International Orthopaedics (2024) 48:2421–2427
https://doi.org/10.1007/s00264-024-06255-9

ORIGINAL PAPER

Evaluation of interleukin-6 in synovial fluid in periprosthetic joint infection of the elbow

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Received: 5 May 2024 / Accepted: 10 July 2024 / Published online: 20 July 2024

Abstract

Purpose Searching for quick determinable biomarkers with high sensitivity and specificity is necessary to improve and optimise the early diagnosis of periprosthetic elbow infection (PEI). Therefore, this study's objective was to evaluate the diagnostic value of synovial fluid interleukin-6 (IL-6) levels for diagnosing PEI in total elbow arthroplasty.

Method Twelve prospective enrolled patients underwent total elbow arthroplasty revision surgery, during which synovial fluid was obtained. Between the initial implantation and the revision procedure were 33.5 ± 41 months (range, 2–144 months). Synovial fluid was collected for immediate IL-6 analysis parallel to the revision surgery. Furthermore, microbiological samples were obtained and analysed. Two groups were defined based on the microbiological results: non-infection and infection group. The ability of synovial fluid IL-6 analysis to predict infection status was explored using receiver operating characteristic curves and further statistical analysis.

Results Synovial fluid IL-6 analysis had a good diagnostic accuracy of 83% for PEI with an area under the curve of 0,79 and an ideal cutoff value (determined using Youden's criterion) of 15244 pg/mL.

Discussion This is the first study to clinically evaluate IL-6 as a diagnostical marker for periprosthetic joint infection (PJI) in total elbow arthroplasty. Our results suggest a good accuracy and high sensitivity for IL-6 to identify a PEI. The analysis of IL-6 can improve surgical decision-making regarding managing total elbow arthroplasty in terms of one- or two-staged revision.

Conclusion IL-6 can play an important role in the perioperative differentiation of infected and non-infected situations.

Keywords Elbow · Periprosthetic infection · PJI · Cytokines · Total elbow prosthesis · Infection · IL-6

Introduction

The number of total elbow arthroplasties performed has increased in recent years [1]. As a result, complications and revisions of total elbow arthroplasties have increased in frequency and have come under increased scrutiny in recent years [2, 3].

Implant loosening is a common cause of total elbow arthroplasty (TEA) revision, possibly due to an infective or aseptic process [4, 5]. Aseptic loosening is thought to occur due to osteolysis at the cement–bone interface, a failure at the cement-implant interface, or a periprosthetic fracture. These conditions typically can be managed with a single-stage revision [6]. In contrast, septic loosening is often addressed with a two-stage revision procedure and long-term antibiotic therapy [6]. However, this is associated with more significant morbidity, poorer quality of life, and substantially higher costs than single-stage revision [7].

Therefore, it is essential to determine whether a PEI is apparent in every individual case of TEA failure. Diagnosing PEI requires a combination of laboratory procedures, histopathology, microbiology, and imaging studies. However, this appears to be very complex in the elbow because local and systemic complaints of fever or malaise are observed very infrequently, mainly when caused by low-grade infections [8]. In bacterial infection, laboratory markers, including C-reactive protein (CRP) and white-blood-cell counts (WBC), seem important. Unfortunately,

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these serum markers have shown poor correlation with subsequently confirmed infections at the elbow. CRP, an unspecific acute phase protein, can be increased due to numerous side effects such as chronic diseases, nicotine abuse, and obesity [9, 10]. On the other hand, WBC is not elevated in most patients with TEA infection [6, 11, 12].

Joint aspiration (JA) has shown a poor informative value in cases of PEI. Achermann et al. retrospectively analysed a cohort of 27 patients with PEI in a monocenter study. JA identified only six cases of infection (21%). They concluded that JA is an unreliable tool for excluding infections [13].

