

# Relationship between Inflammatory Response and Estimated Complication Rate after Total Hip Arthroplasty

Xu-Xu Chen, Tao Wang, Jian Li, Hui Kang

Department of Sports Medicine, Honghui Hospital, Xi'an Jiaotong University Medical College, Xi'an, Shaanxi 710054, China

## Abstract

**Background:** After total hip arthroplasty (THA), there is a noteworthy inflammatory response. The inflammatory response is associated with postoperative recovery and complications. However, there had been few reports on the relationship between inflammatory response and postoperative complication rate. The aim of the present study was to investigate early inflammatory response in the first 3 days after THA, and to identify the relationship between inflammatory response and estimated complication rate after surgery.

**Methods:** It was a prospective, nonrandomized cohort study. There were 148 patients who underwent unilateral THA in our hospital enrolled. Blood samples were collected preoperatively in the morning of the surgery and at 24, 48, and 72 h after surgery. C-reactive protein (CRP) and interleukin-6 (IL-6) in peripheral blood were measured. The modified physiological and operative severity score for the enumeration of the morbidity (POSSUM) was recorded pre- and intra-operatively. Based on the score, estimated complication rate was calculated. Harris score was used to assess hip function before and after surgery.

**Results:** IL-6 levels reached the peak at 24 h after surgery and CRP at 48 h. After that, both of the levels decreased. The mean Harris scores significantly increased from  $41.62 \pm 23.47$  before surgery to  $72.75 \pm 9.13$  at 3 days after surgery. The Harris scores after surgery did not have a significant relation with either IL-6 or CRP peak levels ( $P = 0.165$ ,  $P = 0.341$ , respectively). Both CRP and IL-6 peak levels significantly and positively correlated with estimated complication rate after surgery. The estimated complication rate calculated using the POSSUM system was 43 cases of 148 patients. Actually, there were only 28 cases that were observed to get postoperative complications during hospitalization. However, there was no significant difference between estimated and observed complication rates ( $P = 0.078$ ). In the group with complications, the CRP and IL-6 peak levels were significantly higher than those in the group without complications (both  $P < 0.001$ ).

**Conclusions:** There were significantly positive relationships between both peak levels of CRP and IL-6 and estimated complication rate after THA. Inflammatory response could predict the incidence of complications after THA.

**Key words:** Complicated Rate; Inflammatory Response; Total Hip Arthroplasty

## INTRODUCTION

Total hip arthroplasty (THA) is commonly used to recover joint structure and function. As a kind of surgical intervention and a form of programmed trauma, it can cause a variety of physiological changes, including increased stress hormones, various humoral mediators, and acute-phase proteins, such as C-reactive protein (CRP).<sup>[1]</sup> Especially, the pro-inflammatory cytokines, such as interleukin-6 (IL-6),<sup>[2,3]</sup> tumor necrosis factor- $\alpha$ ,<sup>[4]</sup> and IL-1 $\beta$ ,<sup>[5]</sup> are considered important mediators of the pathological changes associated with surgery. They play an important role in controlling the immune system in inflammatory response. In many studies, IL-6 has been recognized as a major mediator of the acute-phase protein response and a marker of postoperative tissue trauma.<sup>[1,2]</sup>

THA is associated with a noteworthy inflammatory response. As reported by Larsson *et al.*,<sup>[6]</sup> this response might last more than 6 weeks after surgery. Some researchers suggested that the inflammatory response might determine postoperative recovery and complications.<sup>[7,8]</sup> However, to our knowledge, there have been few reports

**Address for correspondence:** Prof. Hui Kang,  
Department of Sports Medicine, Honghui Hospital, Xi'an Jiaotong  
University Medical College, No. 555 East Youyi Road, Xi'an,  
Shaanxi 710054, China  
E-Mail: dockanghui@126.com

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on the relationship between inflammatory response and postoperative complication rate.

