Combined Serum and Synovial C-Reactive Protein Tests: An Economical and Efficient Adjunct to the Diagnosis of Chronic Prosthetic Joint Infection

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Abstract

Background Diagnosis of Periprosthetic joint infection (PJI) is very complex and challenging, especially for chronic PJI. The value of C-reactive protein (CRP) in infectious diseases has been recognized, but the diagnostic value of CRP in chronic PJI is unknown. Our objective was to investigate the effectiveness of synovial CRP in chronic PJI and to determine the optimal combination of serum and synovial CRP in distinguishing chronic PJI from aseptic failure after knee and hip arthroplasties.

Methods From January 2018 to December 2019, we prospectively included patients scheduled to have a revision surgery for chronic PJI or aseptic loosening of an implant, in which synovial CRP was additionally measured along with routine preoperative diagnostic serum and synovial biomarkers. The receiver operating characteristic (ROC) curves and area under the curve (AUC) were analyzed for each biomarker to determine diagnostic efficacy.

Results There were no statistically significant differences in demographic data among the 97 cases we eventually included. the synovial CRP levels were significantly higher in the infection group than in the aseptic group (median: 19 mg/l vs. 9.25 mg/l; p = .001). The optimal cut-off value for detecting chronic PJI of synovial CRP was of 7.26 mg/l with a sensitivity of 84.62%, a specificity of 93.10%. The combined model I (Serum CRP > 10.2 mg/l OR SF CRP > 7.2 6 mg/l) had a negative predictive value (NPV) of 96.67%, and a sensitivity of 97.44%. The combined model II (Serum CRP > 10.2 mg/l AND Synovial CRP > 7.26 mg/l) led to a specificity of 1, and a positive predictive value (PPV) of 1.

Conclusion The present study demonstrated that the combination of serum and synovial CRP can be used as an adjunct to the diagnosis of chronic PJI.

Introduction

Prosthetic joint infection (PJI) is a devastating complication that can occur following total joint replacement[1]. However, discrimination between infected and aseptic failed total joint replacements can be difficult in some cases, especially in patients with chronic PJI[2]. Establishing a diagnosis of chronic PJI is challenging due to atypical symptoms, which may lead to infection with delayed healing, severe bone defects, joint dysfunction and even a higher risk of short-term mortality[3]. To date, there was no “gold standard” tests or protocol for diagnosing chronic PJI[4]. So, an accurate and timely diagnosis of chronic PJI is a key step toward implementing an effective treatment.

Patients with chronic PJI, elevated serum inflammatory biomarkers, such as serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be the primary indications of PJI due to atypical clinical symptoms such as joint effusion, pain, swelling, and redness. However, due to insufficient specificity, these tests are not sufficient to diagnose PJI alone[5]. They also need to be supplemented by more specific tests, such as synovial fluid analysis, microbial culture, and histopathology. Among them, the detection of synovial fluid (such as IL-6, CD64, and alpha-defensin) has shown great attraction in recent studies[4, 6, 7]. CRP is one of the most widely used inflammatory markers in the identification of

infectious diseases, which is synthesized primarily in liver hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes[8, 9]. Its physiological role is to bind to lysophosphatidylcholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via C1q[10]. C-reactive protein is a marker for inflammation, and its levels increase during bacterial infection. And studies have shown that, CRP is deposited at sites of inflammation and tissue damage in both naturally occurring and experimental conditions[11]. Therefore, the deposition of CRP at the site of infection can be detected, especially in the liquid phase[12]. Recent studies have shown that measuring CRP levels in synovial fluid may be a valuable and cost-effective means to improve the diagnosis of PJI[1, 13, 14]. However, synovial CRP studies to date were limited to small sample sizes, and studies on chronic low-toxicity PJI were insufficient.

In this study, we thus sought to (1) determine the utility of serum and synovial CRP in distinguishing between aseptic failure and chronic infections in patients undergoing revision surgery for failure of total joint arthroplasty, and (2) establish combined cut-off values of serum and synovial CRP in confirming chronic PJI.

