

Serum C-reactive protein relationship in high- versus low-virulence pathogens in the diagnosis of periprosthetic joint infection

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Abstract

Little is known about the relationship between the virulence of pathogens in periprosthetic joint infection (PJI) and C-reactive protein (CRP) levels. In this context, we assessed the performance of CRP for PJI. We collected the following data from 987 cases of total joint revision due to PJI and 386 cases of aseptic revision: age, gender, comorbidities, values for serum CRP, leukocytes, microbiology for preoperatively taken aspirations and at least 2 intraoperative biopsies, and presence or absence of a draining sinus. The mean CRP value in the PJI group was 50.2 mg l⁻¹ (SD=62.2), while a lower CRP value of 11.6 mg l⁻¹ (SD=25.3) was found in the control group. There were no significant differences for the CRP values between patients with and without draining sinus ($P=0.4423$). The difference in CRP between high-virulence and low-virulence micro-organisms was significant for both the hip and the knee ($P<0.0001$). For the hip, the area under the receiver operating characteristic curve (AUC) of CRP as a diagnostic marker for PJI was 0.830 and, for the knee, the AUC was 0.884. The optimal cutoff point for CRP as a diagnostic marker of PJI, calculated using Youden's index, was 8.90 mg l⁻¹ for the hip and 9.99 mg l⁻¹ for the knee. The study results add valuable new information regarding the organism profile that may help with the diagnostic workup and with the research and development of new strategies for diagnosing and treating PJI.

INTRODUCTION

C-reactive protein (CRP) and other serum markers, such as erythrocyte sedimentation rate (ESR) and white blood cells (WBCs), have long been considered to be part of the diagnostic workup for periprosthetic joint infection (PJI). In an attempt to standardize the definition of PJI for clinical and research purposes, the Musculoskeletal Infection Society (MSIS) published their criteria for PJI, which include two major and five minor criteria, with CRP as a minor criterion [1]. Although more accurate and more specific methods are available for the diagnosis of PJI, such as the alpha-defensin test, CRP measurement remains an important component of the diagnostic procedures. This is due to its wide availability and lower cost. In comparison

to more invasive methods using synovial fluid aspiration, it is the first choice from a clinical perspective.

However, there are certain aspects to consider when using CRP as a marker for PJI diagnosis. CRP can be influenced by comorbidities such as rheumatoid arthritis, smoking and chronic or acute infections. It is also elevated in the postoperative setting. In contrast to a false-positive elevated CRP level, there is the fear of misdiagnosing a PJI due to moderate or non-elevated CRP (false negative), especially in chronic infections [2].

Few studies assessing the diagnostic value of CRP in verified chronic PJI based on the MSIS major criteria are currently available. Moreover, little is known about the relationship

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Abbreviations: AUC, area under curve; CNS, coagulase-negative staphylococci; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; FN, false negative; FP, false positive; HIPAA, Health Insurance Portability and Accountability Act; LR, likelihood ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; MSIS, Musculoskeletal Infection Society; NPV, negative predictive value; PJI, periprosthetic joint infection; PPV, positive predictive value; ROC, receiver operating characteristics; SD, standard deviation; SE, sensitivity; SP, specificity; WBC, white blood cells.