Thus, the aim of the present study was to investigate the early inflammatory response in the first few days after THA and to identify the relationship between inflammatory response and complication rate. Just like what had been done in previous studies, IL-6 and CRP were adopted as the markers of the inflammatory response because they elevated markedly and were easy to be detected in systemic circulation even after mild inflammation.<sup>[2]</sup>

## METHODS

### Subjects

The investigation was designed as a prospective, nonrandomized cohort study, with the approval of the clinical research committee of our hospital. Inclusion criteria were as follows: patients needing THA; no history of THA; be able to tolerate anesthetics and surgery; no taking nonsteroid anti-inflammatory drugs or immunosuppressive drug within 4 weeks before surgery; no history of tumor; and no previous surgery in 3 months before surgery. On admission, all patients that met inclusion criteria were informed about the clinical study. They decided to be enrolled or not and signed the consent forms. Finally, 148 patients scheduled for unilateral THA were enrolled from August 2009 to March 2013.

All patients underwent the unilateral THA. All of the operations were performed by the same surgeon through the posterolateral approach to reduce the difference in surgical trauma. Each case received epidural anesthesia and a patient controlled epidural analgesia pump at the end of the operation.

### Clinical assessment

Harris score was used to assess hip function before surgery and at 3 days after surgery. The Numeric Rating Scale was used to help patients communicate how much pain they were experiencing at moving the operated limb. The measuring was conducted at the admission and at 3 days postoperatively. On the basis of scores, there were four grades: none (0), mild (1–3), moderate (4–6), and severe (7–10). Data, including age, gender, weight, and height, were collected upon admission. The surgery duration and the total blood loss and transfusion were also recorded. The incision length was measured with an aseptic paper ruler after suture.

### Measurement of serum CRP and IL-6 levels

Blood samples were obtained preoperatively in the morning of the surgery and at 24 h, 48 h, and 72 h postoperatively. The CRP concentrations were determined using the latex particle-enhanced nephelometric immunoassay on the BN ProSpec analyzer (Dade Behring, Germany) and were expressed in mg/L. IL-6 was measured in serum samples by a sandwich quantitative enzyme immunoassay technique (R&D Systems, Camarillo, CA, USA). The assay had a sensitivity of 2–500 pg/ml for IL-6.

## Calculation of estimated complication rates

The modified physiological and operative severity score for the enumeration of the morbidity (POSSUM) was recorded pre- and intra-operatively<sup>[9]</sup> [Tables 1 and 2]. Based on the score, estimated complication rate was calculated according to the morbidity formula depicted by Mohamed *et al.*<sup>[9]</sup> The morbidity ( $R$ ) formula is as follows.

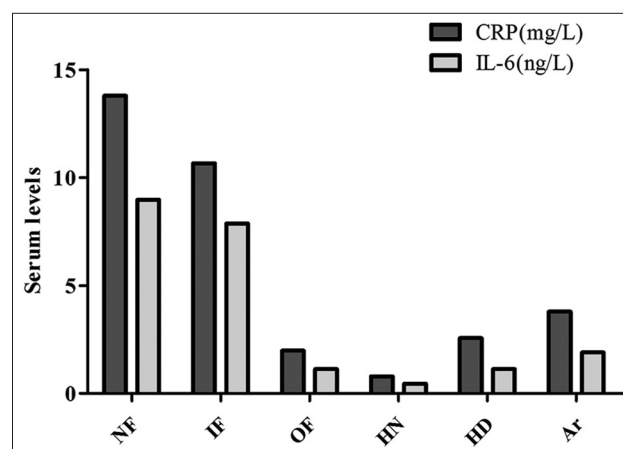
$$\ln R/(1 - R) = -5.91 + (0.16 \times \text{physiological score}) + (0.19 \times \text{operative severity score}).$$

## Statistical analysis

The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS version 15.0 for Windows, SPSS Inc., Chicago, IL, USA). The data were expressed as mean  $\pm$  standard deviation (SD) or as a percentage of patients. The changes of variables before and after surgery were compared using analysis of variance or  $t$ -tests. Correlation analysis was used to analyze relationships between variables.  $P < 0.05$  was considered statistically significant.

