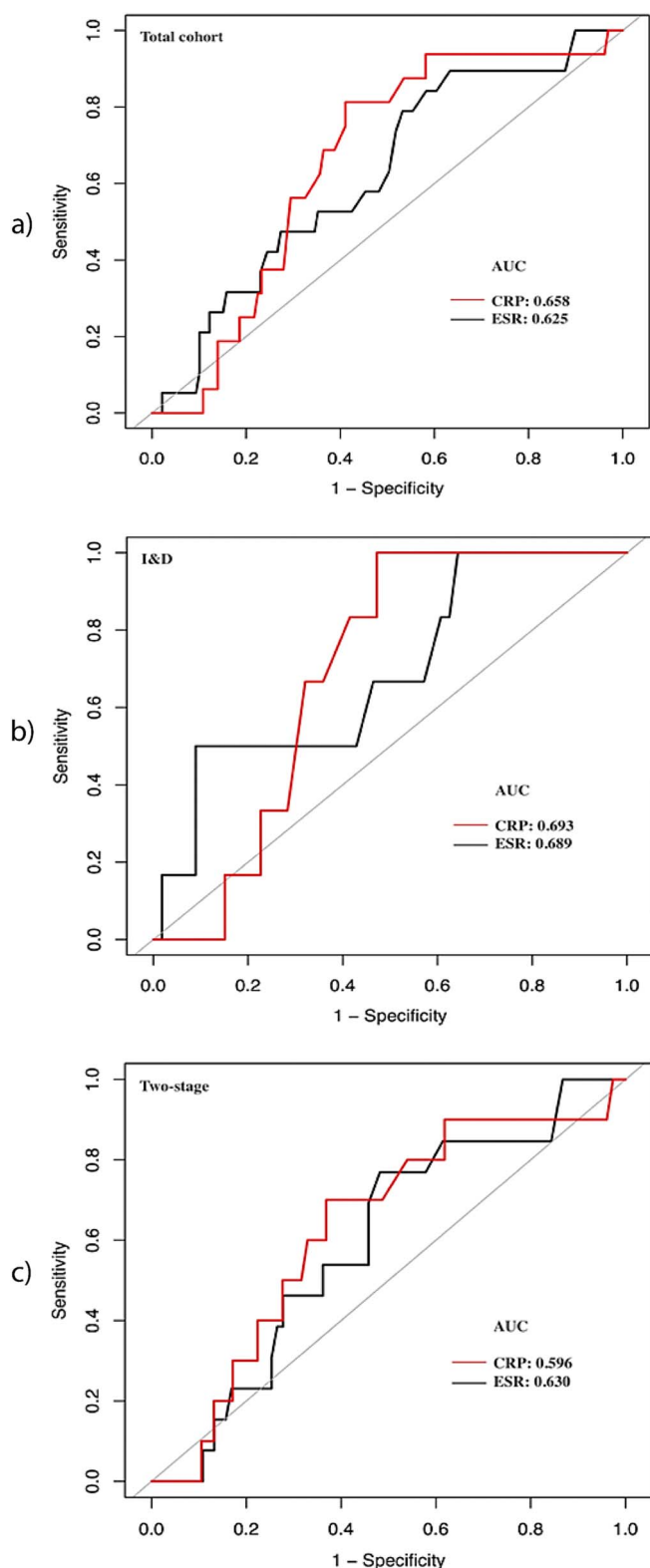


Fig. 2
ROC curve of ESR and CRP in predicting treatment failure for the overall cohort: total cohort (**Fig. 2-A**), 1 stage after irrigation and debridement (I&D) (**Fig. 2-B**), and 2-stage exchange arthroplasty (**Fig. 2-C**).

the infecting microorganism during subsequent development of PJI were the same in 54.2%. The PJI was acute and occurred within 90 days of arthroplasty in 36% of patients (9 of 25).