Table 1. Characteristics of patients in the PJI group

	Female	Male	Overall
<i>n</i>	464	523	987
Age [mean (SD)]	68.7 (10.4)	67.1 (10.1)	67.8 (10.2)
BMI [mean (SD)]	28.2 (5.9)	28.2 (4.2)	28.2 (5.2)
Joint=hip/knee (%)	290/174 (62.5/37.5)	348/175 (66.5/33.5)	638/349 (64.6/35.4)
Sinus (%)			
No Sinus	166 (35.8)	143 (27.3)	309 (31.3)
Sinus	44 (9.5)	41 (7.8)	85 (8.6)
NA	254 (54.7)	339 (64.8)	593 (60.1)
Oxacillin sensitivity (%)			
Oxacillin-resistant	131 (28.2)	147 (28.1)	278 (28.2)
Oxacillin-sensitive	154 (33.2)	169 (32.3)	323 (32.7)
NA	179 (38.6)	207 (39.6)	386 (39.1)
CRP [mean (SD)]	55.7 (70.0)	45.3 (54.0)	50.2 (62.2)
WBC [mean (SD)]	7.9 (2.8)	8.0 (2.5)	7.9 (2.6)
Haemoglobin [mean (SD)]	11.9 (4.1)	12.8 (1.8)	12.4 (3.2)
Intraoperative biopsy (%)			
<i>Candida albicans</i>	1 (0.2)	2 (0.4)	3 (0.3)
Coagulase-negative staph.	35 (7.5)	65 (12.4)	100 (10.1)
<i>Corynebacterium</i>	1 (0.2)	2 (0.4)	3 (0.3)
<i>Escherichia coli</i>	10 (2.2)	4 (0.8)	14 (1.4)
<i>Enterobacter</i>	6 (1.3)	2 (0.4)	8 (0.8)
<i>Enterococcus</i>	34 (7.3)	31 (5.9)	65 (6.6)
Multi-organism	21 (4.5)	26 (5.0)	47 (4.8)
Negative	99 (21.3)	104 (19.9)	203 (20.6)
Other	9 (1.9)	4 (0.8)	13 (1.3)
<i>Peptostreptococcus</i>	6 (1.3)	8 (1.5)	14 (1.4)
<i>Propionibacterium</i>	25 (5.4)	41 (7.8)	66 (6.7)
<i>Proteus mirabilis</i>	1 (0.2)	1 (0.2)	2 (0.2)
<i>Pseudomonas</i>	8 (1.7)	2 (0.4)	10 (1.0)
<i>Salmonella</i>	1 (0.2)	1 (0.2)	2 (0.2)
<i>S. aureus</i>	50 (10.8)	47 (9.0)	97 (9.8)
<i>S. epidermidis</i>	124 (26.7)	157 (30.0)	281 (28.5)
<i>Streptococcus</i>	33 (7.1)	26 (5.0)	59 (6.0)

between the virulent behaviour of PJI bacteria and CRP levels. Chronic PJIs with bacteria considered to be a low virulence are often also related to low CRP levels [2, 3].

Therefore, we conducted a single-centre retrospective clinical study to determine the role of CRP measurements

in PJI. This study was designed to answer the following questions. (1) What is the sensitivity, specificity, and negative and positive predictive value of CRP in PJI? (2) Is there any difference in CRP levels between low-virulence and high-virulence micro-organism? (3) Is the

Table 2. Characteristics of patients in the aseptic group

	Female	Male	Overall
<i>n</i>	182	164	346
Joint=ip/knee (%)	90/92 (49.5/50.5)	75/89 (45.7/54.3)	165/181 (47.7/52.3)
Side=left/right (%)	105/77 (57.7/42.3)	88/76 (53.7/46.3)	193/153 (55.8/44.2)

presence of a draining sinus associated with a lower CRP level?

METHODS

Study design and inclusion and exclusion criteria

The following study was approved by an institutional review board and the Hamburg Medical Chamber Ethics Committee. The study was carried out in accordance with the World Medical Association Declaration of Helsinki. Patient confidentiality was appropriately protected according to German federal law and the US Health Insurance Portability and Accountability Act (HIPAA).

In this retrospective study, we included patients who were treated for PJI between January 2001 and June 2016. They were identified by electronic database query. A total of 1044 cases of patients treated with a septic exchange arthroplasty of the hip or knee joint were identified. Twenty-two patients had more than one case of PJI over the years or a PJI in more than one joint, meaning that a total of 1022 patients had experienced septic revision arthroplasty. All patients were diagnosed according to the standard preoperative protocol of ENDO-Klinik [4] and then selected for aseptic revision or septic exchange. All identified PJI patients with an existing preoperative CRP value were included in this study. Patients without serum CRP levels and patients younger than 18 years were excluded from the study. Additionally, patients were excluded if they were smokers; had any rheumatoid diseases, such as rheumatoid arthritis or psoriasis; had any malignant tumours; or had other infections, such as pneumonia or urinary tract infection. Patients who had suffered a major trauma or had undergone surgery 6 weeks prior to admission were also excluded. In total, 987 patients met the inclusion and exclusion criteria and were included in the study. From the same time interval, we randomly selected a group of 346 patients who had undergone an aseptic revision arthroplasty at our institution. The same inclusion and exclusion criteria were used for the control group.

