THE USE OF PREOPERATIVE CRP AND ESR AS PREDICTIVE MARKERS OF PROSTHETIC JOINT INFECTION IN PRIMARY TOTAL HIP AND KNEE ARTHROPLASTY

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ABSTRACT

Research Question: Do patients who undergo primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) with elevated pre-operative C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) produce a higher incidence of post-operative periprosthetic joint infection (PJI), compared to THA and TKA patients that had normal pre-op labs? Further, what proportion of patients that developed PJI post-operatively had elevations in only CRP, only ESR, or both CRP and ESR? Lastly, we will investigate whether patients had pre-operative elevations in CRP and/or ESR due to the presence of a modifiable risk factor, such as an acute infection or inflammation. How did such conditions correlate with PJI development when compared to patients with non-modifiable risk factors (age, sex, chronic disease)?

Background, significance, rationale: CRP and ESR are commonly utilized indicators of inflammation in the diagnosis and management of PJI among patients undergoing THA and TKA. The frequency of these surgeries is expected to increase significantly, with projections indicating a rise from 400,000 THAs and 700,000 TKAs annually to 635,000 THAs and 1,260,000 TKAs by 2030. PJI poses a notable challenge, contributing to 20% of revision THA cases and 25% of revision TKA cases. The economic burden of PJI is substantial, estimated to reach $753.4 million for THA and $1.1 billion for TKA by 2030. Given the transition to value-based healthcare, optimizing patients before surgery is paramount. This study aimed to evaluate the association between preoperative CRP/ESR levels and the subsequent development of PJI following primary THA and TKA, as well as to identify modifiable and non-modifiable risk factors among patients exhibiting elevated preoperative inflammatory markers.

Materials and methods: A retrospective review was conducted on 806 patients from a single healthcare facility who had undergone either THA (n=291) or TKA (n=515). As part of the preoperative assessment, CRP and ESR levels were measured for all patients. Data regarding patient demographics, medical conditions, and incidences of PJI were collected. A CRP value greater than 0.3 mg/dL and an ESR value exceeding 30 mm/hr were considered positive indicators.

Results: Our study revealed no statistically significant correlation between pre-operative CRP or ESR and PJI. However, it is worth mentioning that a greater percentage of patients diagnosed with PJI exhibited elevated preoperative CRP levels (70.6%) compared to PJI cases with normal CRP levels (29.4%).

Conclusions: This study did not validate the use of preoperative CRP and ESR as reliable predictors of PJI in primary THA and TKA. However, it offers valuable quantitative data on the prevalence of elevated preoperative CRP and ESR levels in all patients undergoing THA and TKA, with a significant portion having modifiable risk factors. Given that a significant number of patients with elevated CRP and ESR levels did not develop PJI, we do not advise cancellation of THA and TKA unless there are obvious modifiable risk factors significantly increasing the risk of PJI.

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Research Question:

Do patients who undergo primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) with elevated pre-operative C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) produce a higher incidence of post-operative periprosthetic joint infection (PJI), compared to THA and TKA patients that had normal pre-op labs? Further, what proportion of patients that developed PJI post-operatively had elevations in only CRP, only ESR, or both CRP and ESR? Lastly, we will investigate whether patients had pre-operative elevations in CRP and/or ESR due to the presence of a modifiable risk factor, such as an acute infection or inflammation. How did such conditions correlate with PJI development when compared to patients with non-modifiable risk factors (age, sex, chronic disease)?

Introduction and Significance:

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are among the most common orthopedic surgeries in the United States. They are associated with various complications, including aseptic loosening, instability, dislocation, periprosthetic fracture, stiffness, chronic pain, DVT/PE, and prosthetic joint infection (PJI).[1,2,3,4] Currently, over 400,000 THAs and more than 700,000 TKAs are performed annually, with projections showing an increase to approximately 635,000 THAs and 1,260,000 TKAs by 2030.[5]

Despite advancements, PJI remains a prevalent and one of the most serious complications in patients undergoing total joint arthroplasty (TJA).[6,7,8,9,10] The overall incidence of PJI in THA and TKA ranges from 1% to 2% and 2% to 3%, respectively, with its occurrence increasing alongside the rising number of TJAs nationwide.[11] PJI accounts for approximately 20% of all revision THA cases and 25% of all revision TKA cases.[10] Apart from the substantial impact on patient health, the projected annual economic burden of PJI by 2030 is estimated to reach $753.4 million for THA and $1.1 billion for TKA.[12]

