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Original article

Evaluation of the serum level of C-reactive protein for diagnosing acute periprosthetic infection after total knee arthroplasty

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Abstract

Objective: To determine the serum level of C-reactive protein (CRP) with greater accuracy for diagnosing acute periprosthetic infection after total knee arthroplasty (TKA). Method: Case-control study evaluating serum levels of CRP after TKA in infected and uninfected groups. The serum levels of CRP were assessed in patients submitted to TKA who had been readmitted in the acute phase for surgical debridement with implant retention and had their diagnosis of periprosthetic infection confirmed. These values were compared with a control group, which did not present infectious complications. Results: Between March 2014 and March 2016, 1,373 TKAs were performed in the institution, and 28 patients (0.49%) were readmitted in the acute phase with a diagnosis of periprosthetic infection. Sixteen patients met the inclusion criteria. Gender, skin color, age, and body mass index (BMI) were similar between the groups. The patients in the acute periprosthetic infection group had significantly higher mean serum levels of CRP than the control group ($p<0.001$). For CRP levels = 30.615, the test's highest sensitivity (75%) and specificity (77%) were achieved, with an accuracy of 77.3% for the diagnosis of infection. The area under the 0.762 Receiver Operating Characteristics (ROC) curve showed satisfactory performance of the proposed test. Conclusion: Serum levels of CRP greater than 30.615 mg/L in the third week after TKA associated with clinical signs are highly suggestive of acute periprosthetic infection.

Keywords: Knee; Osteoarthritis; Arthroplasty; Infection; CRP.

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Introduction

Total knee arthroplasty (TKA) is a surgical procedure to treat advanced cases of osteoarthritis, from refractory to conservative treatment. Its effectiveness and safety are widely proven in the literature.[1-5]

Increases in life expectancy[6] and the growth of obesity[7] have exponentially increased the demand for TKAs. Since the end of the 1980s, the number of surgeries performed in the United States (USA) rose by up to 10% per year.[4] As a result, between 1990 and 2002, the number of TKA per 100,000 inhabitants tripled.[4]

In 2019, more than 13,000 knee prostheses were implanted in Brazil, and this number is expected to increase exponentially, driven by increased longevity and growth of obesity.[3] Although the clinical satisfaction rate can reach up to 92% of operated patients,[1-3], complications occur in between 0.4%[8] and 7% of cases.[3,9,10] Among the difficulties, infection is the most frequent and feared, accounting for up to 25.2% of revisions and reaching mortality rates of 18%.[11] In addition, the cost of treating a prosthesis-associated infection is about three to four times the value of a primary arthroplasty.[11]

The diagnosis of infection after TKA is difficult in the immediate postoperative period since clinical signs, such as edema and erythema, can occur even in a normal postoperative period.[12] In addition, laboratory tests traditionally used to diagnose periprosthetic infections, such as C-reactive protein (CRP) and serum erythrocyte sedimentation rate (ESR), are usually elevated in the immediate postoperative period.[13] Early diagnosis allows treatment with surgical debridement and implant retention (D+R), a less aggressive strategy, with lower cost and a success rate of up to 36%,[14] as long as it is performed until the third week.[15] Although serum

CRP is part of the periprosthetic infection protocol,[16] its level may be altered without any relation to infection in up to two-thirds of patients.[17]

The objective of this study was to determine the serum value of CRP with greater accuracy to assist in the diagnosis of acute periprosthetic infection after TKA.

Materials and methods

After the approval by the institution Ethics and Research Committee under number 804.216, the medical records of all hospitalized patients diagnosed with acute periprosthetic infection between March 2014 and March 2016 were evaluated retrospectively and for convenience.

The study included all patients submitted to TKA who evolved to acute postoperative infection within 30 days after surgery and required surgical intervention. The diagnosis of periprosthetic infection was confirmed according to the criteria established by the Center for Disease Control (CDC).[18]

Patients who did not have a diagnosis of infection confirmed by the results of the cultures obtained intraoperatively, who had been diagnosed for over 30 days, or with incomplete data in the medical record were excluded.

