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# Changes in perioperative C-reactive protein levels in patients with rheumatoid arthritis undergoing total knee arthroplasty in the biologic era

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## ABSTRACT

This study aimed to investigate changes in and factors associated with perioperative serum C-reactive protein (CRP) levels in rheumatoid arthritis (RA) patients undergoing total knee arthroplasty (TKA) in the biologic era. A total of 173 patients (228 knees) with RA underwent elective primary TKA at our institute between January 1, 2006 and December 31, 2018. Of these, 214 cases among 161 patients were examined in this retrospective study after excluding 3cases among 3 patients who developed postoperative complications and 11 cases among 9 patients who were treated with tocilizumab. Factors associated with changes in CRP levels between baseline (preoperative) and day 7 after TKA [ΔCRP (0–7days)] were assessed by multiple regression analysis. Median (interquartile range) CRP levels were 0.69 (0.21, 1.82) mg/dl preoperatively, 5.66 (4.21, 7.61) mg/dl on postoperative day 1, 12.75 (9.79, 16.74) mg/dl on postoperative days 3–4, 3.26 (2.21, 4.85) mg/dl on postoperative day 7, and 0.87 (0.45, 1.81) mg/dl on postoperative day 14. Multivariate regression analysis revealed that body mass index ≥25 [partial regression coefficient (B)=1.03, *P*=0.012] and use of glucocorticoids (B=–0.86, *P*=0.017) were independently associated with ΔCRP (0–7days), whereas use of methotrexate and targeted drug modifying antirheumatic drugs and preoperative CRP levels (an objective biomarker of RA activity) were not. In conclusion, serum CRP levels increased rapidly after TKA and peaked on postoperative days 3–4, followed by a return to preoperative levels by postoperative day 14 in patients with RA. Obesity and the use of glucocorticoids were independently associated with changes in CRP levels.

Keywords: arthroplasty, C-reactive protein, glucocorticoids, obesity, rheumatoid arthritis

Abbreviations:
CRP: C-reactive protein
RA: rheumatoid arthritis
TKA: total knee arthroplasty
OA: osteoarthritis
SSI: surgical site infection

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IL-6: interleukin-6
MTX: methotrexate
TCZ: tocilizumab
DMARDs: drug modifying antirheumatic drugs
BMI: body mass index
GCs: glucocorticoids
MMP3: matrix metalloproteinase-3
IQRs: interquartile ranges



## INTRODUCTION

Orthopedic procedures are performed in patients with rheumatoid arthritis (RA) who have functional disability due to severe joint destruction.[1] Total knee arthroplasty (TKA), a common orthopedic procedure, improves function and pain in patients with RA, as well as those with osteoarthritis (OA).[2] Patients with RA are at high risk of postoperative complications, including surgical site infection (SSI), after TKA.[3] According to previous studies, the rate of SSIs after TKA was 3-fold higher in patients with RA compared to those with OA due to immune disorders from RA itself and anti-rheumatic drug use.[4,5] Orthopedic SSIs are associated with substantial morbidity and prolonged hospital stays, resulting in an economic burden on both patients and society.[6] SSIs after TKA are difficult to treat, and thus their early detection is crucial for reducing the severity and duration of infection.

C-reactive protein (CRP) is an acute phase reactant synthesized in the liver in response to pro-inflammatory cytokines [eg, interleukin-6 (IL-6)],[7] and is widely used as an indicator of infection. Tissue damage and SSIs can increase serum CRP levels in patients undergoing major surgery,[8,9] and thus distinguishing between the two is difficult. Changes in perioperative CRP levels without SSIs may allow for the assessment of increases in CRP levels owing to SSIs. In addition, RA activity and antirheumatic drugs may influence perioperative CRP levels in RA patients since RA is a systemic inflammatory disease and antirheumatic drugs have anti-inflammatory effects. Treatment strategies for RA have greatly advanced over the last few decades, and aggressive therapies including methotrexate (MTX) and biologics have enabled more patients to achieve a controlled disease state. We recently reported that preoperative CRP levels showed a significant decreasing trend with more aggressive treatment with MTX and biologics in RA patients undergoing total joint replacement.[10] While a number of studies have examined changes in CRP levels after TKA in RA patients, those studies were conducted before the biologic era[11,12] and did not address the impact of RA activity and antirheumatic drugs on perioperative CRP levels.

This study aimed to investigate changes in perioperative serum CRP levels in RA patients undergoing elective primary TKA in the biologic era. We also examined the influence of patient characteristics, including preoperative CRP levels (an objective biomarker of disease activity in RA), and drugs used to treat RA on perioperative CRP levels.