Patients And Methods

Before beginning this study, we obtained Institutional Review Board approval for collection of all patient samples. We enrolled patients who were scheduled to have a revision surgery for indications of chronic infection of knee and hip arthroplasties or aseptic loosening of an implant from January 2019 to December 2020. The patients were divided into two groups, “aseptic” and “infection”, based on the 2013 Musculoskeletal Infection Society (MSIS) criteria for the diagnosis of PJI[15]. The “aseptic revision” group was defined as patients who did not fulfill the definition of PJI and did not develop infection or undergo a reoperation for at least 1 year following the index arthroplasty. A postoperative infection was considered 'chronic' when PJI symptoms occurred beyond 6 weeks after implantation[16-18].

To rule out diseases associated with elevated inflammatory markers, patients with the following conditions were excluded: malignancy, rheumatism, renal failure, autoimmune disease, chronic infectious disease (such as human immunodeficiency virus or hepatitis C virus), and patients with recent antibiotic use (less than two weeks).

All synovial fluid aspirates were collected either preoperatively or in the operating room at the time of revision surgery. And blood samples were obtained preoperatively. To assess CRP levels, plasma and synovial fluid were stored in lithium-heparin vacuum collection tubes. The CRP was tested using a particle-enhanced turbidimetric immunoassay with a HITACHI 7600 Series Automatic Biochemical Analyzer (Hitachi, Tokyo, Japan) and diagnostic kit (DiaSys Diagnostic Systems GmbH, Shanghai, China). Synovial fluid was examined for WBCs and PMNs using a haematology analyzer (Symex XE-5000 haematology analyzer, Symex, Japan), and the synovial fluid is cultured for 14 days on Columbia agar, chocolate agar, and Schaedler agar. At least three suspected tissue specimens were obtained

intraoperatively by a stationary surgeon for culture, and the tissue specimens were subjected to intraoperatively frozen section and histopathological examination.

Statistical Analysis

Data were recorded using Microsoft Excel (Microsoft Corporation, Richmond, VA), and statistical analysis was carried out using SPSS version 24. The data are presented as medians and interquartile ranges (IQRs). The results of the diagnostic tests were compared between the groups using an independent-samples t-test. We used receiver operating characteristic (ROC) curve analyses, with Wald CIs, to assess the ability of serum and synovial fluid CRP concentration to determine the presence of PJI. Youden's J statistic was used to determine optimum cut-off values for the diagnosis of chronic infection. The area under the curves (AUCs) of each test were compared using MedCalc 13.2.2 Software (MedCalc Software BV, Ostend, Belgium), and based on the cut-off values, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of these makers were calculated from contingency tables. A p-value ≤ 0.05 was considered statistically significant.

Result

Between January 2018 to December 2019, 122 patients with revision surgery after knee and hip arthroplasties in our department were screened, of which 97 were eligible. Reasons for exclusion include: acute infection within 6 weeks after primary arthroplasties (11, 44%), inadequate synovial fluid acquisition (8, 32%), revision surgery for periprosthetic fractures (2, 8%), local or intravenous antibiotics within two weeks (3,12%) and 1 patient developed infection 273 days after aseptic revision. 58 patients were assigned to the "aseptic" group and 39 to the "infection" group. The patients' demographics were shown in Table 1. Data in Table 1 did not show a significant difference in Ages, Gender, Joint type and BMI between the groups. Mean time since prosthesis implantation was 9.868 years (SD 2.668) in the group with aseptic revision and 2.958 years (SD 1.052) in the group with infection ($p < 0.01$). In the infection group, the causative organism could be identified in 87.18% of the cases (34/39). The most commonly isolated pathogens were coagulase-negative staphylococci (n = 13, 38.24%), Staphylococcus aureus (n = 11, 32.35%), Staphylococcus epidermidis (n = 3, 8.82%), Methicillin-resistant Staphylococcus aureus (MRSA) (n = 2, 5.88%), Candida tropicalis (n = 2, 5.88%), Streptococcus agalactiae (n = 2, 5.88%) and Carbapene-resistant Acinetobacter baumannii (1, 2.95%).

