Periprosthetic infection risks and predictive value of C-reactive protein / albumin ratio for total joint arthroplasty

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Abstract. *Background and aim:* There are no gold standard markers to estimate the risk of developing periprosthetic infections. Our aim is to compare the risks of periprosthetic infection in patients with THA and THA and to investigate the predictive significance of the CRP / albumin ratio. *Methods:* This is a retrospective study containing data from 241 osteoarthritis patients and 19 patients with periprosthetic infections who underwent TKA and THA in our hospital from January 2014 to January 2019.12 risk factors(CRP/ albumin, albumin, CRP, age, gender, BMI, DM, ASA, nasal culture, urine culture, hospital stay, operation time) were analyzed. *Results:* In the binary logistic regression model and multivariate regression analysis, the rate of CRP / albumin was 17.161 times higher than the patients with ≤0.16 cut-off value. (CRP / albumin ratio (odds ratio (OR) = 17.16, 95% CI: 1.55-189.03, P: 0.02). High BMI increased the risk of periprosthetic infection 1.3 times. Nasal bacterial colonization (OR = 0.99, 95% CI: 0.868-1.38, P: 0.7) and bacterium in urine (OR = 0.502, 95% CI: 0.07-3.598, P: 0.703) did not pose a significant risk for periprosthetic infection. *Conclusion:* According to our findings, the CRP / albumin ratio has a more prognostic capacity than other risks in determining the risk of periprosthetic infection for total joint arthroplasty. CRP / albumin ratio is a cheap and easy to apply marker. Routine urine and nasal bacteria screening is not required before total joint arthroplasty.

Key words: CRP/ albumin ratio, periprosthetic infection, risk factors, total joint arthroplasty

Introduction

Total knee arthroplasty (TKA) and total hip arthroplasty (THA) are effective surgical procedures that improves the quality of life of patients with end-stage gonarthrosis and coxarthrosis. Total joint arthroplasty (TJA) is generally usually procedure with a low complication rate, but periprosthetic infection (PPI) is the most common and difficult to treat complication. Although periprosthetic infection rates have decreased recently because of antibiotic prophylaxis, new surgical techniques, and laminar airflow in operating theaters, the number of absolute infections is also increasing (1). The rate of periprosthetic infection is in primary THA 1.6%, and in primary THP is 0.2-1.1% (2).

Risk factors primary TJA surgery are nasal bacterial carriage, bacterium in urine, the patient's general medical condition (eg body mass index (BMI), additional diseases (diabetes mellitus(DM), heart failure and other diseases), trauma in the joint and prior surgeries(3). A recent study showed that the most important biodemographic factors that increase the risk of PPI after TJA are body mass index (BMI) and American Society of Anesthesiologists(ASA)(4). Nasal S.aureus carriage varies between 10-30% in the normal population (5,6). There is study in the literature showing that there is a risk of perioperative symptomatic urinary tract infection and increased PPI (7).

Serum C-reactive protein (CRP) is an acute phase reactant, and in the presence of infection, its amount in the blood increases (8). Unlike CRP, albumin is a

negative phase reactant that decreases during inflammation. The relationship between inflammation severity and low albumin has been demonstrated in the literature (9). Knowing the risk of PPI development early can facilitate the follow-up and early detection of the infection that may occur. An easy-to-apply and without additional costs scoring system may be needed to determine the PPI development risk rate. As far as we know, there is no study investigating the relationship of this marker with PPI risk in the literature. Our aim is to evaluate the risks of periprosthetic infections in TJA patients and compare them with the CRP / albumin ratio and to investigate the predictive importance of the CRP / albumin ratio.

Methods

This is a retrospective and observational study that includes data from 241 osteoarthritis patients who underwent TKA and THA in our hospital from January 2014 to January 2019. There were 19 patients in group 1 (patients who develop infections after TJA) and 222 patients in group 2 (patients who did not develop infection after TJA). Patient data included age, gender, operation time, length of hospital stay, blood values (pre-operative CRP (mg/dl) and albumin (g/dl)), BMI, nasal and urine cultures, American Society of Anesthesiologists (ASA) scores, additional diseases (DM), infection time (early, delayed and late), and culture results of infected TJA. The inclusion criteria were the absence of a history of infection in the joint, and primary joint arthroplasty. Patients with incomplete patient data, secondary osteoarthritis, and for any reason (trauma, cancer, and infection) previously had a history of surgical treatment in the joint were excluded.