## MATERIALS AND METHODS

*Subjects*

A total of 173 RA patients (228 knees) underwent elective primary TKA at our institute between January 1, 2006 and December 31, 2018. All patients met the 1987 American College

of Rheumatology (ACR) classification criteria[13] or the new ACR/European League Against Rheumatism (EULAR) diagnostic criteria.[14] A flow chart of case selection is provided in Figure 1. Given our focus on assessing perioperative changes in CRP levels, we excluded 3 cases among 3 patients who developed perioperative infections (1 SSI and 2 urinary tract infections) because perioperative infections are known to affect serum CRP levels.[9] Moreover, given that tocilizumab (TCZ), a monoclonal anti-IL-6 receptor antibody, is known to decrease serum CRP levels by inhibiting IL-6 even after surgery,[15,16] we excluded 11 cases among 9 patients who were treated with TCZ. Thus, the final study population for this retrospective study consisted of 214 cases among 161 patients.

This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine (2018-0260) and complied with the principles set forth in the Declaration of Helsinki. Informed consent was obtained by an opt-out procedure. Subject anonymity was maintained during data collection, and the security of personal information was strictly controlled.

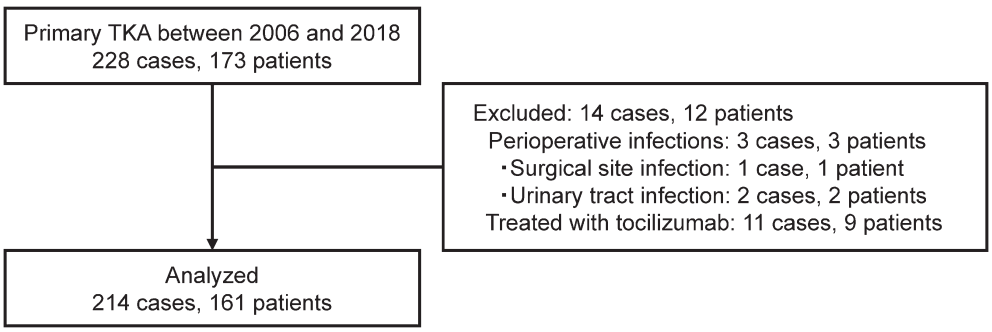


**Fig. 1** Flowchart of patient selection

TKA: total knee arthroplasty

*Surgical method and perioperative management*

All TKAs were performed with an inflated tourniquet under general anesthesia. Femoral, tibial, and patellar components (Nexgen, Zimmer Inc., Warsaw, IN, USA) were fixed using polymethylmethacrylate cement. An intra-articular suction drain was used for 1–2 days, and intravenous antibiotics were administered for 2 days after TKA. Postoperatively, full weight bearing was allowed after drain removal depending on the degree of pain. MTX and targeted drug modifying antirheumatic drugs (DMARDs) were typically withheld for one dosing interval before surgery, and restarted postoperatively if the surgical wound was healing and there were no local or systemic signs of infection.

*Data collection*

Demographic and clinical data of patients at the time of TKA were retrospectively collected from clinical records, and included the following: age, sex, body mass index (BMI), diabetes, disease duration of RA, use of MTX, glucocorticoids (GCs), and/or targeted DMARDs, serum matrix metalloproteinase-3 (MMP3) levels, surgery time, and amount of intraoperative blood loss. Data on serum CRP levels before and 1, 3–4, 7, and 14 days after TKA were also retrospectively collected. For postoperative day 7 and day 14 assessments, a margin of ±1 day was allowed.

*Statistical analysis*

Continuous variables are expressed as median and interquartile ranges (IQRs), while categorical variables are expressed as percentages. Previous studies showed that serum CRP levels were still higher at 1 to 2 weeks after TKA in patients with postoperative complications (eg, SSIs) than in those without,[9,17] and that serum CRP levels in most patients without complications return to preoperative levels by 2 weeks after surgery.[18] A recent study found no significant difference in CRP levels during the first 5 days after TKA between patients with early prosthetic joint infection and those without.[19] Hence, subgroup analyses were also performed in which changes in CRP levels from baseline (preoperative) to postoperative day 7 [ΔCRP (0–7days)] were compared according to the following variables using the Mann-Whitney U test: use of MTX [MTX (+/–) groups], GCs [GC (+/–) groups], and/or targeted DMARDs [targeted DMARD (+/–) groups], and preoperative CRP levels (>1.0 mg/dl [CRP (+) group] vs ≤1.0 mg/dl [CRP (–) group] based on ACR/EULAR remission criteria). Factors associated with ΔCRP (0–7days) were assessed by multiple regression analysis with the above described variables, as well as the following variables at the time of TKA: age (≥65 vs <65 years), sex, BMI (≥25 vs <25, based on the cut-off point for obesity in Japan), diabetes, disease duration (≥10 vs <10 years), serum MMP-3 levels [ ≤121.0 (male) and 59.7 (female) ng/ml vs >121.0 (male) and 59.7 (female) ng/ml, based on normal upper limit), surgery time (≥120 vs <120 minutes, based on the median time), and amount of intraoperative blood loss (≥70 vs <70 ml, based on the median amount).