Fresh frozen histological examination is one of the few real-time diagnostic tools to evaluate inflammatory soft tissue for suspected PEI. Unfortunately, the results of a review of 227 revision TEA showed a sensitivity of only 51.3% with a specificity of 93.1%, indicating a low clinical value [14].

Therefore, the gold standard tool still seems to be a microbiological tissue culture to rule out infection, which entails a prolonged two-stage protocol in nearly all cases [6, 14]. However, Wee et al. showed a 7.5% chance of an unsuspected positive microbiological result in revision surgery, complicating further decisions for the surgeon [15].

To improve and optimise the early diagnosis of PJI, a search for biomarkers with a fast response, high sensitivity, and specificity is necessary. Several studies described the suitability of interleukins in serum for diagnosing PJIs after knee, hip, and shoulder arthroplasty [16–20].

In this context, cytokines appear to be a promising category of biomarkers since they play a vital role in the immune response during infections. Until now, no studies have evaluated the use of cytokines for PJI of the elbow. Interleukin (IL)-6 is described as one of the primary mediators of acute-phase protein production [21].

This study aimed to evaluate the diagnostic value of synovial fluid interleukin (IL)-6 levels for diagnosing PEI.

Material and methods

From January 2020 to March 2024, 30 prospectively enrolled patients underwent total elbow arthroplasty revision surgery. Synovial fluid was obtained just before the incision by needle aspiration. The mean age of the patients at the time of surgery was 63 ± 15 years (range 31 to 88 years). The average time between the initial implantation and the revision procedure was 28.9 months (range 2 to 144 months). Inclusion criteria were an age of 18 and above and TEA revision surgery. Exclusion criteria were infections in other parts of the body and organs, active autoimmune diseases and current antibiotic or immunomodulatory therapy.

All patients underwent a routine preoperative workup for PEI, including serum measurements of WBC and CRP levels. Synovial fluid was obtained for culture and IL-6 analysis by direct aspiration at the time of the revision. In addition, a minimum of five tissue specimens were obtained intraoperatively from all patients (range 5 to 9). These included samples along the ulnar and humeral components, intramedullary tissue of the stems after removal, and capsular or pseudo-capsular tissue.

Fluid and tissue specimens were processed according to standard laboratory protocols, with cultures incubated for fourteen days. The IL-6 analysis was performed in a delayed manner, using the analysis protocol described below. Consequently, the results were unavailable to the surgeon for clinical decision-making and were analysed strictly for this study.

For the analysis of IL-6 levels, samples were taken to our laboratory immediately after collection and analysed within 30 Minutes after extraction by a standard sandwich immunoassay, Elecsys IL-6, Cobas E801 (Roche Diagnostics, Switzerland). It utilises an electrochemiluminescence immunoassay (ECLIA) technology. This standard laboratory procedure was certified by DIN ISO EN 15189 and has shown to be a clinically reliable method for analysing IL-6 levels.

IRB approval was obtained from our institutional review board.

All cases required complete medical records, radiographs, blood lab (WBC, CRP), and the results of intraoperative tissue cultures after a two-week incubation. Based on the results of the microbiological analysis, two groups were defined: a non-infection group and an infection group. The non-infection group described patients with no evidence of infection. The infection group included patients who met the criteria for infection, defined as positive microbiological results in more than three intraoperatively collected samples. In addition, these samples needed to show the same pathogen. All cases were discussed in our interdisciplinary infection board.

Statistical analysis was performed using IBM SPSS Statistics Version 27 (IBM, New York, USA). Means, standard deviations, and ranges were calculated. The statistical ability of synovial fluid IL-6 analysis to identify infection was analysed using receiver operating characteristic curves. The accuracy, sensitivity, and specificity were calculated for IL-6, WBC and CRP. Youden's criterion was used to choose an ideal cutoff value for determining infection status based on the IL-6 level. According to this criterion, the point on the receiver operating characteristic curve that maximises the sum of sensitivity and specificity is the ideal cutoff level.