## RESULTS

Totally, 148 patients enrolled and no one dropped out during hospitalization. The average time of hospital stay after surgery was 6.7 days. There were nine cases (6.08%) of intracapsular femoral neck fracture, 17 cases (11.49%) of intertrochanteric fracture, 11 cases (7.43%) of old femoral neck or intertrochanteric fracture, 72 cases (48.65%) of femoral head necrosis, 18 cases (12.16%) of hip dysplasia, 15 cases (10.14%) of hip osteoarthritis, three cases (2.03%) of hip rheumatoid arthritis, and three cases (2.03%) of ankylosing spondylitis. Before surgery, both CRP and IL-6 levels in patients of intracapsular neck fracture and intertrochanteric fracture were significantly higher than



**Figure 1:** Preoperative serum CRP and IL-6 levels for different diseases. Both CRP and IL-6 levels in NF and IF groups are significantly higher than those in OF, HN, HD, and Ar groups (all  $P < 0.05$ ). CRP: C-reactive protein; IL-6: Interleukin-6; NF: Intracapsular femoral neck fracture; IF: Intertrochanteric fracture; OF: Old fracture; HN: Femoral head necrosis; HD: Hip dysplasia; Ar: Arthritis including hip osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis.

**Table 1: The physiological assessment in the orthopedic POSSUM system**

Items	Physiological score			
	1	2	4	8
Age (years)	<60	60–70	>70	-
Cardiac signs	Normal	On cardiac drugs or steroid	Edema, warfarin, borderline cardiomegaly	Raised JVP Cardiomegaly
Respiration signs	Normal	SOB exertion	SOB stairs	SOB rest
Chest radiograph	Normal	Mild COAD	Model COAD	Any other chang (Fibrosis or consolidation)
Systolic BP (mmHg)	110–130	130–170	≥171	≤89
Pulse (beats/min)	50–80	100–109 81–100 40–49	90–99 100–120	≥121 ≤39
Coma score	15	12–14	9–11	≤8
Blood urea (mmol/L)	≤7.5	7.6–10.0	10.1–15.0	≥15.1
Blood Na (mmol/L)	≥136	131–135	126–130	≥125
Blood K (mmol/L)	3.5–5.0	3.2–3.4 5.1–5.3	2.9–3.1 5.4–5.9	≥2.8 ≥6
Hb (g/dl)	13–16	11.5–12.9 16.1–17.0	10.0–11.4 17.1–18.0	≤9.9 ≥18.1
White cell count (×10 <sup>12</sup> /L)	4–10	10.1–20.0 3.1–3.9	≥20.1 ≤3	-
ECG	Normal	-	Atrial fibrillation (rate 60–90)	Any other abnormal rhythm or ≥5 ectopics/min Q waves or ST/T wave changes

1 mmHg = 0.133 kPa. POSSUM: Physiological and operative severity score for the enumeration of the morbidity; BP: Blood pressure; Hb: Hemoglobin; ECG: Electrocardiograph; JVP: Jugular venous pressure; SOB: Shortness of breath; COAD: Chronic obstructive airway disease. -: Not applicable.

**Table 2: The operative severity assessment in the orthopedic POSSUM system**

Items	Operative severity score			
	1	2	4	8
Magnitude	Fasciotomy, ganglion/ bursa, tenotomy/tendon repair, arthroscopic surgery, carpal tunnel/ nerve release, removal of metal, closed reduction of fracture	Excision/osteotomy small bone, minor joint replacement, amputation digit/digits, closed reduction with external fixation, open reduction of fracture of small bone	Osteotomy long bone, Ligamentous reconstruction + prosthesis, arthrodesis large joint, major joint replacement, amputation limb, disc surgery, open reduction of fracture of a long bone	Radical tumorectomy, major spinal reconstruction, revision prosthetic replacement, major joint, hindquarter/ forequarter amputation
Number of operative variables within 30 days	1	-	2	>2
Blood loss (ml)	≤100	101–500	501–999	≥1000
Contamination	None	Incised wound	Minor contamination or necrosis tissue	Gross contamination or necrosis tissue
Presence of malignancy	None	Primary lesion	Node metastases	Distant metastases
Timing of operation	Elective	-	Emergency, resuscitation possible ≤48 h	Emergency, immediate ≤6 h

-: Not applicable; POSSUM: Physiological and operative severity score for the enumeration of the morbidity.

other group patients [Figure 1]. Table 3 summarizes the main population characteristics, including age, gender, body mass index (BMI), surgery duration, incision length, blood loss, and transfusion. Neither of these background variables had a significant correlation with CRP nor IL-6 peak levels after surgery.