Table 3. Micro-organisms identified from the intraoperative biopsy classified according to their virulence

	High virulence	Low virulence	Negative biopsy	Other micro-organisms
<i>n</i>	383	388	203	13
Intraoperative iopsy (%)				
<i>Candida albicans</i>	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Coagulase-negative staph.	100 (26.1)	0 (0.0)	0 (0.0)	0 (0.0)
<i>Corynebacterium</i>	0 (0.0)	3 (0.8)	0 (0.0)	0 (0.0)
<i>E. coli</i>	0 (0.0)	14 (3.6)	0 (0.0)	0 (0.0)
<i>Enterobacter</i>	0 (0.0)	8 (2.1)	0 (0.0)	0 (0.0)
<i>Enterococcus</i>	65 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multi-organism	47 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)
Negative	0 (0.0)	0 (0.0)	203 (100.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	13 (100.0)
<i>Peptostreptococcus</i>	0 (0.0)	14 (3.6)	0 (0.0)	0 (0.0)
<i>Propionibacterium</i>	0 (0.0)	66 (17.0)	0 (0.0)	0 (0.0)
<i>Proteus mirabilis</i>	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)
<i>Pseudomonas</i>	10 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)
<i>Salmonella</i>	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
<i>S. aureus</i>	97 (25.3)	0 (0.0)	0 (0.0)	0 (0.0)
<i>S. epidermidis</i>	0 (0.0)	281 (72.4)	0 (0.0)	0 (0.0)
<i>Streptococcus</i>	59 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)