With the shift to value-based care and alternative payment models, the need to prioritize optimizing patients before surgery has grown significantly in order to decrease the risk of postoperative complications. [13,14,15,16] Common components of an optimization panel include a thorough history and physical exam, complete blood count, comprehensive metabolic panel, coagulation studies (PT/INR), electrocardiogram, assessment of body mass index (BMI), mental health screening, dental assessment, screening for nicotine use, as well as screening for alcohol and illicit drug use.[15,16]

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly utilized markers for inflammation and infection across various fields in medicine. [17,18,19,20,21,22] In orthopedic surgery, CRP and ESR are frequently employed to diagnose and monitor infection, including PJI in TKA and THA. Extensive literature exists on their use specifically in diagnosing PJI within the realm of TJA. [23,24,25,26,27] However, there is limited data concerning their preoperative use specifically in primary TJA. Previous studies have reported a correlation with elevated CRP and PJI, while others have found no correlation.[6,28,29,30,31] This study aims to further explore any association between preoperative CRP/ESR levels and PJI in primary THA and TKA, as well as to assess risk factors among patients with elevated preoperative inflammatory markers to enhance understanding of overall PJI incidence in this patient population.

Materials and Methods:

A retrospective chart review was conducted to analyze patients who underwent primary THA or TKA at John Peter Smith Hospital between 2016 and 2020. Data regarding patient demographics, acute infections, laboratory results, and medical history were extracted from their medical records. Exclusion criteria included cases involving THA for femoral neck fracture, follow-up periods less than 1 year, and patients who were federal inmates due to inadequate follow-up documentation. After applying these exclusion criteria, a total of 806 patients were included in the final analysis cohort, all of whom had a minimum follow-up period of 1 year. All surgeries were exclusively performed at John Peter Smith Hospital in Fort Worth, Texas, by one of two attending orthopedic surgeons specialized in adult reconstruction and with fellowship training in adult reconstruction.

Baseline patient demographics, medical history, preoperative laboratory results (including CRP, ESR, and urinalysis), and outcomes (specifically, the occurrence of PJI) were retrieved from their medical records. Past medical history was analyzed to evaluate the impact of documented conditions such as obesity, smoking, rheumatoid arthritis, liver disease, renal disease, HIV, as well as other relevant conditions like deep vein thrombosis/pulmonary embolism, coagulopathy, stroke, transient ischemic attacks, and coronary artery disease. To establish an objective threshold, positive CRP was defined as any value exceeding 0.3 mg/dL, and positive ESR as any value surpassing 30 mm/hr. Prosthetic joint infection was defined according to the Musculoskeletal Infection Society (MSIS) criteria.

A logistic regression analysis was conducted to examine the influence of ESR on positive CRP laboratory results. To establish a comprehensive model, all variables extracted from the medical records underwent initial univariate pre-filtering. Each variable was individually analyzed using univariate regression, and those with a p-value of 0.2 or lower were included in the subsequent multivariate models. Backwards stepwise regression was employed to create parsimonious models. Analyses were performed separately for each type of surgery (THA and TKA) based on the distribution of the data. When appropriate, statistical tests including the Wilcoxon-Mann-Whitney U test, chi-square test, or Fisher's exact test were utilized.

This chart review received approval from the North Texas Regional Institutional Review Board (IRB), with waiver of informed consent granted by the IRB under approval number 1354130-2. All PHI reviewed in this study adhered to the HIPAA regulations.

Results:

Demographics and THA vs TKA:

A total of 806 patients underwent primary THA (291) and TKA (515). Patient demographics and medical comorbidities categorized by the type of surgery performed are summarized in Table 1. Significant differences were observed when comparing patient age (p-value < 0.0001) between the two surgery types. The median age for patients undergoing THA was 55 (IQR: 49 to 60), whereas for those undergoing TKA, it was 62 (IQR: 56 to 69). Additionally, there was a significant difference in the distribution of BMI across the two surgery types (p-value = 0.0001). A higher proportion of patients undergoing TKA (70.1%) were obese compared to those undergoing THA (49.1%). Similarly, the incidence of avascular necrosis differed significantly (p-value < 0.0001) between the two groups, with none of the TKA patients experiencing avascular necrosis compared to 22.3% of THA patients. Among the total 65 patients with avascular necrosis, two had prosthetic joint infection (PJI). Furthermore, the proportion of patients with PJIs was significantly lower (p-value = 0.0487) among those undergoing TKA (1.4%) compared to THA (3.4%). Patients with prior surgeries constituted a significantly higher proportion (p-value = 0.0001) of the TKA group (22.1%) compared to the THA group (11.4%). When evaluating smoking status, a significantly higher proportion (p-value < 0.0001) of TKA patients (61.9%) reported never smoking compared to THA patients (44.8%). Additionally, there were significantly more patients with diabetes mellitus undergoing TKA (28.0%) compared to THA (17.5%) (p-value = 0.0009).

