



C-reactive protein misdiagnoses delayed postoperative spinal implant infections in patients with low-virulent microorganisms

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Abstract

Purpose C-reactive protein (CRP) has been shown to be a powerful parameter for detecting acute postoperative spinal implant infections (PSII) with a high sensitivity and specificity. However, little data are available on the performance of CRP in the diagnosis of delayed PSII. The aim of the current study was therefore to establish cutoff values for diagnosing delayed infection based on serum CRP.

Methods All patients who underwent a revision surgery after instrumented spinal fusion from January 2013 through January 2016 were included. Demographic data, laboratory values, type of infection (including microbiological and pathological results), comorbidities and clinical manifestation were collected. The European Bone and Joint Infection Society criteria, proposed to diagnose periprosthetic joint infection, were used to diagnose PSII.

Results A total of 257 patients were included. PSII was diagnosed in 61 patients, representing 24% of the study cohort. There was a significant difference in serum CRP levels between septic and aseptic cohorts (19.3 vs. 4.8 mg/l, $p < 0.001$). However, 26 patients (43%) from the PSII group had a normal (< 5 mg/l) serum CRP level prior to revision surgery. According to the ROC curve, a serum CRP threshold of 4.05 mg/l had a sensitivity of 64% and specificity of 68%. The most common isolated microorganism was *Propionibacterium* spp. followed by coagulase-negative staphylococci.

Conclusion Serum CRP showed low sensitivity and specificity for diagnosis of delayed PSII, even after applying cutoffs optimized by using receiver operating curve analysis, because of the high incidence of low-virulent pathogens.

Graphical abstract

These slides can be retrieved under Electronic Supplementary Material.

Key points

1. The performance of serum CRP in the diagnosis of delayed PSII remains in spine surgery unknown.
2. In this analysis of 257 patients, serum CRP had a sensitivity of 64% and specificity of 68%.
3. The most common isolated microorganism was *Propionibacterium* spp. followed by coagulase-negative staphylococci.

Figure 2: Receiver operating characteristics curve for serum C-reactive protein (CRP). Sensitivity is plotted against 100% specificity.

| Variable | AS patients (n=227) | PSII group (n=61) | Non-PSII group (n=196) | p value |
|---|----------------------|---------------------|------------------------|---------|
| Age at the time of revision (years) | 42.1 ± 19.3 | 38.6 ± 20.5 | 43.2 ± 18.8 | 0.1 |
| Male/Female | 96 (42%) / 131 (58%) | 37 (61%) / 24 (39%) | 59 (30%) / 137 (70%) | <0.001 |
| Charlson comorbidity index (mean ± SD) | 3.5 ± 2.2 | 3.5 ± 2.6 | 3.6 ± 2.1 | 0.98 |
| CRP at revision (mg/l)* | 8.3 ± 19.1 | 19.3 ± 34.8 | 4.8 ± 7.6 | <0.001 |
| Serum leukocyte count at admission (10 ⁹ /l) | 7.8 ± 2.5 | 7.9 ± 3 | 7.8 ± 2.3 | 0.83 |
| Time from index surgery to revision (months) | 37.4 ± 46 | 27.5 ± 30 | 40.8 ± 50 | 0.68 |

*The values are given as the mean and the standard deviation

**The values are given as the number with the percentage of the group as parenthesis

Table 1: Patient demographics, clinical and laboratory findings

Take Home Messages

1. Pre-operative diagnosis of delayed PSII remains challenging in daily routine.
2. Serum CRP is not relevant in the diagnosis of delayed PSII due to the low sensitivity and specificity.
3. Standardized criteria for diagnosis of delayed PSII and peri-operative routines should be established.

Keywords Infection · Spine surgery · CRP · Diagnostic · Posterior fusion · Revision surgery

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Introduction

Postoperative spinal implant infection (PSII) following instrumented fusion remains a common complication after spinal surgery. Although acute postoperative infection after instrumented spinal surgery is readily detectable, delayed

infection presents a unique diagnostic and therapeutic challenge [1]. In these cases, specific clinical signs, radiographic changes and, especially, elevated inflammatory blood parameters may be absent.

