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ORIGINAL STUDY

C-reactive protein kinetics and its predictive value in orthopedic (trauma) surgery: A systematic review

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In Orthopedic Trauma Surgery (OTS), C-reactive-protein (CRP) is a widely used marker for the diagnosis of postoperative wound infections (POWI's) and other complications. The aim of this systematic review was to describe specific CRP kinetics and to evaluate the diagnostic value of CRP for te detection of post-operative complications in OTS. The same pattern is reported consistently, where the highest levels of CRP are found at post-operative-day two or three, returning to normal in three weeks. Amplitude varies per procedure. Persistently high CRP levels or secondary increases may indicate complications. A low CRP may be used to rule out complications.

Keywords : C-reactive protein ; diagnostic tool ; orthopedic surgery ; surgical site infection.

INTRODUCTION

Postoperative wound infections (POWI) form one of the biggest challenges in orthopedic (trauma) surgery (OTS). It is estimated that POWI's occur in 1-7% of all arthroplasty patients *(8,11)* and in approximately 3.3 % of patients following internal fixation for fracture treatment *(7)*. Early diagnosis of POWI's can be challenging, laboratory tests however may reveal POWI's and other complications before clinical signs become apparent. Examples of these tests are Erythrocyte Sedimentation Rate (ESR), Leukocyte count and C-Reactive Protein (CRP). More recently revealed markers (e.g. Interleukine-6) also show promise as an accurate predictor of infection *(5,11,14)*. To date, CRP is the most widely used marker for infection in daily practice.

C-reactive protein is an acute phase protein with a half-time of 4-6 hours. Serum levels in healthy individuals do not exceed 10mg/L *(29)*. The serum levels can increase by a thousand-fold within 24-48 hours *(26)*. A rise in CRP levels can be the result of a wide array of conditions, including local and general infections, and also tissue damage. An increase of CRP is a physiological phenomenon after surgical interventions, and its magnitude depends on the amount of surgical trauma *(23)*. CRP levels may be also elevated by default in patients with underlying infections or systemic diseases, such as rheumatoid arthritis *(25,32)*. Even though CRP is a sensitive test for the detection of post-operative complications, its low specificity

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limits its predictive value *(12,34)*. Early detection of POWI's may lead to better treatment outcomes, as early treatment may avert serious adverse events such as chronic osteomyelitis or unplanned removal of implants.

Primary aim of this systematic review was to determine CRP kinetics after various types of OTS. Secondary aim was to evaluate the diagnostic value of post-operative CRP measurements in detecting POWI's in orthopedic (trauma) surgery.

METHODS

This systematic review was performed according to the PRISMA guidelines *(21)*. A literature search was conducted up to the 8th of December 2016 to identify studies that concerned the postoperative course of CRP after OTS. The electronic databases of Pubmed, Cochrane and Embase were explored, using the following keywords and combinations (each modified to fit use in the different databases): 'orthopedic surgery', 'trauma surgery, 'fracture', 'arthroplasty surgery', 'surgical wound infection', and 'C-reactive protein'. The full search is provided in the appendix. Using the Covidence online tool for reviews (www.covidence.org), all abstracts were reviewed by two independent researchers (JK and SD).

Eligible articles were those that considered patients undergoing fracture surgery or primary arthroplasty, with follow-up of the serum CRP of at least 5 days after surgery and on at least 3 separate days. A pre-operative CRP measurement was mandatory to rule out pre-existing elevated CRP levels. Only full versions of original articles were considered, there were no restrictions concerning publication date.

Articles concerning pediatric populations, spinal surgery and all revision arthroplasty surgery were excluded. Authors who did not exclude patients who suffered from any condition that might obscure the course of post-op CRP levels, such as rheumatic or chronic infectious diseases, were also excluded. Language was restricted to English, German and Dutch. In case of disagreement between the two reviewers, the differences were resolved through discussion. The search flowchart is shown in Figure 1. Of each study, data was extracted regarding the number of patients, the location of the fracture or arthroplasty, treatment, the number and timing of CRP measurements, the peak CRP moment and test accuracy if calculated. A separate analysis of total hip arthroplasty, total knee arthroplasty and open & closed fractures was performed. Studies that calculated test specifics (sensitivity, specificity and predictive values) were subjected to bias risk analysis using the QUADAS-2 questionnaire for diagnostic accuracy studies *(37)*. Four different domains were used to screen these studies; patient selection, index test, reference test and flow & timing. In each domain, a different number of signaling questions were answered, resulting in a high, low or unclear risk for bias in that domain. CRP kinetics were pooled for the uncomplicated THA and TKA using a fixed effect model.