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[20] $P<0.05$ was considered statistically significant.

## RESULTS

*Demographic and clinical characteristics*

Table 1 summarizes the demographic and clinical characteristics of the 214 cases among 161 patients included in the study. Among the analyzed cases, 137 (64%) received MTX at a median (IQR) dose of 8 (6, 8) mg/week, 109 (51%) received GCs at a median (IQR) dose of 5 (3, 5) mg/day, and 72 (34%) received targeted DMARDs (ie, etanercept, 41; infliximab, 14; adalimumab, 4; golimumab, 5; abatacept, 7; tofacitinib, 1). The median (IQR) preoperative CRP level was 0.69 (0.21, 1.82) mg/dl.

**Table 1** Demographics and clinical characteristics

| Characteristics | Total (n=214) | |
|---|---|---|
| Age, years | 65 | (61, 71) |
| Female, % | 84 | |
| Body mass index | 23 | (20, 26) |
| Disease duration, years | 12 | (7, 20) |
| Diabetes, % | 6 | |
| Use of methotrexate, % | 64 | |
| Methotrexate dose, mg/week* | 8 | (6, 8) |
| Use of glucocorticoids, % | 51 | |
| Glucocorticoid dose, mg/day* | 5 | (3, 5) |
| Use of targeted DMARDs, % | 34 | |
| Preoperative CRP, mg/dl | 0.69 | (0.21, 1.82) |
| Preoperative MMP3, ng/ml† | 166 | (91.6, 835) |
| Surgery time, min | 119 | (102, 135) |
| Intraoperative blood loss, ml | 71 | (31, 133) |

Data are presented as median values (interquartile range) or percentages.
*Median among subjects receiving the drug.
†Data were available for 202 cases.
DMARDs: disease modifying antirheumatic drugs
CRP: C-reactive protein
MMP3: matrix metalloprotease 3

*Changes in perioperative CRP levels*

Changes in perioperative CRP levels are shown in Figure 2. Among the analyzed cases, 3 (1.3%) had disease flares within 1week after TKA. Serum CRP levels on postoperative days 1, 3–4, 7, and 14 were available for 203, 192, 151, and 119 cases, respectively. CRP levels increased from postoperative day 1, peaked on postoperative days 3–4, and then returned to preoperative levels by postoperative day 14. Median (IQR) CRP levels were 5.66 (4.21, 7.61) mg/dl, 12.75 (9.79, 16.74) mg/dl, 3.26 (2.21, 4.85) mg/dl, and 0.87 (0.45, 1.81) mg/dl on postoperative days 1, 3–4, 7, and 14, respectively. A case with SSI was more likely to have higher CRP levels on postoperative days 3–4 to 14 relative to those without SSIs (Supplementary Fig. 1a). Increases in CRP levels were suppressed during the perioperative period in patients treated with TCZ (Supplementary Fig. 1b).