The efficacy of IL-6 analysis in identifying infection status was described by the area under the curve (AUC). To classify the diagnostical value of the AUC, we defined limits to rate the values. An AUC of 0.91–1.00 was considered excellent, 0.81–0.90 good, 0.71–0.80 decent, and < 0.61–0.70 insufficient.

Results

The total number of revision surgeries was 30. Four different models of TEA were included ($n = 23$ Latitude, Stryker; $n = 5$ Nexel, Zimmer/Biomet, $n = 1$ Coonrad/Morrey, Zimmer/Biomet, $n = 1$ Discovery, Enovis). 10 men (33,3%) and 20 women (66,6%) were treated (Fig. 1). The most frequent indication for TEA in the study population was trauma ($n = 23$), which is shown in Fig. 1. In 11 cases (36,6%), we included the patients in the infection group (septic loosening), and 19 (63,4%) patients did not meet the criteria with no microbiological evidence for infection. All other causes for revision surgery are shown in Fig. 2. The mean number of surgeries, excluding the current revision surgery, was 6.33 ± 5.12 (range 1 – 20). In the infection group, the microbiological incubation provided at least 3 positive samples for Staphylococcus epidermidis ($n = 7$), Cutibacterium acnes ($n = 2$), and Staphylococcus aureus (MSSA) ($n = 2$).

IL-6 was significantly elevated in the infection group ($p = 0{,}001$), as shown in Fig. 3. At the same time, CRP ($p = 0.03$) and WBC ($p = 0.02$) were also significantly elevated in the infection group (Fig. 3).

The mean intraarticular IL-6 level for both groups was 50810.43 pg/mL ± 183716.29 (range 89–1000000 pg/mL), while the CRP value averaged 24.855 mg/L ± 53.148 (range; 0.8 – 209.7 mg/L) and leukocyte count 8.36×10^9/L ± 3.71 (range: 4.75–24.47 × 10^9/L).

IL-6 analysis of synovial fluid demonstrated a diagnostic accuracy of 83.33% (95% CI: 65%—94%) for infections with an AUC of 0.79 and an ideal cutoff value (determined using Youden's criterion) of 15244,36 pg/mL. IL-6 analysis showed a sensitivity of 94.74% and a specificity of 63.64%, with a positive predictive value of 81.82% and a negative predictive value of 87.50%.

CRP evaluation revealed a diagnostic accuracy of 73.33% (95% CI: 54%—88%) for PEI with an AUC of 0.67, an ideal cutoff value of 22.38 mg/L, a sensitivity of 89.47%, a specificity of 45.45%, a positive predictive value of 73.91%, and a negative predictive value of 71.43%.

The analysis of WBC for the identification of PEI showed an accuracy of 71.24% (95% CI: 55%—87%). The AUC was 0,71 with a sensitivity of 78.95%, a specificity of 63.64%, a positive predictive value of 77.85%, and a negative predictive value of 63.42%. The ideal cutoff value of 9.92×10^9/L was identified for PEI. The individual ROC for IL-6, CRP and WBC are shown in Fig. 4.