RESULTS

The search yielded a total of 1580 articles, of which 482 were duplicates, which were removed. One thousand ninety-eight titles and abstracts were screened, after which 1020 articles were excluded. The remaining 78 articles were eligible for full-text review. Fifty-five articles were excluded after reading full text for following reasons: incompatible intervention (n = 10) (i.e. revision surgery, spinal surgery, implant removal), incompatible study design (n = 29) (i.e. no exclusion of possible influential factors such as rheumatic disease or chronic infections, infection at baseline, short follow-up and insufficient post-surgical CRP measurements), language other than English, Dutch or German (n = 10) and full text unavailable (n = 6). The remaining 23 articles were cross-checked for references, and no additional articles of interest were identified.

CRP kinetics

Total hip arthroplasty (THA) was the most extensively researched procedure. We found 16 articles describing CRP kinetics after THA, with a total number of 629 patients *(1,2,5,10,13,18–20,22,23,27,30,33,35,36,39)*. Results are available in Table I. Serum CRP peaked at postoperative day

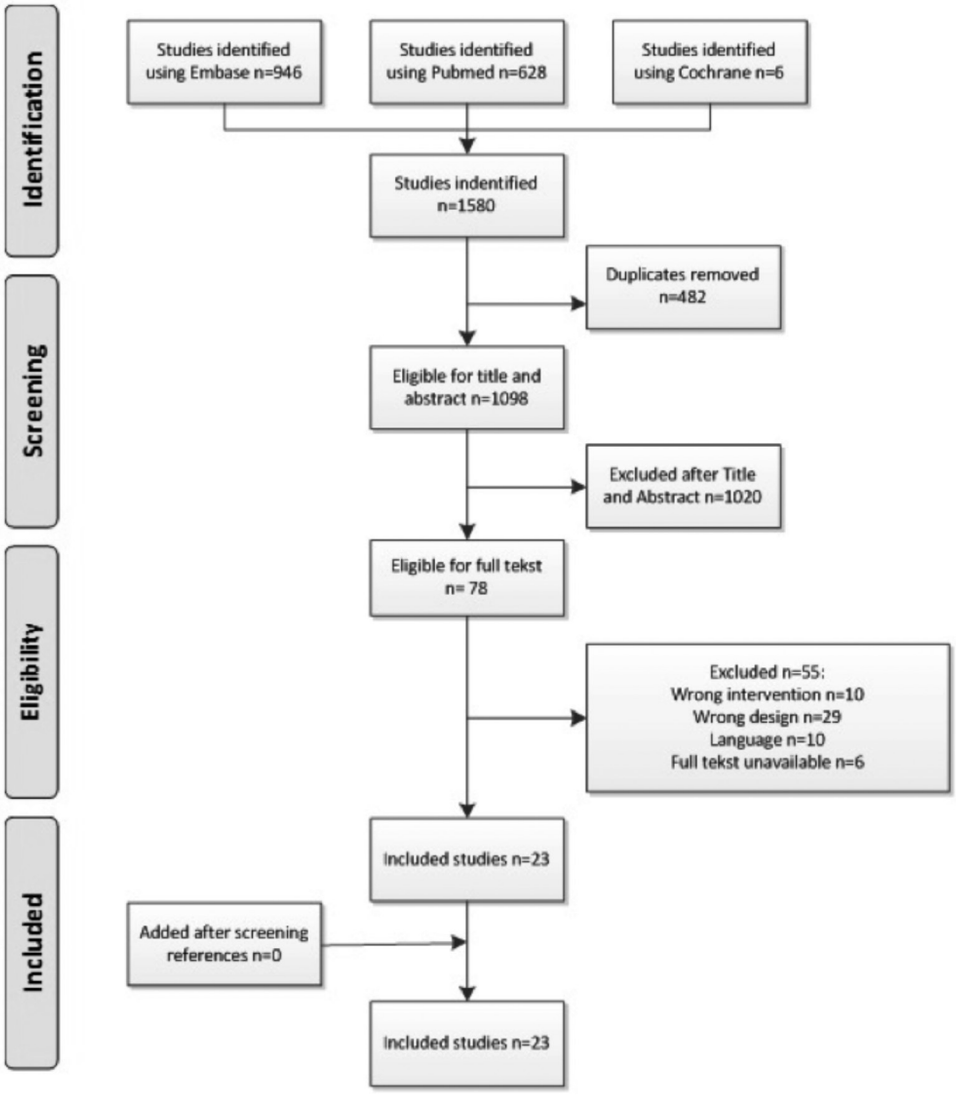

Fig. 1. — Flow-chart literature search according to the PRISMA 2009 Guidelines

(POD) two or three, and reached a mean peak amplitude ranging from 66 mmol/L *(22)* to 185 mmol/L *(18)*. In uncomplicated cases, there was a relatively rapid decline after the peak on day 2-3, to POD 5-7, after which CRP returned slowly to pre-operative levels in three weeks (figure 1). One study analyzed 32 hip fractures in elderly patients of whom 23 were treated by intramedullary nailing and 9 by hemiarthroplasty. CRP peaked at 48-60 hours post-surgery at 165 mg/L (± 15) *(3)*. Pooled CRP kinetics following uncomplicated THA are shown in figure 2.

Twelve authors studied CRP kinetics after total knee arthroplasty (TKA) in a total number of 1607 patients (Table II) *(13,15,18–20,22,28,30,35,36,38,39)*. CRP kinetics in uncomplicated cases were similar to those in THA patients. Pooled CRP kinetics following uncomplicated TKA are shown in figure 3.