The mean concentration of CRP in the synovial fluid for the infection group was 9.93 mg/ml and was significantly higher ($p < 0.001$) than the aseptic group with a mean concentration of 3.58 mg/ml (Table 2). Serum CRP and synovial fluid percentage of polymorphonuclear neutrophils (PMN%) were significantly higher in the infection group than in the aseptic group (Table 2 and Fig. 1). While the ESR did not differ significantly between the two groups (p=.097).

To visualize the sensitivity and specificity of the measured biomarkers to predict the cause of revision (aseptic or infection), a conventional ROC curve and the area under the curve (AUC) were calculated (Figure 2). The ROC curve analysis revealed the highest AUC for synovial fluid CRP, at 0.937 (95%

confidence interval (95% CI), 0.869–0.976). Using Youden's index, the optimal cut-off values were 7.26 mg/l, 10.2 mg/l, 69.79% and 34 mm/h, for synovial CRP, serum CRP, synovial PMN% and ESR, respectively, discriminating between PJI and aseptic failure.

As shown in Table 3, the synovial CRP level (7.26 mg/l) demonstrated a mean sensitivity of 84.62% (95% CI 69.5 to 94.1) and a mean specificity of 93.10% (95% CI 83.3% to 98.1%). The optimal serum CRP cut-off value was calculated at 10.02 mg/l, with sensitivity, specificity, and negative predictive value (NPV) of 84.62% (95% CI 69.5 to 94.1), 56.90% (95% CI 43.2 to 69.8), and 84.6% (95% CI 71.8 to 92.2), respectively. To a better evaluation of the combined application of serum and synovial CRP, we designed two combined models, model I (Serum CRP > 10.2 mg/l OR SF CRP > 7.2 6 mg/l) and model II (Serum CRP > 10.2 mg/l AND Synovial CRP > 7.26 mg/l), respectively. The combined model I (Serum CRP > 10.2 mg/l OR Synovial CRP > 7.2 6 mg/l) had a negative predictive value (NPV) of 96.67%, and a positive predictive value (PPV) of 56.72%. The combined model II (Serum CRP > 10.2 mg/l AND Synovial CRP > 7.26 mg/l) had an NPV of 84.06%, and a PPV of 1 (Table 3).

Discussion

In this prospective study, we analyzed and compared serum and synovial inflammatory factors in patients with chronic infection and aseptic after knee and hip arthroplasties. Our data indicate that serum and synovial CRP was significantly higher in the chronic infected group than in the aseptic group (35 mg/l vs 21.5 mg/l, and 9.93 mg/l vs 3.58 mg/l, $p < 0.001$, Table 2). We found a strong correlation between serum and synovial fluid CRP level ($r = 0.523$, $P = .0012$). This suggests that the circulatory system CRP is detected by spreading to the synovial fluid through increased vascular and synovial permeability due to infection[13, 19]. We determined that the serum CRP threshold for diagnosing chronic PJI was 10mg/l, which was significantly lower than the results (39.8 mg/l) of a recent multicentric study conducted by Parvizi[20]. We found that when the threshold of synovial CRP was 7.26 mg/l, the AUC area of chronic PJI was as high as 93.70% (95□CI 0.869 to 0.976). However, the thresholds for synovial CRP that we determined were different from previous studies[13, 21] (2.8mg/l to 9.5mg/ml), which may be due to reduced inflammatory response in chronic PJI patients with low-toxic infections, as well as differences in measurement.

Meanwhile, we also show that when serum CRP > 10.2mg/l or synovial CRP > 7.26mg/l, the diagnosed NPV value reached 96.67%. This combination can significantly improve diagnostic sensitivity, but specificity will be sacrificed. In our cohort, there will be 29 aseptic patients who will be misdiagnosed with an infection. Accordingly, when serum and synovial CRP were both high than 10.2 mg/l and 7.26 mg/l, respectively, the diagnostic PPV value reached 1, and the specificity of diagnosis was improved to 1. This combination can be prepared to exclude non-infected patients and improve the efficiency of clinical diagnosis. To our knowledge, this is the first study to use different predictive models of serum and synovial CRP in the identification of chronic PJI.