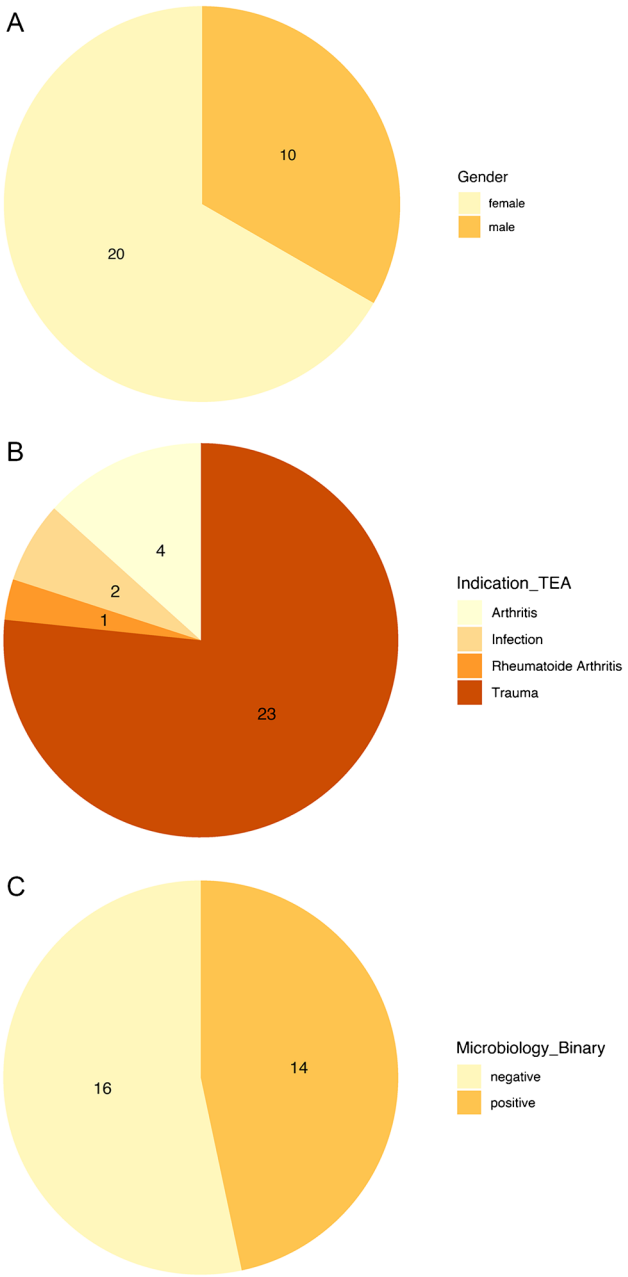

Fig. 1 **A** The Figure shows the gender distribution in the study population. **B** The indications for the initial implantation of the TEA. **C** Shows the results of microbiological testing of samples, of which 14 were considered positive

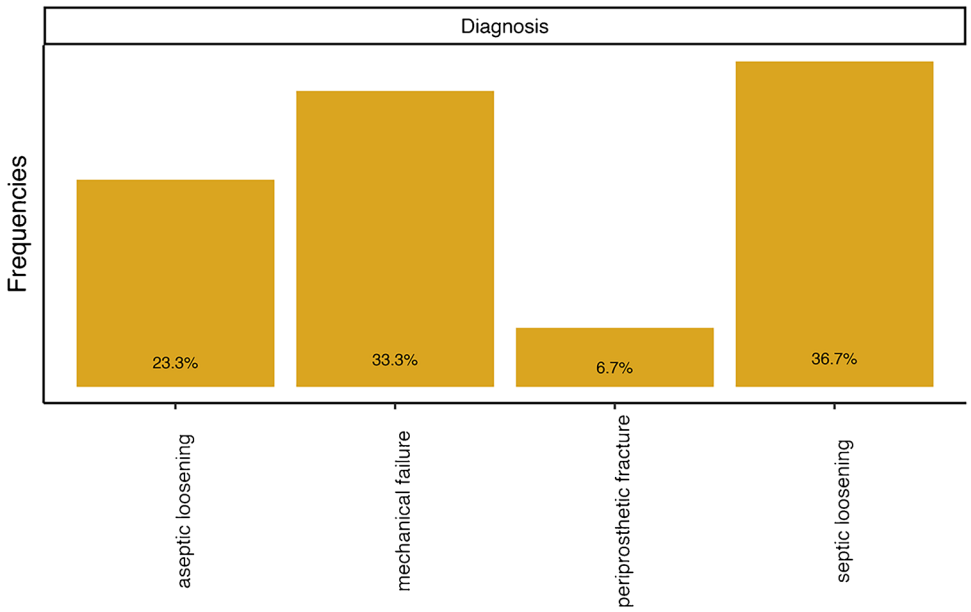

Fig. 2 Causes for failure of TEA based on all diagnostical information. 36.7% were identified as cases of septic loosening by positive microbiology