There were six studies describing fracture surgery and other miscellaneous procedures *(6,9,20,24,31,39)*. All of these authors excluded multi-trauma patients. It was reported that operative treatment of fractures of the Femur, Tibia, Humerus, Forearm, Ankle and small bones have a lower CRP peak than THA and

Table 1. — CRP kinetics after THA

	No. of THA	Peak POD	Peak amplitude (mean, in mg/L)
Aalto 1984	35	2	134
Battistelli 2014	31	3	107
Bouaicha 2013	31	2	130
Chapman 2016ǂ	50	2	141
Giehl, 2000	20	2	123
Hughes 2013	5	3	101
Kolstad 1995*ǂ	5	2	185
Kragsbjerg 1995*	5	2	160
Larsson 1992	109	3	116
Neumaier 2006	87	2	160
Nazem 2016ǂ	45	2	66ǂ
Okafor 2014	33	2	146
Sastre 2005*	68	2	129
Shih 1986	50	2	135
Wasko 2015	49	2	107
White 1990	13	3	100
Yoon 1993*ǂ	9	2 - 3	60

ǂ Both complicated and uncomplicated cases.*Authors pooled results of THA and TKA procedure

Table II. — CRP kinetics after TKA

	Peak day	No. of TKA	Peak amplitude (mean, in mg/L)
Giehl, 2000	2	20	138
Hughes 2013	3	5	131
Kolstad 1995*ǂ	2	5	185
Kragsbjerg 1995*	2	5	160
Larsson 1990^	2	39	140
Nazem 2016ǂ	2	35	81ǂ
Park 2008ǂ	2	320	158
Sastre 2006*	2	75	129
Wasko 2015	2	51	121
White 1990	2	13	155
Yoon 1993*ǂ	2-3	5	60
Windisch 2016	2	1034	170

ǂ= Both complicated and uncomplicated cases *Authors pooled results of TKA and THA procedures. ^Unicondilar procedure.

TKA surgery (Table III). CRP kinetics however after fracture surgery follow a similar pattern to joint arthroplasty surgery. The magnitude of the CRP response is different for each intervention. Two studies describe multiple types of fracture surgery separately *(24,31)*. These studies report highest peak levels in proximal femur fractures (165 *(9)* and 154 mg/L *(31)*), followed by Humerus (82 mg/L) *(24)* and Tibia fractures (79 mg/L) (Table 3) *(31)*.

Open and closed fractures

Bourguignat et al. analyzed a population of open fractures, and reported a peak mean CRP of 77,3 mg/L. The population consisted of Femur,

