



**Postoperative IL-6 levels cannot predict early onset periprosthetic hip/knee infections: an analysis of 7661 patients at a single institution**

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Abstract:	<p>Prior studies have outlined C-reactive protein (CRP) within the first 5 days following TKA as an inappropriate indicator for an early periprosthetic joint infection (PJI). In recent years, Interleukin-6 (IL-6) as a potential inflammatory marker following total joint arthroplasty (TJA) has gained increasing interest, particularly due to its considerably shorter half-life. The aim of the present study was to assess the predictive value of IL-6 measured on postoperative day 3 following TJA to predict an early onset PJI. A total of 7661 patients who underwent total hip or knee arthroplasty (THA, TKA) at a single institution between 2016 and 2019 were evaluated. Serum IL-6 values were taken on postoperative day 3 and compared between patients with and without early onset PJI in the postoperative follow-up, matched for age, gender, Surgical Site Infection Risk Score (SSIRS), and the Charlson Comorbidity Index. Overall (n=7661), there was no statistically significant difference in serum IL-6 levels comparing patients with and without early onset PJI following THA [38.9 (IQR: 40.4) pg/ml vs. 32.0 (IQR: 25.9) pg/ml, p=0.116] and TKA [30.6 (IQR: 20.7) pg/ml vs. 28.2 (IQR: 24.3) pg/ml, p=0.718]. Male gender and high BMI were associated with an increased risk for early onset PJI following THA (p=0.027, p=0.002). Matched cohort analysis (n=86) showed no statistically significant difference in serum IL-6 levels between patients with and without early onset PJI following THA (p=0.680) and TKA (p=0.910). Serum IL-6 values on postoperative day 3 following total hip or knee arthroplasty cannot predict early onset periprosthetic joint infections.</p>

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1 **Postoperative IL-6 levels cannot predict early onset periprosthetic**  
2 **hip/knee infections: an analysis of 7661 patients at a single**  
3 **institution**

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1 **Postoperative serum IL-6 levels cannot predict early onset periprosthetic**  
2 **hip or knee infections: an analysis of 7661 patients at a single institution**

3  
4 **ABSTRACT**

5 Prior studies have outlined C-reactive protein (CRP) within the first 5 days following TKA as  
6 an inappropriate indicator for an early periprosthetic joint infection (PJI). In recent years,  
7 Interleukin-6 (IL-6) as a potential inflammatory marker following total joint arthroplasty (TJA)  
8 has gained increasing interest, particularly due to its considerably shorter half-life. The aim of  
9 the present study was to assess the predictive value of IL-6 measured on postoperative day 3  
10 following TJA to predict an early onset PJI. A total of 7661 patients who underwent total hip  
11 or knee arthroplasty (THA, TKA) at a single institution between 2016 and 2019 were evaluated.  
12 Serum IL-6 values were taken on postoperative day 3 and compared between patients with and  
13 without early onset PJI in the postoperative follow-up, matched for age, gender, Surgical Site  
14 Infection Risk Score (SSIRS), and the Charlson Comorbidity Index. Overall (n=7661), there  
15 was no statistically significant difference in serum IL-6 levels comparing patients with and  
16 without early onset PJI following THA [38.9 (IQR: 40.4) pg/ml vs. 32.0 (IQR: 25.9) pg/ml,  
17 p=0.116] and TKA [30.6 (IQR: 20.7) pg/ml vs. 28.2 (IQR: 24.3) pg/ml, p=0.718]. Male gender  
18 and high BMI were associated with an increased risk for early onset PJI following THA  
19 (p=0.027, p=0.002). Matched cohort analysis (n=86) showed no statistically significant  
20 difference in serum IL-6 levels between patients with and without early onset PJI following  
21 THA (p=0.680) and TKA (p=0.910). Serum IL-6 values on postoperative day 3 following total  
22 hip or knee arthroplasty cannot predict early onset periprosthetic joint infections.

