POSTOPERATIVE IL-6 LEVELS CANNOT PREDICT EARLY ONSET PERIPROSTHETIC HIP/KNEE INFECTIONS: AN ANALYSIS OF 7,661 PATIENTS AT A SINGLE INSTITUTION

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Abstract

Prior studies have outlined C-reactive protein (CRP) within the first 5 d following total hip arthroplasty (THA) as an inappropriate indicator of an early periprosthetic joint infection (PJI). Recently, 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 IL-6 measured on postoperative day 3 following TJA as a prediction marker of early onset PJI. 7,661 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 measured 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 and Charlson comorbidity index. Overall (n = 7,661), there was no statistically significant difference in serum IL-6 levels comparing patients with and without early onset PJI following THA [38.9 pg/mL $vs.$ 32.0 pg/mL, p = 0.116] and TKA [30.6 pg/mL $vs.$ 28.2 pg/mL, p = 0.718]. Male gender and high body mass index were associated with an increased risk of 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 THA or TKA could not predict early onset PJIs.

List of Abbreviations

ASA	American Society of Anesthesiologists
BMI	body mass index
CCI	Charlson comorbidity index
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
IL-6	interleukin-6
IQR	interquartile range
MSIS	Musculoskeletal Infection Society
PJI	periprosthetic joint infection
SSIRS	surgical site infection risk score
THA	total hip arthroplasty
TJA	total joint arthroplasty
TKA	total knee arthroplasty
WBC	white blood cell count

Introduction

Early detection of acute PJI following TJA is crucial for the patient outcome. Serum parameters, including CRP, measured during the postoperative period play an important role in the diagnosis of PJIs (Parvizi *et al.*, 2018). However, reports have showed their limited accuracy and low specificity (Sigmund *et al.*, 2021). Previous studies have demonstrated a slow normalisation in the postoperative levels of CRP following primary TJA, representing a drawback with regard to diagnosing acute PJIs (Azboy *et al.*, 2021). The serum levels of CRP have been reported to reach a peak during the second postoperative day. This is followed by a slow normalisation rate to baseline levels (Wirtz *et al.*, 2000) over the following 3 weeks

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(Larsson *et al.*, 1992) up to 5 months (Herrero *et al.*, 2008). As a result, CRP measured within the first 5 d following TKA is considered to be an inappropriate indicator for an early PJI (Windisch *et al.*, 2017).

Another commonly used serological parameter is the ESR, which, however, has been reported to be associated with a low accuracy when detecting PJIs (Sigmund *et al.*, 2021). The main problem is the fact that it can be normal in patients with chronic PJI due to low-virulence organisms (Pérez-Prieto *et al.*, 2017). A similar problem has been reported for the diagnostic value of WBC, D-dimer, procalcitonin and fibrinogen, with poor accuracy to reliably diagnose a PJI (Sigmund *et al.*, 2021).

In recent years, IL-6 as a potential inflammatory marker following TJA has gained increasing interest, particularly due to its half-life being 4 times shorter compared to CRP (Wirtz *et al.*, 2000). In fact, the peak of IL-6 serum levels is measured after 6 h, with a mean half-life of 15 h (Wirtz *et al.*, 2000). The aim to identify cut-off values of serum markers with a short half-life to predict PJI in the postoperative period is further reinforced by the progressive trend towards a significantly decreased hospital length of stay due to rapid-recovery protocols (Berend *et al.*, 2004). Based on these considerations, a standardised protocol was adapted in 2016 at the Orthopaedic Hospital Vienna-Speising, Department of Orthopaedic Surgery II to measure IL-6 levels prior to discharge on postoperative day 3 following TJA in each patient.

The aim of the present study was to evaluate average serum IL-6 levels on postoperative day 3 following uneventful THA and TKA in a large subset of patients at a single institution, in context with patient-related risk factors. Patients with an early acute PJI during the first 90 d following TJA were further identified. Then, a matched-cohort analysis was performed, aiming at assessing the ability of IL-6, measured prior to discharge on postoperative day 3 following TJA, to predict an early onset PJI in a large subset of patients.