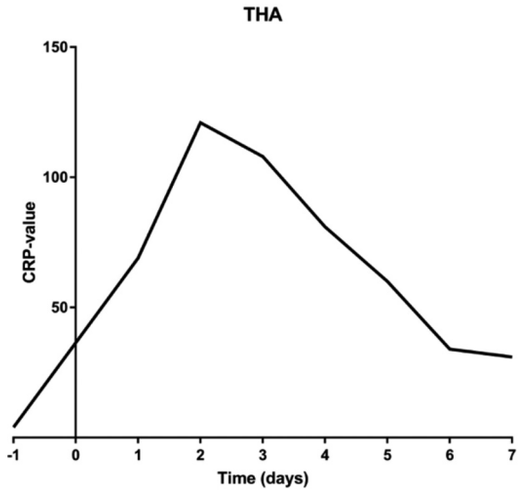

Fig. 2. — Pooled CRP kinetics following uncomplicated THA

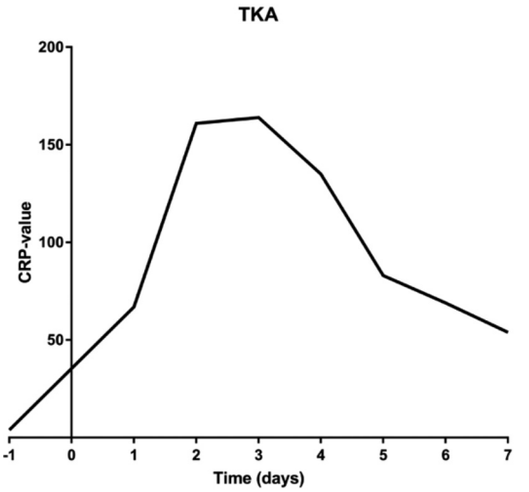

Fig. 3. — Pooled CRP kinetics following uncomplicated TKA

Table III. — CRP kinetics after miscellaneous procedures

	Fracture site	Peak day	Peak amplitude (mean, in mg/L)
Bourguignat 1996[i]	Femur (n = 4) Knee (n = 6) Tibia (n = 51) Ankle (n = 15) Foot (n = 4)	4	71.5
Bulut 2010	Proximal femur (n=29)	2	165
Kallio 1990	Tibia: Conservative (n = 27) Tibia: Intramedullairy nailing (n= 10) Tibia: Open reduction, internal fixation (n = 5)	2 6 2	42 67 105
Larsson 1992	THA (n = 109) TKA revisions (n = 9) Knee, unicondilar (n = 39) Microdiscectomy (n = 36)	3 3 2 2	116 136 140 48
Neumaier 2008[i]	Femur (n=362) Tibia (n =113) Humerus (n=88) Elbow & forearm (n=61) Ankle & small bones (n=163)	2 2 2 2 2	136 78 82 44 39
Scherer 2001[i]	Femur (n=81) Tibia + anterior cruciate ligament rupture (n=57) Humerus (=17) Elbow + fore arm (n=40) Ankle + small bones (n=85)^ Implant removal (n=24)	2 2 2 2 2 2	154 79 71 46 65 34
Yoon 1993[i]	Long bone fractures (n=57) (Humerus n = 6, forearm n = 8, femur n = 19 tibiofibular n = 24)	2	53

ǂ= Both complicated and uncomplicated cases ^Including open fractures

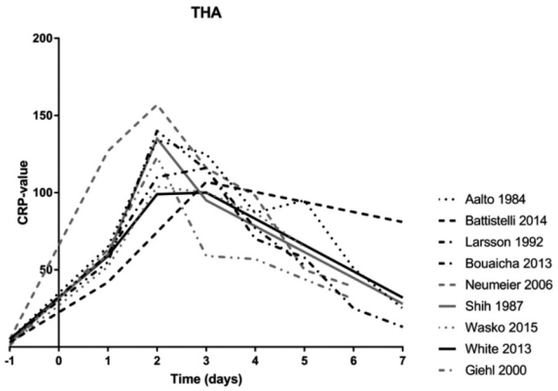

Fig. 4. — Different CRP kinetics after THA

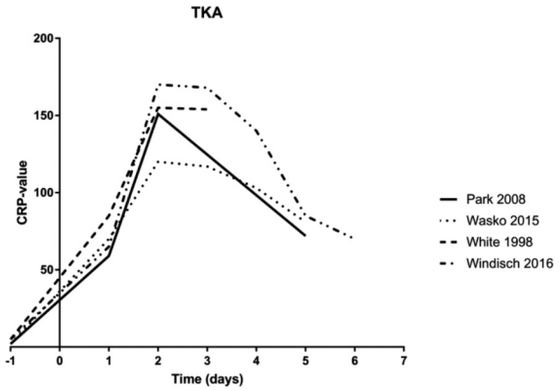

Fig. 5. — Different CRP kinetics after TKA

Table IV. — Diagnostic test characteristics

Author	Intervention(s)	POD nr.	Cutoff (mg/L)	Sens	Spec	PPV	NPV
Beloosesky 2004	Intramedullary nailing (n = 23) Hemiarthroplasty (n = 9)	From day 3	150	93%	65%	-	-
Bourguignat* 1996	Femur (n = 4) Knee (n = 6) Tibia (n = 51) Ankle (n = 15) Foot (n = 4)	From day 8	100	67%	89%	-	-
Neumaier* 2008	Femur (n = 362) Tibia (n = 113) Humerus (n = 88) Elbow/forearm (n = 61) Ankle/small bones (n = 163)	From day 3	96	92%	93%	-	-
Sastre 2006	THA (n = 68) TKA (n = 75)	From day 5	60	60%	92%	98%	17%
Scherer 2001	Femur (n = 81) tibia fractures & anterior cruciate ligament ruptures (n = 57) Humerus (n = 17) Elbow & forearm (n = 40) spinal surgery (n = 26) ankle & small bones (n = 85) implant removal (n = 24)	From day 4	140	100%	98.4%	-	-