23  
24 Key Words: joint infection; IL-6; total hip arthroplasty; total knee arthroplasty

## 1 INTRODUCTION

2 Early detection of acute periprosthetic joint infections (PJI) following total joint arthroplasty  
3 (TJA) is crucial for patient outcome. Serum parameters measured during the postoperative  
4 period play an important role in the diagnosis of PJI, including CRP among others (Parvizi et  
5 al., 2018), with however reports on their limited accuracy and low specificity. (Sigmund et al.,  
6 2021) Previous studies have demonstrated a slow normalization in the postoperative levels of  
7 CRP following primary TJA, representing a drawback with regard to diagnosing acute PJI.  
8 (Azboy et al., 2021) The serum levels of CRP have been reported to reach a peak during the  
9 second postoperative day. This is followed by  
10 a slow normalization rate to baseline levels (Wirtz et al., 2000) over the following 3 weeks  
11 (Larsson et al., 1992) up to 5 months (Herrero et al., 2008). As a result, CRP measured within  
12 the first 5 days following TKA is considered an inappropriate indicator for an early PJI  
13 (Windisch et al., 2017).

14 Another commonly used serological parameter is the Erythrocyte Sedimentation Rate  
15 (ESR), which however, has been reported to be associated with a low accuracy to detect PJI.  
16 (Sigmund et al., 2021) A main problem is the fact that it can be normal in patients with chronic  
17 PJI due to low virulence organisms. (Pérez-Prieto et al., 2017) A similar problem has been  
18 reported for the diagnostic value of white blood cell count (WBC), D-Dimer, Procalcitonin and  
19 Fibrinogen with poor accuracy to reliably diagnose a PJI. (Sigmund et al., 2021)

20 In recent years, Interleukin-6 (IL-6) as a potential inflammatory marker following TJA  
21 has gained increasing interest, particularly due to its half-life being four times shorter compared  
22 to CRP (Wirtz et al., 2000). In fact, the peak of IL-6 serum levels is measured after 6 hours with  
23 a mean half-life of 15 hours (Wirtz et al., 2000). The aim to identify cutoff values of serum  
24 markers with a short half-life to predict PJI in the postoperative period is further reinforced by  
25 the progressive trend towards a significantly decreased hospital length of stay via rapid recovery  
26 protocols. (Berend et al., 2004) Based on these considerations, a standardized protocol was

1 adapted in 2016 at our institution to measure IL-6 levels prior to discharge on postoperative day  
2 3 following TJA in each patient.

3 The aim of the present study was to evaluate average serum IL-6 levels on postoperative  
4 day 3 following uneventful total hip and knee arthroplasty (THA, TKA) in a large subset of  
5 patients at a single institution, in context with patient related risk factors. We further identified  
6 patients with an early acute PJI during the first 90 days following TJA. A matched-cohort  
7 analysis was then performed, aiming at assessing the ability of IL-6 measured prior to discharge  
8 on postoperative day 3 following TJA to predict an early onset PJI in a large subset of patients.

1 **MATERIALS AND METHODS**

2

3 ***Institutional Arthroplasty Registry***

4 The present study was approved by the institutional review board. Our institutional arthroplasty  
5 registry and PJI database were retrospectively evaluated from 01/2016 to 12/2019 for patients  
6 who underwent total joint arthroplasty (TJA) for the hip (THA) or knee (TKA). Patients with  
7 no revision surgery following TJA (n=7618) were compared with patients who underwent a  
8 revision surgery for an early PJI within 90 days following primary surgery (n=43). The 2018  
9 Musculoskeletal Infection Society (MSIS) criteria (Parvizi et al., 2018) were applied for the  
10 definition of a periprosthetic joint infection. Furthermore, only patients with serum IL-6 levels  
11 measured on day 3 were included. Data were further collected on age, gender, body mass index  
12 (BMI), the interval between primary total joint arthroplasty and revision surgery, the Surgical  
13 Site Infection Risk Score (SSIRS) (van Walraven and Musselman, 2013), , the ASA score  
14 (American Society of Anesthesiologists classification of physical status), and the  
15 microbiological analysis. Furthermore, the Charlson Comorbidity Index (CCI) was evaluated.  
16 This index was initially described - consisting of 19 weighted separate comorbidities (including  
17 peripheral vascular disease, cerebrovascular disease, diabetes, renal disease, liver disease,  
18 among others) - as a prognostic score to predict patient mortality. (Charlson et al.,; Charlson et  
19 al., 1987)

20 In a sub-analysis, both sub-groups were finally matched (1:1) for age, gender, operated  
21 joint, SSIRS, and the Charlson Comorbidity Index, and the serum IL-6 values on day 3 were  
22 then compared (Figure 1).

