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# Variation of synovial fluid leucocyte cell count and polymorphonuclear percentage in patients with aseptic revision total knee arthroplasty

**M. Fuchs,  
F. Kirchhoff,  
H. Reichel,  
C. Perka,  
M. Faschingbauer,  
C. Gwinner**

From RKU Department of Orthopaedic Surgery, University Ulm Medical Centre, Ulm, Baden-Württemberg, Germany

## Aims

Current guidelines consider analyses of joint aspirates, including leucocyte cell count (LC) and polymorphonuclear percentage (PMN%) as a diagnostic mainstay of periprosthetic joint infection (PJI). It is unclear if these parameters are subject to a certain degree of variability over time. Therefore, the aim of this study was to evaluate the variation of LC and PMN% in patients with aseptic revision total knee arthroplasty (TKA).

## Methods

We conducted a prospective, double-centre study of 40 patients with 40 knee joints. Patients underwent joint aspiration at two different time points with a maximum period of 120 days in between these interventions and without any events such as other joint aspirations or surgeries. The main indications for TKA revision surgery were aseptic implant loosening (n = 24) and joint instability (n = 11).

## Results

Overall, 80 synovial fluid samples of 40 patients were analyzed. The average time period between the joint aspirations was 50 days (SD 32). There was a significantly higher percentage change in LC when compared to PMN% (44.1% (SD 28.6%) vs 27.3% (SD 23.7%);  $p = 0.003$ ). When applying standard definition criteria, LC counts were found to skip back and forth between the two time points with exceeding the thresholds in up to 20% of cases, which was significantly more compared to PMN% for the European Bone and Joint Infection Society (EBJIS) criteria ( $p = 0.001$ ), as well as for Musculoskeletal Infection Society (MSIS) ( $p = 0.029$ ).

## Conclusion

LC and PMN% are subject to considerable variation. According to its higher interindividual variance, LC evaluation might contribute to false-positive or false-negative results in PJI assessment. Single LC testing prior to TKA revision surgery seems to be insufficient to exclude PJI. On the basis of the obtained results, PMN% analyses overrule LC measurements with regard to a conclusive diagnostic algorithm.

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## Introduction

Periprosthetic joint infection (PJI) continues to be a devastating complication. Recently, the rising scientific questions with regard to the best diagnostic strategies to determine PJI were considered as one of the research priorities for problematic knee arthroplasty.<sup>1</sup> An accurate differentiation between septic and aseptic conditions prior to total knee

arthroplasty (TKA) revision remains crucial for an optimal outcome, as it potentially implies dire consequences. The diagnosis of PJI is based on various examinations, considering clinical findings, individual serum CRP levels, synovial leucocyte counts, and microbial identifications of bacterial pathogens, as well as histopathological examinations.<sup>2-4</sup> There is a growing body of evidence, including

Correspondence should be sent to Michael Fuchs; email: Michael.fuchs@rku.de

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current guidelines, which advocate that synovial analysis of joint aspirates, including leucocyte cell count (LC), as well as polymorphonuclear percentage (PMN%). However, the respective cut-off values for LC and PMN% show substantial differences in the setting of either septic or aseptic conditions, and remain the subject of current scientific debate.<sup>5-8</sup> The first publications reported on a cut-off value for synovial fluid leucocyte count of 1,700  $\mu\text{L}$  to 2,500  $\mu\text{L}$  and a polymorphonuclear percentage of 60% to 65% in order to differentiate between aseptic TKA failure and PJI.<sup>9-11</sup>

Within the last decade, these defined cut-off levels were extensively discussed as lower thresholds potentially increase the percentage of false-positive results, while higher cut-off values could lead to undiagnosed PJI, with potentially devastating progressions of the disease. Surprisingly, little has changed, and there is still an obvious variation with regard to LC cut-off values, with thresholds ranging from 2,000 to 3,000 cells  $\mu\text{L}$ . With regard to PMN%, cut-off values of 70% to 80% have been described.<sup>2,4,6,8,12</sup> While several studies further adjusted the above-mentioned cut-off values of LC and PMN%,<sup>13-17</sup> there is considerably paucity in current literature if these biomarkers are subject to individual variation at different time points, thus potentially contributing to inconclusive results and ultimately to incorrect therapeutic decisions. The timing of aseptic revision TKA, as well as the time span between the joint aspirations, is mainly dictated by three parameters: 1) patient-specific preferences with regard to the timing of surgical planning; 2) hospital related organizational circumstances such as theatre planning and ordering of special surgical instruments; and 3) in 2020, there may have been huge organizational difficulties due to the COVID-19 pandemic, which led to substantial delays of scheduled aseptic surgeries.<sup>18,19</sup> By implication, the current study aims to delineate the individual variation of LC and PMN% in patients with scheduled aseptic TKA revision surgery. The working hypothesis is that these biomarkers are subject to a substantial variation over time.