*= exclusively postoperative wound infections Sens = sensitivity. Spec = specificity. PPV = positive productive value. NPV = negative predictive value.

Table V. — Risk of bias analysis, using Quadas-2 tool

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Beloosesky 2004	☺	☺	☺	☹	☺	☺	☺
Bourguignat 1996	☹	☺	☺	☹	☺	☺	☺
Neumaier 2008	☺	☺	☹	☹	☺	☺	☺
Scherer 2001	☺	☺	☺	☹	☺	☺	☺
Sastre 2006	?	☺	☹	☹	☺	☺	☺

☹ = high risk ☺ = low risk ? = unclear

Tibia and foot fractures *(6)*. Kallio et al. reported a slightly higher CRP in open fractures (58,4 mg/L) compared to closed fractures (54,7 mg/L). However, this difference was not significant *(17)*. Yoon et al. reported a secondary CRP rise in conservatively treated fractures. Authors attribute this second rise to the required repeated debridement of the open wounds and secondary closure. There was no difference in CRP levels at the three-week mark *(39)*.

The global pattern of CRP behavior was similar in all types of fractures and interventions. There is a peak at POD two or three. In uncomplicated cases, CRP will then decline to normal levels in two to three weeks. The decline is initially rapid, and evens out when it approaches normal levels. A secondary peak was explicitly found to be indicative of post-operative complications in 5 studies *(3,17,20,31,36)*.

Diagnostic value of CRP

Five studies evaluated CRP measurements as a diagnostic tool for detecting complications (table IV) *(3,6,24,30,31)*. Neumaier and Bourguinat were

the only authors to exclusively look at POWI's, the other authors assessed complications in general (including POWI's). All authors used different cut-off values for different procedures on different time points. There was no uniform gold standard test, i.e. authors used different endpoints for the detection of POWI's. Some authors used a positive wound culture as a reference test, others used clinical parameters such as redness, pain and purulent drainage. Sensitivity of CRP measurements ranged from 60 to 100% and specificity from 65 to 98,4%. Sastre et al. also calculated negative and positive predictive values; these were 17 and 98% respectively *(30)*. Due to the heterogeneity between the studies a meta-analysis of test characteristics was not possible.

Risk of Bias

Bourguignat et al was considered to have high risk of bias in the patient selection for not defining exclusion criteria *(6)*. Neumaier et al. did not describe reference testing sufficiently and therefore is prone to bias in the reference test section *(24)*. Sastre et al. did not describe reference testing and is therefore susceptible to bias in that area *(30)*. All studies pooled outcomes from different procedures although we know that different procedures know different CRP kinetics. Therefore all studies are prone for bias in the flow & timing domain (Table IV).

DISCUSSION

In this study we present a comprehensive systematic review of the current literature regarding post-operative CRP levels in patients undergoing orthopedic (trauma) surgery. We found that in uncomplicated cases, CRP follows a similar pattern after every orthopedic (trauma) intervention. There is a sharp increase in CRP levels, peaking after 48 to 72 hours, followed by a rapid decline, returning to normal levels after 2 to 3 weeks. The type of trauma and surgery correlates with CRP levels. For instance, the highest CRP levels were reached in femur fractures with mean peak values between 136 and 154 mg/L, as opposed to ankle fractures, with amplitude with a mean peak of 34 – 39 mg/L in uncomplicated cases *(24,31)*. After POD 3, CRP declines in uncomplicated cases and in case of stagnation or secondary increase, an underlying complication may be present. There were five studies calculating test characteristics, with a sensitivity between 60% and 100% and specificity between 65% and 98%. Only one study provided predictive values, with a PPV of 98% and NPV of 17% *(3,6,24,30,31)*.

CRP kinetics follow the same pattern after different types of surgical procedures. The amplitude of the CRP peak however, differs between the procedures. Notably, it has been stated that even an untreated femur fracture causes a rise in CRP and thus the total post-surgical increase can be partly explained by the trauma itself *(17)*. Therefore, we believe that the different CRP peak is partially the consequence of the trauma mechanism and partially of the surgical treatment, with both factors causing a certain amount of tissue damage. CRP kinetics after abdominal surgery follow a similar pattern, also with a peak at POD two or three *(12,34)*.