23

24 ***Statistical Analysis***

25 Categorical variables are reported as frequencies and percentages, and continuous variables as  
26 median with the interquartile range (IQR). The Pearson's chi squared test was used for the

1 comparison of proportions. The Kolmogorov Smirnov test was used to test for a normal  
2 distribution. Due to a non-parametric distribution, the Mann-Whitney U test was used for the  
3 comparison of continuous variables. A p-value of  $<0.05$  was defined as the level of statistical  
4 significance. Correlation analysis was performed via bivariate Pearson correlation. Data  
5 analysis was performed using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY).



1 **RESULTS**

2

3 ***Overall Study Population (n=7661)***

4 Overall, 7661 patients met the study's inclusion criteria. Between 01/2016 and 12/2019, 3710  
5 primary THA and 3908 primary TKA were performed with no revision following primary  
6 surgery. In 29 (0.8%) and 14 (0.4%) patients, a revision surgery was performed for an early  
7 acute PJI within the first 90 days following primary THA and TKA, respectively (29/3739 vs.  
8 14/3922;  $p=0.014$ ). In patients with no infection following TJA, the IL-6 values on  
9 postoperative day 3 were significantly higher ( $p<0.001$ ) in patients following THA (32.0, IQR:  
10 25.9 pg/ml) versus TKA (28.2, IQR: 24.3 pg/ml). There was no statistically significant  
11 difference ( $p=0.325$ ) in IL-6 values on postoperative day 3 following THA (38.9, IQR: 41.7  
12 pg/ml) versus TKA (30.6, IQR: 30.3 pg/ml) with an early acute PJI in the postoperative  
13 followup.

14

15 ***Total Hip Arthroplasty Group (n=3739)***

16 In the group of THA patients, the mean age was 68.7 (IQR: 17.5) years, and the median BMI  
17 was 26.8 (IQR: 6.5)  $\text{kg/m}^2$ . Overall, the proportion of male patients was 38.7%. ASA category  
18 I was identified in 18.4%, ASA II in 73.0%, and ASA III in 8.5%. In ASA categories IV and V  
19 there was only 1 patient each. The mean value of IL-6 on postoperative day 3 was 32.0 (IQR:  
20 26.0) pg/ml.

21 There were no statistically significant differences with regard to age ( $p=0.436$ ), IL-6  
22 values ( $p=0.116$ ), and distribution of ASA categories ( $p=0.718$ ) compared between patients  
23 with versus without a revision within 90 days following primary THA due to an early acute PJI.  
24 There was a significantly higher BMI in patients with a revision ( $p=0.002$ ), in addition to a  
25 higher proportion of male patients ( $p=0.027$ ). (Table 1) In THA patients with no early acute  
26 PJI, IL-6 levels were significantly higher in patients with an ASA category  $\geq 3$  vs. ASA  $<3$

1 (54.4±50.7 vs. 38.5±32.2;  $p<0.001$ ). In THA patients with an early acute PJI, no statistically  
2 significant difference was observed ( $p=0.758$ ). There was a longer duration of surgery in  
3 patients with versus without an early acute PJI (81.8±32.2 vs. 71.5±31.8 minutes;  $p=0.03$ ).  
4 Bivariate correlation however only demonstrated a weak correlation between length of surgery  
5 and IL-6 measured on postoperative day 3 ( $r=0.118$ ).