A control group was created, consisting of 103 patients submitted to TKA, with the same pre- and postoperative protocol, the same surgical technique, and who did not present infectious complications.

Data on age, gender, BMI, and ethnicity were obtained from all patients. In the "case" group, both the CRP value and the postoperative interval to collect the CRP that led to reoperation were recorded. In addition, preoperative CRPs on the third and 21st postoperative days were evaluated in the control group.

Quantitative CRP, evaluated in a 2 mL sample of venous blood, was used for analysis, which was performed in the institution's laboratory. The turbidimetric method was used in the BT3000 *Plus* ® biochemistry analyzer (Wiener Lab – Rosario, Santa Fe, Argentina), with reference levels in adults of 5 mg/L for infectious diseases.

The data collected were analyzed using the Statistical Package for the Social Science (SPSS) program, version 22.0, and Microsoft Excel 2011. The data were synthesized for sample characterization and descriptive analysis of the variables' behavior by calculating descriptive statistics (mean, median, minimum, maximum, standard deviation, coefficient of variation, proportions of interest), distributions of simple frequencies, and cross tables and descriptive graphs.

The Receiver Operating Characteristics (ROC) curve was used to identify an optimal CRP cutoff point for diagnosing the infection. The performance measure of the diagnostic test proposed using this cutoff point was the area under the ROC curve, and the significance of this area was evaluated by the test that judges the null hypothesis H0: the area under the ROC curve is equal to 50. Under the null hypothesis, the proposed test has no power to discriminate between infected and uninfected individuals and is therefore expected to reject H0. In addition to the significance test, an asymptotic confidence interval was obtained for the area under the ROC curve, which was expected not to contain the value of 0.5. The data were analyzed considering a maximum significance level of 5%.

Results

Between March 2014 and March 2016, 1,373 primary knee TKAs were performed. Twenty-eight readmissions (0.49%) occurred with a diagnosis of acute periprosthetic infection and indication for surgical debridement and implant retention. After the application of inclusion and exclusion criteria, 16 patients were selected for the study.

The statistical analysis showed that the case and control groups were similar in gender ($p = 0.535$), age ($p = 0.833$), skin color ($p = 0.264$), and BMI ($p = 0.453$) (Figures 1 and 2).

Table 1 shows the main CRP statistics of infected and uninfected patients. Both groups show a high variability of values, as shown by the sample amplitude and coefficients of variation. However, the mean and median values of the infected group are higher ($p = 0.001$) (Figure 3).

The ROC curve identified as the optimal cutoff point the CRP level equal to 30.615 mg/L, where sensitivity and specificity simultaneously reach their highest level (Figure 4).

The test based on the proposed cutoff point has sensitivity equal to 0.75 and specificity equal to 0.777. Therefore, the accuracy of the proposed test is 77.3%. In addition, the proportion of false negatives is equal to 25.0%.

In this analysis, the area under the ROC curve was 0.762, showing satisfactory performance of the proposed test with the new CRP cutoff point. Table 2 shows the significance analysis of this area under the curve.

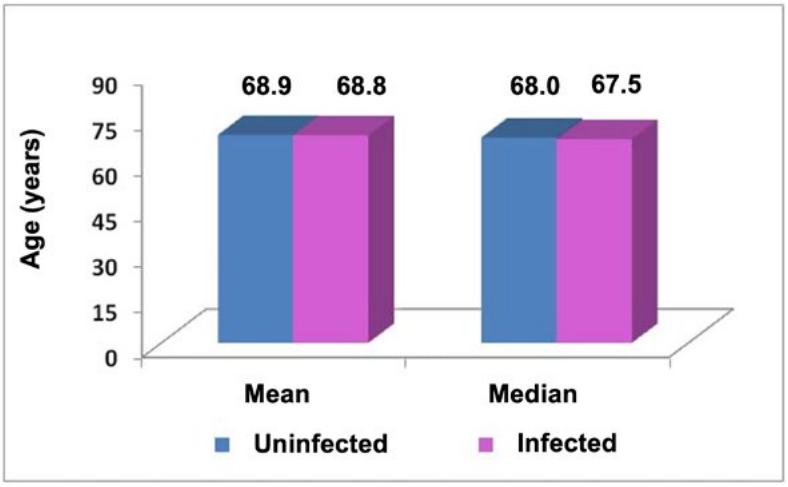

Figure 1. Mean and median ages of uninfected and infected patients
Source: The authors (2022).