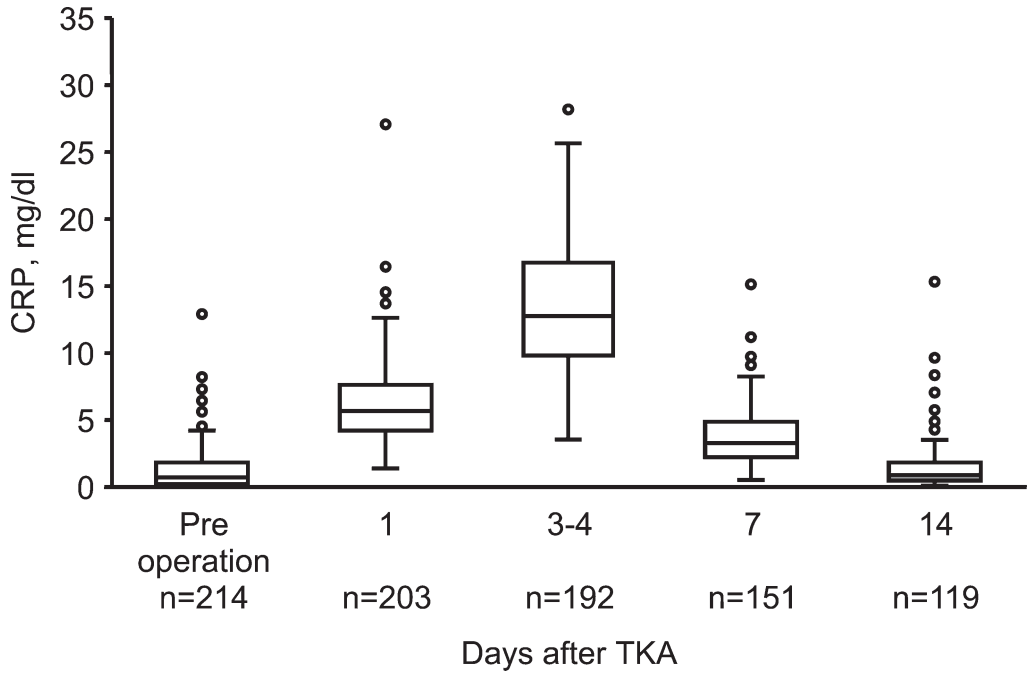


**Fig. 2** Changes in C-reactive protein (CRP) levels after total knee arthroplasty (TKA)
The box plot shows the median value (central line) and 25th and 75th percentiles (horizontal lines); whiskers indicate minimum and maximum values; and circles represent outliers.

*Factors associated with perioperative CRP levels*

Factors associated with change in perioperative CRP levels were analyzed in 151 cases among 123 patients from whom data for serum CRP levels were available on postoperative day 7. There were no significant differences in most baseline characteristics, except for MTX dose and preoperative CRP levels, between the analyzed cases and those excluded due to missing data (Supplementary Table 1).

A significantly lower ΔCRP (0–7days) was observed in the GC (+) group (n=74) relative to the GC (–) group (n=77) [median (IQR), 2.07 (1.14, 3.05) vs 2.99 (1.39, 4.22), *P*=0.015] (Fig. 3b), and in the CRP (+) group (n=49) relative to the CRP (–) group (n=102) [median (IQR), 2.66 (1.6, 4.04) vs 2.05 (0.49, 3.37), *P*=0.017] (Fig. 3d). There was no significant difference in ΔCRP (0–7days) when stratified by use of MTX and targeted DMARDs (Figs. 3a, 3c). Partial regression coefficient (B) for ΔCRP (0–7days) was calculated using multiple regression analysis. Preoperative CRP and MMP-3 levels were entered separately as variables in Models 1 and 2, respectively, in order to avoid multicollinearity. BMI ≥25 (B=1.03, *P*=0.012) and use of GCs (B=–0.86, *P*=0.017), but none of the other assessed variables, were independently associated with ΔCRP (0–7days) in Model 1 (Table 2). Similar results were observed in Model 2 (Supplementary Table 2). In addition, multiple regression analysis was performed in 101 cases among 85 patients from whom data for serum CRP levels were available on at all time points (ie, preoperative, postoperative days 1, 3–4, 7, and 14 after surgery) (Supplementary Table 3). BMI ≥25 was independently associated with ΔCRP (0–7days) (B=1.35, *P*=0.011), and use of GC tended to be so (B=–0.81, *P*=0.070).