### 6 7 ***Total Knee Arthroplasty (n=3922)***

8 In the group of TKA patients, the mean age was 71.2 (IQR: 13.3) years, and the median BMI  
9 was 29.1 (IQR: 7.2). Overall, the proportion of male patients was 33.8%. ASA category I was  
10 identified in 8.3%, ASA II in 84.0%, and ASA III in 7.7%. There were 3 patients assigned to  
11 ASA category IV, and no patient assigned to ASA category V. The mean value of IL-6 on  
12 postoperative day 3 was 28.2 (IQR: 24.3) pg/ml.

13 There were no statistically significant differences with regard to age ( $p=0.925$ ), gender  
14 ( $p=0.064$ ), BMI ( $p=0.375$ ), IL-6 values ( $p=0.718$ ), and distribution of ASA categories  
15 ( $p=0.829$ ) compared between patients with versus without a revision within 90 days following  
16 primary TKA due to an early acute PJI. (Table 2) In TKA patients with no early acute PJI, IL-  
17 6 levels were significantly higher in patients with an ASA category  $\geq 3$  vs. ASA  $<3$  (60.7±92.7  
18 vs. 36.7±48.9;  $p<0.001$ ). In TKA patients with an early acute PJI, no statistically significant  
19 difference was observed ( $p=0.088$ ). There was a trend towards a longer duration of surgery in  
20 patients with versus without an early acute PJI (91.6±22.1 vs. 80.8±22.4 minutes;  $p=0.06$ ).  
21 Bivariate correlation however only demonstrated a weak correlation between length of surgery  
22 and IL-6 measured on postoperative day 3 ( $r=0.084$ ).

### 23 24 ***Matched-Cohort Analysis (n=86)***

25 In the group of THA patients, matching was performed for age ( $p=0.907$ ), gender ( $p=1.000$ ),  
26 SSIRS ( $p=1.000$ ), and the Charlson Comorbidity Index ( $p=0.979$ ), and the serum IL-6 values

1 on day 3 was then compared between patients with and without early onset PJI in the  
2 postoperative follow-up. Matched cohort analysis in the group of THA patients (n=58; 29 cases  
3 vs. 29 controls) showed no statistically significant difference in serum IL-6 levels between  
4 patients with (38.9, IQR: 41.7 pg/ml) versus without (40.2, IQR: 21.5 pg/ml) early onset PJI  
5 following THA (p=0.680).

6 In the group of TKA patients, matching was performed for age (p=0.804), gender  
7 (p=1.000), SSIRS (p=1.000), and the Charlson Comorbidity Index (p=1.000), and the serum  
8 IL-6 values on day 3 was then compared between patients with and without early onset PJI in  
9 the postoperative follow-up. Matched cohort analysis in the group of TKA patients (n=28; 14  
10 cases vs. 14 controls) showed no statistically significant difference in serum IL-6 levels between  
11 patients with (30.6, IQR: 30.3 pg/ml) versus without (28.5, IQR: 30.5 pg/ml) early onset PJI  
12 following TKA (p=0.910).

## 1 **DISCUSSION**

2 Prior studies have outlined C-reactive protein (CRP) within the first 5 days following TKA as  
3 an inappropriate indicator for an early periprosthetic joint infection (PJI). (Windisch et al.,  
4 2017) Due to a considerably shorter half-life with regard to normalization to baseline levels  
5 (Azboy et al., 2021; Herrero et al., 2008), Interleukin-6 has gained increasing interest in the  
6 setting of diagnosing PJI. The aim of the present study therefore was to assess the ability of IL-  
7 6 measured prior to discharge on postoperative day 3 following TJA to predict an early onset  
8 PJI in a large subset of patients. We therefore evaluated an overall number of 7661 patients who  
9 underwent primary THA or TKA between 01/2016 and 12/2019 at a single institution, thereby  
10 representing the largest series of its kind.