Materials and Methods

Institutional arthroplasty registry

The present study was approved by the institutional review board. The institutional arthroplasty registry and PJI database were retrospectively evaluated from January 2016 to December 2019 for patients who underwent THA/TKA. Patients with no revision surgery following TJA (*n* = 7,618) were compared with patients who underwent a revision surgery for an early PJI within 90 d following the primary surgery (*n* = 43). The 2018 MSIS criteria (Parvizi *et al.*, 2018) were applied for the definition of a PJI. Furthermore, only patients with serum IL-6 levels measured on day 3 were included. Data on age, gender, BMI, interval between primary TJA and revision surgery, SSIRS (van Walraven and Musselman, 2013), ASA score and microbiological analysis were further collected. Furthermore, the CCI was evaluated. This index – consisting of 19 weighted separate comorbidities (including peripheral vascular disease, cerebrovascular disease, diabetes, renal disease, liver disease, among others) – was initially described as a prognostic score to predict patient mortality (Charlson *et al.*, 1987).

In a sub-analysis, both sub-groups were finally matched (1:1) for age, gender, operated joint, SSIRS and CCI and, then, the serum IL-6 values on day 3 were compared (Fig. 1).

Statistical analysis

Categorical variables are reported as frequencies and percentages and continuous variables as median with the IQR. The Pearson's chi-squared test was used for the comparison of proportions. The Kolmogorov-Smirnov test was used to test for normal distribution. Due to a non-parametric distribution, the Mann-Whitney U test was used for the comparison of continuous variables. A $p < 0.05$ was defined as the level of statistical significance. Correlation analysis was performed using a bivariate
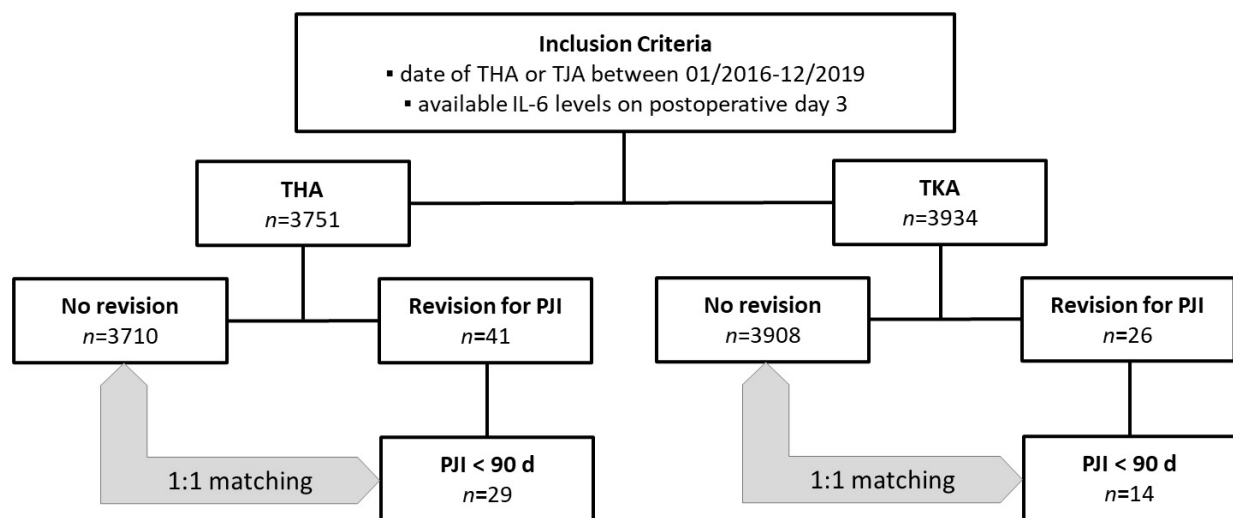

Fig. 1. Flow-chart diagram of patient inclusion and exclusion criteria.