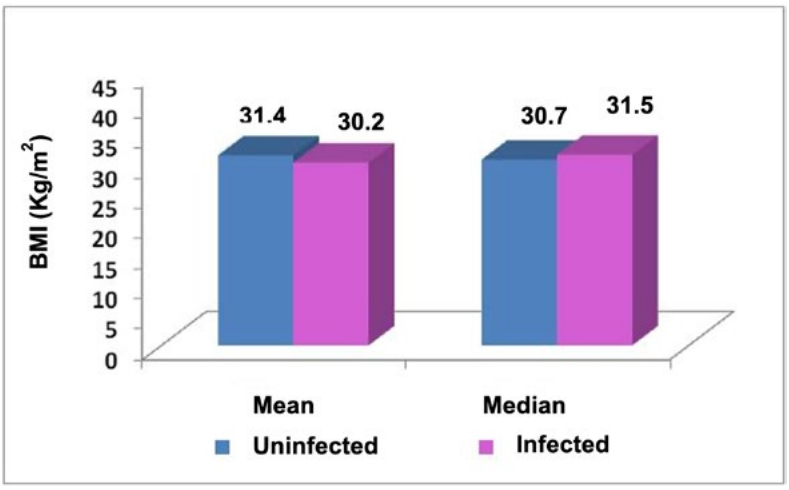

Figure 2. Mean and median BMI of uninfected and infected patients
Source: The authors (2022).

Table 3 shows, for different values of CRP cutoff points, the measures of false positive, sensitivity, and specificity, resulting in tests with stricter and less strict criteria. The serum level of CRP of 30.615 mg/L is the one that presented the greatest balance between sensitivity and specificity.

Discussion

Increased life expectancy and the desire for greater activity, associated with favorable results, have motivated the increased demand for TKA surgeries in recent years. Unfortunately, however, the number of complications continues to rise in equal proportion.

The diagnosis of infection after knee arthroplasty in the immediate postoperative period is particularly difficult since clinical signs can occur even in the normal postoperative period.[13] The laboratory tests traditionally used for diagnostic of periprosthetic infections, such as CRP, are usually elevated in the immediate postoperative period.[12]

The definition and performance of studies on this subject in Brazil are important in order to adopt

Table 1. Main CRP statistics in the infected and uninfected groups

CRP Statistics	Uninfected	Infected
Mean	27.4	57.3
Median	15.4	39.1
Standard deviation	36.9	49.4
Minimum	0.7	5.4
Maximum	263.9	154.0
Sample amplitude (Range)	263.2	148.6
CV	1.4	0.9
p-value of KS test	0.000	0.029
p-value of SW test	0.000	0.003
p-value of Mann Whitney test	0.001	

Legend: CV: Coefficient of variation. KS test: Kolmogorov–Smirnov test. SW test: Shapiro-Wilk test.
Source: The authors (2022).

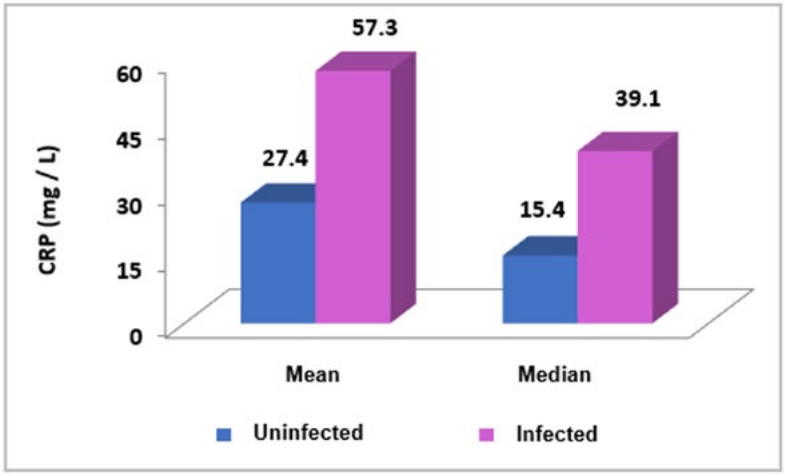

Figure 3. Mean and median CRP dosages in uninfected and infected patients
Source: The authors (2022).