Some studies have compared uncomplicated procedures with complicated procedures, calculating test accuracy ratings for post-operative CRP *(3,6,10,24,31)*. Authors calculated different optimal cutoff values for CRP on different post-operative days. Unfortunately there were methodological differences between those studies and authors used different patient groups for their analysis. Four authors pooled different procedures. We believe their results are inaccurate, since each procedure produces a different CRP peak *(4,6,24,31)*.

Chapman et al. developed a predictive model for the expected CRP value on a certain POD, accurate between POD five and thirty; 500/d (d = POD). A CRP higher than the predicted value raises suspicion for post-operative complications *(10)*.

Five studies exclusively considered POWI's, with incidence rates ranging from 2.7% to 11.4% *(6,9,10,27,31)*. Others also considered other complications as an endpoint, these include urinary tract infections and pneumonia. This reflects the main weakness of CRP as a diagnostic tool, namely its low specificity.

Open fractures produce a slightly higher CRP peak *(17)*. This may be caused by the increased energy of the trauma in these injuries. Wound

debridement and secondary closure may cause a secondary increase of serum-CRP, as a results of surgical trauma *(39)*. Evidence on open versus closed fractures is limited.

Blood transfusions, amount of blood loss, type of anesthesia and administered drugs do not correlate with a higher CRP peak *(20,24)*. The use of a tourniquet seems to increase CRP production in the first 15 minutes after perfusion, but it is unclear whether longer-term CRP is affected *(16)*. A high body mass index (BMI) seems to significantly increase post-operative CRP levels after both THA and TKA procedures *(35)*. The largest cohort study on uncomplicated TKA so far found significantly higher CRP values in men on POD 2-5 and 7-8 *(38)*.

One earlier systematic review by Nunes et al. was performed on CRP kinetics after surgery including orthopedic trauma surgery. A pooled test sensitivity and specificity were calculated, resulting in a sensitivity of 85% and a specificity of 86%. The validity of the calculations may be disputed, as the authors pooled results from both gastrointestinal and orthopedic trauma studies. Also, no references are provided to the original studies and their outcomes *(26)*.

In gastro-intestinal surgery, two systematic reviews calculated test characteristics for CRP. They found very similar kinetics to orthopedic and trauma surgery. Pooled cutoff values were 159 mg/L *(12)* and 140 mg/L on POD 3 *(34)*. Authors state that the positive predictive value is limited, but a low CRP can be used to rule out complications with high certainty. Furthermore, additional diagnostic evaluation is recommended in case of a CRP > 215 mg/L on POD 5 *(34)*. We believe that the same characteristics may apply to CRP in OTS, but the cutoff value may vary per trauma/intervention.

In OTS several authors have pooled different surgical procedures to establish a 'common' cutoff-value. We believe such cut-off values are certainly useful in clinical practice but should be intervention specific. Another option would be to follow CRP levels on designated moments after surgery. A deviation from the 'normal' course is more predictive for complications than one single CRP value. If there is a higher-than-expected peak at day 2 or 3, or if there is a secondary increase in CRP, a complication may be present and additional diagnostics might be indicated.

Several limitations have to be taken into account. Firstly, there is no standard definition for the diagnosis of POWI's. Many studies use different diagnostic criteria, hampering interpretation of the different test characteristics (i.e. sensitivity and specificity). Secondly, the studies we included in our analysis show great methodological heterogeneity, making it impossible to perform meta-analysis. Thirdly, most of the reports in our review are not designed to look at POWI's specifically. The incidence of POWI's is usually low and most authors focus on any major complication, including general infections such as urinary tract infections and pneumonia.

However, this is the first attempt to establish a practical interpretation of CRP values in OTS, following similar studies in abdominal surgery.

We believe that the high negative predictive value of a normal CRP is the most valuable asset and CRP is less suitable to differentiate between various types of complications, as any septic complication will cause an increase in CRP level. Clinical evaluation remains the prime tool for a patient with suspected post-operative complications. In order to establish an accurate model for the predictive value of CRP testing after orthopedic trauma surgery, a large prospective study is needed, with regular CRP evaluation at fixed intervals and a uniform golden standard for clinical evaluation of POWI's and other complications. This could especially be of value in high-risk surgery such as surgery for open fractures or calcaneal fractures.