Table 1. Demographic Distribution by Surgery Performed

	Total Hip Arthroplasty N = 291	Total Knee Arthroplasty N = 515	P-Value
Median Age (IQR)[1]	55 (49 - 60)	62 (56 - 69)	<.0001
Gender[2]			
Female	161 (55.3%)	354 (68.7%)	0.0001
Male	130 (44.7%)	161 (31.3%)	
Body Mass Index[3]			
Underweight	5 (1.7%)	0 (0.0%)	<.0001
Normal	56 (19.2%)	44 (8.5%)	
Overweight	87 (29.9%)	110 (21.4%)	
Obese	143 (49.1%)	361 (70.1%)	
Avascular Necrosis[2]			
No	226 (77.7%)	515 (100.0%)	<.0001
Yes	65 (22.3%)	0 (0.0%)	
Postive Urinalysis[2]			
No	241 (82.8%)	424 (82.3%)	0.861
Yes	50 (17.2%)	91 (17.7%)	
Periprosthetic joint infection[2]			
No	281 (96.6%)	508 (98.6%)	0.0487
Yes	10 (3.4%)	7 (1.4%)	
Had Prior Surgery[2]			

No	257 (88.6%)	401 (77.9%)	0.0001
Yes	33 (11.4%)	114 (22.1%)	
Smoking Status[2]			
Former	90 (31.0%)	137 (26.6%)	<.0001
Never	130 (44.8%)	319 (61.9%)	
Current	70 (24.1%)	59 (11.5%)	
Diabetes Mellitus[2]			
No	240 (82.5%)	371 (72.0%)	0.0009
Yes	51 (17.5%)	144 (28.0%)	
Rheumatoid Arthritis[2]			
No	278 (95.5%)	501 (97.3%)	0.1851
Yes	13 (4.5%)	14 (2.7%)	
HIV[2]			
No	279 (95.9%)	503 (97.7%)	0.1502
Yes	12 (4.1%)	12 (2.3%)	
Renal Disease[2]			
No	264 (90.7%)	459 (89.1%)	0.4741
Yes	27 (9.3%)	56 (10.9%)	
Liver Disease[2]			
No	263 (90.4%)	470 (91.3%)	0.6744
Yes	28 (9.6%)	45 (8.7%)	
Congestive Heart Failure[2]			
No	270 (92.8%)	494 (95.9%)	0.0541
Yes	21 (7.2%)	21 (4.1%)	
Coagulation Condition[2]			
No	271 (93.1%)	486 (94.4%)	0.2486
Yes	20 (6.9%)	29 (5.6%)	
Positive CRP[2]			
Negative (lab of 0.3 or less)	132 (45.4%)	270 (52.4%)	0.054
Positive (lab greater than 0.3)	159 (54.6%)	245 (47.6%)	
Positive ESR[2]			
Negative (lab of 30 or less)	240 (82.5%)	427 (82.9%)	0.8743
Positive (lab greater than 30)	51 (17.5%)	88 (17.1%)	

1. Wilcoxon-Mann-Whitney U test performed
2. Chi Square was performed
3. Fisher's Exact Test was performed

Table 1 – Distribution of patient demographics and comorbidities by surgery performed (THA vs. TKA)

CRP and ESR distribution:

Table 2 provides a breakdown of patient CRP and ESR results. In total, 49.9% of patients exhibited normal CRP levels (<0.3 mg/dL), while 50.1% showed elevated CRP levels (>0.3 mg/dL). Similarly, 82.8% of patients had normal ESR levels (30 mm/hr or lower), whereas 17.3% had elevated ESR levels (>30 mm/hr). Of all patients,

53.7% demonstrated elevation in either CRP or ESR, 46.3% had normal levels of both CRP and ESR, and 13.7% displayed elevation in both CRP and ESR.

Upon examining CRP and ESR elevation across various laboratory results, no significant differences in PJI occurrence were observed. Additionally, when combining ESR and CRP results, no significant differences in PJI status were noted across the combined laboratory profiles.