The sensitivity of serum CRP reached 84.62% was in line with that of a previously published study, included 4934 participants, by Parvizi J et al[22]. However, the serum CRP showed false-positive cases and, hence, a reduced specificity in our study, resulting in a potential overtreatment with unnecessary surgical revisions and prolonged antimicrobial treatment if used alone. The reasonable explanation is that CRP, a factor secreted by a variety of cells, increases to different degrees when the body is stimulated by inflammation[3, 5]. Therefore, we investigated inflammatory markers of local synovial fluid in joints with higher specificity[4]. Based on previous studies, detection time and economic benefits, we focused on the value of synovial CRP in differentiating chronic PJI[13, 14, 23, 24]. Our study indicated the synovial CRP possess a 93.10% diagnostic specificity and 89.69% diagnostic accuracy in identifying chronic PJI (Table 3). However, the analysis found that synovial-CRP sensitivity in differentiating chronic PJI was only 84.62%, ranging from 69.5% to 94.1%. A possible reason for the low sensitivity is the formation of mature biofilms in patients with chronic infection, which protect the pathogen against the host immune system resulting in a weakened immune response and, hence, reduced release of CRP[25, 26]. Therefore, we also do not recommend the use of synovial CRP alone for the diagnosis of chronic PJI.

Therefore, we recommend the combined application of serum CRP and synovial CRP to timely detect chronic PJI. The current data suggested that the combination model I of serum and synovial CRP (Serum CRP > 10.2 OR Synovial CRP > 7.26) be first used to achieve higher diagnostic sensitivity and to reduce the false negative rate of diagnosis. And then using the combined model II of serum and synovial CRP (Serum CRP > 10.2 AND Synovial CRP > 7.26) to improve diagnostic specificity and thus reduce the false positive rate. The effectiveness of this joint diagnostic approach was recently recognized in a systematic review by Abdelbary et al[27]. After this screening, histopathology and other tests can be used in the remaining patients to minimize missed and misdiagnosis. There was no consensus on the optimal thresholds of serum CRP alone and its combination with synovial CRP for the detection of chronic PJI. The current study established thresholds for serum and synovial CRP (10.2mg/l and 7.26mg/l, respectively), and developed two predictive models for the diagnosis of chronic PJI that were highly valuable. In addition, based on the premise of effectiveness, serum and synovial CRP have low cost-effectiveness, (USD $12 per test) and the detection ability of CRP is available in many hospitals. Therefore, this combination method has the potential to be widely used.

There were some limitations in the present study. First of all, there is no clear consensus on the exact time of postoperative chronic PJI. Although the time of biofilm maturation and previous published studies were used as references in this study, cases of acute infection in included chronic PJI patients could not be completely excluded[4, 28, 29]. Second, this study involved a single center, and the sample size was relatively small, with only 39 cases in the chronic PJI group and 58 cases in the aseptic group. However, this preliminary trial shows valuable results and warrants a larger multicentric study to verify the efficacy of serum and synovial CRP in the diagnosis of chronic PJI. Finally, patients with recent antibiotic use were excluded from this study for the elimination of confounding factors. However, this may reduce the number of patients enrolled, limiting the generalizability of the results of this study.

Conclusions

This is the first study concentrating on the diagnoses of even low-grade infections against aseptic failure of knee and hip arthroplasty. Synovial CRP is a valuable test that can well exclude chronic PJI through a combination of serum and synovial CRP (Serum CRP ≤ 10.2mg/l AND Synovial CRP ≤ 7.26mg/l). Therefore, this study is a valuable addition to the current diagnostic criteria developed by the International Consensus Conference on Musculoskeletal Infection (ICM)[30]. And we concluded that preoperative testing for ESR had no benefit for the diagnosis of chronic PJI.

Declarations

Author contributions

Wei Huang: Conceptualized the study, Carried out the statistical analysis, Reviewed the manuscript, Lead author of original trial data.

Hai Wang: Collected and analyzed the data, Wrote the manuscript.

Leilei Qin and Ning Hu: Carried out the statistical analysis, Reviewed the manuscript.

Jiawei Wang: Collected and analyzed the data.