Before surgery, both IL-6 and CRP levels were lower. After surgery, both IL-6 and CRP levels rose immediately and

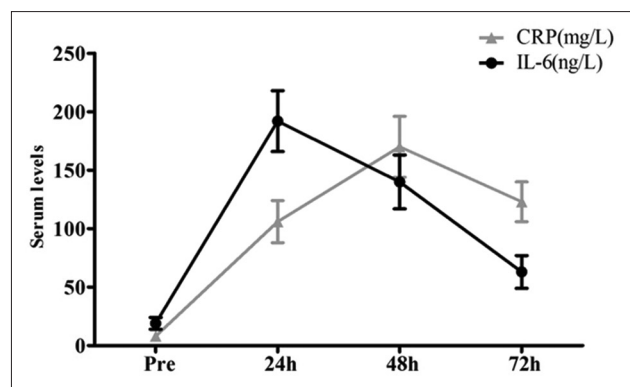
reached the peak at 24 and 48 h, respectively. After that, both levels decreased. Both IL-6 and CRP levels at each time point after surgery were significantly higher than that before surgery (all  $P < 0.05$ ) [Figure 2].

The mean Harris score was  $41.62 \pm 23.47$  before surgery and  $72.75 \pm 9.13$  at 3 days after surgery. There was a significant increase of Harris scores after surgery ( $P < 0.001$ ). The mean pain scores decreased significantly after surgery ( $5.46 \pm 1.61$ ),

compared with that before surgery ( $6.90 \pm 3.11$ ,  $P = 0.012$ ). The Harris scores after surgery did not have a significant relation with either IL-6 or CRP peak levels ( $P = 0.165$ ,  $P = 0.341$ , respectively).

The average physiological score was  $18.79 \pm 4.93$ . The average operative severity score was  $14.01 \pm 2.86$ . The estimated complication rate was 43 cases of 148 patients. Actually, there were only 28 cases who were observed to get postoperative complications during hospitalization, including eight cases of pulmonary infection, five cases of wound infection, and 17 cases of digestive system diseases (five cases of diarrhea, five cases of abdominal distention, and seven cases of constipation). There were 2 cases with both pulmonary infection and digestive system diseases. Moreover, there was one case that got prosthesis-related infection and underwent debridement and two-stage revision surgery. There was no significant difference between estimated and observed complication rates ( $P = 0.078$ ). In the group with complications, the CRP and IL-6 peak levels were significantly higher than those in the group without complications (both  $P < 0.001$ ) [Figure 3]. The estimated complication rates for patients of intracapsular neck and intertrochanteric fracture were consistent with observed rates. As for patients of other diseases, the estimated rates were higher than the observed rates [Table 4].

The scatter diagrams of the correlations between both IL-6 and CRP peak levels and estimated complication rates

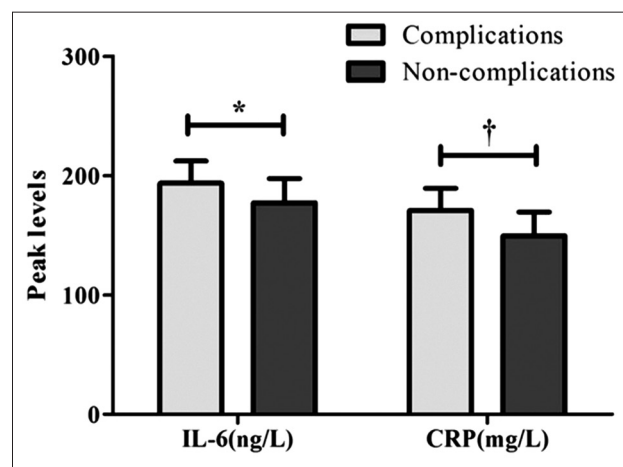


**Figure 2:** Pre- and post-operative serum CRP and IL-6 levels. CRP: C-reaction protein; IL-6: Interleukin-6.

showed linear trends [Figure 4]. The Pearson correlation analysis resulted that there was a significant positive relationship between IL-6 peak levels and estimated complication rates ( $r = 0.558$ ,  $P < 0.001$ ). A similar relationship could also be observed between CRP peak levels and estimated complication rates ( $r = 0.577$ ,  $P < 0.001$ ). After multivariate linear regression analysis, the IL-6 variable was rejected out and a regression equation could be got as follows: Estimated complication rate =  $-4.037 + 0.064 \times \text{CRP (mg/L)}$  ( $P < 0.001$ ).