Pearson correlation. Data analysis was performed using IBM SPSS Statistics, Version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Overall study population (*n* = 7,661)

Overall, 7,661 patients met the study's inclusion criteria. Between January 2016 and December 2019, 3,710 primary THA and 3,908 primary TKA were performed, with no revision following primary surgery. In 29 (0.8 %) and 14 (0.4 %) patients, a revision surgery was performed for an early acute PJI within the first 90 d following primary THA and TKA, respectively (29/3,739 *vs.* 14/3,922; *p* = 0.014). In patients with no infection following TJA, the IL-6 values on postoperative day 3 were significantly higher (*p* < 0.001) following THA (32.0, IQR: 25.9 pg/mL) *versus* TKA (28.2, IQR: 24.3 pg/mL). There was no statistically significant difference (*p* = 0.325) in IL-6 values on postoperative day 3 following THA (38.9, IQR: 41.7 pg/mL) *versus* TKA (30.6, IQR: 30.3 pg/mL) with an early acute PJI in the postoperative follow-up.

THA group (*n* = 3,739)

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

There were no statistically significant differences with regard to age (*p* = 0.436), IL-6 values (*p* = 0.116) and distribution of ASA categories (*p* = 0.718) compared between patients with *versus* without a revision within 90 d following primary THA due to an early acute PJI. There was a significantly higher BMI in patients with a revision (*p* = 0.002), in addition to a larger proportion of male patients (*p* = 0.027) (Table 1). In THA patients with no early acute PJI, IL-6 levels were significantly higher in patients with an ASA category ≥ 3 *vs.* ASA < 3 (54.4 ± 50.7 *vs.* 38.5 ± 32.2; *p* < 0.001). In THA patients with an early acute PJI, no statistically significant difference was observed (*p* = 0.758). There was a longer duration of surgery in patients with *versus* without an early acute PJI (81.8 ± 32.2 *vs.* 71.5 ± 31.8 min; *p* = 0.03). However, bivariate correlation only demonstrated a weak correlation between length of surgery and levels of IL-6 measured on postoperative day 3 (*r* = 0.118).

TKA (*n* = 3922)

In the group of TKA patients, the mean age was 71.2 (IQR: 13.3) years and the median BMI was 29.1 (IQR: 7.2). The proportion of male patients was 33.8 %. ASA category I was identified in 8.3 %, ASA II in 84.0 % and ASA III in 7.7 % of the patients. There were 3

patients assigned to ASA category IV and no patient assigned to ASA category V. The mean value of IL-6 on postoperative day 3 was 28.2 (IQR: 24.3) pg/mL.

There were no statistically significant differences with regard to age (*p* = 0.925), gender (*p* = 0.064), BMI (*p* = 0.375), IL-6 values (*p* = 0.718) and distribution of ASA categories (*p* = 0.829) compared between patients with *versus* without a revision within 90 d following primary TKA due to an early acute PJI (Table 2). In TKA patients with no early acute PJI, IL-6 levels were significantly higher in patients with an ASA category ≥ 3 *vs.* ASA < 3 (60.7 ± 92.7 *vs.* 36.7 ± 48.9; *p* < 0.001). In TKA patients with an early acute PJI, no statistically significant difference was observed (*p* = 0.088). A trend towards a longer duration of surgery was observed in patients with *versus* without an early acute PJI (91.6 ± 22.1 *vs.* 80.8 ± 22.4 min; *p* = 0.06). However, bivariate correlation only demonstrated a weak correlation between length of surgery and IL-6 measured on postoperative day 3 (*r* = 0.084).

Matched-cohort analysis (*n* = 86)

In the group of THA patients, matching was performed for age (*p* = 0.907), gender (*p* = 1.000), SSIRS (*p* = 1.000) and CCI (*p* = 0.979) and, then, the serum IL-6 values on day 3 were compared between patients with and without early onset PJI in the postoperative follow-up. Matched cohort analysis in the group of THA patients (*n* = 58; 29 cases *vs.* 29 controls) showed no statistically significant difference in serum IL-6 levels between patients with (38.9, IQR: 41.7 pg/mL) and without (40.2, IQR: 21.5 pg/mL) early onset PJI following THA (*p* = 0.680).