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Availability of data and materials

We do not wish to share our data, because some of the patient's data regarding individual privacy, and according to the policy of our hospital, the data could not be shared with others without permission. An anonymised form of the data could be made available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This trial was approved by the institutional review board (the institutional ethical review board of The First Affiliated Hospital of Chongqing Medical University 20187101).

Written informed consent was obtained from all participants.

Trial registration: International Clinical Trial Registry (ChiCTR1800020440). Registered 29 December 2018, http://www.chictr.org.cn

Consent to Publish

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table I. Demographic data for the study population. Variables are expressed as means (SDs) or absolute numbers and percentages.

	aseptic(n=58)	infected（n=39）	P value
Age (years)			
MEAN	69.37	73.28	0.078#
SD	12.633	6.177	
Gender			
Male	28	22	0.535†
Female	30	17	
Joint type			
Hip	33	28	0.198†
Knee	25	11	
Height(cm)			
MEAN	161.28	161.95	0.680#
SD	7.777	7.98	
Weight（kg）			
MEAN	60.69	59.97	0.775#
SD	12.743	10.854	
BMI（kg/m2）			
MEAN	23.343026	22.903791	0.632#
SD	4.6574813	4.0354309	
Time Frame (year)			
MEAN	9.868	2.959	<0.01#/*
SD	2.668	1.052	

“*” means statistically significant values “#” Independent-samples t-test. “†” Fisher's exact test. Variables are expressed as mean ± SD (standard deviation), or numbers (percentage), BMI (Body Mass Index)

Table 2. Analysis of inflammatory markers in patients with infected and aseptic revision arthroplasty

Inflammatory marker	Hip + Knee		
	Aseptic (n=58)	Infection (n=39)	p value
ESR (mm/h)			
median	21.5	35	0.097
P25, P75	(16.25, 34)	(15, 50)	
Serum CRP (mg/L)			
median	9.25	19	0.001*
P25, P75	(3.36, 21.15)	(13.8, 28.6)	
PMN% (%)			-
median	54.155	78.75	<0.001*
P25, P75	(49.85, 70.06)	(70.73, 89.81)	-
Synovial CRP (mg/L)			
median	3.58	9.93	<0.001*
P25, P75	(2.4025, 5.785)	(8.115, 12.35)	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMN%: Percentage of Polymorphonuclear Cells

Table III. Sensitivity, Specificity, PPV, NPV, and accuracy of inflammatory markers

Parameters	ESR (mm/h）	Serum CRP (mg/L)	Synovial PMN (%)	Synovial CRP (mg/L)	Serum CRP OR Synovial CRP (mg/L)	Serum CRP AND Synovial CRP (mg/L)
AUC (95%CI）	0.600 (0.495, 0.698)	0.703 (0.601, 0.791)	0.810 (0.718, 0.882)	0.937 (0.869, 0.976)	/	/
Cut-off level	34	10.2	69.79	7.26	Serum CRP > 10.2 OR Synovial CRP > 7.26	Serum CRP > 10.2 AND Synovial CRP > 7.26
Sensitivity (%) (95%CI）	51.28 (34.8, 67.6)	84.62 (69.5, 94.1)	84.62 (69.5, 94.1)	84.62 (69.5, 94.1)	0.974359	0.717949
Specificity (%) (95%CI）	77.59 (64.7, 87.5)	56.90 (43.2, 69.8)	74.14 (61.0, 84.7)	93.10 (83.3, 98.1)	0.5	1
PPV (%)	60.6 (46.6, 73.1)	56.9 (48.8, 64.6)	68.7 (58.2,77.6)	89.2 (76.0, 95.5)	0.567164	1
NPV (%)	70.3 (62.5, 77.1)	84.6 (71.8, 92.2)	87.8 (77.2, 93.8)	90.0 (81.1, 95.0)	0.966667	0.84058
Accuracy (%)	0.670103	0.680412	0.783505	0.896907	0.690722	0.886598

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMN%: Percentage of Polymorphonuclear Cells；CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