## DISCUSSION

In the present study, we estimated all patients' complication rates by the POSSUM scores before surgery and investigated the early inflammatory response in the first 3 days after THA. Results showed that there was a significantly positive relationship between the level of inflammatory response and estimated complication rate. There was no significant difference between estimated and observed complication rates. The CRP and IL-6 peak levels in the group with complications were significantly higher than those in the group without complications.

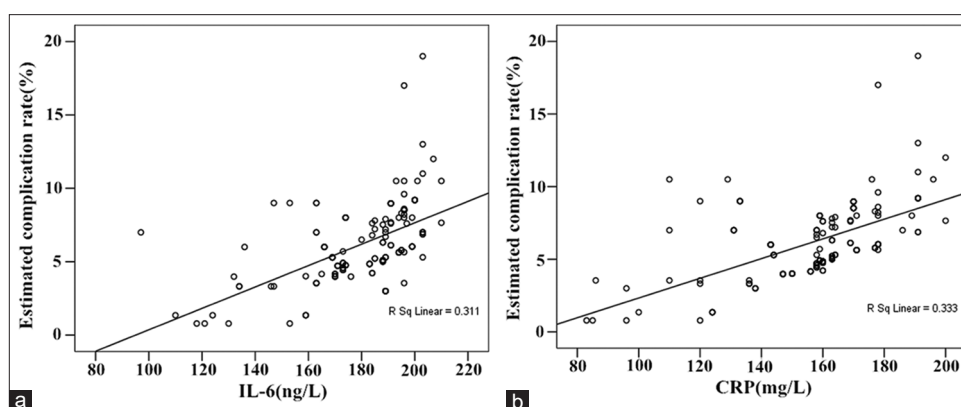


**Figure 3:** Comparisons of CRP and IL-6 peak levels after surgery between the group with complications and the group without complications. In the group with complications, the IL-6 (\*) and CRP (†) peak levels were significantly higher than those in the group without complications (both  $P < 0.001$ ). IL-6: Interleukin-6; CRP: C-reaction protein.

**Table 3: Demographic characteristics, operative parameters, and their correlations with CRP and IL-6 levels ( $n = 148$ )**

Parameters	Values	CRP		IL-6	
		<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age (years)	$61.62 \pm 15.35$	0.140	0.64	0.165	0.85
Male*	84 (56.76%)	-0.168	0.94	-0.273	0.82
BMI ( $\text{kg}/\text{m}^2$ )	$25.31 \pm 3.72$	0.077	0.46	0.132	0.13
Surgery duration (min)	$91.66 \pm 15.13$	0.200	0.90	0.314	0.90
Incision length (cm)	$12.26 \pm 2.39$	0.066	0.94	0.089	0.73
Blood loss (ml)	$612.34 \pm 220.64$	0.193	0.76	0.199	0.94
Blood transfusion (IU)	$2.17 \pm 1.39$	0.097	0.84	0.112	0.97

All data are shown as mean  $\pm$  SD or  $n$  (%) unless otherwise indicated. \*Spearman correlation coefficient test was used in correlation analysis. The others used Pearson correlation coefficient test. CRP: C-reaction protein; IL-6: Interleukin-6; BMI: Body mass index; SD: Standard deviation.



**Figure 4:** The scatter diagrams of the correlations between both IL-6 (a) and CRP (b) peak levels and estimated complication rates ( $n = 148$ ). IL-6: Interleukin-6; CRP: C-reaction protein.

**Table 4: Physiological and operative severity scores, estimated and observed complication rates for different diseases ( $n = 148$ )**

Diseases	Physiological score	Operative severity score	Complication rates	
			Estimated	Observed
Intracapsular neck fracture	19.01 ± 4.90	14.88 ± 3.01	4	4
Intertrochanteric fracture	19.90 ± 4.96	14.60 ± 2.84	7	8
Old fracture	18.92 ± 4.28	13.69 ± 2.67	3	2
Head necrosis	18.71 ± 4.96	14.00 ± 2.97	16	10
Hip dysplasia	16.94 ± 3.51	13.03 ± 2.14	6	2
Arthritis	17.95 ± 4.04	13.67 ± 2.88	7	2

All data are shown as mean ± SD unless otherwise indicated. SD: Standard deviation.