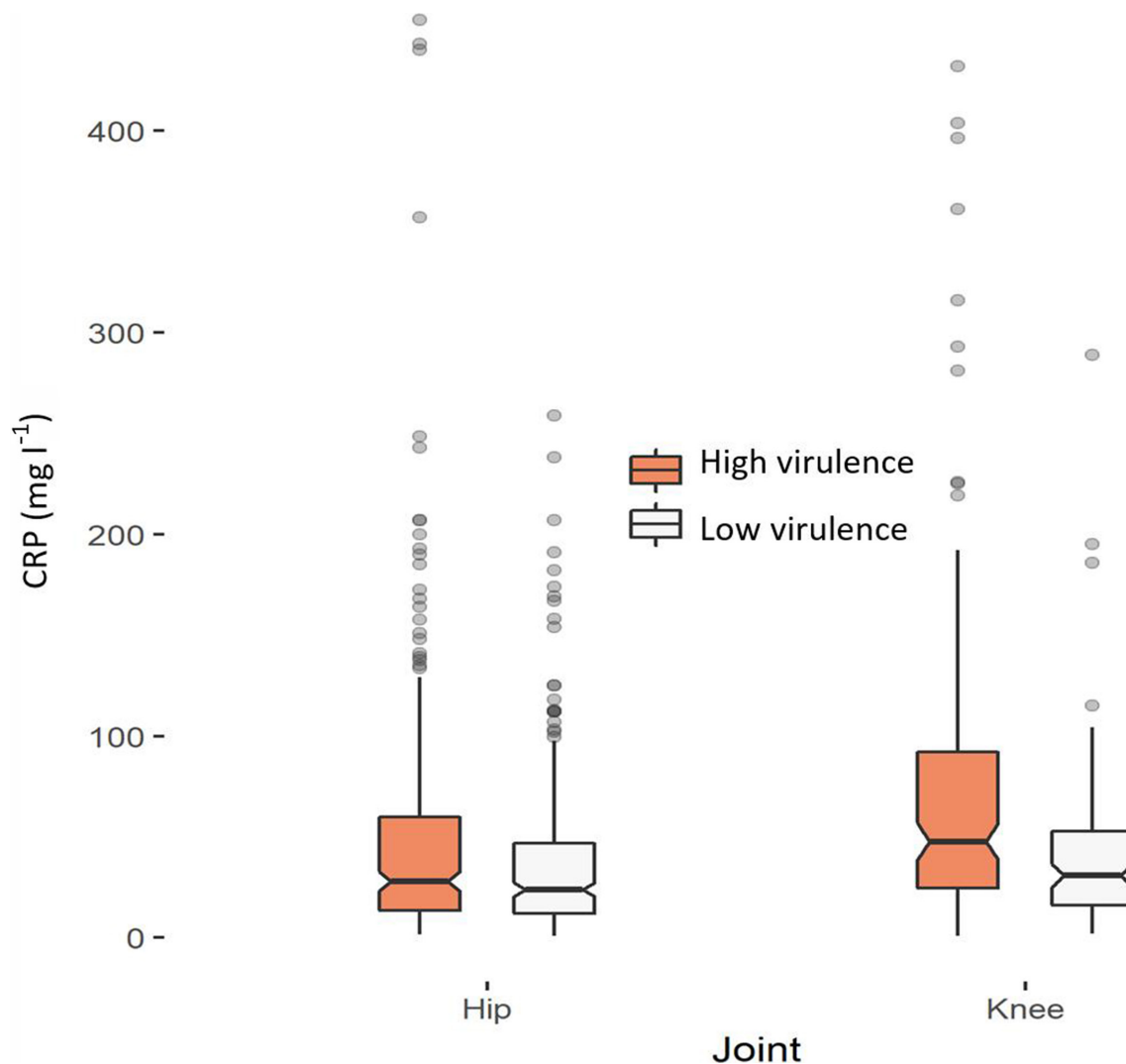


Fig. 1. Box plots showing the CRP values in cases of infection with high-virulence compared to low-virulence micro-organisms.

Patients' charts were reviewed to obtain the following information: age, gender, comorbidities, surgical history, clinical findings (presence of draining sinus), microbiological findings and laboratory tests, including serum CRP at admission. The threshold for elevated serum CRP was greater than 10 mg l^{-1} according two published meta-analyses [5, 6]. In all septic cases, the pathogens were divided in high-virulence pathogens [*Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), pseudomonas, enterococci, streptococci, candida] and low-virulence pathogens (propionibacterium, coagulase-negative Staphylococci (CNS), including *Staphylococcus epidermidis*).

Statistical analysis

All variables were expressed in terms of the mean and the standard deviation (SD) of the mean. To assess the diagnostic performance of serum CRP statistically, the specificity (SP), sensitivity (SE), positive predictive value (PPV), negative predictive

value (NPV) and area under the receiver operating characteristic curve (AUC) were calculated. The differences in CRP between high- and low-virulence micro-organisms and patients with and without draining sinus were calculated using the Wilcoxon rank-sum test. Statistical significance for the analyses was set at a *P* value less than 0.05. All analyses were conducted using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 1333 (987 PJI cases, 346 aseptic revisions) patients were recruited for the final analysis. The overall cohort consisted of 803 hips and 530 knees, of which 638 hips and 349 knees were in the PJI group (Table 1). The mean age in the PJI group was 67.8 years (range from 23 to 93 years; SD=10.2 years). The mean age in the aseptic group was 69.8 years (range from 38 to 90 years; SD=10.9 years).