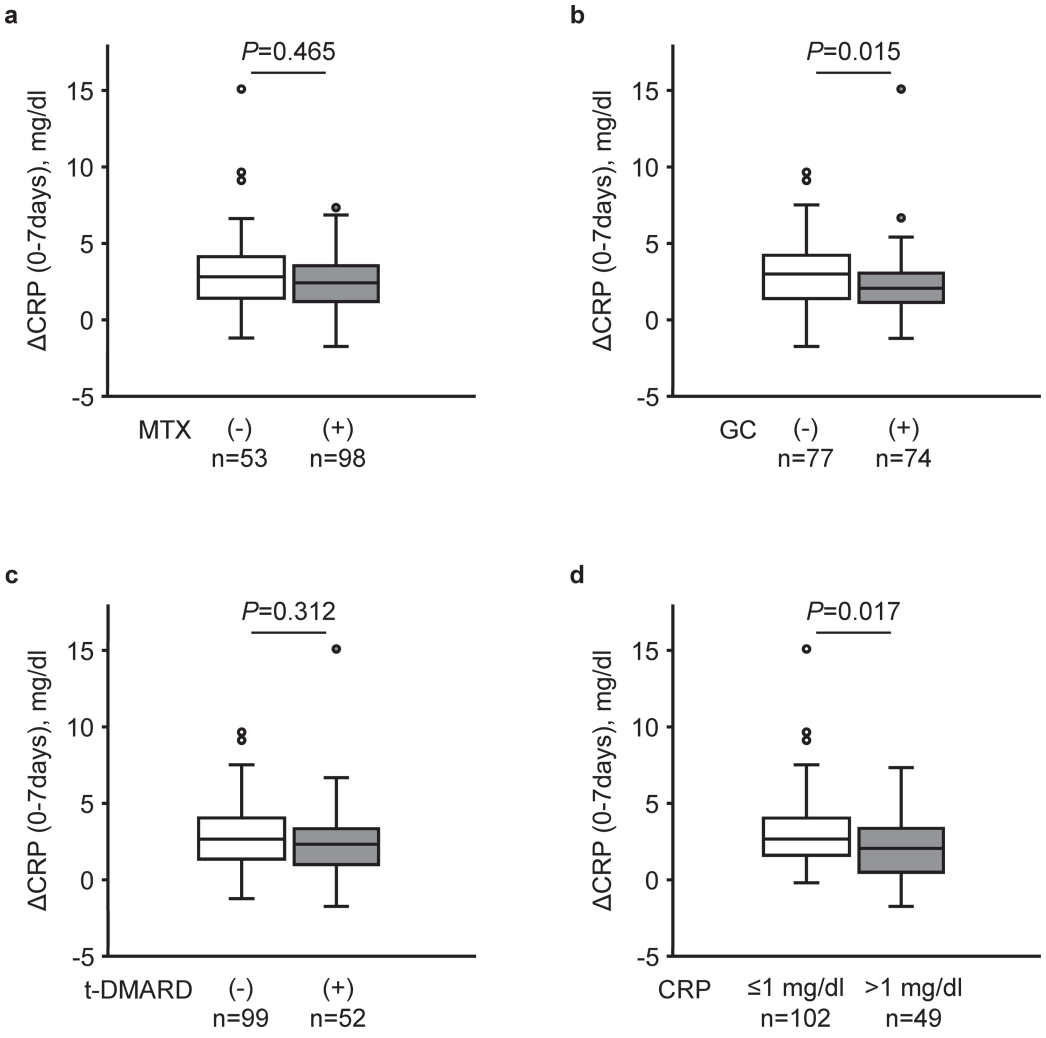


**Fig. 3** Perioperative changes in C-reactive protein (CRP) levels
Changes in serum CRP levels from 0 to 7 days after total knee arthroplasty (TKA) [ΔCRP (0–7days)] stratified by (a) use of methotrexate (MTX), (b) use of glucocorticoids (GCs), (c) use of targeted DMARDs (t-DMARDs), and (d) preoperative CRP levels. Data were compared using the Mann-Whitney U test.

**Table 2** Factors associated with changes in serum CRP levels from day 0 (preoperative) to day 7 after total knee arthroplasty

| | B (95% CI) | | SE | β | *P* value |
|---|---|---|---|---|---|
| Intercept | 3.18 | (1.67, 4.68) | 0.76 | 3.16 | <0.001 |
| Age, ≥65 years | –0.23 | (–0.95, 0.49) | 0.37 | –0.05 | 0.530 |
| Female | 0.14 | (–0.85, 1.14) | 0.50 | 0.02 | 0.774 |
| Body mass index, ≥25 | 1.03 | (0.22, 1.83) | 0.41 | 0.22 | 0.012 |
| Diabetes | –0.67 | (–2.19, 0.85) | 0.77 | –0.07 | 0.384 |
| Disease duration, ≥10 years | 0.56 | (–0.21, 1.32) | 0.39 | 0.12 | 0.151 |
| Use of methotrexate | –0.52 | (–1.28, 0.24) | 0.38 | –0.11 | 0.180 |
| Use of glucocorticoids | –0.86 | (–1.57, –0.16) | 0.36 | –0.19 | 0.017 |
| Use of targeted DMARDs | –0.21 | (–0.96, 0.53) | 0.38 | –0.05 | 0.568 |
| Preoperative CRP, >1 mg/dl | –0.68 | (–1.45, 0.10) | 0.39 | –0.14 | 0.086 |
| Surgery time, ≥120 min | 0.26 | (–0.50, 1.01) | 0.38 | 0.06 | 0.503 |
| Intraoperative blood loss, ≥70 ml | –0.42 | (–1.20, 0.36) | 0.40 | –0.09 | 0.292 |

B: partial regression coefficient
CI: confidence interval
SE: standard error
β: standardized partial regression coefficient
DMARDs: disease modifying antirheumatic drugs
CRP: C-reactive protein

## DISCUSSION

In this study, we found that serum CRP levels changed after primary TKA in RA patients. Serum CRP levels are known to increase in response to tissue damage after major orthopedic surgery and RA synovitis. A recent study also demonstrated changes in perioperative CRP levels in 40 joints of RA patients who underwent orthopedic surgery.[15] Given the variability in degree of changes in perioperative CRP levels by type of surgery, evaluation by type of surgery could provide meaningful information.[8] The present study, which had a large sample size and focused on elective TKA, found that serum CRP levels increased from postoperative day 1, peaked on postoperative days 3–4, and then returned to preoperative levels by postoperative day 14. Obesity and use of GCs were independently associated with these changes, whereas use of MTX and targeted DMARDs and preoperative CRP levels were not.