CONCLUSION

In uncomplicated cases, CRP values peak at POD two or three. Each intervention has its own distinct peak value. In current literature, authors established a sensitivity between 60% and 100% and specificity between 65% and 98% for CRP as a diagnostic tool. Low CRP levels following OTS may rule out- and a secondary rise may be indicative of postoperative complications. However more prospective research towards the clinical value of CRP measurements as a diagnostic tool is needed especially in the light of its low specificity.

Compliance with ethical standards:

- The authors declare that they have no conflict of interest.
- No funding was received for this project
- Research involving human participants and/or animals: This article does not contain any studies with human participants or animals performed by any of the authors.

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REFERENCES

1. **Aalto K, Osterman K, Peltola H, Räsänen J.** Changes in erythrocyte sedimentation rate and C-reactive protein after total hip arthroplasty. *Clin Orthop Relat Res.* 1984 ; 118-120.
2. **Battistelli S, Fortina M, Carta S** *et al.* Serum C-reactive protein and procalcitonin kinetics in patients undergoing elective total hip arthroplasty. *Biomed Res Int.* 2014.
3. **Beloosesky Y, Grinblat J, Pirotsky A** *et al.* Different C-Reactive Protein Kinetics in Post-Operative Hip-Fractured Geriatric Patients with and without Complications. *Clin Sect Gerontol.* 2004 ; 50 : 216-222.
4. **Beloosesky Y, Hendel D, Weiss A** *et al.* Cytokines and C-Reactive Protein Production in Hip-Fracture-Operated Elderly Patients. *Journal of Gerontology: Medical Sciences.* 2007 ; 62 : 420-426.
5. **Bouaicha S, Blatter S, Moor BK** *et al.* Clinical Study Early Serum Procalcitonin Level after Primary Total Hip Replacement. *Mediators Inflamm.* 2013.
6. **Bourguignat A, Ferard G, Jenny J-Y** *et al.* Diagnostic value of C-reactive protein and transthyretin in bone infections of the lower limb. *Clin Chim Acta.* 1996 ; 255 : 27-38.
7. **Boxma H, Broekhuizen T, Patka P** *et al.* Randomised controlled trial of single-dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch Trauma Trial. *Lancet.* 1996 ; 347 : 1133-1137.
8. **Buchheit J, Uhring J, Sergent P** *et al.* Can preoperative CRP levels predict infections of bipolar hemiarthroplasty performed for femoral neck fracture? A retrospective, multicenter study. *Eur J Orthop Surg Traumatol.* 2014.
9. **Bulut G, Yasmin D, Ak D, Yldz M.** Value of procalcitonin in differentiating post-surgical systemic and infectious complications from inflammatory reaction caused by surgical trauma in fracture surgery: preliminary report. *Eur J Orthop Surg Traumatol.* 2010 ; 20 : 1-10.
10. **Chapman G, Holton J, Chapman A.** A threshold for concern? C-reactive protein levels following operatively managed neck of femur fractures can detect infectious complications with a simple formula. *Clin Biochem.* 2016 ; 49 : 219-224.
11. **Elgeidi A, Elganainy AE, Abou Elkhier N** *et al.* Interleukin-6 and other inflammatory markers in diagnosis of periprosthetic joint infection. *Int Orthop.* 2014 : 38 : 2591–2595.
12. **Gans SL, Atema JJ, Van Dieren S** *et al.* Diagnostic value of C-reactive protein to rule out infectious complications after major abdominal surgery: a systematic review and meta-analysis. *Int J Colorectal Dis.* 2015 ; 30 : 861–873.
13. **Giehl JP, Kluba T, Lebherz C.** Entzundungs-parameterverlauf nach elektiven orthopadischen Eingriffen. *Z Orthop.* 2000 ; 138 : 181-184.
14. **Honsawek S, Deepaisarnsakul B, Tanavalee A** *et al.* Relationship of serum IL-6, C-reactive protein, erythrocyte sedimentation rate, and knee skin temperature after total knee arthroplasty: A prospective study. *Int Orthop.* 2011 : 35 : 31-35.
15. **Hughes SF, Hendricks BD, Edwards DR** *et al.* Lower limb orthopaedic surgery results in changes to coagulation and non-specific inflammatory biomarkers, including selective clinical outcome measures. *Eur J Med Res.* 2013 ; 18:1.
16. **Hughes SF, Hendricks BD, Edwards DR** *et al*. Tourniquet-applied upper limb orthopaedic surgery results in increased inflammation and changes to leukocyte, coagulation and endothelial markers. *PLoS One.* 2010 (5,7).
17. **Kallio P, Michelsson J-E, Lalla M** *et al.* C-Reactive protein in tibial fractures natural response to the injury and operative treatment. 1990;72.
18. **Kolstad K, Levruider H.** Inflammatory Laboratory Tests after Joint Replacement Surgery. *Upsala J Med Sci.* 1995 ; 100 : 243-248.
19. **Kragsbjerg P, Holmberg H, Vikerfors T.** Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *Eur J Surg.* 1995 ; 161 : 17-22.
20. **Larsson S, Thelander U, Friberg S.** C-Reactive Protein (CRP) Levels After Elective Orthopedic Surgery. *Clin Orthop Relat Res1.* 1992 ; 275 : 237-242.
21. **Liberati A, Altman DG, Tetzlaff J** *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009 ; 6 : e 1000100.
22. **Nazem K, Motififard M, Yousefian M.** Variations in ESR and CRP in total knee arthroplasty and total hip arthroplasty in Iranian patients from 2009 to 2011. *Adv Biomed Res.* 2016 ; 5 : 148.
23. **Neumaier M, Metak G, Scherer MA.** C-reactive protein as a parameter of surgical trauma CRP response after different types of surgery in 349 hip fractures. *Acta Orthop.* 2006 ; 77 : 788-790.
24. **Neumaier M, Scherer MA.** C-reactive protein levels for early detection of post- operative infection after fracture surgery in 787 patients. *Acta Orthop.* 2008 ; 79 : 428-432.
25. **Ng T.** Erythrocyte sedimentation rate, plasma viscosity and C-reactive protein in clinical practice. *Br J Hosp Med.* 1997; 58:521-523.

