Thieme

Retrospective Evaluation of C-reactive Protein for Ruling Out Infection After Cesarean Section

Eine retrospektive Evaluierung von CRP-Werten zum Ausschluss von Infektionen nach der Kaiserschnittentbindung

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ABSTRACT

Introduction
Infection after cesarean section is a major contributor to maternal morbidity. Measurement of C-reactive protein (CRP) is a laboratory test frequently conducted to rule out or confirm postoperative infection. The present study aimed to evaluate whether CRP is a suitable tool for ruling out infection after cesarean section and whether there are any reliable cut-off values.

Materials and Methods
2056 patients with cesarean section (CS) over a 3-year period were included in a retrospective analysis. Outcome parameters and risk factors for postoperative infection were collected. CRP values from preoperative and postoperative tests were compared. Cut-offs for ruling out infection were assessed.

Results
Among 2056 CSs, postoperative infection occurred in 78 cases (3.8%). The prevalence of infection in emergency CS was lowest, at four out of 134 (2.9%), and the highest prevalence was seen in secondary CS, at 42 of 903 (4.6%; $p = 0.35$). CRP values in the infection group were significantly higher (preoperative, 1.01 mg/dl vs. 0.62 mg/dl; day 1 postoperative, 7.91 mg/dl vs. 6.44 mg/dl; day 4 postoperative, 8.44 mg/dl vs. 4.09 mg/dl; $p = 0.01$). A suitable cut-off value for ruling out infection was not identified.

Conclusions
Although CRP values were significantly higher in the infection group, the clinical relevance of this appears to be negligible. CRP testing does not appear to be a reliable tool for diagnosing or ruling out postoperative infection.

ZUSAMMENFASSUNG

Einleitung

Infektionen nach einer Kaiserschnittentbindung tragen wesentlich zur mütterlichen Morbidität bei. Die Messung von C-reaktivem Protein (CRP) ist ein häufig durchgeführter Labortest, um postoperative Infektionen auszuschließen oder zu bestätigen. Ziel dieser Studie war es, herauszufinden, ob CRP ein geeignetes Instrument zum Ausschließen von Infektionen nach einer Kaiserschnittentbindung sein könnte, und ob es verlässliche Cut-off-Werte dafür gibt.

Material und Methoden

Es wurden 2056 mit Kaiserschnitt entbundene Patientinnen über einen Zeitraum von 3 Jahren in die retrospektive Analyse aufgenommen. Outcome-Parameter und Risikofaktoren für eine postoperative Infektion wurden gesammelt. Die CRP-Werte der prä- und postoperativen Tests wurden verglichen. Es wurden Cut-off-Werte für den Ausschluss einer Infektion bewertet.

Ergebnisse

Bei 2056 mit Kaiserschnitt entbundenen Frauen gab es in 78 Fällen (3,8 %) eine postoperative Infektion. Die Infektionsprävalenz war beim Notfallkaiserschnitt am niedrigsten mit insgesamt 4 Fällen von 134 Patientinnen (2,9 %). Die höchste Prävalenz fand sich bei sekundären Kaiserschnittentbindungen mit 42 aus 903 Fällen (4,6 %; p = 0,35). Die CRP-Werte der Infektionsgruppe waren signifikant höher (präoperative Werte: 1,01 mg/dl vs. 0,62 mg/dl; 1. postoperativer Tag: 7,91 mg/dl vs. 6,44 mg/dl; 4. postoperativer Tag: 8,44 mg/dl vs. 4,09 mg/dl; p = 0,01). Es ließ sich aber kein geeigneter Wert identifizieren, der verlässlich Infektionen ausschloss.

Schlussfolgerungen

Obwohl die CRP-Werte in der Infektionsgruppe signifikant höher waren, scheint dessen klinische Relevanz vernachlässigbar. CRP-Tests stellen kein verlässliches Instrument für die Diagnose oder den Ausschluss von postoperativen Infektionen dar.

