



Synovial C-reactive protein features high negative predictive value but is not useful as a single diagnostic parameter in suspected periprosthetic joint infection (PJI)



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SUMMARY

Objectives: Synovial fluid C-reactive protein (syCRP) has been recently described as a new biomarker in preoperative diagnostics to identify periprosthetic joint infections (PJI). The aim of this study was to evaluate syCRP in a large cohort of patients with suspected PJI and to calculate the optimal cut-off to diagnose PJI.

Methods: Between September 2015 and June 2017, we prospectively included patients with suspected PJI, in which syCRP was additionally measured along with routine preoperative diagnostic serum and synovial biomarkers. We analysed the sensitivity and specificity of syCRP using receiver operating characteristic curves.

Results: We included 192 cases (hip $n=80$, knee $n=91$, shoulder $n=21$) with a final diagnosis of PJI in 26 cases (14.0%). Combined for all joints, the syCRP values were significantly higher in the PJI group than in the no PJI group (median: 13.8 vs. 0 mg/l; $p < 0.001$). The optimal cut-off (Youden Index: 0.71) for the PJI diagnosis combined for all joints was at a syCRP value of 2.9 mg/l with a sensitivity of 88%, a specificity of 82%, and a negative predictive value of 98%.

Conclusions: SyCRP features high negative predictive value but is not useful as a single diagnostic parameter in suspected periprosthetic joint infection (PJI).

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Introduction

The numbers of total joint arthroplasties (TJA) have steadily increased over the last decade, and concomitantly, there has been an increase in the absolute numbers of periprosthetic joint infections (PJI).¹ For clinicians, it is crucial to distinguish between septic and aseptic causes of joint pain because treatment options differ regarding antibiotic therapies and surgical procedures.² Several societies published guidelines for the diagnosis of PJIs. Most commonly, the guideline of the Infectious Diseases Society of America (IDSA)³ and the adapted Musculoskeletal Infection Society (MSIS) guideline by the consensus meeting 2013 are currently used.^{4,5} In the latter, diagnosis of a PJI is based on preoperative and/or intraoperative laboratory, histopathology and microbiological findings, as well clinical signs of a sinus tract. Preoperative

diagnosis can only be made with accuracy lower than that of additional intraoperative diagnostics. Therefore, a single biomarker that can reliably predict the absence of a PJI appears useful because a significant proportion of patients with a painful joint arthroplasty would not inevitably require a septic operative revision of the affected joint. To improve the preoperative diagnostic accuracy, there is ongoing research seeking an optimal diagnostic biomarker,^{6,7} including inflammatory cytokines and antimicrobial peptides. Synovial fluid C-reactive protein (syCRP) is one of these biomarkers that has already been examined in several studies.^{7–14} In two recently published meta-analyses, syCRP has a sensitivity of 85–86% and specificity of 88–90% in patients with hip or knee arthroplasties.^{15,16} However, the numbers of included studies, as well as the numbers of patients, were generally small.

The aim of this study was to evaluate syCRP in a larger cohort of patients who presented with pain before a potential surgical revision after hip, knee, and shoulder arthroplasty and to calculate the optimal cut-off to diagnose a PJI.

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Methods

Study design and population

Between September 2015 and June 2017, we conducted a prospective study at the Orthopedic University Hospital Balgrist, Zurich. We consecutively investigated the syCRP of all patients with a TJA and symptoms suspicious for a PJI (pain, joint swelling, wound secretion, erythema, and sinus tract) or other reasons for joint pain independent of the need for surgical revision. In addition to routine preoperative clinical work-up (serum CRP, erythrocyte sedimentation rate (ESR), leucocyte counts), as well as fluoroscopy-guided synovial aspirates (leucocyte count, neutrophil granulocyte percentage, crystals, and microbiological culture) in patients presenting with joint pain, syCRP was measured in all patients. To decrease viscosity, synovial fluid was treated with hyaluronidase (Merck, Darmstadt, Germany).

In case of an operative revision surgery, tissue specimen was intraoperatively obtained for microbiological and/or histological analyses. If foreign material was removed, sonication fluid was used for microbiological analysis. Cases with dry synovial aspiration were excluded ($n = 39$). Histology was positive if signs of acute inflammation with dominance of neutrophils in at least one tissue sample were present.