When comparing the surgical treatments, patients treated with a 2-stage exchange arthroplasty compared with the group that had undergone 1-stage TJA after irrigation and debridement were more likely to be younger, to have a hip infection, and to have a lower BMI and ASA score, but were more likely to be smokers (Table V). There was no difference in the infection rate between the 2 surgical treatments: 10.3% (10 of 97) for the 2-stage exchange arthroplasty group and 13.6% (15 of 110) for the group that had undergone 1-stage TJA after irrigation and debridement ($p = 0.665$).

Discussion

TJA following native joint septic arthritis results in an increased rate of complications, especially PJI^{1,3}. In this high-risk population, it is important to assess and mitigate the risk of PJI prior to a patient undergoing arthroplasty. However, minimal literature exists with regard to which patients are safe to undergo arthroplasty and when this can be performed. The International Consensus Meeting (ICM) on Periprosthetic Joint Infection in 2013 determined that research on the optimal timing of elective arthroplasty for patients with prior septic arthritis remains one of the most important areas of future research¹⁴.

Given the low rate of arthroplasty for native joint septic arthritis, patient and surgical factors that influence the development of PJI have been rarely investigated^{1,4}. In the largest series of patients with septic arthritis undergoing TJA, Kim et al. investigated 170 hips in 161 patients with previous childhood septic arthritis and concluded that there should be a quiescent period of 10 years after the infection before an arthroplasty is performed¹⁵. The rationale was that the only patient with a quiescent period of <10 years developed a bilateral infection and the remaining 168 hips with a period of ≥ 10 years had no reinfection. Although the 10-year cutoff may apply to childhood septic arthritis, this lengthy period can be problematic or impractical in adults with severe joint pain. Furthermore, Sultan et al. also investigated risk factors and the influence of the timing from septic arthritis to arthroplasty in a series of 62 patients¹⁶. They recommended that arthroplasty be delayed for 2 years, as they found that arthroplasty occurring before 2 years demonstrated an odds ratio of 3.02 (95% CI, 1.33 to 48.67) for PJI, which was not significant. When applying the recommended 2-year cutoff suggested by Sultan et al. to the present study with a much larger sample size, there was no difference with an odds ratio of 1.11 (95% CI, 0.31 to 4.01). This suggests that delaying arthroplasty may not lead to a substantial reduction in the development of PJI.

The current ICM recommendation⁵ stated that “in the absence of concrete evidence, we recommend that arthroplasty be delayed at least until completion of antibiotic treatment and resolution of clinical signs of infection, but no earlier than three months from the inciting event.” Furthermore, the PJI rates of patients with septic arthritis who underwent 2-stage arthroplasty as definitive treatment did not differ across the delayed

TABLE IV PJI Rate by Organism Profile

	Total (N = 157)*	Non-PJI Group (N = 137)*	PJI Group (N = 20)*	P Value
Polymicrobial organisms	15 (9.6%)	12 (8.8%)	3 (15.0%)	0.375
Resistant organisms	13 (8.3%)	10 (7.3%)	3 (15.0%)	0.243
<i>Staphylococcus aureus</i>	38 (24.2%)	30 (21.9%)	8 (40.0%)	0.077
Coagulase-negative staphylococci	18 (11.5%)	15 (10.9%)	3 (15.0%)	0.595
Streptococcus	12 (7.6%)	12 (8.8%)	0 (0.0%)	0.168
Gram-negative organisms	17 (10.8%)	14 (10.2%)	3 (15.0%)	0.52
Others	17 (10.8%)	13 (9.5%)	4 (20.0%)	0.158
Culture-negative	51 (32.5%)	47 (34.3%)	4 (20.0%)	0.202

*The values are given as the number of patients, with the percentage in parentheses.

time frames to TJA, which is in concordance with results recently published on the optimal timing of reimplantation after 2-stage exchange procedures that did not reveal any benefit in delaying reimplantation¹⁷.