Table 2. Distribution of CRP and ESR Elevation[1]

	Total Patient Population N = 806	No PJI N = 789	PJI N = 17	P-Value
Percent of Patients With Elevation of CRP				
Negative (lab of 0.3 or less)	402 (49.9%)	397 (50.3%)	5 (29.4%)	0.1392
Positive (lab greater than 0.3)	404 (50.1%)	392 (49.7%)	12 (70.6%)	
Percent of Patients With Elevation of ESR				
Negative (lab of 30 or less)	667 (82.8%)	667 (82.8%)	12 (58.8%)	0.1796
Positive (lab greater than 30)	139 (17.3%)	139 (17.3%)	5 (29.4%)	
Percent of Patients With Elevation of CRP or ESR				
Positive ESR or Postive CRP	373 (46.3%)	421 (52.2%)	5 (0.6%)	0.0557
Both ESR and CRP are Negative	433 (53.7%)	368 (45.7%)	12 (1.49%)	
Percent of Patients With Elevation of CRP and ESR				
Positive ESR and Positive CRP	696 (86.4%)	105 (13.0%)	5 (0.6%)	0.1586
Either ESR or CRP are Negative	110 (13.7%)	684 (84.9%)	12 (1.49%)	
Percent of Patients With Elevation of CRP but ESR is Negative				
Positive CRP and Negative ESR	294 (36.5%)	287 (35.6%)	7 (0.9%)	0.6841
CRP is Negative, and ESR can be positive/negative	512 (63.5%)	502 (62.3%)	10 (1.2%)	
Percent of Patients With Elevation of ESR but CRP is Negative				
Positive ESR and Negative CRP	29 (3.6%)	29 (3.6%)	0 (0.0%)	0.4208
ESR is Negative, and CRP can be positive/negative	777 (96.4%)	760 (94.3%)	17 (2.1%)	

1. Chi Square was performed

Table 2 – Distribution of elevated CRP and/or ESR according to post-operative development of PJI vs. no PJI vs. total patient population

Modifiable and Non-modifiable Risk factors:

Table 3 presents the distribution of modifiable and non-modifiable causative risk factors associated with elevations in CRP and ESR. When considering all potential causative risk factors (including increased BMI, urinalysis results, current smoking status, diabetes, rheumatoid arthritis, HIV, renal disease, liver disease, congestive heart failure, or coagulopathy), no significant differences were observed across any combination of ESR and CRP levels.

Elevations in ESR (p-value < 0.0001) and patients with positive CRP but negative ESR (p-value = 0.0132) were significantly associated with an increased likelihood of having an unmodifiable risk factor (such as diabetes, rheumatoid arthritis, HIV, renal disease, liver disease, congestive heart failure, or coagulopathy). Similarly,

elevations in ESR (p-value = 0.0039) along with positive CRP but negative ESR (p-value = 0.0051) were significantly associated with an increased likelihood of having a modifiable risk factor (such as increased BMI, positive urinalysis, or current smoking status).

Table 3. Distribution of CRP and ESR Labs, by Risk Factors[1]