The gold standard for the diagnosis of a PJI was the criteria of the Musculoskeletal Infection Society, revised at the consensus meeting in 2013.⁵

Microbiological evaluation

Microbiological techniques and standard biochemical methods for detection and identification of microorganisms were performed as previously described.¹⁷ The incubation time was seven days for synovial and sonication fluid and 10 days for tissue biopsies with a blind subculture of thioglycolate broth for another 2–4 days (final cultivation time of 12–14 days). CRP was measured by immunoturbidimetry (Siemens Advia 1800; Siemens Healthcare AG, Zurich, Switzerland).

Ethics

The local ethics committee of Zurich, Switzerland approved the study protocol (Kantonale Ethikkommission Number 2015-0357, 2016-00145), and all patients signed a study-specific informed consent.

Statistics

The sensitivity and specificity of syCRP as a diagnostic tool were calculated using receiver operating characteristic (ROC) curves. The optimal cut-off was subsequently determined by using the Youden index. We calculated the ROC curve for each joint separately (shoulder, hip, and knee) and as a combined group of hip and knee patients, as well as for a combined group including all patients irrespective of the affected joint. The Mann–Whitney *U*-Test with unequal variances was used to compare the groups. For these analyses, we used Stata/SE 15.1 (StataCorp, College Station, TX, USA). The statistical significance level was established at $p < 0.05$.

Results

Patient characteristics and standard diagnostic findings

Between September 2015 and June 2017, we analysed a total of 192 patients (91 knees, 80 hips and 21 shoulders). The mean age at the time of the diagnostic workup was 67 years (range: 41–91

Table 1

Final diagnosis of the 166 included patients in which PJI could be excluded.

Diagnosis	Cases ($n = 166$)
Aseptic loosening	59 (35.6%)
Joint instability ^a	39 (23.5%)
Pain of unknown origin	14 (8.4%)
Knee arthrofibrosis	10 (6%)
Periprosthetic fractures or delayed union	8 (4.8%)
Wound healing disorder (no PJI)	8 (4.8%)
Tendinopathy	5 (3%)
Metallosis	4 (2.4%)
Patella problems	4 (2.4%)
Heterotopic ossifications	2 (1.2%)
Component fracture	2 (1.2%)
Complex regional pain syndrome (knee)	1 (0.6%)
Rheumatological diseases	
Crystal deposition disease	5 (3%)
Psoriasis, rheumatoid arthritis	2 (1.2%)
Other ^b	3 (1.8%)

^a All patients in this group had joint instability due to muscular insufficiency.

^b Contact allergy ($n=1$); painful scar ($n=1$); lower back pain with radiation ($n=1$). Abbreviations: *n*, number of patients.

years), and half of the patients were male. Neither gender nor age differed between the groups ($p = 0.54$ and $p = 0.57$, respectively).

We diagnosed 26 (14%) PJIs (6 knees, 17 hips and 3 shoulders). In the remaining 166 patients, PJI could be excluded. In this latter group, most patients had aseptic loosening (35%) or joint instability (23%) (Table 1).

All serum (CRP and ESR) and synovial fluid parameters (leucocytes, neutrophils) were significantly higher in the PJI group than in the no PJI group (all $p < 0.001$) (Table 2 and Fig. 1). Surgical revision was done in 93/192 (48%) patients (22/26 PJI cases, and 71/166 no PJI cases). In the PJI group, histology was positive in 68% and ≥ 2 positive cultures with the same microorganisms were detected in 82%.

Microbiology findings

In the PJI group, the causative organism could be identified in 88% of the cases (23/26). The most commonly isolated pathogens were coagulase-negative staphylococci ($n = 10$), *Staphylococcus aureus* ($n = 6$), *Streptococcus agalactiae* ($n = 1$), *Cutibacterium avidum* ($n = 1$), and *Candida tropicalis* ($n = 1$). In four cases, the infection was caused by several pathogens (polymicrobial infection).