C-reactive protein (CRP) has been shown to be a powerful parameter for detecting acute periprosthetic joint infections and PSII with high sensitivity and specificity [2–4]. However, a recent study showed normal CRP levels in more than one-third of the patients with periprosthetic joint infections, especially if caused by indolent organisms [5]. There is a paucity of studies on the diagnostic value of CRP in delayed PSII. Recently, Hahn et al. [6] have reported that normal CRP following spinal instrumentation does not rule out late infections of *Propionibacterium acnes*. Understanding the limitations of the CRP can lower our threshold to use further diagnostic tools.

Therefore, the aim of the current study was to (1) establish cutoff values for diagnosing delayed infection based on serum CRP and (2) determine the infecting microorganisms in delayed spinal infection. To our knowledge, no study has investigated this important issue.

Methods

This retrospective study has been conducted at a single-center university clinic. An analysis of all patients who underwent a revision surgery after instrumented spinal fusion from January 2013 through January 2016 was performed. Demographic data such as age and gender, type of infection (acute postoperative or delayed spinal implant infection) [1], comorbidities, the Charlson Comorbidity Index score (CCI) [7], surgical history and clinical and radiological manifestation were collected. Furthermore, laboratory values including serum CRP, blood leukocytes, microbiological and pathological results of revisions and time from index surgery to revision were recorded for all patients. Patients with missing data and those with an acute postoperative infection were excluded. The mean variables of the present study were the serum CRP level and infecting organism. The total number of intraoperative tissue samples and the incidence of positive cultures were also recorded for each patient. The study protocol was reviewed and approved by the institutional ethics committee and was done in accordance with the Declaration of Helsinki (EA2/012/18). A data extraction based on the Standards for Reporting of Diagnostic Accuracy Studies (STARD) checklist was used to appraise the overall quality of the current study (Fig. 1) [8]. A quality assessment tool was developed on the basis of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and used to assess reported study quality [9].

The European Bone and Joint Infection Society (EBJIS) criteria [10], proposed to diagnose periprosthetic joint infection, were modified and used in this cohort study to diagnose PSII. According to this classification system, PSII was confirmed when at least one of the following criteria was fulfilled: (1) macroscopic purulence around the implants; (2) presence of sinus tract; (3) significant microbial growth in tissue around implants or sonication culture of retrieved implants; and (4) positive histopathology defined as ≥ 23 granulocytes per ten high-power fields, corresponding to the type II or type III classification of the periprosthetic membrane [11]. Low-virulent microorganisms such as coagulase-negative staphylococci (CNS), *Bacillus* species, *Corynebacterium* species or *Propionibacterium* species were considered relevant if the same microorganism was isolated in at least two samples or in one sample if another criterion of PSII diagnosis was fulfilled. Sonication was performed for 1 min at 40 kHz (BactoSonic, BANDELIN electronic, Berlin, Germany); the resulting sonication fluid was plated onto aerobic and anaerobic sheep blood agar plates and incubated for 14 days. According to the local laboratory, the CRP level was considered normal if the value was under 5 mg/l.

Chi-squared and Fisher's exact tests were used to find significant differences between categorical variables. The two-sample *t* test (for parametric distribution) or Mann–Whitney *U* test (for nonparametric distribution) was used to compare continuous variables between groups. Receiver operating characteristic (ROC) curves were constructed to display sensitivity and specificity of serum CRP level for PSII. The area under the curve was calculated, and the optimum cutoff point was determined by the maximized Youden's index. The results were expressed as mean and standard deviation (SD) or as number and percentage. A *p* value < 0.05 was considered significant. SPSS version 20 (SPSS Inc., Chicago, Illinois) was used for the statistical analyses.

Results

During the study period, 302 patients were identified. After exclusion of seven patients due to missing data and 38 presence of an acute infection, 257 patients were included. The mean age of the study cohort was 62.1 years old (SD, 19.3 years), and there were 161 females (63%). PSII was diagnosed in 61 patients, representing 24% of the study cohort. Interestingly, 77% of these patients with diagnosed PSII preoperatively showed no obvious clinical signs of infection such as redness, swelling, sinus tract formation and fever and were operated on as presumed aseptic due to hardware failure, pseudoarthrosis or adjacent segment instability and stenosis revealed on the imaging studies. There was a significant difference in serum CRP levels between septic and aseptic cohorts (19.3 vs. 4.8 mg/l, $p < 0.001$).