Potential Identifying Risk Factor: increased BMI, urinalysis, current smoking status, diabetes, rheumatoid arthritis, HIV, renal, liver, CHF, or coagulopathy			
	Potentially Causative Risk Factor	**No Causative Risk Factor**	**P-Value**
Percent of Patients With Elevation of CRP			
Negative (lab of 0.3 or less)	376 (46.7%)	26 (3.2%)	0.1093
Positive (lab greater than 0.3)	388 (48.1%)	16 (2.0%)	
Percent of Patients With Elevation of ESR			
Negative (lab of 30 or less)	633 (78.5%)	34 (4.2%)	0.7509
Positive (lab greater than 30)	131 (16.3%)	8 (1.0%)	
Percent of Patients With Elevation of CRP or ESR			
Positive ESR or Positive CRP	414 (51.4%)	19 (2.4%)	0.2574
Both ESR and CRP are Negative	350 (43.4%)	23 (2.9%)	
Percent of Patients With Elevation of CRP and ESR			
Positive ESR and Positive CRP	105 (13.0%)	5 (0.6%)	0.7354
Either ESR or CRP are Negative	659 (81.8%)	37 (4.6%)	
Percent of Patients With Elevation of CRP but ESR is Negative			
Positive CRP and Negative ESR	283 (35.1%)	11 (1.4%)	0.1549
CRP is Negative, and ESR can be positive/negative	481 (59.7%)	31 (3.9%)	
Percent of Patients With Elevation of ESR but CRP is Negative			
Positive ESR and Negative CRP	26 (3.2%)	3 (0.4%)	0.2052
ESR is Negative, and CRP can be positive/negative	738 (91.6%)	39 (4.8%)	
Unmodifiable Identifying Risk Factors: diabetes, rheumatoid arthritis, HIV, renal, liver, CHF, or coagulopathy			
	Potentially Causative Risk Factor	**No Causative Risk Factor**	**P-Value**
Percent of Patients With Elevation of CRP			
Negative (lab of 0.3 or less)	178 (22.1%)	224 (27.8%)	0.4755
Positive (lab greater than 0.3)	189 (23.5%)	215 (26.7%)	
Percent of Patients With Elevation of ESR			
Negative (lab of 30 or less)	277 (34.4%)	390 (48.4%)	<.0001
Positive (lab greater than 30)	90 (11.2%)	49 (6.1%)	
Percent of Patients With Elevation of CRP or ESR			
Positive ESR or Positive CRP	207 (25.7%)	226 (28.0%)	0.1628
Both ESR and CRP are Negative	160 (19.9%)	213 (26.4%)	
Percent of Patients With Elevation of CRP and ESR			

Positive ESR and Positive CRP	72 (8.9%)	38 (4.7%)	<.0001
Either ESR or CRP are Negative	295 (36.6%)	401 (49.8%)	
Percent of Patients With Elevation of CRP but ESR is Negative			
Positive CRP and Negative ESR	117 (14.5%)	177 (22.0%)	0.0132
CRP is Negative, and ESR can be positive/negative	250 (31.0%)	262 (32.5%)	
Percent of Patients With Elevation of ESR but CRP is Negative			
Positive ESR and Negative CRP	18 (2.2%)	11 (1.4%)	0.0686
ESR is Negative, and CRP can be positive/negative	349 (43.3%)	428 (53.1%)	
Modifiable Identifying Risk Factors: increased BMI, urinalysis, or current smoking status,			
	Potentially Causative Risk Factor	**No Causative Risk Factor**	**P-Value**
Percent of Patients With Elevation of CRP			
Negative (lab of 0.3 or less)	359 (44.5%)	43 (5.3%)	0.0039
Positive (lab greater than 0.3)	383 (47.5%)	21 (2.6%)	
Percent of Patients With Elevation of ESR			
Negative (lab of 30 or less)	616 (76.4%)	51 (6.3%)	0.4985
Positive (lab greater than 30)	126 (15.6%)	13 (1.6%)	
Percent of Patients With Elevation of CRP or ESR			
Positive ESR or Positive CRP	407 (50.5%)	26 (3.2%)	0.1022
Both ESR and CRP are Negative	335 (41.6%)	38 (4.7%)	
Percent of Patients With Elevation of CRP and ESR			
Positive ESR and Positive CRP	102 (12.7%)	8 (1.0%)	0.7804
Either ESR or CRP are Negative	640 (79.4%)	56 (6.9%)	
Percent of Patients With Elevation of CRP but ESR is Negative			
Positive CRP and Negative ESR	281 (34.9%)	13 (1.6%)	0.0051
CRP is Negative, and ESR can be positive/negative	461 (57.2%)	51 (6.3%)	
Percent of Patients With Elevation of ESR but CRP is Negative			
Positive ESR and Negative CRP	24 (3.0%)	5 (0.6%)	0.0592
ESR is Negative, and CRP can be positive/negative	718 (89.1%)	59 (7.3%)	
1. Chi Square was performed			

Table 3 – Distribution of elevated CRP and/or ESR according to whether this elevation was associated with a potentially causative risk factor as cause for that elevation. Table then breaks this data down into modifiable vs. unmodifiable identified risk factors.

Odds of PJI with elevated CRP and/or ESR:

Table 4 presents the full logistic regression model, indicating that a positive preoperative ESR significantly increases the likelihood of a positive preoperative CRP test (p-value < 0.0001). Specifically, for each unit increase in ESR, the odds of a positive CRP lab increase by a factor of 1.056 (95% CI: 1.040, 10.072).

Furthermore, the odds of a positive CRP test were 1.973 times higher in patients who THA compared to those who underwent TKA (95% CI: 1.389, 2.803; p-value = 0.0001). Former smokers had 46% lower odds of a positive CRP test compared to current smokers (95% CI: 0.328, 0.888; p-value = 0.0116).