Additionally, we investigated the role that serological markers at the time of arthroplasty may play in predicting the development of PJI. Unfortunately, we could not assess the role of aspiration, as this was performed in a minority of patients (16.9%) and was not amenable to statistical analysis because of the low numbers. The AUC for both ESR and CRP was fair in predicting PJI, and, therefore, their optimal cutoff values were in the normal clinical ranges and thus of no diagnostic value. One possible explanation for this is that the serological values may have been affected by prior therapeutic antibiotic treat-

ment. Wang found that, in 24 patients undergoing total hip arthroplasty for quiescent septic arthritis, 2 of 3 patients with an ESR of >40 mm/hr developed reinfection and none of the remaining 21 patients did¹⁸. We run into a similar dilemma during the reimplantation procedure of a 2-stage exchange performed to treat PJI. In these instances, the literature is mixed with regard to the role of serology and surgeons rely on the serial trending of serological markers, although the optimal cutoffs are unknown^{5,19-23}. Ghanem et al. determined that ESR and CRP prior to reimplantation poorly predicted persistent infection in a series of 109 patients with prior PJI²¹. Kusuma et al. demonstrated that ESR (54%) and CRP (21%) often remained elevated in patients in whom the infection was controlled²³. Furthermore,

TABLE V Demographic Characteristics and Characteristics by Surgical Treatment

	1 Stage After Irrigation and Debridement (N = 97)	2-Stage Exchange (N = 110)	P Value
Age* (yr)	58.2 ± 12.2	53.7 ± 15.4	0.046
BMI* (kg/m ²)	29.1 ± 6.6	25.7 ± 5.0	<0.001
Male sex†	37 (38.1%)	66 (60.0%)	0.325
Knee†	72 (74.2%)	25 (22.7%)	<0.001
ASA class*	2.6 ± 0.6	2.2 ± 0.9	<0.001
Smoking habit†	8 (8.2%)	20 (18.2%)	0.041
Diabetes†	14 (14.4%)	17 (15.5%)	0.816
Rheumatoid arthritis†	5 (5.5%)	6 (5.5%)	0.798
Etiology of septic arthritis†			0.327
Intra-articular injection	20 (20.6%)	19 (17.3%)	
Postoperative	36 (37.1%)	46 (41.8%)	
Others or unknown	24 (24.7%)	34 (30.9%)	
Hematogenous	17 (17.5%)	11 (10.0%)	

*The values are given as the mean and the standard deviation. †The values are given as the number of patients, with the percentage in parentheses.

Lonner et al. found that aspiration after a resection arthroplasty had a sensitivity and positive predictive value of 0% and concluded that a negative result thus does not rule out ongoing infection²⁰.

Several limitations were present that should be considered when interpreting the results of this study. First, the study was retrospective and thus relies on accurate documentation of the initial infection, which may be inaccurate (i.e., recall bias), especially in patients with a quiescent infection that was treated many years ago. Second, the study was multicenter in nature and thus there may have been slight variations in the treatment protocols for native joint septic arthritis. Although serological test results were obtained prior to arthroplasty in most patients (>75%), there were many cases in which an aspiration was not performed prior to the surgical procedure. Third, we were not able to obtain information on whether serological tests or aspirations were performed while the patient was taking antibiotics or if a drug holiday was performed. Antibiotic use may have resulted in lower inflammatory markers and may explain the low threshold found with the Youden index. Although there are no clear guidelines to determine when the TJA after treatment of septic arthritis should occur, it can be assumed that arthroplasty was performed when the joint was in the quiescent phase. Furthermore, although we found that the absolute ESR and CRP at the time of the arthroplasty were not predictive of infection, we were unable to look at the change in ESR and CRP from the initial infection as the laboratory values from the initial infection were frequently unavailable because many of the surgical procedures for the initial infection were performed at an outside hospital. Lastly, there were undoubtedly variables that were unaccounted for when determining the timing of the arthroplasty, which included the antibiotic treatment and duration and an antibiotic holiday.

In summary, the present study found that serological markers obtained at the time of the arthroplasty have little value in predicting the development of PJI after TJA for septic arthritis, although the study demonstrates that there is no

protective effect (reduction in PJI rates) of delaying the TJA for an extended period of time. ■

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