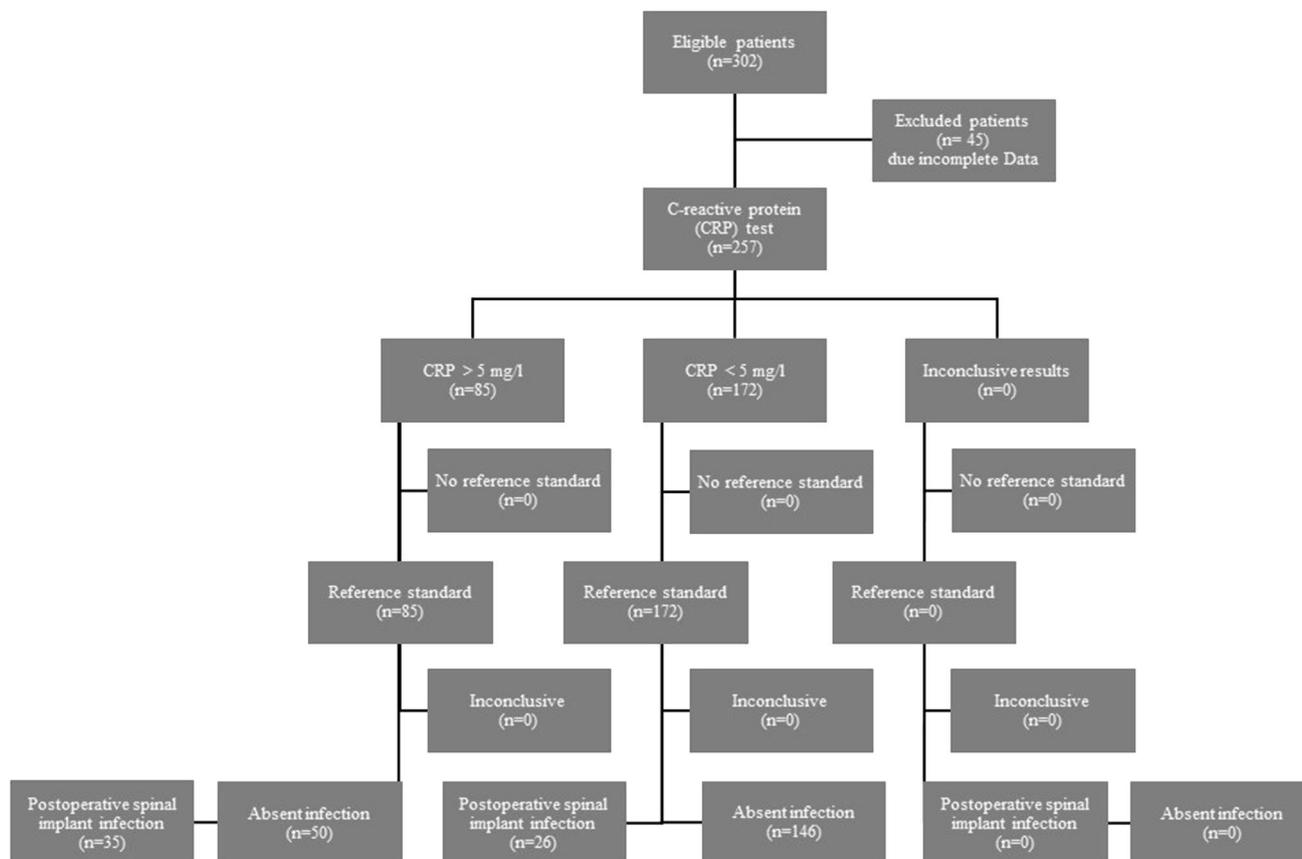


Fig. 1 Data extraction based on the STARD flow diagram illustrated

However, 26 patients (43%) from the PSII group had a normal (< 5 mg/l) serum CRP level prior to revision surgery. Further demographic data and clinical and laboratory findings of both groups (PSII vs. non-PSII) are summarized in Table 1. Interestingly, the mean time to revision from the index surgery was significantly shorter in those with PSII than in those without (27.5 vs. 40.5 months, $p = 0.03$). According to the ROC curve, a serum CRP threshold of 4.05 mg/l had a sensitivity of 64% and specificity of 68% (Fig. 2). The area under the curve was 0.67. The most common isolated microorganism was *Propionibacterium* spp., followed by CNS. *Staphylococcus aureus*, which is the most commonly isolated microorganism in acute postoperative spinal infections [1, 12–14], was isolated in only two patients. Table 2 summarizes the causative pathogens.