Abbreviations

CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
CS	cesarean section
GBS	group B streptococcus
GDM	gestational diabetes mellitus
PPROM	preterm premature rupture of membranes
PROM	preterm rupture of membranes
ROC	receiver operating characteristic
SSI	surgical site infection

Introduction

Cesarean section (CS) is one of the most frequent major operations worldwide, with a rate that is still rising [1]. The results of the nosocomial infection surveillance system in Germany show that there is an infection rate of 1.8 % after CS, with endometritis, wound infections, mastitis, and urinary tract infections being most frequent [2]. The rate of surgical site infection (SSI) after CS ranges from 3 % to 15 %, and SSI is a major contributor to maternal morbidity [3]. SSI can be categorized as superficial incisional SSI, deep incisional SSI, and organ/space SSI, using the criteria recommended by the Centers for Disease Control and Prevention (CDC) [4]. Risk factors that are associated with a higher risk of SSI are a high body mass index, diabetes, high number of previous CSs, emergency CS, and the surgeon's grade, among others [5, 6]. Several perioperative strategies and infection control policies have been introduced and evaluated in order to reduce the risk of postoperative infections [7, 8]. Many studies have recommended the use of prophylactic antibiotics to reduce the risk of postpartum endometritis, wound complications, and urinary tract infections [9, 10, 11, 12]. The use of extended-spectrum prophylaxis with azithromycin in nonelective CS is also suggested to further reduce the risk of postpartum infections [13]. Although the optimal timing of antibiotic administration requires careful consideration, due to unknown long-term effects for the neonate when it is carried out before cord clamping, most authors suggest that antibiotics should be given within 60 minutes before surgery if possible [14, 15].

C-reactive protein (CRP) levels increase in response to injury, inflammation, and infection [16, 17]. CRP testing is frequently carried out to exclude or confirm infection. Many studies have investigated the value of postoperative CRP testing after major gastrointestinal surgery [18, 19, 20]. Raised CRP levels are expected after surgery, with peaks 48 hours postoperatively [21, 22]. As the CRP response in patients is highly variable, it does not appear to be a good indicator of the presence of early SSI [21, 23]. Attempts have been made to develop reference ranges, but it is not clear whether these are generally applicable [24]. Nevertheless, CRP testing is still an important tool for monitoring the clinical response to treatment when infection is diagnosed [25]. Investigations of CRP in the postpartum period have shown that levels are higher after CS than after spontaneous birth [26, 27]. To the best of our knowledge, no previous studies have focused on the role of CRP solely after CS.

The aim of the present study was to evaluate the potential of CRP for diagnosing early infection after CS and to determine thresholds for the prevalence of infection, so that early administration of antibiotics can be avoided.

Materials and Methods

Study protocol

A retrospective analysis of patients' records was conducted using data from the hospital information system (i.s.h. med.; SAP Austria Ltd., Vienna, Austria). All patients who had undergone cesarean sections at Kepler University Hospital, Linz, Austria (formerly Landesfrauenklinik) over a 3-year period were included in the study. Primary CS, in contrast to secondary CS, was defined as CS before the onset of labor or rupture of membranes. Emergency CS is an operation conducted within 20 minutes due to fetal or maternal risk, in accordance with the clinical practice guidelines of the Austrian Society for Gynecology and Obstetrics [28].

Analyzed data

Maternal serum levels of CRP (in mg/dl) were measured using immunochemical testing with a cobas 6000 analyzer (cobas e analyzers; Roche Diagnostics, Mannheim, Germany). Patients underwent routine CRP testing preoperatively and on the first and fourth postoperative days. CRP values ranging up to 0.5 mg/dl are classified as normal. Baseline clinical characteristics and laboratory parameters were recorded. Patients with incomplete data records, intraoperative complications (such as intestinal or urinary lesions), pregnancies with abnormally invasive placenta, and patients needing revision surgery were excluded.

The gestational week was calculated on the basis of crown–rump length using ultrasound during the first trimester. Preterm birth was defined as delivery before 37 + 0 weeks of gestation. Premature rupture of membranes (PROM) is defined as rupture of the amniotic membranes at least 6 hours before onset of labor. Preterm premature rupture of membranes (PPROM) refers to PROM before 37 + 0 weeks of gestation. The diagnosis of gestational diabetes mellitus (GDM) was based on a pathological oral glucose tolerance test with oral administration of 75 g glucose.