Synovial fluid CRP

The syCRP values combined for all joints were significantly higher in the PJI group than in the group without PJI (median: 13.8 mg/l vs. 0 mg/l; $p < 0.001$) (Table 2 and Fig. 1). There was a strong correlation between the syCRP and serum CRP ($r = 0.735$), and moderate correlations between both serum ESR and synovial fluid leucocytes ($r = 0.420$ and $r = 0.463$ respectively) (Table 3).¹⁸

Using ROC analysis combined for all the joints, we calculated a syCRP of 2.9 mg/l as being the optimal threshold for the diagnosis of a PJI, with a sensitivity of 88% and a specificity of 82% (Youden index 0.71, AUC 0.93, 95% CI 0.88–0.97). Looking at the various joints, the optimal cut-offs differed for the shoulder (lower with 2.4 mg/l) and the knee (higher with 12.9 mg/l) arthroplasties.

Taking the cut-off for all joints combined, the negative predictive value to exclude an infection was 98%; however, the positive predictive value was only 43%. Furthermore, we analysed a separate group with all hip and knee patients because, to date, most of the literature reported data for this combination and not for each joint separately. The values of this separate group were similar to those the overall group (optimal cut-off at syCRP of 2.9 mg/l) (Table 4 and Fig. 2).

Table 2

Basic characteristics, serum and synovial parameters of all 192 included patients at the time of the preoperative diagnostic work-up.

Characteristics	Total, n = 192	PJI, n = 26	No - PJI, n = 166	P-value
Male gender, n (%)	96 (50)	18 (69)	78 (46.9)	
Age, m (range)	67 (41–91)	67.5 (44–87)	65.5 (41–91)	
Joints, n (%)				
Hip	80 (41.7)	17 (64.4)	63 (38)	
Knee	91 (47.4)	6 (23.1)	85 (52.1)	
Shoulder	21 (10.9)	3 (11.5)	18 (10.8)	
Serum parameters				
CRP (mg/l), m (range)	4.7 (0–218.4)	39.4 (2.6–218.4)	2.6 (0–216.8)	<0.001
Available test, n (%)	186 (97)	26 (100)	160 (96)	
ESR (mm/h), m (range)	21 (2–105)	50 (9–75)	19 (2–105)	<0.001
Available test, n (%)	183 (95%)	26 (100)	157 (95)	
Synovial fluid parameters				
CRP (mg/l), m (range)	0 (0–95.4)	13.8 (1–53)	0 (0–95.4)	<0.001
Available test, n (%)	192 (100)	26 (100)	166 (100)	
Leucocytes (µl), m (range)	250 (0–230,600)	36,400 (550–230,600)	200 (0–53,500)	<0.001
Available test, n (%)	172 (90)	23 (88)	149 (90)	
% neutrophils, n				
100%		2	2	
80%		16	9	
>50%		5	15	
<50%		0	55	
n.d.		3	85	
Crystal deposits				
Available test, n (%)	181 (94)	23 (88)	158 (95)	
+Calcium Pyrophosphate	15	0	15	
+Hydroxyapatite	1	0	1	
+Cholesterol	1	0	1	

Abbreviations: m, median; n, number of patients; PJI, periprosthetic joint infection; CRP, C – reactive protein; n.d., not done.

Table 3

Correlation analysis of serum – and synovial fluid parameters.

	syCRP	Serum CRP	Serum ESR	syLeuc
syCRP	1	0.735*	0.420*	0.463*
Serum CRP		1	0.516*	0.352*
Serum ESR			1	0.216*
syLeuc				1

* Correlation is significant at $p = 0.01$ (two sided). Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; syCRP, synovial fluid C-reactive protein; syLeuc, Synovial fluid leucocytes.

Only three out of 26 PJI cases (11.5%) had a syCRP below the cut-off of 2.9 mg/l: one shoulder patient with a polymicrobial PJI (syCRP 2.4 mg/l), one hip patient with a *Cutibacterium avidum* PJI (syCRP 1.3 mg/l), and one patient with a culture-negative knee PJI (syCRP 1.0 mg/l). In the last case, the diagnosis was based on histopathology showing acute inflammation and high intraoperative synovial cell count (61,000 leucocytes/µl), 80% neutrophils, and exclusion of crystal deposit disease as a differential diagnosis. Applying the joint-specific syCRP cut-off, the shoulder PJI mentioned above would have been classified correctly.