Discussion

Serum CRP has long been an important parameter for the diagnosis of infection. Although it has a high relevance in the diagnosis of periprosthetic joint infection and acute postoperative spine infection, its role in delayed PSII was

not investigated in the literature. This current study demonstrated a low sensitivity and specificity for serum CRP in detecting delayed PSII. Thus, serum CRP is an unreliable diagnostic marker of delayed PSII, especially when caused by low-virulent pathogens. To our knowledge, this is the first study in the literature dealing with this topic.

Previously, Piper et al. performed a similar study and found an optimized serum CRP cutoff of 4.6 mg/l with a sensitivity and specificity of 79% and 68%, respectively, for diagnosing PSII. They gave no information about the type of causative microorganisms, and only 54 patients were included in his study, of which 14 had a PSII. The possible reason our threshold as well as sensitivity was lower than reported by Piper et al. [2] may be because they included not only delayed but also acute infections. Thus, a direct comparison of this study with our results would be incorrect. Hu et al. [15] recently showed that occult infections could easily be misdiagnosed in patients who underwent revision spine surgery and hardware removal due to the lack of preoperative clinical signs of infection. Similarly, 77% of our cases with diagnosed PSII showed no clinical signs of infection preoperatively.

Table 1 Patient demographics, clinical and laboratory findings

| Variable | All patients (n = 257) | PSII group (n = 61) | Non-PSII group (n = 196) | p value |
|--|------------------------|---------------------|--------------------------|---------|
| Age at the time of revision (years) ^a | 62.1 ± 19.3 | 58.6 ± 20.5 | 63.2 ± 18.8 | 0.1 |
| Sex ^b | | | | <0.001 |
| Male | 96 (37) | 37 (61) | 59 (37) | |
| Female | 161 (63) | 24 (39) | 137 (63) | |
| Charlson comorbidity index (age adjusted) ^a | 3.5 ± 2.2 | 3.5 ± 2.6 | 3.6 ± 2.1 | 0.58 |
| CRP at admission (mg/l) ^a | 8.3 ± 19.1 | 19.3 ± 34.8 | 4.8 ± 7.6 | <0.001 |
| Serum leukocyte count at admission (nl) ^a | 7.8 ± 2.5 | 7.9 ± 3 | 7.8 ± 2.3 | 0.83 |
| Diagnosis of primary surgery | | | | |
| Degenerative | 180 (70) | 44 (72) | 136 (69) | |
| Fracture | 26 (10) | 7 (11) | 19 (10) | |
| Primary deformity | 12 (5) | 2 (3) | 10 (5) | |
| Secondary deformity | 21 (8) | 3 (5) | 18 (9) | |
| Tumor | 6 (2) | 2 (3) | 4 (2) | |
| Unknown | 12 (5) | 3 (5) | 9 (5) | |
| Area of the index surgery ^b | | | | |
| Cervical | 6 (2) | 3 (5) | 3 (2) | |
| Thoracic | 10 (4) | 4 (7) | 6 (3) | |
| Lumbar | 127 (49) | 23 (38) | 104 (53) | |
| Cervicothoracic | 1 (0) | 1 (2) | – | |
| Thoracolumbar | 41 (16) | 11 (18) | 30 (15) | |
| Lumbosacral | 57 (22) | 15 (24) | 42 (21) | |
| Thoracolumbosacral | 15 (6) | 4 (7) | 11 (6) | |
| Time from index surgery until revision (months) ^a | 37.4 ± 46 | 27.5 ± 30 | 40.5 ± 50 | 0.03 |

^aThe values are given as the mean and the standard deviation

^bThe values are given as the number with the percentage of the group in parentheses