During the study period, all women undergoing CS were given antibiotic prophylaxis with parenteral ampicillin/sulbactam (Unasyn, 3 g). Patients with a penicillin allergy were given an alternative (cefuroxime, clindamycin). In patients receiving a primary CS, antibiotic prophylaxis was administered after cord clamping. Patients with PROM received antibiotics, with administration starting 12 hours after rupture of the membranes; in patients with a positive test for group B streptococcus (GBS), antibiotics were started at the onset of labor or premature rupture of the membranes. Patients with PPROM received antibiotics immediately after hospitalization. In secondary or emergency CS, antibiotic prophylaxis was also administered after cord clamping if it had not yet been started for the other reasons mentioned above. Postoperative antibiotic therapy was administered as prescribed by the clinician on duty.

CS was conducted following standard surgical procedures and international guidelines. Povidone-iodine-based solutions were used on a standard basis for antiseptic skin preparation; vaginal disinfection is not routinely conducted. Uterine exteriorization after uterotomy was not performed on a standard basis. Cord traction is used to deliver the placenta.

Early infection was defined as new-onset postoperative infection occurring during days 1–4 after surgery; late infection was defined as infection on days 5–8. Fever was defined as an axillary temperature higher than 38.0 °C.

Statistical analyses

All data for continuous variables were checked for normal distribution (test of normality: Kolmogorov–Smirnov with Lilliefors significance correction, type I error = 10 %) and for heteroscedasticity (Levene test, type I error = 5 %). Since none of the variables fulfilled the criteria for parametric analysis, subgroup comparisons (infection vs. noninfection; early infection vs. late infection vs. noninfection) were carried out either using the Mann–Whitney U test or with Kruskal–Wallis one-way analysis of variance followed by Nemenyi's multiple comparisons. Data for categorical variables were compared either using Fisher's exact test or with the chi-square test (with provision of adjusted residuals).

The suitability of CRP values for predicting early and late infections was checked by means of receiver operating characteristic (ROC) curves; cut-off values were assessed using the Youden index. The robustness of the ROC results was investigated by means of modified bootstrapping approaches (1000 runs per calculation).

The type I error was not adjusted for multiple testing. The results of inferential statistics are therefore only descriptive. Statistical analysis was performed using the open-source R statistical software package, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

The study was approved by the local ethics committee of Upper Austria (K-32–13). Due to its retrospective design, the study was not registered in a public trial registry, but it was conducted in accordance with the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network guidelines.

Results

Study participants and characteristics

During the study period, 9981 deliveries took place at Kepler University Hospital, Linz, and 2186 CSs were performed (21.9 %). After application of the exclusion criteria, 2056 patients were enrolled in the study. Postoperative infection was documented in 78 cases (3.8 %), with 50 early infections (2.4 %) and 28 late infections (1.4 %). Out of this group, 42 patients (53.8 %) had postoperative fever without any special focus of infection, 21 (26.9 %) showed SSI or infected hematoma, mastitis occurred in eight patients (10.3 %), and urinary tract infection in seven patients (9.0 %). There were no documented cases of endometritis. The rate of infections was stable over the study period, varying from 3.1 % to 4.9 % (p = 0.22).

Of the 2056 patients, 973 (47.3 %) underwent primary CS, 945 (46.0 %) secondary CS, and 138 (6.7 %) had an emergency CS. The prevalence of infection in the study group was lowest among emergency CSs, at four of 134 (2.9 %), in comparison with 32 of 941 (3.4 %) in the primary CS group and 42 of 903 (4.6 %) in the

▶**Table 1** Risk factors associated with postoperative infection after cesarean section.

	Infection (n = 78)	**No infection** (n = 1978)	**Total** (n = 2056)	**p**
Preterm birth	24 (30.8%)	441 (22.3%)	465 (22.6%)	0.10
DM/GDM	10 (12.8%)	182 (9.2%)	192 (9.3%)	0.32
Multiple pregnancy	10 (12.8%)	184 (9.3%)	194 (9.4%)	0.32
GBS	11 (17.5%)	330 (20.3%)	341 (20.2%)	0.75
PROM/PPROM	18 (23.1%)	316 (16.0%)	334 (16.3%)	0.12
Postoperative complications	8 (10.4%)	1 (0.1%)	9 (0.4%)	**< 0.01**
Packed red blood cell administration	0 (0.0%)	1 (0.1%)	1 (0.0%)	> 0.99

DM = diabetes mellitus; GBS = group B streptococcal infection; GDM = gestational diabetes mellitus; PPROM = preterm premature rupture of membranes; PROM = preterm rupture of membranes.

secondary CS group, but there were no significant correlations (p = 0.35).