In all three PJI cases with lower syCRP as our calculated cut-off of 2.9 mg/l, serum CRP values correlated and were below or at the standard threshold of 10 mg/l (10.7 mg/l, 4.7 mg/l and 2.6 mg/l, respectively).

Table 4

Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of correctly detecting periprosthetic joint infections with an optimal threshold of synovial CRP calculated by Roc analysis.

Joint	n	AUC (95% CI)	Sens	Spec	PPV	NPV	ACC	Threshold
All	192	0.93 (0.88–0.97)	0.88	0.82	0.43	0.98	0.83	2.9 mg/l
Shoulder	21	0.93 (0.77–1)	1	0.78	0.43	1	0.81	2.4 mg/l
Hip	80	0.95 (0.90–0.99)	0.93	0.86	0.64	0.98	0.88	2.9 mg/l
Knee	91	0.92 (0.8–1)	0.83	0.98	0.71	0.99	0.97	12.9 mg/l
Hip and knee	171	0.93 (0.89–0.98)	0.91	0.82	0.44	0.98	0.83	2.9 mg/l

n, number of patients; AUC, area under the curve; CI, confidence interval; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy.

In the no PJI group, 30 out of 166 cases (18.1%) had a syCRP above the cut-off of 2.9 mg/l. These were cases with aseptic loosening ($n = 9$), muscular insufficiency ($n = 6$), superficial wound healing disorders ($n = 5$), knee arthrofibrosis ($n = 3$), patella problems ($n = 2$), pain of unknown origin ($n = 2$), crystal deposit disease ($n = 1$), complex regional pain syndrome ($n = 1$), and painful scar ($n = 1$).

Synovial fluid CRP as additional criterion for PJI diagnosis

Adding the syCRP as an additional diagnostic criterion to the MSIS criteria in the preoperative setting, one additional case (shoulder PJI with *S. epidermidis*) could have been detected preoperatively. By contrast, one case (knee TJA) without infection, but crystal deposit disease, would have met the criteria for PJI, leading to a false-positive decision, as shown in one of our seven cases with rheumatological diseases (Fig. 1). In patients with intraoperative diagnostics, the syCRP had no additional advantage to the established MSIS criteria.

Due to the good correlation of serum and syCRP (Table 3), we compared the AUC for both biomarkers using ROC analysis curves. The AUC for serum CRP was similar to that of syCRP (0.92 and 0.93, respectively), indicating no benefit of syCRP compared to serum CRP.