All patients were routinely evaluated preoperatively. Anamnesis and clinical examination data were reviewed. Routine blood tests are performed before and after surgery, and urine and nasal cultures are taken. TKA was performed using standard medial parapatellar approach with using a tourniquet. THA was performed using either a direct lateral (modified Hardinge) or direct posterior (Kocher-langenbeck) approach. Antibiotic prophylaxis with 1 g of cefazolin every 8 hours was continued up to 48 hours after surgery. Clindamycin was given if the patient had a history of allergy to penicillin. One day after the operation, the drain was removed, muscle exercises were started and the patient was mobilized. All patients without any early complications were included in the physical therapy program at the 4th week after the operation. Clinical and radiographic follow-up was performed routinely in all patients at 2nd, 4th, 8th and 12th weeks after surgery.

The presence of PPI is defined according to the criteria of the international consensus(10). A certain PPI is present when: 1. A sinus tract associated with a prosthesis, or 2. A bacterial growth in 2 or more fluid or tissue cultures from an infected prosthetic joint, or 3. if there are 3 of 5 criteria: 1) increased serum ESR and serum CRP; 2) increased synovial white blood cell count, or ++ change in the leukocyte esterase test strip; 3) increased synovial polymorph nuclear percentage; 4) positive histological analysis of periprosthetic tissue; and 5) a single positive culture. PPIs were classified as "early" (first 3 months after surgery), "delayed" (between 3 months and 2 years after surgery) or "late" (more than 2 years after surgery) in terms of infection time(11).

The study was approved by the Ethics Review Committee of our faculty (187/04.06.2020). All data were obtained without a personal identification document and made in accordance with the Declaration of Helsinki regulation.

SPSS23.0 statistical software was used to analyze the measured data. Numerical data obtained in the study are shown as mean ± SD, (min-max), categorical data as frequency and percentage values. Chi-square test and Student test were used to compare categorical data. Univariate Binary Logistic regression analysis was used to determine the effects of potential prognostic factors on infection. The diagnostic separation of CRP / albumin in infection was examined by area under the curve (AUC) and ROC curve analysis (12). In statistical analysis, $P < 0.05$ was considered statistically significant with 95% confidence interval and 5% margin of error.

Results

56 (23.2%) of 241 patients were male and 185 (76.7%) were female. We had 19 (7.8%) patients

with periprosthetic infections. 12 patients had early, 6 patients had delayed and 1 patient had late periprosthetic infection. The distribution of patients according to TKA and THA are given in table 1 (Table 1).

In the nasal culture, 9 *Staphylococcus epidermidis* (SE), 1 *Moraxella Caterrhal*, 4 *Coagulase-negative Staphylococcus (*CNS), 7 *Methicillin Resistant Staphylococcus Aureus* (MRSA) and 2 methicillin-susceptible *S aureus* (MSSA) bacteria strains were produced. PPI developed in the patient whose CNS bacterium strain was growing in the nasal culture. In the wound culture, SE bacterium strain was grown. PPI developed in one patients who had SE bacterium strains in nasal culture. *Staphylococcus Haemolticus (SH)* strain of bacteria was grown in wound culture. In urine culture, 3 *Staphylococcus epidermidis*, 13 *E. Coli*, 3 *Klebsiella Pneumoniae*, 5 *Streptococcus Agalactiae* bacteria strains were grown. PPI developed in a patient whose E.Coli reproduced in urine culture. MRSA bacterial strain was produced in wound culture. PPI did not develop in a patient who produced SE in both urine and nasal cultures. In infected wound culture 1 *SH*, 5 MRSA, 2 MSSA and 3 *SE* bacterial strains were grown. No bacterial growth occurred in other infected cases.

Evaluation of univariate risk factors for PPI

CRP / albumin ratio (P: 0.01) and BMI (P <0.01) also showed a significant difference between group 1 and group 2 according to the Student T test. There was no significant difference between group 1 and group 2 according to Student T test in age (P: 0.07), albumin (P: 0.405), CRP (P: 0.101), hospital stay (P: 0.102)

and operation time (P: 0.507). There was no significant difference between group 1 and group 2 according to Chi-Square test for gender (P: 0.398), nasal culture, (P: 0.70), urine culture (P: 0.703) and DM (P: 0.06). There was a significant difference between group 1 and group 2 according to Chi-Square test in ASA (P: 0.03) (Table 2).

Cut off values periprosthetic infection

The cut-off value for the ratio of CRP / albumin to infection was 0.16. The area below the curve (AUC) was 0.664 (P: 0.018) with moderate accuracy. For CRP (P: 0.060), it was for albumin (P: 0.029). ROC analysis, AUC and P values are given in table 3. The AUC corresponding to CRP / albumin has proven to be the best indicator for PPI. Sensitivity and specificity were 0.68 and 0.56, respectively. Although there was broad AUC corresponding to CRP by itself, it was found that there was no significant indicator for PPI. We had 131 patients below the cut-off 0.16, and 5 of them had PPI. We had 110 patients above the cut-off 0.16, and 14 of them had PPI (P: 0.01).