Additionally, patients classified as obese had significantly higher odds of having a positive CRP test (p-value < 0.0001). Specifically, the odds of a positive CRP test were 4.102 times higher in obese patients compared to those with a normal body mass index (95% CI: 2.442, 6.89).

Table 4. Full Logistic Model Assessing Positive C-Reactive Protein Labs	**Crude Odds Ratio**			**Adjusted Odds Ratio**		
	Estimate	**95% Confidence Interval**	**P-value**	**Estimate**	**95% Confidence Interval**	**P-value**
Erythrocyte Sedimentation Rate	1.057	(1.043, 1.072)	<.0001	1.056	(1.040, 1.072)	<.0001
Gender						
Female	1.684	(1.259, 2.253)	0.0004	1.063	(0.749, 1.509)	0.732
Male	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Rheumatoid Arthritis						
Yes	6.036	(2.068, 17.612)	0.001	3.034	(0.873, 10.547)	0.0807
No	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Procedure						
Total Hip Arthroplasty	1.311	(0.982, 1.750)	0.0664	1.973	(1.389, 2.803)	0.0001
Total Knee Arthroplasty	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Periprosthetic joint infection						
Yes	2.442	(0.852, 6.995)	0.0964	1.641	(0.488, 5.519)	0.4235
No	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Urinalysis						
Positive	1.543	(1.068, 2.231)	0.021	1.209	(0.794, 1.84)	0.3762
Negative	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Smoking Status						
Former	0.695	(0.450, 1.073)	0.0397	0.54	(0.328, 0.888)	0.0116
Never	0.96	(0.648, 1.423)	0.3312	0.762	(0.482, 1.203)	0.8311
Current	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Body Mass Index						
Underweight	0.478	(0.051, 4.446)	4.446	0.197	(0.015, 2.625)	0.1106
Normal	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Overweight	0.906	(0.543, 1.511)	0.6108	0.977	(0.551, 1.732)	0.9197
Obese	2.906	(1.850, 4.565)	0.0006	4.102	(2.442, 6.89)	<.0001

Renal Disease			
Yes	1.207	(0.765, 1.904)	0.4186
No	*Reference*	*Reference*	*Reference*
Prior Surgery			
Yes	1.162	(0.812, 1.662)	0.4123
No	*Reference*	*Reference*	*Reference*
HIV			
Yes	1.187	(0.526, 2.683)	0.6795
No	*Reference*	*Reference*	*Reference*
Diabetes Mellitus			
Yes	0.885	(0.641, 1.223)	0.4594
No	*Reference*	*Reference*	*Reference*
Avascular Necrosis			
Yes	0.761	(0.455, 1.273)	0.2984
No	*Reference*	*Reference*	*Reference*
Revision			
Yes	1.134	(0.642, 2.001)	0.6647
No	*Reference*	*Reference*	*Reference*
Congestive Heart Failure			
Yes	0.695	(0.368, 1.315)	0.264
No	*Reference*	*Reference*	*Reference*
Coagulation Condition			
Yes	1.044	(0.586, 1.862)	0.8828
No	*Reference*	*Reference*	*Reference*

Table 4 – Full logistical model assessing positive CRP labs

Table 5 summarizes the results of the reduced model derived from stepwise regression. The most parsimonious model comprised of ESR, procedure type, smoking status, and BMI. The odds of a positive CRP test significantly increase by 1.061 for each unit increase in ESR (p-value < 0.0001; 95% CI: 1.046, 1.076).

Additionally, the odds of a positive CRP test are 2.014 times higher (p-value < 0.0001; 95% CI: 1.425, 2.845) in patients who underwent THA compared to those who underwent TKA Moreover, former smokers have 44.8% lower odds of a positive CRP test compared to current smokers (p-value = 0.0137; 95% CI: 0.336, 0.904).

Furthermore, patients classified as obese have significantly higher odds of having a positive CRP test (p-value < 0.0001). Specifically, the odds of a positive CRP test are 4.203 times higher in obese patients compared to those with a normal BMI (95% CI: 2.502, 7.059).