## Methods

**Study design.** We conducted a retrospective analysis of prospectively collected data in this double-centre study to investigate the variation of LC and PMN% after joint aspiration in patients with scheduled aseptic revision TKA surgery. Aseptic revision surgery was indicated on the basis of previous examinations by the use of the European Bone and Joint Infection Society (EBJIS)-based PJI definition criteria.<sup>4,6</sup> Every patient received clinical examinations, systemic blood sampling, a radiological evaluation, and a joint aspiration on a routine basis prior to further planning of the therapeutic options. Before surgery, all patients received standard radiological examinations (standing long leg anterior-posterior (AP) radiograph, AP

and lateral knee radiograph). In the case of an unclear radiological examination, CT imaging was performed to confirm implant loosening. Joint instability was assessed via AP and sagittal stress radiographs. Data were collected from September 2018 to October 2020.

In all, 62 patients who underwent aseptic revision TKA were included after retrospective identification regarding study participation suitability. The inclusion criterion was a minimum age of 18 years and scheduled aseptic one-stage revision surgery of either the femoral, tibial, or both implant components as well as liner exchange surgery. Furthermore, only patients with negative microbiological and histopathological testing during revision surgery and written informed consent were included for further evaluation. With the exception of LC and PMN%, which were subject of this study, the exclusion criterion was revision surgery due to PJI, as defined by the EBJIS.<sup>6</sup> Patients that received preoperative antibiotic treatment, any immunosuppressive drugs or an additional joint puncture in between the evaluated time points were excluded from this study. Additionally, patients with an underlying rheumatic disease (with or without immunosuppressive medication) were excluded from further evaluation. Obtained LC and PMN% values were put in context to the PJI definitions of the Musculoskeletal Infection Society (MSIS),<sup>12</sup> as well as the EBJIS criteria. All cell counts were generated automatically by the use of a special analyzer (ABX Micros 60; Horiba Medical, France). A maximum time period of 120 days between the joint aspirations was accepted for study inclusion. The different time points under consideration are the result of various parameters interfering with a consistent timing of revision TKA, as described in the introduction. Taken together, individual patient-specific preferences, as well as hospital-related organizational circumstances, especially in 2020 due to the COVID-19 pandemic partly led to substantial delays of scheduled aseptic surgeries in our institutions.

**Revision surgeries and sample collection.** A total of 62 patients were enrolled in this study. Of these, 22 (35%) were excluded for the following reasons: confirmed PJI due to relevant microbiological growth in prosthetic tissue or sonication culture of the retrieved components ( $n = 5$ ); a time period between the joint punctures of greater than 120 days ( $n = 5$ ); underlying rheumatic disease ( $n = 3$ ); and immunosuppressive medication ( $n = 2$ ). In seven patients, no determination of LC could be performed due to sample clotting. After applying the above-mentioned exclusion criteria, 40 patients with 40 aseptic TKA revisions were included in this study. The indications for TKA revision surgery were aseptic implant loosening ( $n = 24$ ), joint instability ( $n = 11$ ), polyethylene liner wear ( $n = 3$ ), and secondary arthrosis of the patella ( $n = 2$ ). Each patient underwent joint aspiration at two different time points. The first sample collection of synovial fluid was performed under sterile conditions on an outpatient