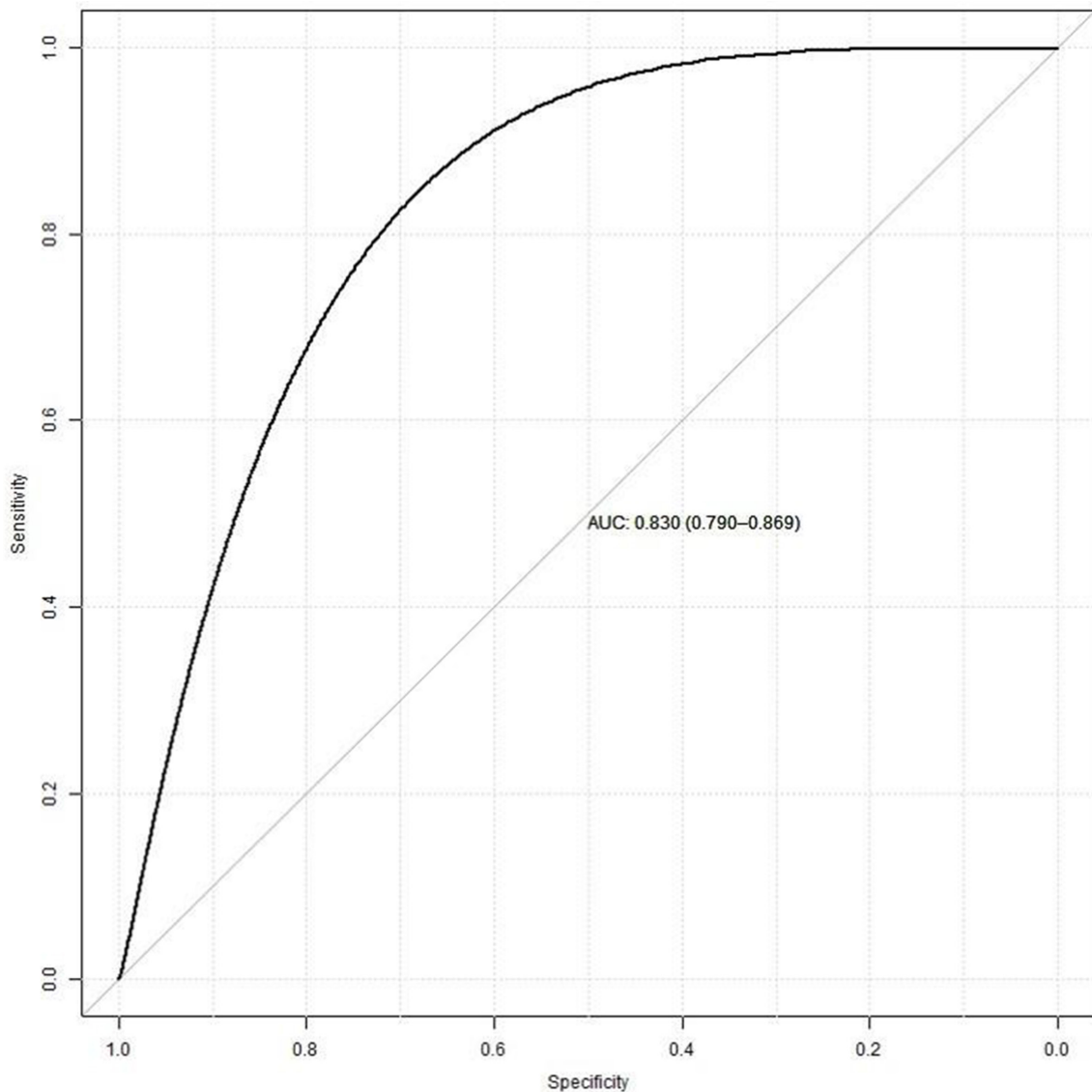


Fig. 2. Receiver operating characteristic (ROC) curve of CRP as a marker of PJI in the hip. The area under the ROC curve (AUC) was 0.830.

Further detailed information about patient characteristics is given in Table 2.

In the PJI group, 203 cases had negative intraoperative biopsies. However, in 168 out of 203 cases, preoperative aspiration revealed a growth of germ. Only 35 had negative aspirations and negative intraoperative biopsies. Fifty-seven had preoperative negative aspirations, of which 22 had intraoperative proof of infection. Thirteen patients had a draining sinus but negative intraoperative biopsies. Eighty-five patients had a persisting draining sinus. Intraoperative specimens were grouped into high- and low-virulence pathogens (Table 3).

The mean CRP value in the PJI group was 50.2 mg l⁻¹ (range from 0.9 to 455 mg l⁻¹; SD=62.2). The CRP values in the aseptic group were significantly lower with 11.6 mg

l⁻¹ (range from 0 to 204 mg l⁻¹; SD=25.3, $P<0.05$). There were no significant differences for the CRP values between patients with and without draining sinus ($P=0.4423$). The difference in CRP between high-virulence and low-virulence micro-organisms was significant for both the hip and the knee (Wilcoxon rank-sum test: $P<0.0001$) (Fig. 1).

We calculated the AUC of blood serum CRP as a marker of PJI in the hip and knee. For the hip, the AUC was 0.830 (Fig. 2) and for the knee it was 0.884 (Fig. 3).

Using the method described by Youden [7], we calculated the optimal cutoff point for CRP as a diagnostic marker of PJI. For the hip, 8.90 mg l⁻¹ was the optimal CRP cutoff point. For the knee, the value was 9.99 mg l⁻¹. Table 4 presents the sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, positive (LR+) and