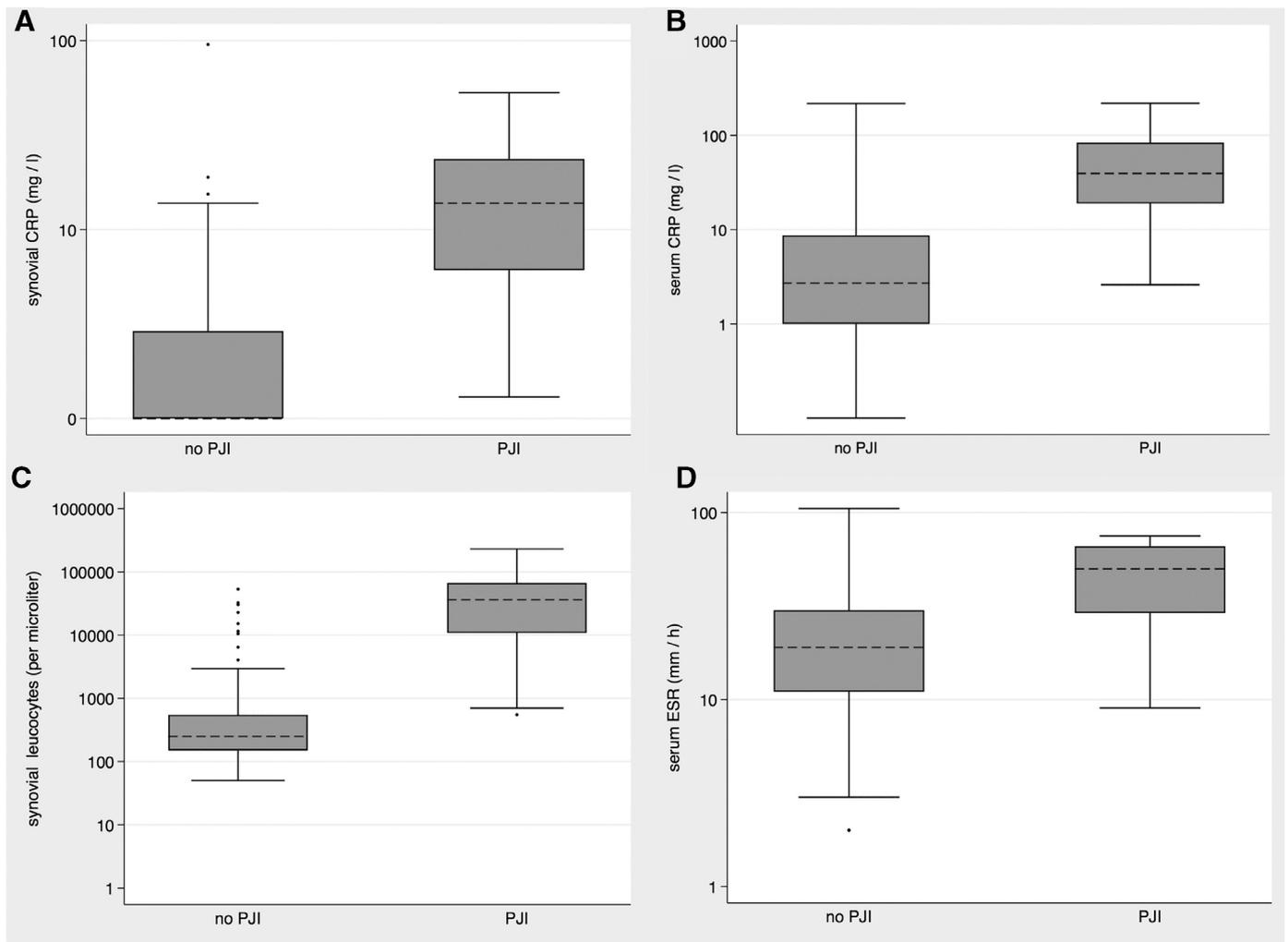


Fig. 1. Box plot comparing synovial fluid CRP (A), serum CRP (B), synovial fluid leucocytes (C), and serum ESR (D) in patients with PJI and without PJI. The difference of the medians in all panels is $p < 0.001$. The outlier (synovial fluid CRP: 95.4 mg/l) in panel 1A in the no PJI group represents a case with the diagnosis of a crystal deposit disease.

Discussion

We found a high negative predictive value of the syCRP (98%), allowing the exclusion of PJI when using the optimal cut-off of 2.9 mg/l or joint-specific cut-offs. Nevertheless, the calculated positive predictive value was low; therefore syCRP alone cannot be recommended as a single biomarker.

Our calculated sensitivity of 88% was in line with that of a previously published study by Stone et al.¹⁹ and with two recent meta-analyses (71–96%).^{15,16} Two of three PJI cases with a syCRP level below the cut off were caused by low-virulence organisms appearing to have lower syCRP values compared to high-virulence organisms.²⁰ In this recent large study by Deirmengian et al. comparing the synovial fluid CRP values in low- and high-virulence organisms, the mean synovial fluid CRP value was 15.1 mg/l detecting low-virulence organisms, similar to our calculated syCRP for low-virulence organisms (mean 19.3 mg/l). However, they did not include PJIs caused by *Cutibacterium acnes*.

In our study, we found a specificity of 82%, a value lower than that reported in most of the included studies in a meta-analysis by Ahmad et al. (79–99%).¹⁵ For syCRP they calculated a pooled sensitivity of 86% and specificity of 90% in patients with knee or hip arthroplasties for the diagnosis of a PJI. Nevertheless, an ideal cut-off value could not be determined.^{15,16} The reported cut-offs in

the included studies ranged from 2.5 mg/l to 16.6 mg/l.¹⁶ However, the included studies varied in their inclusion and exclusion criteria as well as the diagnostic gold standard for the definition of a PJI. Most often, the MSIS criteria^{7,8,12,13} or the AAOS criteria^{10,11} were used.