Associations between maternal and pregnancy characteristics and the occurrence of postoperative infection are presented in ▶ **Table 1**. A significant correlation was observed between postoperative complications such as hematoma, paralytic ileus, and wound dehiscence and infection (p < 0.01). There were no significant associations between other risk factors that were investigated.

Among the 2056 patients, 339 (16.5%) received antibiotics within the first four postoperative days and 184 (9.0%) within postoperative days 4–8.

Parameters and outcomes

Preoperative and postoperative CRP and leukocyte values are listed in ▶ **Table 2**. The mean CRP level was significantly higher in the infection group preoperatively and postoperatively (p = 0.01). A similar trend was seen in the leukocyte values, with significant results only being observed on the fourth day after CS (p = 0.01). In view of the unequal size samples, a subgroup analysis comparing postoperative CRP and leukocyte measurements between early and late infection was also conducted. The results are presented in ▶ **Table 3**, showing significant results on the first postoperative day (p < 0.05).

The suitability of CRP values for predicting early and late infections was checked using ROC curves, which are shown in ▶ **Fig. 1** and ▶ **Fig. 2**. On the basis of the Youden index, a cut-off value of 6.7 mg/dl was calculated for the first postoperative day (▶ **Fig. 1**), with a sensitivity of 68% (95% CI, 53.3 to 80.5) and a specificity of 60.87% (95% CI, 58.8 to 63.0) (p < 0.01). The cut-off value calculated for the fourth postoperative day (▶ **Fig. 2**) was 7.3 mg/dl, with a sensitivity of 34.78% (95% CI, 16.4 to 57.3) and a specificity of 91.81% (95% CI, 90.4 to 93.1) (p = 0.02).

Discussion

In the group of patients included in the study, those with postoperative infection after CS were found to have significantly higher CRP values than those without infection. However, the clinical relevance of this is unclear. The mean CRP on the first postoperative day in the infection group was 7.91 mg/dl, in comparison with 6.44 mg/dl in the group with no infection, so that the differences are small. This might be due to unequal size samples, with only 78 infections out of a total of 2056 cesarean deliveries. A subgroup analysis of early infection versus late infection was carried out in addition, to provide similar sample sizes, but the differences in the CRP values were also negligible in that subgroup (▶ **Table 3**).

An attempt was made using ROC analysis to identify an optimal cut-off value for CRP in order to rule out infection after CS. A bootstrap approach was used in view of the dissimilar sample sizes. As ▶ **Fig. 1** and ▶ **Fig. 2** show, there are no valid cut-off values for ruling out infection using CRP testing on either the first or fourth postoperative days.

In clinical management, CRP levels are frequently tested routinely after surgery. As the present data confirmed, an elevated CRP value does not always correlate with the occurrence of clinical infection. Preoperatively and on postoperative day 1, the maximum CRP values were observed in the group without infection. Clinicians' awareness of postoperative CRP test values may influence their decision-making regarding antibiotic administration, and this should be avoided. In particular, inexperienced residents might initiate antibiotic therapy purely because of laboratory results, which would be inappropriate and could lead to the development of resistance mechanisms [29, 30]. This situation is also reflected in the data from the present study. Although only 78 patients had clinical signs of infection, antibiotics were administered in 339 cases during postoperative days 1–4 and in 184 cases during postoperative days 5–8. Whether or not to administer antibiotic therapy lies in the responsibility of the clinician who is on duty. Preoperatively initiated antibiotic therapy might therefore

▶**Table 2** CRP and leukocyte measurements: infection vs. no infection. The mean CRP level was significantly higher in the infection group preoperatively and postoperatively. The mean leukocyte level was significantly higher on postoperative day 4.

	Infection (n = 78)	**No infection** (n = 1978)	**p**
CRP, preoperative (mg/dl)			
▪ Mean	1.01	0.62	**0.01**
▪ SD	1.38	0.8	
▪ Maximum	7.8	9.6	
CRP, postoperative day 1 (mg/dl)			
▪ Mean	7.91	6.44	**0.01**
▪ SD	4.84	3.66	
▪ Maximum	21.3	24.2	
CRP, postoperative day 4 (mg/dl)			
▪ Mean	8.44	4.09	**< 0.01**
▪ SD	6.19	2.35	
▪ Maximum	25.1	22.3	
Leukocytes, preoperative (G/l)			
▪ Mean	9.35	9.52	0.11
▪ SD	3.42	2.62	
▪ Maximum	28.7	23.8	
Leukocytes, postoperative day 1 (G/l)			
▪ Mean	12.32	11.7	0.47
▪ SD	4.28	3.06	
▪ Maximum	26.0	26.3	
Leukocytes, postoperative day 4 (G/l)			
▪ Mean	9.52	8.0	**0.01**
▪ SD	4.06	2.02	
▪ Maximum	27.3	19.0	

CRP = C-reactive protein; SD = standard deviation.