Table 5. Reduced Logistic Model Assessing Positive C-Reactive Protein Labs			
	Estimate	**95% Confidence Interval**	**P-Value**
Erythrocyte Sedimentation Rate	1.061	(1.046, 1.076)	<.0001
Procedure			
Total Hip Arthroplasty	2.014	(1.425, 2.845)	<.0001
Total Knee Arthroplasty	*Reference*	*Reference*	*Reference*
Smoking Status			
Former	0.552	(0.336, 0.904)	0.0137
Never	0.773	(0.492, 1.215)	0.8103
Current	*Reference*	*Reference*	*Reference*
Body Mass Index			
Underweight	0.193	(0.015, 2.542)	0.1015
Normal	*Reference*	*Reference*	*Reference*
Overweight	1.028	(0.582, 1.817)	0.8377
Obese	4.203	(2.502, 7.059)	<.0001

Table 5 - Reduced logistical model resulting from a stepwise regression assessing positive CRP

Discussion and Innovation:

To date, only a limited number of studies have investigated the relationship between preoperative ESR or CRP levels and their potential association with PJI. The literature reveals mixed results; some studies have found a positive correlation while others have found no correlation.[6,28,29,30,31,32] Xu et al. specifically examined TKA in osteoarthritis patients, reporting an overall prevalence of elevated preoperative inflammatory markers of 4.1% in their retrospective review of 3,376 cases. The rate of PJI was higher in patients with elevation of both CRP and ESR (12.5%) compared to either high (0.9%) or both normal groups (1.4%).[28] Pfitzner et al., in a retrospective review of 50 matched patients, found the average preoperative CRP level to be 1.3 mg/dL in the PJI group versus 0.4 mg/dL in the non-infected group. They recommended performing CRP testing on all patients before THA/TKA and suggested a threshold of 0.5 mg/dL, warranting further investigation into potential causes.[29] Although not specific to PJI, Ghosh et al. observed in their study that patients with high preoperative CRP levels (>3 mg/dL) may be at a heightened risk of developing complications after postoperative day 14.[31] Similarly, Ackland et al. noted in their study that patients with elevated preoperative CRP levels experienced increased rates of delayed post-operative complications and longer hospital stays.[32]

In a retrospective review of 351 TKAs, Godroy et al. reported no significant difference in CRP or ESR levels in association with any complications.[6] Within this cohort, there were a total of eight infections, two of which were classified as deep infections. In another study investigating preoperative CRP levels in patients undergoing hemiarthroplasty for femoral neck fracture, the overall infection rate was 4.85%.[30] However, their findings did not validate the use of CRP or propose a definitive threshold for the presence of pre-existing infection ahead of hemiarthroplasty for femoral neck fracture.[30]

Our study of 806 primary TJA cases (515 TKA, 291 THA), the second largest cohort to date exploring preoperative inflammatory markers before primary TJA, revealed no statistically significant association between elevation of preoperative CRP or ESR and development of PJI. The incidence of PJI was 2.1%. We did find that a higher incidence of patients with PJI had elevated preoperative CRP (70.6%) compared to those with normal CRP (29.4%); however, among patients without PJI, elevated preoperative CRP (>0.3 mg/dL) was still present in half of the cohort (49.7%). ESR showed a different pattern, with only 29.4% of patients with PJI having elevated preoperative ESR. In our whole data set over half of all patients (regardless of PJI status) had elevated preoperative CRP (50.1%), while only 17.3% of all patients had elevated ESR.

While our study of the correlation of preoperative CRP and ESR with PJI did not show statistical significance, the results do highlight an important finding. There is a significant proportion of patients in our data set with elevated preoperative CRP and ESR that undergo primary TJA without eventually developing a PJI. Given these findings, we investigated potential risk factors among our cohort of patients to see if there was a correlation. No study to date on the topic of TJA and preoperative CRP/ESR has investigated this, to our knowledge. Among all patients with elevated preoperative CRP or ESR, we identified a potential risk factor in 95.6% of cases. These risk factors

included current smoking status, increased BMI, positive urinalysis, diabetes mellitus, rheumatoid arthritis, HIV, renal disease, liver disease, CHF, and coagulopathy. We also differentiated between modifiable and non-modifiable risk factors. As such, 94.0% of the time, at least one *modifiable* risk factor was present, which we defined as increased BMI, positive urinalysis, and current smoking status. This can be explained by the fact that CRP/ESR serve as nonspecific markers of inflammation, often elevated in patients with chronic diseases involving a systemic inflammatory response. Watson et al. addressed this in a study focusing on idiopathically elevated CRP and ESR levels in patients undergoing primary TKA. They found a correlation between higher BMI and elevated preoperative CRP and ESR levels.[33] Our study reaffirms this correlation; patients categorized as obese (BMI >30) were more likely to exhibit elevated preoperative CRP levels (OR 4.2, $p < 0.0001$).