Figures

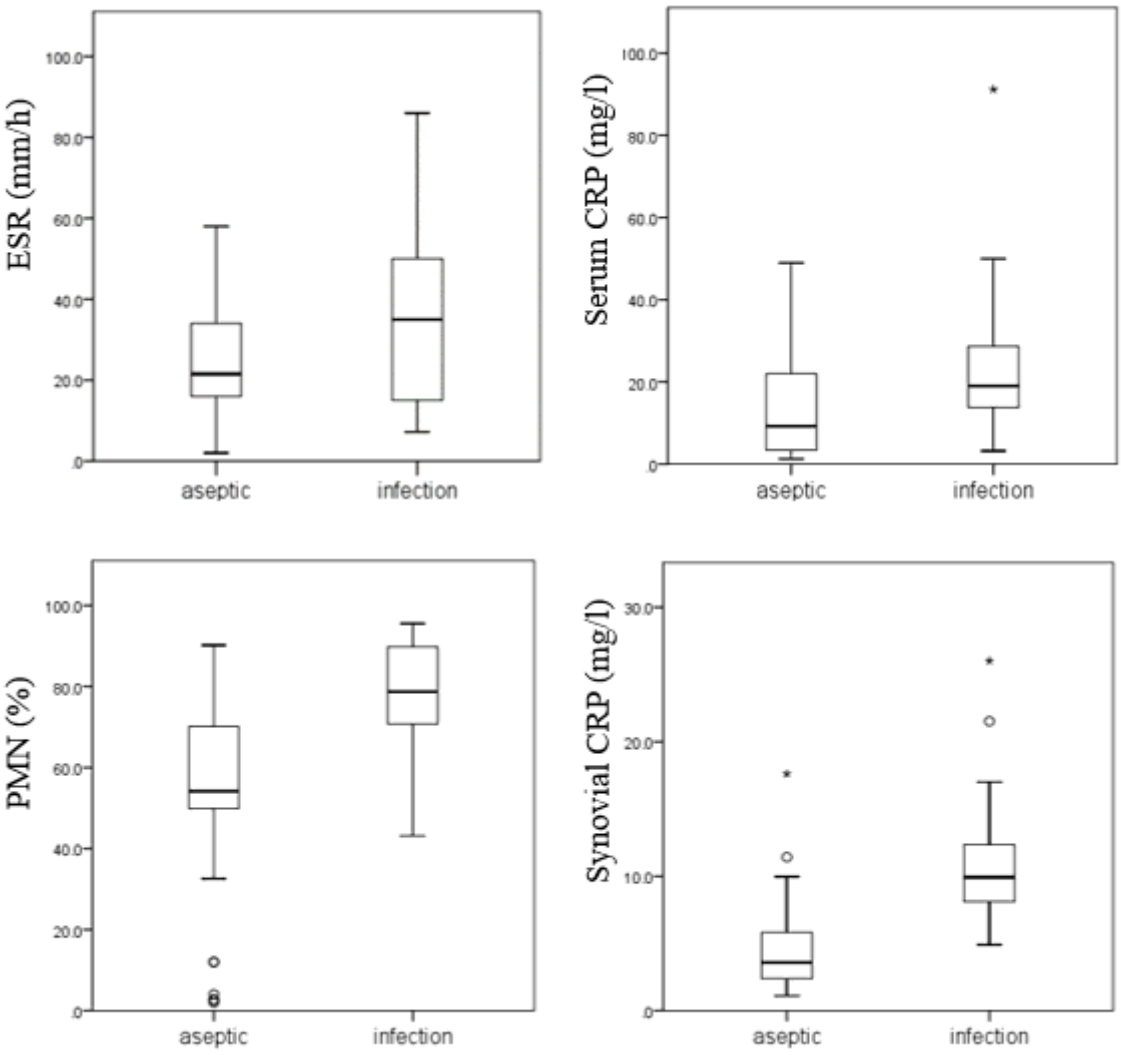

Figure 1

Boxplots of serum CRP, ESR, synovial CRP and PMN% levels in the two groups. The horizontal line represents the median level, the black box the interquartile range, the whiskers the minimum and maximum and the cross outliners.