After THA, previous reports describe that circulating concentration of IL-6 significantly increases, which concurs with our findings. Moreover, IL-6 can regulate the generation of the acute-phase response, including CRP. Consistent with the present study, many studies show that the increase in IL-6 is followed by a rise in CRP in patients who undergo THA. Moreover, there is usually a significant relationship between both markers.<sup>[2]</sup> Besides, the releases of IL-6 and CRP correlate with the severity of tissue trauma. Therefore, in many studies, IL-6 or CRP is detected as the marker of surgery magnitude.<sup>[10]</sup> Many previous studies have been performed to evaluate the postoperative inflammatory response, adopting IL-6 and CRP as the markers.<sup>[11]</sup> Hall *et al.*<sup>[11]</sup> studied the relationship between hip functional recovery and inflammatory response after hip arthroplasty and suggested that the inflammatory response was correlative with postoperative pain and early functional recovery. In the study of Feng *et al.*,<sup>[12]</sup> patients undergoing elective total knee replacement were investigated and it was found that peripheral IL-6 level significantly correlated with pain score at 48 h after surgery. Besides, Ugras *et al.*<sup>[13]</sup> found that early functional recovery after total knee replacement was affected by the local inflammatory response. However, in this study, the early functional recovery did not significantly correlate with either IL-6 or CRP levels. This might be because our study has a small sample and the functional scores at 3 days after surgery are too early to be distinguished.

Furthermore, many researchers have observed that IL-6 and CRP are useful risk factors and indicators of infectious

complications. Scherer *et al.*<sup>[14]</sup> studied 330 patients who had operative fracture treatment and suggested that a cutoff CRP level of 140 mg/L on the 4<sup>th</sup> day after surgery was recorded for patients with deep wound infection. This evidence suggested that inflammatory response more or less gave a prediction for the incidence of complications. However, these results did not clearly prove the relationship between inflammatory response and the morbidity of complications after THA. In this study, we correlated the level of inflammatory response with estimated complication rate by POSSUM and found there was a significantly positive relationship between them, which was in accordance with previous results. Moreover, the CRP and IL-6 peak levels in the group with complications were significantly higher than those in the group without complications, which additionally noted the predictive role of inflammatory response.

The POSSUM system was first depicted by Copeland as a measurable method of assessing outcomes of surgical intervention based on symptoms and signs, physiological parameters, and operative severity parameters.<sup>[15]</sup> Mohamed *et al.*<sup>[9]</sup> modified the score system and made it applicable in orthopedic surgeries. They applied the modified POSSUM in a study of 2336 cases who underwent orthopedic surgeries and found that the estimated morbidity and mortality were nearly the same with the observed rates.<sup>[9]</sup> In our study, we calculated the estimated complication rate by POSSUM and analyzed its correlation with the level of inflammatory response. Our results showed that the estimated complication

rates were consistent with the observed rates, indicating the applicability of the modified POSSUM in orthopedic surgeries.

Some previous studies observed that the levels of CRP and IL-6 were relative with age,<sup>[16]</sup> gender,<sup>[17]</sup> BMI,<sup>[18]</sup> the total blood loss<sup>[19,20]</sup> or transfusion,<sup>[21]</sup> or postoperative pain.<sup>[12]</sup> However, in this study, there were no significant relationships between these background variables and CRP or IL-6 levels. This might be because the relationship is so weak that it is not significant in a small-sample study. Several other limitations of the study should also be acknowledged. First, the main limitation of the present study is a small size and heterogeneous character of patient population. There are some confounding factors that might have an influence on levels of CRP and IL-6 after surgery. However, the inclusion criteria are so strict that the investigation is too time consuming to find a larger enough patient population. Second, it would be better if the drained fluid samples were collected to detect local inflammatory factors. As reported in a previous study,<sup>[22,23]</sup> there was a 1000-fold increase of IL-6 levels in drained fluid, comparing to the systemic concentrations in arterial blood of patients operated in thoracic scoliosis. Furthermore, what period of complications after surgery the CRP and IL-6 levels could predict is still unclear. The answer cannot be gotten in this study, either. More attention should be given on this problem in further studies.

In conclusion, we concluded that the early inflammatory response significantly correlated with the estimated complication rate and it could give predictions for complications after THA.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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