A number of studies have examined changes in CRP levels after primary TKA in patients with OA.[8,9,21,22] Curves depicting perioperative CRP levels were similar across all of these studies, with levels peaking on postoperative days 2–3 followed by a rapid fall to preoperative levels by 2–3 weeks postoperatively, although the amplitude of the curves varied. A similar curve was observed for RA patients in this study, although the peak timing in CRP levels after TKA was shifted. This difference in peak timing may be due to differences in the timing of data collection, since serum CRP data were not available for postoperative day 2. Previous studies conducted before the biologic era also reported similar CRP curves after TKA in RA patients, despite higher preoperative CRP levels compared to the present study.[11,23] Moreover, consistent with a previous study,[23] there was no association between preoperative CRP levels and changes in serum CRP levels. Taken together, serum CRP levels after TKA appear to be less affected

by RA activity than surgical invasion.

Among the entire study population, only one case had an SSI postoperatively. In that case, serum CRP levels were high during the postoperative period and did not normalize to preoperative levels by postoperative day 14. Similar to this finding, a previous study also reported on a patient who had a deep infection post-TKA and high CRP levels even after 21 days postoperatively.[24] Another study, which included patients who underwent total knee or hip arthroplasty, found that serum CRP levels peaked at 1 and 2 weeks after surgery among patients with postoperative complications, including SSIs.[9] These findings collectively suggest that a serious complication should be suspected if serum CRP levels remain high at 1–2 weeks after TKA.

GCs suppress inflammation, and have been used for decades to treat RA. The rise in CRP levels after total knee or hip arthroplasty has been shown to be slightly weaker in RA patients administered GCs daily compared to those not administered GCs.[25] According to recent randomized controlled studies, administering GCs preoperatively reduced the postoperative elevation of CRP levels in patients with OA.[26] These prior reports support our finding that use of GCs was inversely associated with the elevation of serum CRP levels after TKA. In contrast, use of targeted DMARDs other than TCZ was not associated with changes in serum CRP levels after TKA. This finding is also consistent with that reported in a previous study showing no significant difference in changes in CRP levels after orthopedic surgery between patients treated with tumor necrosis factor inhibitors and conventional synthetic DMARDs.[15] ACR guidelines recommend withholding biologics for one dosing cycle prior to total knee and hip arthroplasty until wound healing.[27] Notably, TCZ suppressed the elevation of CRP levels after surgery despite preoperative withholding in the present study as well as in previous studies.[15,16] Based on the above, we conclude that withholding targeted DMARDs other than TCZ, especially biologics, according to ACR guideline recommendations has no major impact on postoperative serum CRP levels.

Obesity is another factor that was associated with the elevation of serum CRP levels after TKA. In the general population, a greater BMI is associated with higher serum CRP levels, especially among females.[28] Adipose tissue has been shown to produce IL-6, which promotes CRP production in the liver, in obese individuals.[29] Moreover, obesity is associated with higher serum CRP levels in female, but not male, RA patients.[30] In the present study, obesity increased postoperative serum CRP levels, possibly because over 80% our cases were female.

Procalcitonin, a peptide hormone, has been used as a biomarker for the diagnosis of bacterial infection.[31] MMP-3 and inflammatory cytokines, such as IL-6, are potential biomarkers for disease activity of RA.[32-34] Those biomarkers are not measured frequently during the perioperative period because of high cost. By contrast, measurement of serum CRP levels is relatively inexpensive and performed frequently in clinical practice. Frequent measurement during the perioperative period should be advantageous for early detection of SSI.[8,9,23]

This study has some limitations worth noting. First, since this was a retrospective study using data obtained in clinical settings, data on CRP levels were collected only at limited time points. Assessment of serum CRP levels at more time points may provide better resolution of the changes in perioperative serum CRP levels. Second, 63 (29%) cases were excluded from the analysis of factors associated with changes in serum CRP levels due to missing data on postoperative day 7, and the excluded cases had higher preoperative CRP levels than the analyzed cases. This difference may have influenced our results, particularly in view of the lack of association between preoperative CRP levels and changes in serum CRP levels. However, we note that a similar lack of association was also reported in a previous study.[23]

In conclusion, serum CRP levels increased rapidly after TKA with a peak on postoperative days 3 to 4, followed by a fall to preoperative levels by postoperative day 14, in RA patients undergoing TKA. Obesity was positively associated, and the use of GCs inversely associated, with

the elevation of serum CRP levels. Our findings may contribute to the detection of postoperative complications such as SSI by screening for elevated CRP levels following TKA.

## FUNDING

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## CONFLICTS OF INTEREST

SA has received speakers' fees from AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Janssen, Takeda, and UCB Japan. NT has received speakers' fees from AbbVie, Asahi Kasei, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Janssen, Mitsubishi Tanabe, Ono, Pfizer, Takeda, and UCB Japan. YS has received speakers' fees from Astellas, Bristol-Myers Squibb, and Ono. MS has received speakers' fees from Bristol-Myers Squibb, Eisai, and Asahi Kasei. NI has received grant/research support, consulting fees, and/or speakers' fees from AbbVie, Asahi Kasei, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Kaken, Mitsubishi Tanabe, Ono, Otsuka, Pfizer, Taisho Toyama, Takeda, and Zimmer Biomet. TK has received grant/research support and/or speakers' fees from AbbVie, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eli Lilly, Janssen, Mitsubishi Tanabe, Novartis, Pfizer, and Takeda. The other authors declare no conflicts of interest.