Multivariate risk details of patients with PPI

In the binary logistic regression model and multivariate regression analysis, the rate of CRP / albumin was 17.161 times higher than the patients with ≤0.16 cut-off value. (CRP / albumin ratio (odds ratio (OR) = 17.16, 95% CI: 1.55-189.03, P: 0.02). CRP (OR = 2.4, 95% CI: 1.094-5.28, P: 0.028), albumin (OR = 0.291, 95% CI: 0.1-0.83, P: 0.021), BMI (OR =

Table 1. Patents data

	Total knee arthroplasty	Total hip arthroplasty
Gender	128f /19m	57f /37m
Age	64.5 years(range:38-76 years)	57.3(range:28-78 years)
ASA	75 ≤ ASA 2 / 72> ASA 3	60 ≤ ASA 2 /34> ASA 3
BMI	30.8 (range:21-38)	28.1(range:20-38)
Follow-up time	46.8 (range:17-76 months)	50.5(range:17-76 months)
Operation time	135.1±14.9 minutes	173.8±25 minutes
Hospital stay	4.1 days(range:2-12 days)	5.4 days(range:2-25 days)
Periprosthetic infection	14	5

Table 2. Comparison of risk factors between groups

	Group 1	Group 2	P value
CRP/ albumin	0.19±0.14	0.27±0.19	0.01
Albumin	3.32±0.4 g/dl	3.7±1.9 g/dl	0.405
CRP	0.91±0.6 mg/dl	0.66±0.44 mg/dl	0.101
Age	65.5±7.5 years	61.4±9.8 years	0.07
Gender	13f/6m	172f/50	0.398
BMI	33.1±2.7	29.3±3.9	<0.01
DM	7	12	0.06
ASA	6≤ ASA 2 / 13> ASA 3	129 ≤ ASA 2 / 93> ASA 3	0.03
Nasal culture	2	21	0.700
Urine culture	1	23	0.703
Hospital stay	6.8±5.9 days	4.4±2.2	0.102
Operation time	162.3±30.1 minutes	158.4±28.6 minutes	0.507

Table 3. Diagnostic evaluation of independent predictors of PPI by ROC curve analysis.

	Area Under the Curve				
	Test Result Variable(s): crp/alb ratio, crp and albumin respectively				
	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CRP/alb ratio	,664	,064	,018	,538	,790
CRP	,630	,067	,060	,499	,766
Albumin	,651	,063	,029	,528	773

ROC Curve

Diagonal segments are produced by ties.
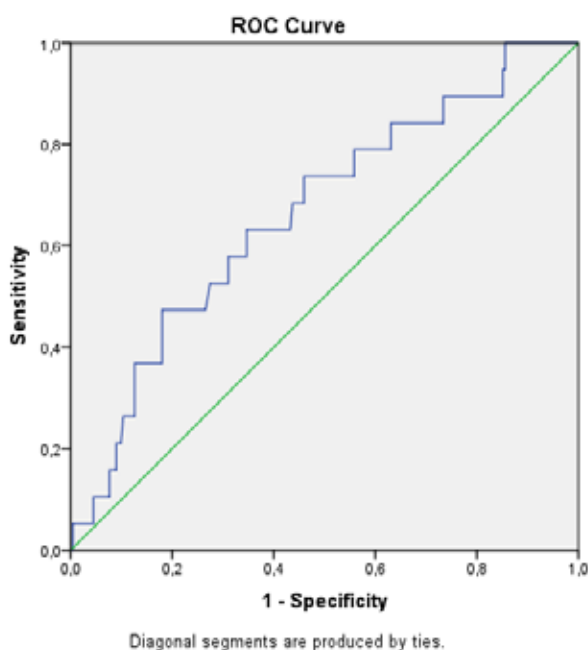
1.3, 95% CI: 1.14- 154, P <0.001), DM (OR = 0.365, 95% CI: 0.135-0.987, P: 0.04) and ASA (OR = 0.086, 95% CI: 0.06-1.12, P <0.001) were risk factures for periprosthetic infection. Nasal bacterial colonization (OR = 0.99, 95% CI: 0.868-1.38, P: 0.7) and bacterium in urine (OR = 0.502, 95% CI: 0.07-3.598, P: 0.703) did not pose a significant risk for periprosthetic infection.

Discusson

The primary finding of this study was found to be a prognostic marker in determining the risk of periprosthetic infection after TJA using the CRP / albumin ratio. CRP / albumin ratio correlated positively with important prognostic markers such as BMI, ASA score, DM, age, gender, bacterial colonization in

the nose, bacteria in the urine, length of hospital stay, serum CRP and albumin values.