11 Based on our results, the rate of early onset PJI within the first 90 days following TJA  
12 was 0.8% for THA and 0.4% for TKA, representing a statistically significant difference. In  
13 patients without a PJI in the early postoperative period, IL-6 levels measured on postoperative  
14 day 3 were significantly higher in patients following THA versus TKA (32.0 vs. 28.2 pg/ml).  
15 A similar trend was detected in patients with an early onset PJI following THA versus TKA,  
16 which however did not reach statistical significance, potentially contributable to a type II error.  
17 Interestingly, Wirtz et al. did not identify a difference in IL-6 following THA versus TKA, with  
18 however a considerably smaller study population (20 vs. 10 patients). (Wirtz et al., 2000)

19 In the subgroup of THA patients, there was a trend towards higher serum IL-6 levels  
20 comparing patients with versus without early onset PJI, which however did not reach statistical  
21 significance. In addition, the observed difference in median values (6.9 pg/ml) can be  
22 considered of limited clinical relevance. Male gender and high BMI were associated with an  
23 increased risk for early onset PJI following THA. This concurs with a prospective evaluation  
24 of a total number of 623253 hip procedures performed over a period of 10 years published by  
25 Lenguerrand et al. The authors identified male gender as being associated with a 1.7-fold  
26 increased risk for a revision due to PJI. Furthermore, an elevated BMI of  $\geq 30$  kg/m<sup>2</sup> was

1 associated with a 1.9-fold increased risk compared to patients with a BMI of  $<25 \text{ kg/m}^2$   
2 (Lenguerrand et al., 2018). In the subgroup of TKA patients, there was no statistically  
3 significant difference in serum IL-6 levels comparing patients with versus without early onset  
4 PJI. Similar to the analysis in THA patients, the proportion of male patients seemed to be higher  
5 in patients with an early onset PJI following TKA, which however did not reach statistical  
6 significance, potentially contributable to a type II error. BMI was not associated with an early  
7 onset PJI following TKA.

8         Despite the study being the largest of its kind limitations need to be considered when  
9 interpreting the presented findings. In fact, especially with regard to the IL-6 levels in patients  
10 with an early postoperative PJI, the sample sizes were too small to perform a multivariate  
11 analysis. This is mainly due to a low incidence of PJI in the early postoperative period. Follow  
12 up studies, ideally with a prospective study design, are warranted.

13         In order to account for potential confounding, matching was performed for a large  
14 number of variables, including age, gender, SSIRS, and the Charlson Comorbidity Index.  
15 Matched cohort analysis showed no statistically significant difference in serum IL-6 levels  
16 between patients with and without early onset PJI, neither following THA nor TKA. We  
17 therefore consider IL-6 as an inappropriate tool to predict the risk for a revision due to an early  
18 onset PJI following primary TJA. The half-life period of IL-6 with regard to normalization to  
19 preoperative baseline values has been reported to be considerably lower compared to CRP. In  
20 a prospective study by Wirtz et al., serum levels of both IL-6 and CRP were measured before  
21 and after total hip and knee arthroplasty. The peak of serum levels were measured after 6 hours  
22 for IL-6 with a mean half-life of 15 hours, in contrast to CRP which peaked during the second  
23 postoperative day with a slow descent and a mean half-life of 62 hours. (Wirtz et al., 2000)  
24 According to Azboy et al., CRP levels returned to baseline levels after 45 days following  
25 uneventful TJA (Azboy et al., 2021), which is in contrast with a study by Herrero et al. in which

1 the authors observed a return to baseline levels over a period of 150 days with still high levels  
2 on postoperative day 42. (Herrero et al., 2008)

3 As previously described in an analysis from our department, 327 two-stage revision  
4 knee and hip arthroplasties in an overall number of 312 patients were evaluated. Ninety  
5 different microorganisms were diagnosed in 74 first and second stage procedures, with 91.1%  
6 gram positive, 7.8% gram negative, and 1.1% Candida species. In initial 2-stage exchange  
7 arthroplasties (first and second), the most commonly detected microorganism was  
8 Staphylococcus epidermidis (30%), followed by Staphylococcus aureus (12.2%), and  
9 Cutibacterium acnes (12.2%). Out of 27 Staphylococcus epidermidis cases, there were 21 cases  
10 of methicillin resistance, and 6 cases of methicillin sensitivity. Out of 11 Staphylococcus aureus  
11 cases, there was one case of methicillin resistance (MRSA). In 21.6% and 16.2% of first and  
12 second stage procedures, a polymicrobial infection was detected. (Frank et al., 2021)

13 In conclusion, based on our findings, serum IL-6 values measured on postoperative day  
14 3 following total hip or knee arthroplasty cannot predict early onset periprosthetic joint  
15 infections within the first 90 postoperative days.