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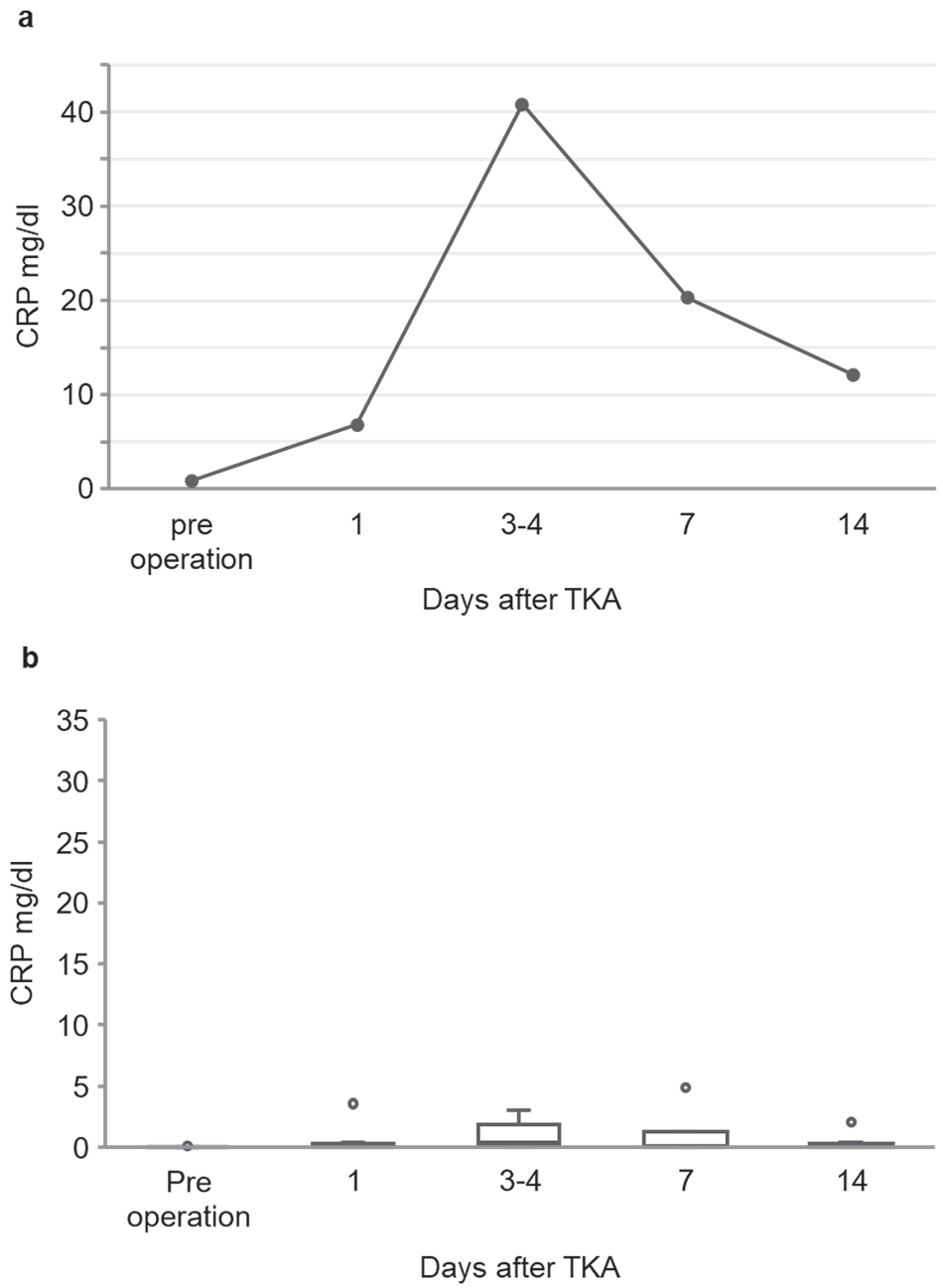
Supplementary Data




**Supplementary Fig. 1** Changes in C-reactive protein (CRP) levels after total knee arthroplasty (TKA) in (a) a patient with surgical site infection, and (b) patients treated with tocilizumab (n=11)