Discussion

A PJI is a significant complication after total elbow arthroplasty and remains a diagnostic challenge because of the frequently subliminal, nonspecific clinical appearance. Low-grade infections usually need multiple positive microbiological samples to be identified [22]. Serum laboratory analysis with CRP and WBC is unreliable in determining PEI [22, 23]. A recent systematic review concluded that total elbow arthroplasty is associated with an increased risk for infection compared to other significant arthroplasties [24]. Future studies of innovative diagnostics are necessary as the current literature is limited in this regard.

Serum markers can easily be misinterpreted because underlying or systemic infections can be apparent. Autoimmune and hematologic diseases also tend to affect the serum levels of the analysed values [25]. Local collection of immune markers in the affected joints may be better diagnostic tests.

Our results support this approach, as CRP and WBC showed poor accuracy in identifying PEI. This result reiterates the insufficiency of the current systemic diagnostic modalities. Nevertheless, serum markers should always be analysed to rule out a septic situation, systemic response or infections in other parts of the body. We are convinced that a septic situation needs an urgent workup since other localisations of infections are always possible and should be noticed.

Our study is the first to evaluate synovial fluid IL-6 as a marker for infection after total elbow arthroplasty. Our results suggest that the analysis of IL-6 in synovial fluid is more accurate than other systemic criteria for identifying a PEI. Early and successful identification of PEI is crucial for determining subsequent medical and surgical management. Nevertheless, in our study, two of the cases of the non-infection group were above the cutoff for IL-6.

According to our results, IL-6 analysis can help differentiate between infective and non-infective processes in total elbow arthroplasty failure in the future.

Preoperative aspiration of synovial fluid can be performed in suspected cases. Intraoperative synovial analysis can be carried out within the first minutes of the operation. This analysis can act as a rapid laboratory test to help surgeons make intraoperative decisions regarding single—or two-stage operations. This leads to a decrease in the number of surgeries for patients and is very cost-effective.

Due to a lack of studies on the elbow joint. our results can only be compared with literature on other joints. Deirmengian et al. identified several synovial fluid biomarkers, including IL-6, whose levels were substantially elevated in patients with periprosthetic hip or knee infections. In their study, synovial fluid IL-6 analysis had a sensitivity and specificity of 100% at a cutoff value of 13,350 pg/mL [26].

Similarly, in a study analysing several biomarkers, Jacovides et al. found synovial fluid IL-6 levels associated with periprosthetic infections at the hip and knee, presenting 87% sensitivity and 100% specificity [27]. Frangiamore et al. found synovial IL-6 to be more sensitive and specific than any other laboratory method in predicting a positive microbiological result for infection of total shoulder arthroplasty [17]. Both studies did not see a significantly elevated IL-6 value in peripheral blood samples. It is difficult to compare our results to those of previous studies due to differences in general analysis and the anatomical region. However, we can report promising results with higher accuracy than CRP and WBC for revision cases.