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

Discussion

Prior studies have outlined CRP within the first 5 d following TKA as an inappropriate indicator for an early PJI detection (Windisch *et al.*, 2017). Due to its considerably shorter half-life with regard to normalisation to baseline levels (Azboy *et al.*, 2021; Herrero *et al.*, 2008), IL-6 has gained increasing interest for PJI diagnosis. Therefore, the aim of the present study was to assess the ability of IL-6 measured prior to discharge on postoperative day 3 following TJA to predict an early onset PJI in a large subset of patients. An overall number of 7,661 patients who underwent primary THA or TKA

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

	THA (*n* = 3739)		
	No infection (*n* = 3710)	Early acute PJI (*n* = 29)	*p*-value
Age in 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^2)	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 d).

	TKA (*n* = 3922)		
	No infection (*n* = 3908)	Early acute PJI (*n* = 14)	*p*-value
Age in 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^2)	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

between January 2016 and December 2019 at a single institution was evaluated, thereby representing the largest series of its kind.

Based on the study results, the rate of early onset PJI within the first 90 d following TJA was 0.8 % for THA and 0.4 % for TKA, representing a statistically significant difference. In patients without a PJI in the early postoperative period, IL-6 levels measured on postoperative day 3 were significantly higher in patients following THA *versus* TKA (32.0 *vs.* 28.2 pg/mL). A similar trend was observed in patients with an early onset PJI following THA *versus* TKA, which however did not reach statistical significance, potentially due to a type II error. Interestingly, Wirtz *et al.* (2020) did not identify a difference in IL-6 following THA *versus* TKA, with however a considerably smaller study population (20 *vs.* 10 patients).

In the subgroup of THA patients, there was a trend towards higher serum IL-6 levels comparing patients with *versus* without early onset PJI, which however did not reach statistical significance. In addition, the observed difference in median values (6.9 pg/mL) could be considered of limited clinical relevance. Male gender and high BMI were associated with an increased risk of early onset PJI following THA. This concurs with a prospective evaluation of a total number of 623,253 hip procedures performed over

a period of 10 years, as published by Lenguerrand *et al.* (2018). The authors identified male gender as being associated with a 1.7-fold increased risk of a revision due to PJI. Furthermore, an elevated BMI of ≥ 30 kg/m^2 was associated with a 1.9-fold increased risk compared to patients with a BMI of < 25 kg/m^2 (Lenguerrand *et al.*, 2018). In the subgroup of TKA patients, there was no statistically significant difference in serum IL-6 levels comparing patients with *versus* without an early onset PJI. Similar to the analysis in THA patients, the proportion of male patients seemed to be larger in patients with an early onset PJI following TKA. However, results did not reach statistical significance, potentially due to a type II error. BMI was not associated with an early onset PJI following TKA.

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

To account for potential confounding factors, matching was performed for a large number of variables, including age, gender, SSIRS and CCI.

Matched cohort analysis showed no statistically significant difference in serum IL-6 levels between patients with and without early onset PJI, neither following THA nor TKA. Therefore, detection of IL-6 was considered as an inappropriate tool to predict the risk of a revision due to an early onset PJI following primary TJA. The half-life period of IL-6 with regard to normalisation to preoperative baseline values has been reported to be considerably lower compared to CRP. In a prospective study by Wirtz *et al.* (2020), serum levels of both IL-6 and CRP were measured before and after both THA and TKA. The peaks of serum IL-6 levels were measured after 6 h with a mean half-life of 15 h, in contrast to CRP that peaked during the second postoperative day with a slow descent and a mean half-life of 62 h (Wirtz *et al.*, 2000). According to Azboy *et al.* (2021), CRP levels return to baseline levels after 45 d following uneventful TJA, which is in contrast to a study by Herrero *et al.* (2008) in which the authors observed a return to baseline levels over a period of 150 d with still high levels on postoperative day 42.

As previously described in an analysis from the Department of Orthopaedic Surgery II, Orthopaedic Hospital Vienna-Speising, 327 two-stage revision knee and hip arthroplasties in an overall number of 312 patients were evaluated. The presence of 90 different microorganisms was diagnosed in 74 first and second stage procedures, with 91.1 % gram positive, 7.8 % gram negative and 1.1 % Candida species. In initial 2-stage exchange arthroplasties (first and second), the most commonly detected microorganism was *Staphylococcus epidermidis* (30 %), followed by *Staphylococcus aureus* (12.2 %) and *Cutibacterium acnes* (12.2 %). Out of 27 *Staphylococcus epidermidis* cases, there were 21 cases of methicillin resistance and 6 cases of methicillin sensitivity. Out of 11 *Staphylococcus aureus* cases, there was one case of methicillin resistance. In 21.6 % and 16.2 % of first and second stage procedures, respectively, a polymicrobial infection was detected (Frank *et al.*, 2021).