26. **Nunes B, Lacerda R, Jardim J.** Systematic review and meta-analysis of the predictive value of c-reactive protein in postoperative infections. *Rev Esc Enferm USP.* 2011 ; 45 : 1480-1485.
27. **Okafor B, MacLellan G.** Postoperative changes of erythrocyte sedimentation rate, plasma viscosity and C-reactive protein levels after hip surgery. *Acta Orthop Belg.* 1998 ; 64 : 52-56.
28. **Park K, Kim T, Chang C** *et al.* Normative temporal values of CRP and ESR in unilateral and staged bilateral TKA. *Clin Orthop Relat Res.* 2008 ; 466 : 179-188.
29. **Pepys M, Hirschfield G.** C-reactive protein: a critical update. *J Clin Invest.* 2003 ;111 : 1805-1812.
30. **Sastre S, Soriano Á, Garcia S, Martínez JA** *et al.* Serum C-reactive protein as predictor of infected arthroplasty. *Eur J Orthop Surg Traumatol.* 2006 ; 16 : 17–19.
31. **Scherer M a, Neumaier M, Gumppenberg S von.** C-Reactive Protein in Patients Who Had Operative Fracture Treatment. *Clin Orthop Relat Res.* 2001 ; 393 : 287-293.
32. **Schwenger V, Sis J, Breitbart A, Andrassy K.** CRP levels in autoimmune disease can be specified by measurement of procalcitonin. *Infection.* 26 : 274-276.
33. **Shih L, Wu J, Yanc D.** Erythrocyte Sedimentation Rate and C-reactive Protein Values in Patients with Total Hip Arthroplasty. *Clin Orthop Relat Res.* 1987.
34. **Straatman J, Harmsen A, Cuesta M** *et al.* Predictive value of C-reactive protein for major complications after major abdominal surgery: A systematic review and pooled-analysis. *PLoS One.* 2015.
35. **Wasko MK, Bobecka-Wesołowska K, Kowalczewski J** *et al.* Measurement of the inflammatory response in the early postoperative period after hip and knee arthroplasty. *Clin Chem Lab Med.* 2015 ; 53 : 1785-1792.
36. **White J, Kelly M, Dunsmuir R.** C-reactive protein level after total hip and total knee replacement. *Bone Jt Surg* [Br]. 1998 ; 8080 : 909-911.
37. **Whiting P, Rutjes A, Westwood M** *et al.* QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Ann Intern Med.* 2011 ; 155 : 529.
38. **Windisch C, Brodt S, Roehner E** *et al.* The C-reactive protein level after total knee arthroplasty is gender specific. Knee Surgery, *Sport Traumatol Arthrosc.* 2016 ; 24 : 3163-3167.
39. **Yoon S, Lim S, Rha J** *et al.* The C-reactive protein (CRP) in patients with long bone fractures and after arthroplasty. *Int Orthop.* 1993 ; 17 : 198-201.