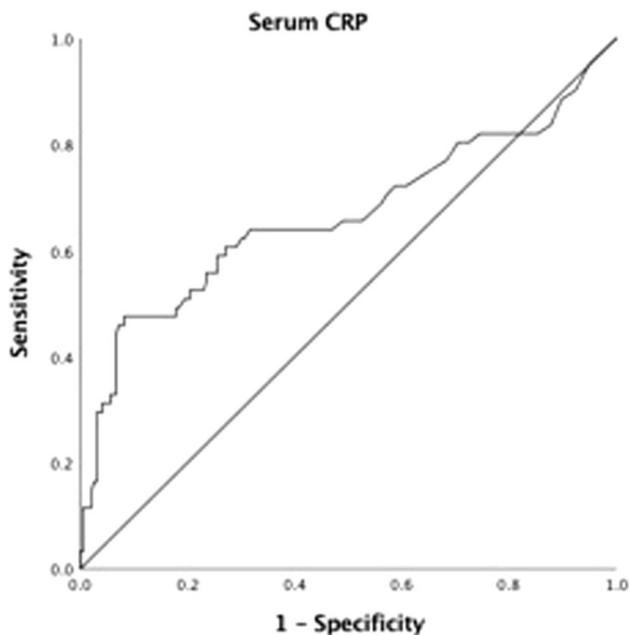


Fig. 2 Receiver operating characteristics curve for serum C-reactive protein (CRP). Sensitivity is plotted against 100% specificity

Table 2 Microorganisms identified

| | |
|-------------------------------|----|
| <i>Propionibacterium</i> spp. | 30 |
| CNS | 22 |
| <i>Streptococcus</i> spp. | 3 |
| <i>Staph. aureus</i> | 2 |
| Others | 9 |
| Polymicrobial | 11 |
| Neg. microbiology | 4 |

Number of patients in whom microorganisms were cultured from intraoperative specimen or sonication fluid culture

Interestingly, 43% of CRP results in the PSII group were within the normal range prior to the diagnosis of infection. Collins et al. reported that 17% of their study cohort was within the normal serum CRP range, and similarly, Hahn et al. [6] found normal CRP level in two of seven patients (29%), who had a late implant infection caused by *Propionibacterium acnes*. Our high rate of 77% with occult infections, who were diagnosed only following implant removal for indications other than overt infection, could conduce to

the high prevalence of seronegative PSII in our cohort. This can be attributed to the biofilm-forming properties of the bacteria in implant-associated infections. An important feature of biofilm-forming bacteria is their resistance to host defense and lack of systemic inflammation in chronic infection [16, 17]. Low-virulent microorganisms reside in biofilm and remain in a dormant state, resulting in a dampened inflammation. In the setting of this latent infection occurring from low-virulent microorganism, patients may have only vague complaints of pain with evidence of pseudoarthrosis or hardware failure after a period of time, even after a number of years without explicit signs of infection [1, 6, 18–20], similarly observed also in our study. Yet, the etiology of failure within the first 2–3 years after index surgery seems more likely to be PSII than aseptic failure, because the PSII group in our cohort underwent revision surgery after a significantly shorter time compared to the non-PSII group. This finding is concordant with the results of the study by Portillo et al. [21] in the field of periprosthetic joint infection; showing a prosthesis failure within 2 years of implantation is highly predictive of infection.

We noted a high prevalence of *Propionibacterium* spp. in our PSII cohort. Although this microorganism has been regarded by some as simply a culture contaminant [22], recent studies have reported propionibacteria as a common cause of late-presenting infection [6, 18, 19]. The incidence becomes obviously higher with improved cultural technique, because propionibacteria require an extended period of incubation before identification [18]. Our high detection rate of propionibacteria reflects the meticulous sampling and culture methods we are using at our institute rather than tissue contamination. However, the question may shift further from whether microorganisms are present to what degree of their presence is indicative of a clinically significant infection [1]. Furthermore, the high prevalence of low-virulent microorganisms in our patient cohort was equivalent to the findings of Kowalski et al. Thus, delayed infections were more typically caused by low-virulent pathogens such as CNS and propionibacteria [1].

This study has several limitations. CRP is a nonspecific marker of inflammation and may be elevated chronically in patients with inflammatory arthropathy, including systemic lupus erythematosus, rheumatoid arthritis and gout, which were not excluded from our study. Thus, their inherently elevated levels of CRP could have altered our results. Serum CRP level was assessed within 1 week prior to revision surgery. Ideally, the timing of CRP measurement should be standardized (e.g., 24 h prior to surgery). It was a retrospective analysis, and seven patients should have been excluded due to missing data. However, this small number of excluded patients would not change our results and statement of the study in a possible worst-case scenario. A further limitation is the lack of a gold-standard definition for PSII, which

can lead to inconsistency between studies and make results incomparable.

Conclusion

Serum CRP showed low sensitivity and specificity for the diagnosis of delayed PSII, even applying cutoffs optimized by using receiver operating curve analysis. Furthermore, infection must always be considered as a possibility in the setting of revision surgery despite the lack of clinical signs.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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