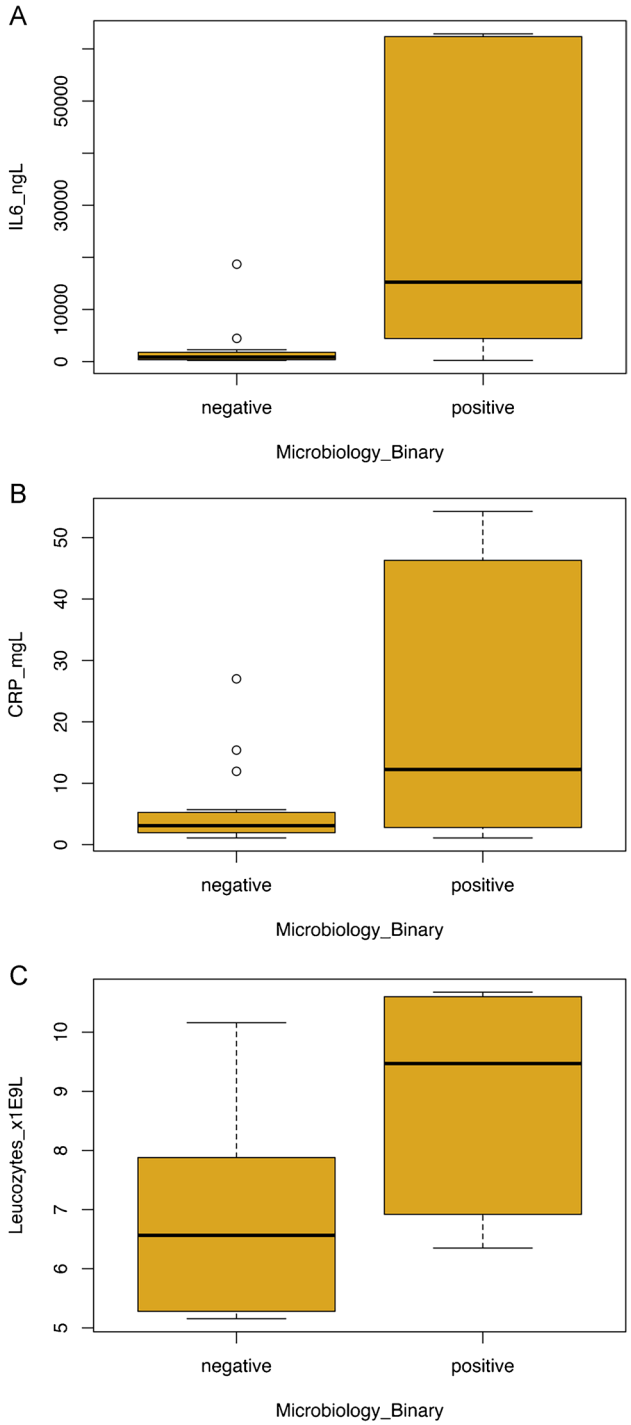

Fig. 3 IL-6 (**A**), CRP (**B**) and Leucocytes (WBC) (**C**) were significantly elevated in the infection group