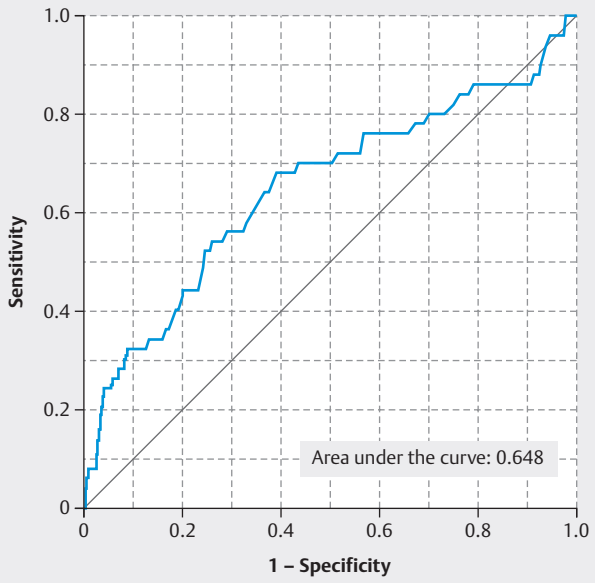
▶**Table 3** CRP and leukocyte measurements: early vs. late infection (subgroup analysis). Significantly higher values were observed on the first postoperative day.

	Early infection (n = 50)	**Late infection** (n = 28)	**p**
CRP, preoperative (mg/dl)			
▪ Mean	1.22	0.64	0.27
▪ SD	1.61	0.74	
▪ Maximum	7.80	3.50	
CRP, postoperative day 1 (mg/dl)			
▪ Mean	8.99	5.98	**0.04**
▪ SD	5.32	3.04	
▪ Maximum	21.30	16.10	
CRP, postoperative day 4 (mg/dl)			
▪ Mean	9.76	6.31	0.15
▪ SD	6.66	4.74	
▪ Maximum	25.10	17.90	
Leukocytes, preoperative (G/l)			
▪ Mean	9.93	8.32	0.09
▪ SD	3.87	2.11	
▪ Maximum	28.70	13.00	
Leukocytes, postoperative day 1 (G/l)			
▪ Mean	13.26	10.64	**0.03**
▪ SD	4.66	2.88	
▪ Maximum	26.00	16.80	
Leukocytes, postoperative day 4 (G/l)			
▪ Mean	9.79	9.10	0.96
▪ SD	4.45	3.41	
▪ Maximum	27.30	20.70	

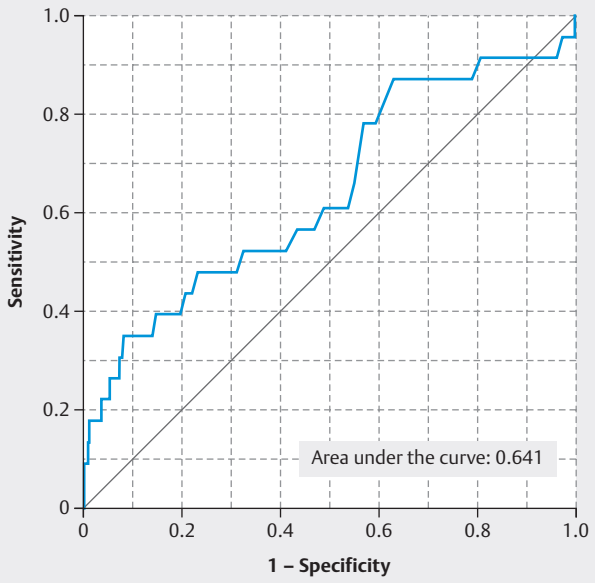
CRP = C-reactive protein; SD = standard deviation.