16

## 17 **FIGURE LEGEND**

18

19 **Figure 1.** Flow-chart diagram of patient inclusion and exclusion.

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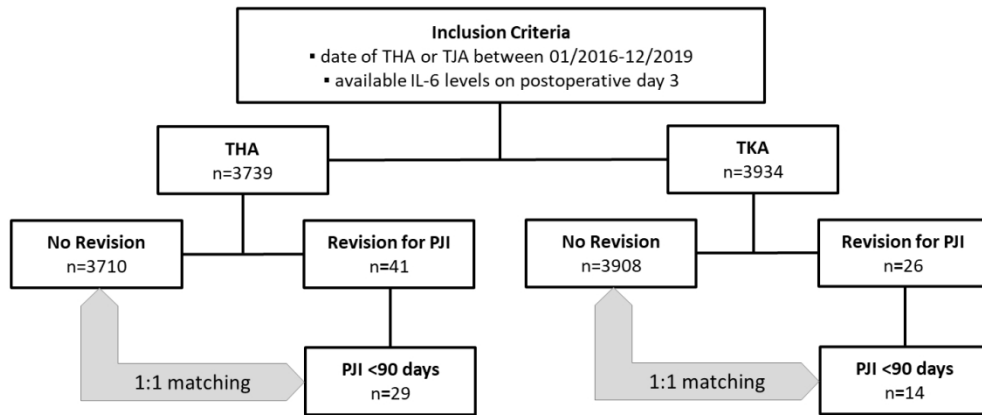
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Flow-chart diagram of patient inclusion and exclusion.

385x166mm (96 x 96 DPI)

**Table 1.** Descriptive statistics of patients with no infection following THA compared with patients with an early acute PJI following THA (<90 days).

	<b>Total Hip Arthroplasty (THA)</b> (n=3739)		<b>p-Value</b>
	<b>no infection</b> (n=3710)	<b>early acute PJI</b> (n=29)	
Age, years Median (IQR)	68.7 (17.4)	68.9 (18.5)	0.436
Male gender (%)	38.5% (1427/3707)	58.6% (17/29)	0.027
BMI (kg/m <sup>2</sup> )	26.8 (6.5)	30.8 (9.6)	0.002
ASA category			0.718
I	18.4% (635/3447)	11.5% (3/26)	
II	73.0% (2516/3447)	73.1% (19/26)	
III	8.5% (294/3447)	15.4% (4/26)	
IV	<0.1% (1/3447)	0.0% (0/26)	
V	<0.1% (1/3447)	0.0% (0/26)	
IL-6, pg/ml	32.0 (25.9)	38.9 (40.4)	0.116

**Table 2.** Descriptive statistics of patients with no infection following TKA compared with patients with an early acute PJI following TKA (<90 days).

	<b>Total Hip Arthroplasty (TKA)</b> (n=3922)		<b>p-Value</b>
	<b>no infection</b> (n=3908)	<b>early acute PJI</b> (n=14)	
Age, years Median (IQR)	71.2 (13.3)	70.4 (4.6)	0.925
Male gender (%)	33.7% (1316/3906)	57.1% (8/14)	0.064
BMI (kg/m <sup>2</sup> )	29.1 (7.2)	31.8 (7.4)	0.375
ASA category			0.829
I	8.3% (298/3598)	7.1% (1/14)	
II	84.0% (3022/3598)	78.6% (11/14)	
III	7.6% (275/3598)	14.3% (2/14)	
IV	0.1% (3/3598)	0.0% (0/0)	
V	0.0% (0/0)	0.0% (0/0)	
IL-6, pg/ml	28.2 (24.3)	30.6 (20.7)	0.718