specific protocols for diagnosing and treating acute postoperative infections after TKA.

Barreto and colleagues[17] evaluated CRP levels in 103 patients undergoing primary TKA. Serum CRP was measured on the day before surgery, as well as on the third and 21st days after the procedure. There was a sudden increase on the third day after surgery, reaching a mean value of 111.9 mg/L, with a median of 75.9 mg/L. Two-thirds of the patients maintained above normal values of serum CRP at the end of the third week. This alteration was not related to infectious complications but to surgical trauma. As this is a quantitative examination, it is important to define a value that presents greater safety for diagnosing acute periprosthetic infection and helps to indicate the need for a new surgical intervention. Our results showed that the value of 36.615 mg/L would be the most reliable for suspecting periprosthetic infection.

Greidanus and colleagues[19] suggest that the serum level of CRP is a good test for establishing the presence

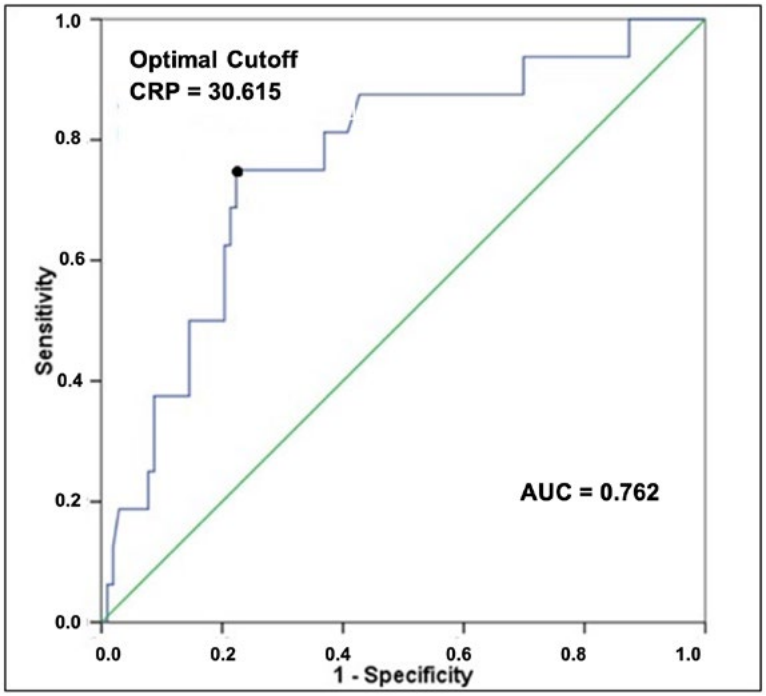

Figure 4. Mean and median CRP dosages in uninfected and infected patients
Source: The authors (2022).

Table 2. Significance analysis of the area under the ROC curve

Area under the ROC curve	Standard error	Asymptotic p-value	Asymptotic confidence interval for the area under the curve	
			Inferior limit	Upper limit
0.762	0.065	0.001	0.636	0.889

Source: The authors (2022).

or absence of infection before surgical intervention in patients with pain at the site of knee arthroplasty. However, this study evaluated the role of CRP in chronic infections and not in the acute scenario, as in our study.

Paul and colleagues[20] evaluated the ideal CRP cutoff point after arthroplasties in the immediate postoperative period (within six weeks of surgery). They showed that adopting a CRP cutoff point of 93 mg/L has ideal sensitivity. However, their study evaluated patients undergoing total hip arthroplasty and not TKA, as in our study. Since these surgeries are different, it is to be expected that the specific level for postoperative follow-up of knee arthroplasty will have a different cutoff point.