**Supplementary Table 1** Demographics and clinical characteristics of analyzed and excluded cases

| Characteristics | Analyzed cases (n=151) | Excluded cases (n=63) | *P* value |
|---|---|---|---|
| Age, years | 66 (61–71) | 64 (57–70) | 0.060 |
| Female, % | 84 | 83 | 0.778 |
| Body mass index | 23 (20–26) | 22 (20–25) | 0.501 |
| Disease duration, years | 12 (7–19) | 11 (8–22) | 0.766 |
| Use of methotrexate, % | 65 | 62 | 0.677 |
| Methotrexate dose, mg/week* | 8 (6–8) | 6 (6–8) | 0.015 |
| Use of glucocorticoids, % | 49 | 56 | 0.382 |
| Glucocorticoid dose, mg/day* | 5 (3–5) | 5 (3–5) | 0.395 |
| Use of targeted DMARDs, % | 34 | 32 | 0.704 |
| Preoperative CRP, mg/dl | 0.62 (0.18–1.42) | 1.12 (0.34–2.65) | 0.004 |
| Surgery time, min | 120 (104–135) | 117 (100–131) | 0.277 |
| Intraoperative blood loss, ml | 65 (30–132) | 100 (39–134) | 0.189 |

Data are presented as median values (interquartile range) or percentages.
*Median among subjects receiving the drug.
CRP: C-reactive protein
DMARDs: disease modifying antirheumatic drugs

**Supplementary Table 2** Factors associated with changes in serum CRP levels from day 0 (preoperative) to day 7 after total knee arthroplasty

| | B (95% CI) | | SE | β | *P* value |
|---|---|---|---|---|---|
| Intercept | 2.9 | (1.2, 4.6) | 0.85 | 2.9 | 0.001 |
| Age, ≥65 years | –0.28 | (–1.03, 0.47) | 0.38 | –0.06 | 0.462 |
| Female | 0.19 | (–0.91, 1.3) | 0.56 | 0.03 | 0.725 |
| Body mass index, ≥25 | 1.08 | (0.26, 1.9) | 0.42 | 0.23 | 0.011 |
| Disease duration, ≥10 years | 0.61 | (–0.18, 1.4) | 0.4 | 0.13 | 0.127 |
| Use of methotrexate | –0.4 | (–1.2, 0.4) | 0.41 | –0.08 | 0.326 |
| Use of glucocorticoids | –0.83 | (–1.62, –0.04) | 0.4 | –0.18 | 0.04 |
| Use of targeted DMARDs | –0.25 | (–1.02, 0.52) | 0.39 | –0.05 | 0.522 |
| Preoperative MMP-3 >normal upper limit | –0.12 | (–1.26, 1.01) | 0.57 | –0.02 | 0.83 |
| Surgery time, ≥120 min | 0.22 | (–0.57, 1.02) | 0.4 | 0.05 | 0.577 |
| Intraoperative blood loss, ≥70 ml | –0.4 | (–1.2, 0.4) | 0.4 | –0.09 | 0.32 |

B: partial regression coefficient
CI: confidence interval
SE: standard error
β: standardized partial regression coefficient
DMARDs: disease modifying antirheumatic drugs
MMP-3: matrix metalloprotease 3

**Supplementary Table 3** Factors associated with changes in serum CRP levels from day 0 (preoperative) to day 7 after total knee arthroplasty

| | B (95% CI) | | SE | β | *P* value |
|---|---|---|---|---|---|
| Intercept | 2.78 | (0.84, 4.72) | 0.97 | 2.78 | 0.005 |
| Age, ≥65 years | 0.07 | (–0.83, 0.98) | 0.46 | 0.02 | 0.875 |
| Female | 0.49 | (–0.89, 1.76) | 0.64 | 0.08 | 0.448 |
| Body mass index, ≥25 | 1.35 | (0.31, 2.38) | 0.52 | 0.27 | 0.011 |
| Disease duration, ≥10 years | 0.35 | (–0.62, 1.33) | 0.49 | 0.07 | 0.473 |
| Use of methotrexate | –0.73 | (–1.69, 0.24) | 0.49 | –0.15 | 0.138 |
| Use of glucocorticoids | –0.81 | (–1.69, 0.07) | 0.44 | –0.17 | 0.07 |
| Use of targeted DMARDs | 0.0001 | (–0.93, 0.93) | 0.47 | 0.0003 | 1.00 |
| Preoperative CRP, >1 mg/dl | –0.67 | (–1.63, 0.3) | 0.49 | –0.14 | 0.173 |
| Surgery time, ≥120 min | 0.49 | (–0.47, 1.46) | 0.49 | 0.11 | 0.312 |
| Intraoperative blood loss, ≥70 ml | –0.49 | (–1.51, 0.51) | 0.51 | –0.11 | 0.334 |

B: partial regression coefficient
CI: confidence interval
SE: standard error
β: standardized partial regression coefficient
DMARDs: disease modifying antirheumatic drugs
CRP: C-reactive protein