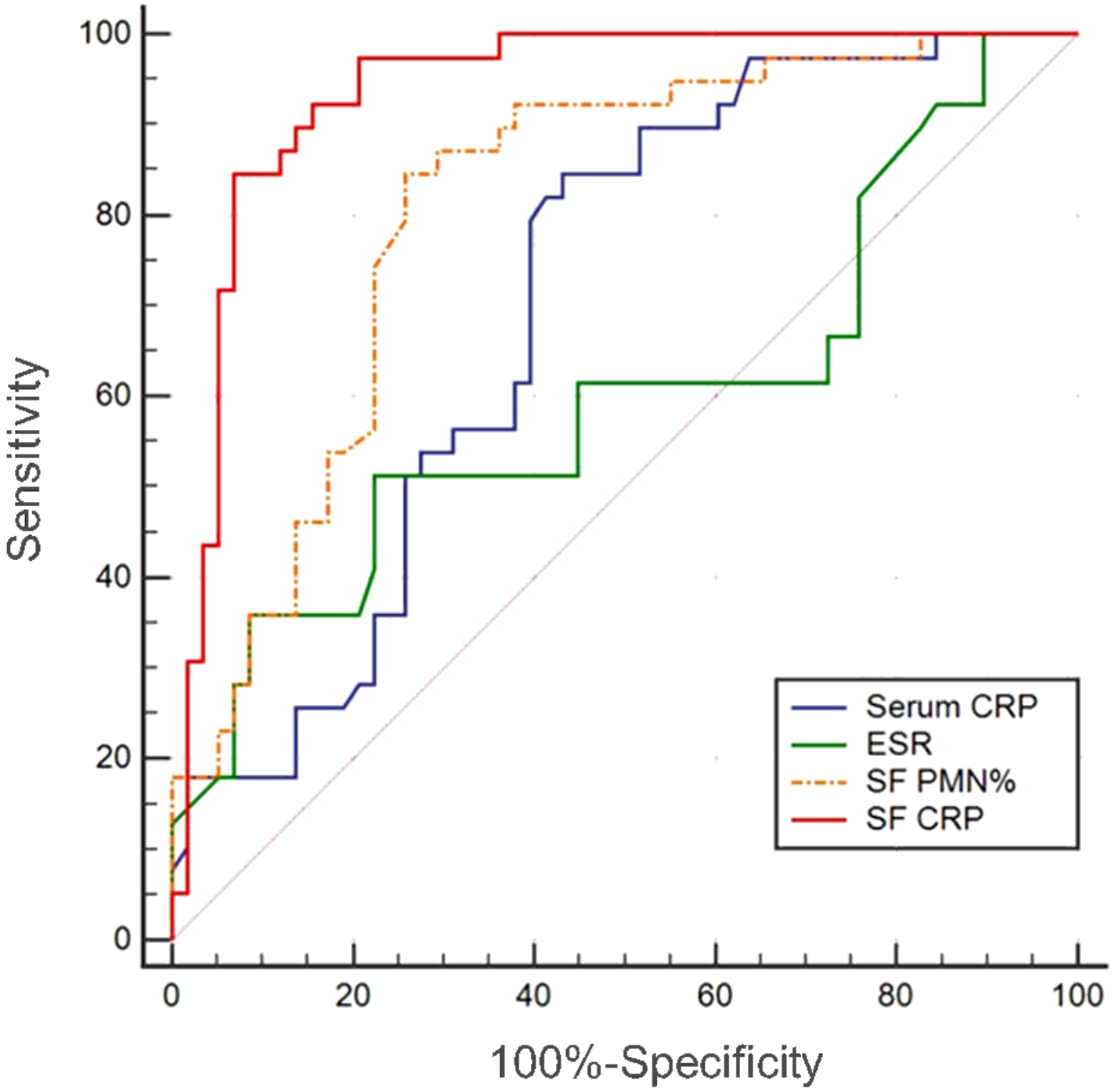

Figure 2

Receiver Operating Characteristic curves (ROCs). ROCs with the corresponding Area under the curve (AUC) of various inflammatory markers of patients with PJI or aseptic failure after TJA. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SF, synovial fluid; SE, serum.