Bedair and colleagues[12] established guidelines for diagnosing infection after TKA in the immediate postoperative period (first six weeks after surgery). In addition, they demonstrated that adopting a CRP cutoff point of 95 mg/L has ideal sensitivity, being substantially higher than those previously published for late periprosthetic infections.[13,21-23]

Cipriano and colleagues[24] suggested a lower CRP cutoff point in patients who underwent knee prosthesis that evolved into periprosthetic infection. The levels found were 15 and 17 mg/L for non-inflammatory and inflammatory arthritis, respectively, with an area under the curve of 88.5% and 85.1%. Unlike our study, these authors did not investigate CRP cutoff levels specific

Table 3. CRP cutoff points for tests with stricter and less strict criteria

	CRP cutoff point	Specificity	Sensitivity	Specificity
Less strict criteria →	0.000	1.000	1.000	0.000
	3.780	0.942	1.000	0.058
	5.060	0.883	1.000	0.117
	6.355	0.825	0.938	0.175
	7.410	0.767	0.938	0.233
	9.730	0,709	0.938	0.291
	11.275	0.660	0.875	0.340
	13.085	0.602	0.875	0.398
	15.000	0.524	0.875	0.476
	17.510	0.456	0.875	0.544
	19.560	0.388	0.813	0.612
	22.860	0.340	0.750	0.660
	26.165	0.282	0.750	0.718
Optimal point	30.615	0.223	0.750	0.777
← Stricter criteria	35.080	0.204	0.500	0.796
	43.000	0.146	0.500	0.854
	55.070	0.107	0.375	0.893
	75.010	0.078	0.188	0.922
	148.000	0.019	0.125	0.981
	264.900	0.000	0.000	1.000

Legend: CRP: C-reactive protein.
Source: The authors (2022).

to acute or chronic infection cases, which may explain the differences between the studies.

Glehr and colleagues,[25] using a CRP cutoff of 23.65 mg/L to diagnose acute infections after knee or hip prostheses, found 80% sensitivity and 79% specificity for the test. The same study suggests that other tests, such as the serum dosage of procalcitonin and IL-6, may help to detect infection in arthroplasty revisions.

In their cohort, Kim and colleagues[26] reported that 13% of patients undergoing primary TKA evolved with a so-called bimodal pattern of increased serum CRP (elevation-depression-elevation) in the first four weeks after operation. However, they concluded that this increase might occur in similar proportions for causes other than periprosthetic infection, so it is necessary to investigate them in a scenario of acute infection after TKA.

Early diagnosis of a periprosthetic infection increases the chances of successful treatment. The performance of the implant debridement and retention procedure (D+R) with polyethylene replacement has a probability of success between 38 and 48%. In addition, if a two-stage revision is necessary, the earlier the diagnosis, the better the result, as demonstrated by Olubsola and colleagues.[26] They showed that the success rate after the two-stage revision procedure in patients submitted to D+R is significantly higher than in those submitted to sequential revision, with failures of 8.7% in the first group versus 17.5% in the second.

This is the first Brazilian study on the subject. A positive aspect of our research is the significant number

of patients, since it addresses a specific and relatively uncommon complication. In addition, the aid of an objective criterion in diagnosing acute infection is extremely desired and awaited by surgeons who perform arthroplasties. The limitations of the research are related to the fact that it is a retrospective study, since the approach protocols have been changed over time, leading to a high rate of exclusion. Nevertheless, we believe that these results can consistently assist in creating future algorithms that increase the reliability of the use of serum CRP in diagnosing acute periprosthetic infection.

Conclusion

Serum levels of CRP higher than 30.615 mg/L in the third week after TKA associated with clinical signs are highly suggestive of acute periprosthetic infection.

Acknowledgments

Study performed at the *Centro de Cirurgia do Joelho, Instituto Nacional de Traumatologia e Ortopedia* (INTO), Rio de Janeiro, RJ, Brazil.

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