Periprosthetic infection (PPI) refers to an infection involving the prosthesis and the tissues surrounding the implant (13). To prevent the most effective strategy against PPI. This strategy should include knowing the preoperative, intraoperative and postoperative risks. Acute infection, inflammatory disease, kidney disease, liver disease and malnutrition are caused by hypoalbuminemia (14). Greene et al. (15) showed that albumin less than 3.5 g / dl preoperatively increased the risk of PPI 7 times after arthroplasty operations. Huang et al.(16) showed in a prospective study of 2161 patients that low albumin level due to malnutrition was not a risk for PPI. In our study, there was no significant relationship between low albumin levels and PPI.

Previous study found that CRP increased slightly in patients with knee and hip osteoarthritis (17). Windish et al. (18) found the preoperative values of CRP as a risk factor for PPI after TKA. Using the CRP / albumin ratio will provide a variable that can combine information created by CRP and albumin in an index that positively correlates with the infection, i.e. a high ratio indicates high inflammation (19). Increased CRP / albumin ratio has been reported to increase hospital mortality in patients with sepsis and cancer and correlate with poor prognosis (20,21). Iwata et al. (22) showed that the increasing CRP / albumin ratio in elderly patients increases the mortality rate in the hospital. Kobayashi et al. (23) found that increased CRP / albumin ratio after spinal instrumentation surgery increased the risk of infection in the surgical field with 57% sensitivity and 90% specificity. In our study, no significant relationship was found between CRP alone and periprosthetic infection. This study showed that the increased CRP / albumin ratio after TJA surgery increased the risk of periprosthetic infection by 17.16 times with 68% sensitivity and 56% specificity and was a prognostic marker. However, new studies are needed to confirm the correlation between PPI risk and CRP / albumin ratio.

Up to one-third of people have S. aureus colonization, most commonly on the nose, skin, and in other parts of the body (6). Skråmm et al. (24) showed that the S aureus colony produced in infected tissue

has genetic features similar to that of strain isolated from the nose. Thus, he claimed that nasal colonization increased the risk of postoperative infection. In the literature, effective iodine or chlorhexidine-based agents or antibiotic therapy are recommended for nasal decolonization based on perioperative nasal culture results (6). In a meta-analysis, Xingyang et al.(25) claimed that S. aureus screening and decolonization decreased the risk of PPI after the primary TKA and THA. None of our patients, whose bacteria were grown in nasal and urine cultures, did not grow the same bacteria in wound cure. We think that nasal colonization is dependent on the patient's environmental conditions, and after the patient is discharged, she/he is exposed to the same environmental conditions, so nasal colonization develops again. Therefore, we did not perform pre-operative decolonization. In our study, the most isolated bacterial strain was Staphylococcus epidermidis different from the literature.

Singh et al. (26) reported increased early complication rates after TKA in women with or without positive urine culture. A study of more than 20,000 patients who underwent total joint arthroplasty found that positive urine culture did not increase the risk of PPI (27). Asymptomatic bacteriuria (ASB) is the presence of bacteria obtained in a urine sample without a urinary infection. It has been shown that ASB varies between 3-19% in patients with total joint arthroplasty (28). We did not apply antibiotic treatment before surgery in patients with positive urinary culture without active urinary complaints. One of 24 patients who had positive urine cultures developed PPI. Another type of bacteria grew in the wound culture of the patient.

Si et al.(29) found that in patients with BMI above 30 kg / m2, the risk of PPI infection increased, and the most risky patients are those with BMI> 40 kg / m2. This is because obese patients take longer operations, hematoma and wound problems are more common, and mobilization becomes more difficult. Wound healing in patients with DM is impaired because microangiopathic pathologies occur, which reduces tissue concentrations and tissue oxygen levels of antibiotics. The rate of PPI in diabetic patients has been reported 3-6 times higher than in non-diabetic patients (30). Jämsen et al. (4) demonstrated that glycemic control is effective in preventing infection in the surgical site.

Claus et al. (31) detected higher postoperative PPI in TKA when ASA grade increased. Namba et al. (32) detected a significant relationship between PPI ratio and ASA grade. Most of our patients had a high ASA score and we found a significant relationship between ASA score and PPI. In our patients with DM, we did not have a significant relationship with the development of PPI in our study, since we successfully provided glucose control for a long time. In our study, the mean BMI indices of our patients were high and we found that high BMI increased the risk of periprosthetic infection 1.3 times.

There are some limitations in our study. As in most retrospective studies, it is a study of 241 patients due to the problem of finding data. It is also a single-center and small group study that can limit the prognostic value of the CRP / albumin ratio. In addition, the rate of infection in our study is higher than in the literature, which may explain why BMI and DMI risk results are not compatible with the literature. Finally, additional studies are required for the prognostic marker value of the CRP / albumin ratio.

Conclusion

According to our findings, the CRP / albumin ratio has a more prognostic capacity than other risks in determining the risk of periprosthetic infection for total joint arthroplasty. CRP / albumin ratio is a cheap and easy to apply marker. Routine urine and nasal bacteria screening is not required before total joint arthroplasty.

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