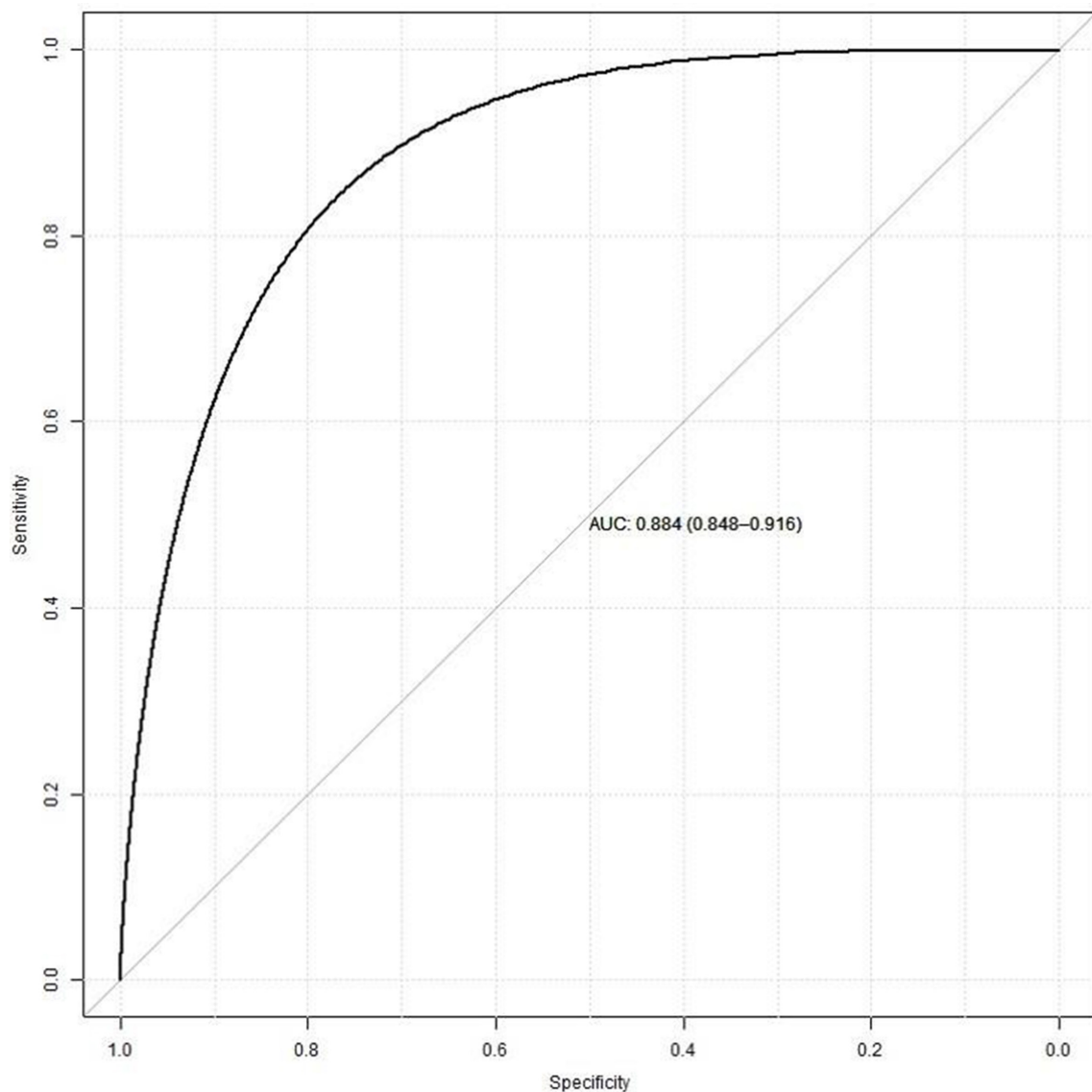


Fig. 3. Receiver operating characteristic (ROC) curve of CRP as a marker of PJI in the knee. The area under the ROC curve (AUC) was 0.884.

negative (LR[−]) likelihood ratios, false positives (FPs) and false negatives (FNs) at the CRP cutoff point for each joint.

DISCUSSION

In recent years, several studies have aimed to identify specific biomarkers for the diagnosis of PJI. Deirmengian *et al.* examined 43 biomarkers and described 100 % sensitivity and specificity for the alpha-defensin enzyme-linked immunosorbent assay (ELISA) Test in detecting PJI [8]. The high accuracy of the alpha-defensin ELISA test was supported by a recent meta-analysis from Wyatt *et al.*, who calculated a sensitivity of 100 % and a specificity of 96 % [9]. In addition to the high accuracy, another advantage of this method is the fact that it delivers consistent results regardless of the organism type,

the virulence of the organism or prior antibiotic therapy [10]. However, the main drawbacks of this test are the high costs and the lack of widespread availability.