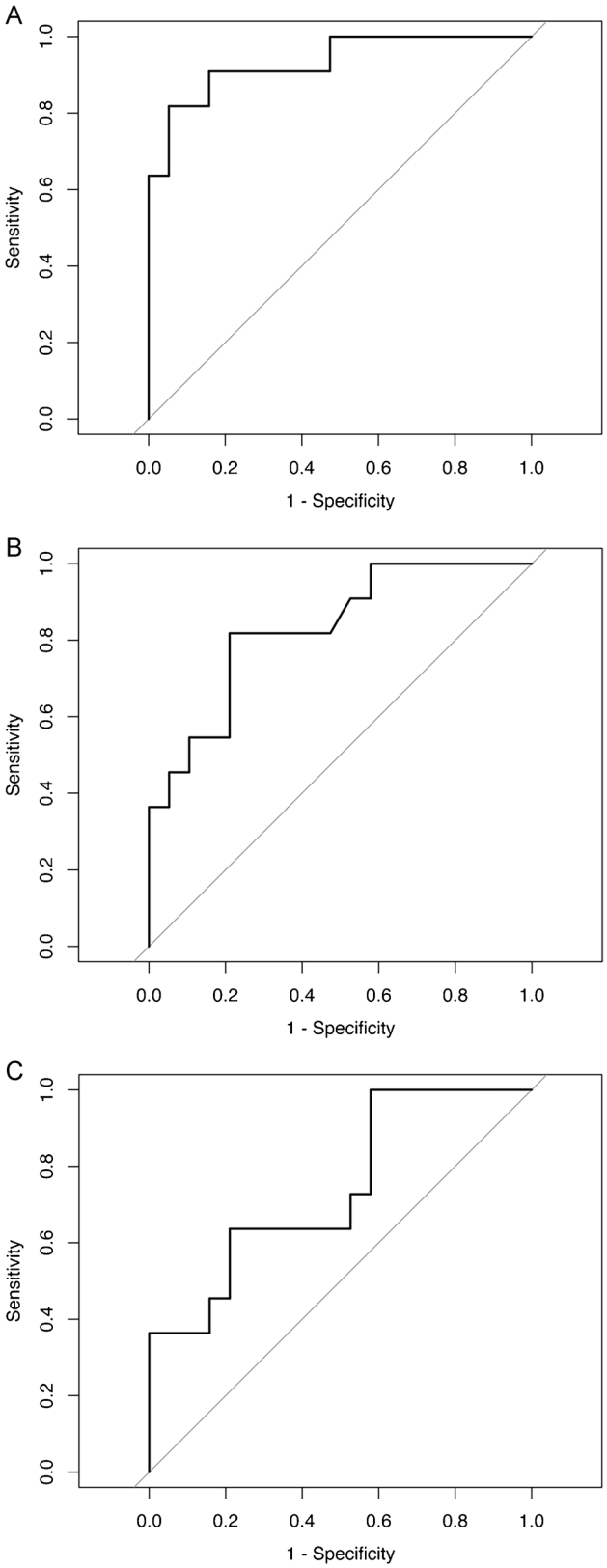

Fig. 4 The IL-6 analysis of synovial fluid demonstrated an AUC of 0.79, as shown on the ROC (**A**). CRP evaluation revealed an AUC of 0.67 (**B**). The analysis of WBC for the identification of PEI showed an AUC of 0.71, which is visualised by a ROC (**C**)

However, the study has limitations due to the small number of cases and the study design. In addition, we could not correlate our findings to histopathological findings due to a lack of specimens ($n=14$). Due to the low volume of samples, we did not perform a qualitative and quantitative analysis of cells.

Nevertheless, we are convinced that IL-6 can be included in a total elbow arthroplasty revision clinical workup. Its potential, fast availability, and low cost (under 50 $ /sample) support the surgeon's intraoperative decision-making and can improve the cost-effectiveness of revision surgeries after TEA. Further studies should be done to support the relevance and reliability of IL-6 as a marker for PEI.

Conclusion

This study is the first to evaluate synovial IL-6 levels as a marker for infection in total elbow arthroplasty. The study demonstrates the potential clinical benefit of synovial fluid IL-6 analysis pre- or intraoperatively to differentiate between an infective or aseptic process in revision total elbow arthroplasty. In addition, synovial fluid IL-6 analysis might be helpful in the postoperative handling of cases with unexpected positive microbiological cultures. It can act as another reliable laboratory value and is helpful in decision-making. The diagnostic accuracy of synovial fluid IL-6 analysis to identify PEI might lead to improved treatments, reduction of costs, and, at this moment, an improvement in patients' quality of life.

Acknowledgements This project did not receive any specific financial support or grants.

Author contributions All authors contributed to the study's conception and design. Felix Krane performed material preparation, data collection, and analysis. The first draft of the manuscript was written by Felix Krane, and all authors commented on previous versions. All authors read and approved the final manuscript.

Funding None.

Data availability The data supporting this study's findings are available on request from the corresponding author, (FK). The data are not publicly available due to heir containing information that could compromise the privacy of research participants.

Declarations

Disclaimer None.

Ethical approval The consent of the institutional ethics committee was granted before this study.

Informed consent Given by the patients.

This study was approved by the University of Cologne ethics committee (Nr. 16–225).

Conflict of interest The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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