Lastly, **Table 2** displays an interesting finding. The presence of elevated CRP or ESR levels (**Table 2**) closely approaches statistical significance ($p = 0.0557$), suggesting a potential association with PJI. This underscores the importance of obtaining these preoperative laboratory values despite not reaching statistical significance, indicating some level of sensitivity in detecting potential correlations with PJI.

Even after identifying numerous potential risk factors for PJI development, there were still nearly 5% of cases in which there were no identifiable risk factors. This can likely be explained by the disease process of osteoarthritis itself inherently leading to an inflammatory response. Takahashi et al. investigated this, as their study demonstrated elevated CRP levels in patients with generalized osteoarthritis and a positive correlation between elevated inflammatory markers and the Kellgren-Lawrence scale of arthritis severity. [34] Similar findings were observed in a study examining CRP and ESR levels in patients with and without knee osteoarthritis, revealing a positive correlation between elevated ESR and CRP levels and higher Kellgren-Lawrence grades in patients with knee osteoarthritis. [35] To our knowledge, no literature has explored this concept in hip osteoarthritis, as both aforementioned studies were specific to knee osteoarthritis. In our study, we observed a slightly higher proportion of hip arthritis patients with elevated preoperative laboratory values compared to knee arthritis patients, with 54.6% of all patients undergoing THA exhibiting elevation in preoperative CRP levels, compared to 47.6% of all TKA patients.

Limitations of our study include its retrospective design and the relatively small number of total PJI cases (n=17). To definitively establish a correlation with PJI, a larger cohort of thousands of patients would be required to investigate a significant number of total PJIs. Nonetheless, our study highlights the significant proportion of patients exhibiting elevated preoperative inflammatory markers, with the majority not progressing to develop PJI following primary TJA. Improved documentation in future studies would be helpful for increasing sample size and thus achieving a high statistical power. This study did not address the frequency with which modifiable risk factors could have been identified and resolved prior to surgery. Inconsistent documentation, likely influenced by the retrospective nature of the study, rendered us unable to do so in our analysis. A prospective analysis might have enabled participating physicians to keep record of a dataset during surgeries, allowing for identification and

resolution of patients' modifiable risk factors. This data could hold clinical relevance when comparing postoperative outcomes in patients whose modifiable risk factors were addressed preoperatively versus those whose risk factors were not addressed prior to surgery.

Future Directions:

Future investigations should strive for high-powered studies to offer a more conclusive resolution on this topic since the results thus far has been mixed. Moreover, extended follow-up periods should be incorporated and exploration of additional complications (such as thromboembolic disease, stiffness, instability, and loosening) warrant investigation. Additionally, a high-powered, prospective study focusing on this topic could prove beneficial, as surgeons could monitor patients' acute modifiable risk factors and potentially postpone surgery until their resolution, thereby assessing any impact on the risk of PJI.

Conclusions:

This study does not validate the use of CRP and ESR as predictive indicators of future PJI risk in TJA. However, it offers quantitative insights into the prevalence of elevated preoperative inflammatory markers among all TJA patients, with a notable portion exhibiting modifiable risk factors. Despite this, some patients show elevated inflammatory markers without an identifiable cause, which may be attributed to the disease process of osteoarthritis itself. Given that nearly half of all patients studied had elevated CRP/ESR, a definitive recommendation regarding the necessity of preoperative labs cannot be made. However, considering the substantial proportion of patients with elevated inflammatory markers who do not develop PJI, routine cancellation of TJA is not advised unless there are identifiable modifiable risk factors increasing PJI risk.

Of note, in our analysis, upon excluding obesity as a modifiable risk factor, many previously significant findings became nonsignificant. This highlights the impact of obesity on inflammatory marker elevation, particularly CRP in cases where ESR was negative. Moreover, we found that elevation in either CRP or ESR approached statistical significance for correlation with PJI, possibly indicating some sensitivity for PJI development. Our study does not dispute the utility of CRP/ESR in diagnosing and treating PJI after TJA, as they remain two of the gold standard biochemical markers in this important and life-altering condition.

Compliance:

This chart review received approval from the North Texas Regional Institutional Review Board (IRB), with waiver of informed consent granted by the IRB under approval number 1354130-2. All PHI reviewed in this study adhered to the HIPAA regulations.

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