Another serum marker that already plays a role in diagnosing PJI is CRP. An elevated blood serum CRP is one minor criterion among the MSIS guidelines for diagnosing PJI. Although the costs of CRP analysis are low and the test itself is widely available, there is a paucity of studies evaluating the role of CRP in PJI diagnosis, especially in terms of the organism type or the virulence of the organism.

In the current study, we assessed the performance of CRP for diagnosing PJI in the hip and the knee. We estimated an AUC of 0.83 for the hip and one of 0.88 for the knee, showing that

Table 4. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, positive (LR+) and negative (LR-) likelihood ratios, false positives (FP) and false negatives (FN) at the optimal CRP cutoff points calculated using Youden's index

	Knee	Hip
CRP cutoff (mg l ⁻¹)	9.99	8.90
Sensitivity	0.86	0.84
Specificity	0.79	0.72
PPV	0.90	0.92
NPV	0.73	0.53
LR+	4.16	3.00
LR-	0.17	0.22
FP	34.00	44.00
FN	48.00	101.00
Youden's index	0.66	0.56

CRP has good accuracy for the detection of infected joints. Furthermore, we calculated the optimal cutoff value of CRP as 8.90 mg l⁻¹ for the hip and 9.99 mg l⁻¹ for the knee using Youden's index [7], which provides the optimal balance of sensitivity and specificity for a given continuous biomarker in a single measure. These cutoff points corresponded to a sensitivity of 84 % and a specificity of 72 % for the hip, and a sensitivity of 86 % and a specificity of 79 % for the knee. In addition, we tested for differences in CRP levels in infections caused by low-virulence micro-organisms compared to high-virulence pathogens. We found that the CRP values were higher, on average, in infections with high-virulence compared to low-virulence micro-organisms.

The results of the current study are consistent with most of the available research on this topic. Several studies have reported sensitivity values below 90 % when the CRP threshold was set at 10 mg/ [5, 6]. Ghanem *et al.* presented a higher sensitivity of 91.1 % when employing a CRP cutoff of 10 mg l⁻¹ [11].

Focusing on the type of micro-organism identified in the biopsy sample, few studies have found that PJIs caused by low-virulence bacteria have normal CRP. In our patient cohort, normal serum CRP was found in 18 % of PJI cases with a low-virulence germ. In a recently published article by Perez-Prieto *et al.*, there was normal CRP in 70 % of PJI cases caused by low-virulence bacteria [2]. However, it must be noted that the number of shoulder arthroplasty cases with *Cutibacterium acnes* was relatively high in this cohort. Piper *et al.* found that shoulder PJIs present a substantial number of cases with normal CRP levels [12]. In our study, we did not include shoulder PJI cases, which might be the reason for the lower number of cases with normal CRP levels in our low-virulence PJI cases.

Interestingly, the presence of a draining sinus did not affect the accuracy of CRP in our patient cohort. This is in contrast to the alpha-defensin test results presented by Gehrke *et al.* [13].

In cases of a draining sinus, the authors found false-negative alpha-defensin results. The authors suggested that missing the accumulation of pathogens due to continuous drainage could affect the number of false negative results for alpha-defensin.

The authors note some limitations of the present study. The first of these is the retrospective study design, with all its inherent limitations. The second is the fact that the total number of patients included in the control group was significantly lower. However, a power analysis conducted prior to the main analyses showed that this sample had sufficient power to conduct our tests. The third limitation was that we did not follow the serum CRP values throughout the hospital stay. However, the main goal of the current study was to determine the overall accuracy of serum CRP values to detect or exclude a PJI, not to monitor longitudinal changes in CRP. Finally, there could be other variables influencing the CRP results between the groups due to their heterogeneity.

While serum CRP has a lower overall accuracy for diagnosing PJI compared to the alpha-defensin test or the leucocyte esterase test, its lower cost and widespread availability justify its use in the workup of patients with suspected PJIs. To the best of the authors' knowledge, this is the largest cohort to date evaluating the relationship between serum CRP and the type of infecting organism or the virulence of the organism. The serum CRP level can be affected by the virulence of the germ. Serum CRP levels may underestimate the diagnosis of PJI in low-virulence organisms. This should be kept in mind before deciding on further treatment. Despite its limitations, this study adds valuable new information to the literature that may help with the diagnostic workup for PJIs and the research and development of new strategies for the diagnosis and treatment of this important complication of arthroplasty procedures.

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Conflicts of interest

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Ethical statement

This study was approved by the ethical review committee. The ethical approval number is PV5556.

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