In conclusion, based on the present findings, serum IL-6 values measured on postoperative day 3 following both THA and TKA cannot predict early onset PJIs within the first 90 postoperative days.

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Discussion with Reviewers

Reeviwer 1: Had the surgical approach in THA patients an influence on the levels of IL-6. Was there

any difference between patients undergoing a lateral *vs.* anterior *vs.* other approaches?

Authors: This is a very interesting question, which however cannot be answered with the present study. At the Orthopaedic Hospital Vienna-Speising, Department of Orthopaedic Surgery II institution, the lateral (transgluteal) approach was the main approach in THA patients before 2012/2013, before it was gradually replaced by the direct anterior approach THA for primary THA and also before IL-6 was introduced as a diagnostic marker in the routine postoperative follow-up. As a result, comprehensive data on IL-6 values in patients following primary lateral THA were not available.

Reeviwer 1: Is procalcitonin part of your diagnostic algorithm for a suspected PJI?

Authors: Procalcitonin can be considered a promising biomarker for diagnosing a PJI. However, th present study used the MSIS criteria by Parvizi *et al.* (2018) for the diagnosis of a PJI. According to these criteria, two positive cultures of the same organism or a sinus tract can be considered as major criteria for PJI diagnosis. Minor criteria for a preoperative diagnosis include serum CRP, serum D-Dimer, serum ESR, synovial WBC, synovial leukocyte esterase, synovial alpha-defensin, synovial polymorphonuclear cells (%) and synovial CRP. Procalcitonin is not part of this diagnostic algorithm.

Reeviwer 2: Why do you even consider measuring IL-6 following primary arthroplasty? Did you change your diagnostic approach following surgery based on your findings? Also, the time of the IL-6 measurement was not discussed. Is it clear that 3 d postoperative is the best time to measure?

Authors: The aim of the Orthopaedic Hospital Vienna-Speising, Department of Orthopaedic Surgery II was to measure the serum levels of CRP prior to discharge to rule out a pathological inflammatory response, potentially requiring further therapy or intervention. With a trend towards a significantly decreased hospital lenth of stay following rapid-recovery protocols, CRP was considered inappropriate due to its prolonged half-life with a slow rate in normalisation in postoperative levels. As a result, the postoperative standard protocol was changed to measuring serum IL-6 levels prior to discharge on postoperative day 3. However, based on the results of the present study, the diagnostic predictive value of IL-6 on day 3 with regard to early acute PJI is limited. In fact, significant outliers with extremely high IL-6 levels were observed in patients with acute gastrointestinal pathologies, rather than in patients with a PJI in the early postoperative period. However, due to a limited sample size, these conclusions need to be evaluated with further studies.

Gowrishankar Muthukrishnan: Can blood-based, non-pathogen-specific biomarkers such as IL-6 and CRP offer the sensitivity and specificity needed to reliably diagnose orthopaedic infections?

Authors: Serum biomarkers are of great importance during the diagnostic steps of PJI, as similarly reported by Gallo *et al.* (2018, additional reference). In a more recent study by Qin *et al.* (2020, additional reference), the authors have identified an accuracy of 96.77 % in diagnosing chronic PJI, when combining synovial and serum IL-6 values. Nevertheless, it is the authors opinion that the major criteria of the MSIS by Parvizi *et al.* (2018) should be applied for the diagnosis of a PJI. According to these criteria, two positive cultures of the same organism or a sinus tract can be considered as major criteria for PJI diagnosis. There are several reports in the literature underlining the limited diagnostic value of serum laboratory values with low sensitivity rates.

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Editor's note: The Scientific Editor responsible for this paper was Fintan Moriarty.