continue for several days after CS if there is a specific condition such as intrapartum fever, foul-smelling amniotic fluid or membranes, or PPROM [31]. In some cases, the clinician may also initiate antibiotic therapy due to raised postoperative inflammatory parameters, without any clinical signs of infection. Clinicians need to bear in mind that raised CRP levels may simply be evoked by tissue damage during the operation [17]. This study shows that postoperative CRP testing should in fact not be carried out routinely after CS, in order to avoid misinterpreting the laboratory results. A nonspecific increase in inflammation levels without a clinical focus is one of the main reasons for the administration of antibiotic therapy, which should be avoided if clinical grounds for it are lacking [32]. However, CRP does have an important role for monitoring or assessing the severity of confirmed infection and for guiding further therapy [25].

This study shows that infections after CS are rather rare, with an overall prevalence of 3.8 % in this group of patients. It should be mentioned that urinary tract infections and puerperal mastitis were also included in the infection group, accounting for 19.3 % of all infections. The fact that no cases of endometritis were diagnosed in the analysis is not reflected in the findings of other studies, in which endometritis appears to be a fairly frequent



▶ **Fig. 1** Receiver operating characteristic (ROC) curve analysis of C-reactive protein values: postoperative day 1. A cut-off value of 6.7 mg/dl for predicting early infection was calculated (sensitivity 68 %, specificity 60.87 %).



▶ **Fig. 2** Receiver operating characteristic (ROC) curve analysis of C-reactive protein values: postoperative day 4. A cut-off value of 7.3 mg/dl for predicting late infection was calculated (sensitivity 34.78 %, specificity 91.81 %).

cause of postpartum infection [33]. The reason for this might be that in the present group of patients there were 42 women with fever, but without any specific focus of infection. Antibiotic therapy was started in these cases, leading to rapid recovery, so that classic symptoms of endometritis such as uterine tenderness or purulent lochia did not occur and the diagnosis was not confirmed.

The rate of CS during the study period was 21.9 % of all deliveries. It should be mentioned that Kepler University Hospital is a tertiary center in Austria, in which many women with high-risk pregnancies are treated. In contrast to other studies that have suggested higher infection rates following emergency CS, the prevalence of infection among emergency cesarean sections was lowest in the study group, at four out of 134 (2.9 %) [34]. This might be explained by the fact that 30 of 134 patients who underwent emergency cesareans (22.4 %) had PROM/PPROM, so that antibiotics had already been administered before surgery.

Increasing rates of CS — leading to higher rates of repeat cesarean deliveries — should also be mentioned at this point. Severe intraperitoneal and intrauterine adhesions may occur more often after a history of postoperative infection, resulting in more intraoperative complications, prolonged hospital stays, and increased postoperative pain. In addition, intrauterine adhesions may lead to decreased pregnancy rates and require hysteroscopic treatment [35, 36].

Strengths and limitations

To the best of our knowledge, this study is the first to focus on CRP solely after CS. The strength of the study is that a large number of patients with CS were included, and the results can therefore be used to guide clinical management, avoiding testing for CRP routinely after CS when there are no signs of infection. The postpartum period is a vulnerable phase for all women, so that adequate management and treatment are indispensable. The present study also has inherent limitations associated with its retrospective design. The fact that endometritis is a common infection after CS is not reflected in the number of cases. This might be because of another limitation, as the clinicians treating the patients were not blinded to the CRP values. Their knowledge could potentially have influenced decision-making, which can be seen in the large number of patients receiving antibiotic therapy without clinical signs of infection. Another problem is that the dissimilar sample sizes only allow limited interpretation of the data collected. Prospective, randomized studies on CRP testing after cesarean section are warranted.

Conclusion

C-reactive protein testing after cesarean sections appears to have limited value for diagnosing postoperative infection. Clinicians should bear in mind that decision-making on initiating antibiotic therapy should be based on clinical criteria and not on laboratory findings alone. However, CRP can be used to monitor the clinical response to treatment and assess the severity of infection.

Statements and Declarations

Details of ethics approval

The study was approved by the local ethics committee of Upper Austria (K-32–13).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributors' Statement

SE: conceptualization, project administration, data curation, validating and writing original draft. PO: review and editing. RBM: conceptualization, methodology, and project administration. EB: data curation and writing original draft. PST: conceptualization, data curation, review, and editing.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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