A potential reason for our lower specificity could be the fact that we did not exclude patients with pre-existing inflammatory disorders that could have high syCRP values.²¹

Except for patients with painful knee arthroplasty (cut-off 12.9 mg/l), all calculated cut-off were approximately 2.9 mg/l. The higher optimal cut-off in knee arthroplasties could be due to the fact that six out of seven patients with inflammatory diseases such as rheumatoid arthritis or crystal deposition disease were in the knee group and high syCRP can be found in patients with crystal deposit diseases.²² Furthermore, no other study to date calculated cut-offs for each joint separately.

Nonetheless, in all of our calculations, the sensitivity ranged from 83% to 100% and the specificity ranged from 78% to 98%. Therefore, we cannot recommend the use of syCRP as a single biomarker for the diagnosis of a PJI. We observed a high correlation between serum and syCRP and a similar AUC for both parameters. Our calculated correlations and AUC were almost identical compared to a large prospective study with a cohort of 150 patients with revision surgery after TJA.¹² As CRP is mainly syn-

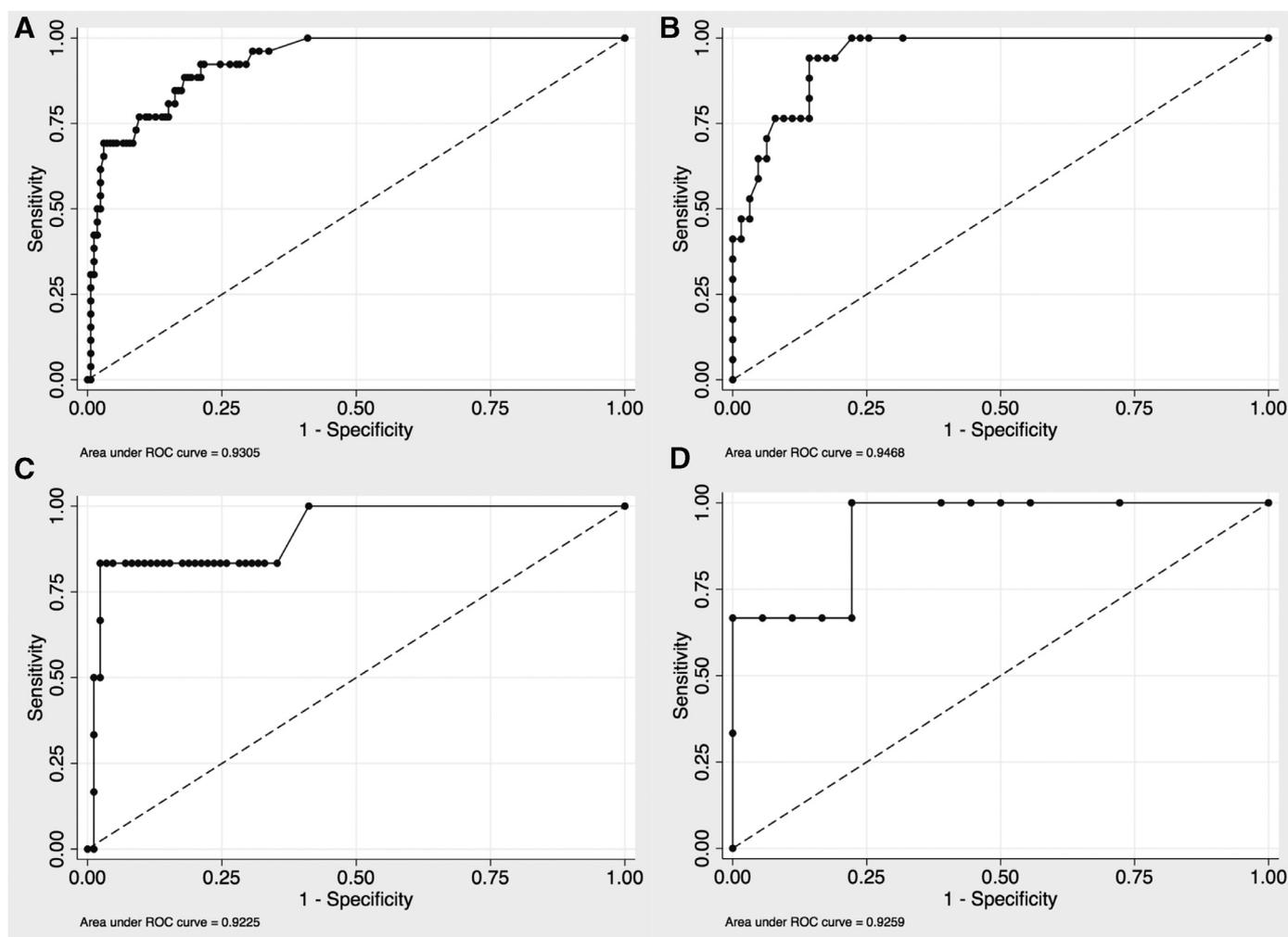


Fig. 2. Receiver operating curves for all joints combined (A), hip (B), knee (C), and shoulder (D) patients.

thesised in the liver and not locally in the joint,^{23,24} and the joint is a compartment with free penetration even of large molecules, it seems evident that there is a strong positive correlation between synovial CRP and serum CRP. Using synovial CRP in combination with the proposed criteria by the adapted consensus meeting 2013, we detected one more shoulder PJI case but also a false positive knee PJI in the preoperative setting. Therefore, we did not see an improvement of preoperative diagnostic using syCRP as an additional biomarker to diagnose a PJI. However, concomitant use of other biomarkers might increase the diagnostic accuracy of MSIS criteria. Deirmengian et al.²⁵ or Stone et al.¹⁹ showed that syCRP in combination with the biomarker α -defensin,⁷ improved diagnostic accuracy. The diagnostic accuracy of syCRP combined with other biomarkers in inconclusive cases need to be evaluated in future trials.

To our knowledge, no previous publications reported syCRP values for patients with a shoulder PJI. In our cohort, we analysed 21 patients with shoulder arthroplasty, of whom 3 had a PJI (14%). At a cut-off of 2.4 mg/l, we calculated an excellent sensitivity of 100% and a specificity of 78%. Nevertheless, the interpretation of the findings remains difficult. On the one hand, the microbiological findings in this cohort did not represent the expected spectrum of causative organisms in shoulder PJIs in which up to 40% were caused by *Cutibacterium acnes*, and the majority of cases were late infections.²⁶ In our cohort, two cases were caused by staphylococci,

and one patient had a polymicrobial infection with a sinus tract. Whether the sensitivity will remain as high as 100% in a cohort of PJIs with a higher proportion of *Cutibacterium acnes*, low-grade infections need to be examined in future trials with larger cohorts of shoulder PJI patients.

Our study has three limitations. First, our prospective study included only patients from a single-centre. A second limitation is the low numbers of PJIs in shoulder arthroplasty in general but particular of *Cutibacterium acnes* PJIs, which precludes a strong recommendation in the performed sub analysis. Third, despite intensive diagnostic work-up, the aetiology of joint pain remained unknown in 14 patients. We cannot absolutely rule out that we missed PJI cases with difficult to cultivate pathogens as a differential diagnosis of culture negative cases. Strengths of our study were the large prospective cohort of 192 included patients with a painful arthroplasty, irrespective of the affected joint and a pre-existing inflammatory diseases. Although interpretation of study results in shoulder arthroplasties was limited, it is the first time that syCRP measurements were reported in patients with shoulder painful arthroplasties to our knowledge.

In summary, syCRP is a biomarker with a high negative predictive value, allowing the exclusion of PJI in the preoperative phase. However, it has a low sensitivity of 88%, a low specificity of 82%, and a similar AUC using ROC analysis as the serum biomarker CRP. Therefore, we conclude that syCRP has no benefit alone and when

using with routine serum (CRP and erythrocyte sedimentation rate) and synovial biomarkers (leucocytes, neutrophils, and microbiological culture) to make a reliable diagnosis of PJI in the preoperative setting. If patients get a surgical revision, intraoperative tissue samples for microbiology and histology should be taken to have a complete diagnostic.

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Declarations of interest

None.

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