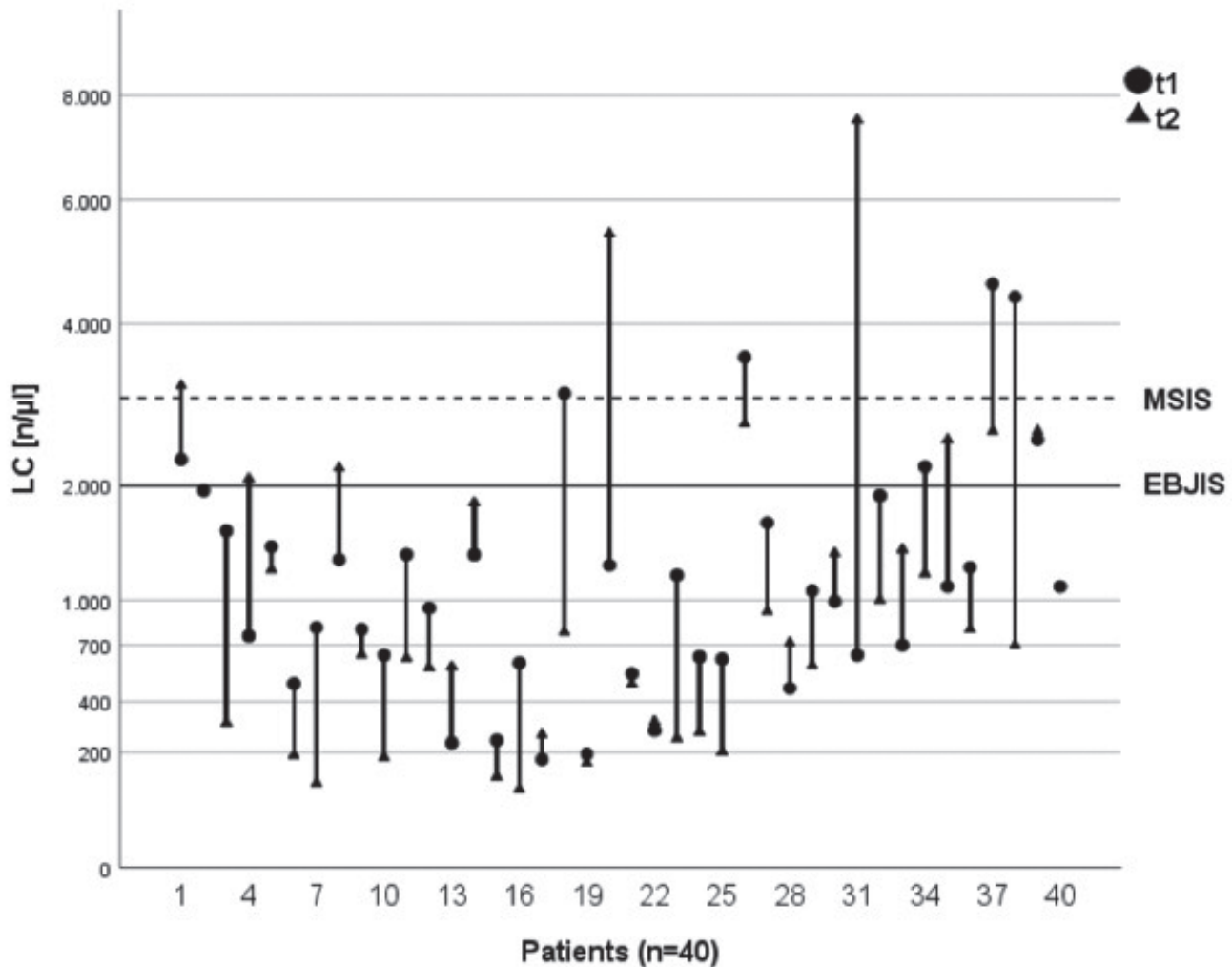


Fig. 1

Variance of leucocyte cell count. Respective leucocyte cell count (LC) values (n/µL) per patient at the first (t1) and second (t2) joint aspiration. Displayed lines illustrate the cut-off levels suggestive for PJI according to the European Bone and Joint Infection Society (EBJIS) (2,000 µL) and Musculoskeletal Infection Society (MSIS) (3,000 µL) criteria.

basis, according to our standard preoperative diagnostic algorithm. The second joint aspiration was undertaken intraoperatively before aseptic revision surgery after skin incision and subcutaneous preparation via intraarticular joint puncture. There were no saline-assisted aspirations or any local anaesthetic agents injected before sample collection. Synovial fluid aspirations were preserved and transported to the laboratory within six hours.

**Statistical analysis.** Statistical analysis was performed using SPSS version 26 (IBM SPSS, USA). Data was expressed as mean (SD) and or median (interquartile range) according to its distribution. Shapiro-Wilk test was used to test Gaussian distribution. The comparison of parametric data was performed with a paired *t*-test and non-parametric data was tested by a Wilcoxon signed rank test or Mann-Whitney U test. Pearson's chi-squared test was used to determine statistically significant differences between

categorical variables. A *p*-value < 0.05 was considered statistically significant.

## Results

The study cohort consisted of 26 females and 14 males. The median age of patients at the time of surgery was 71 years (standard deviation (SD) 8; 55 to 87). In total, 80 synovial fluid samples of 40 patients were analyzed. The average time period between the first and second sample collection was 50 days (mean 48 (SD 33); 1 to 120). Mean LC was 1,306 leucocytes/µL (SD 1,288). Overall, we observed a mean difference in LC count between the respective measurements of 920 leucocytes/µL (mean 480 (SD 1,317); 0 to 6,859) (Figure 1). With respect to the LC difference in relation to the time interval between the first and second joint aspiration, no significant differences were found (*p* = 0.681, paired *t*-test). Mean PMN% was

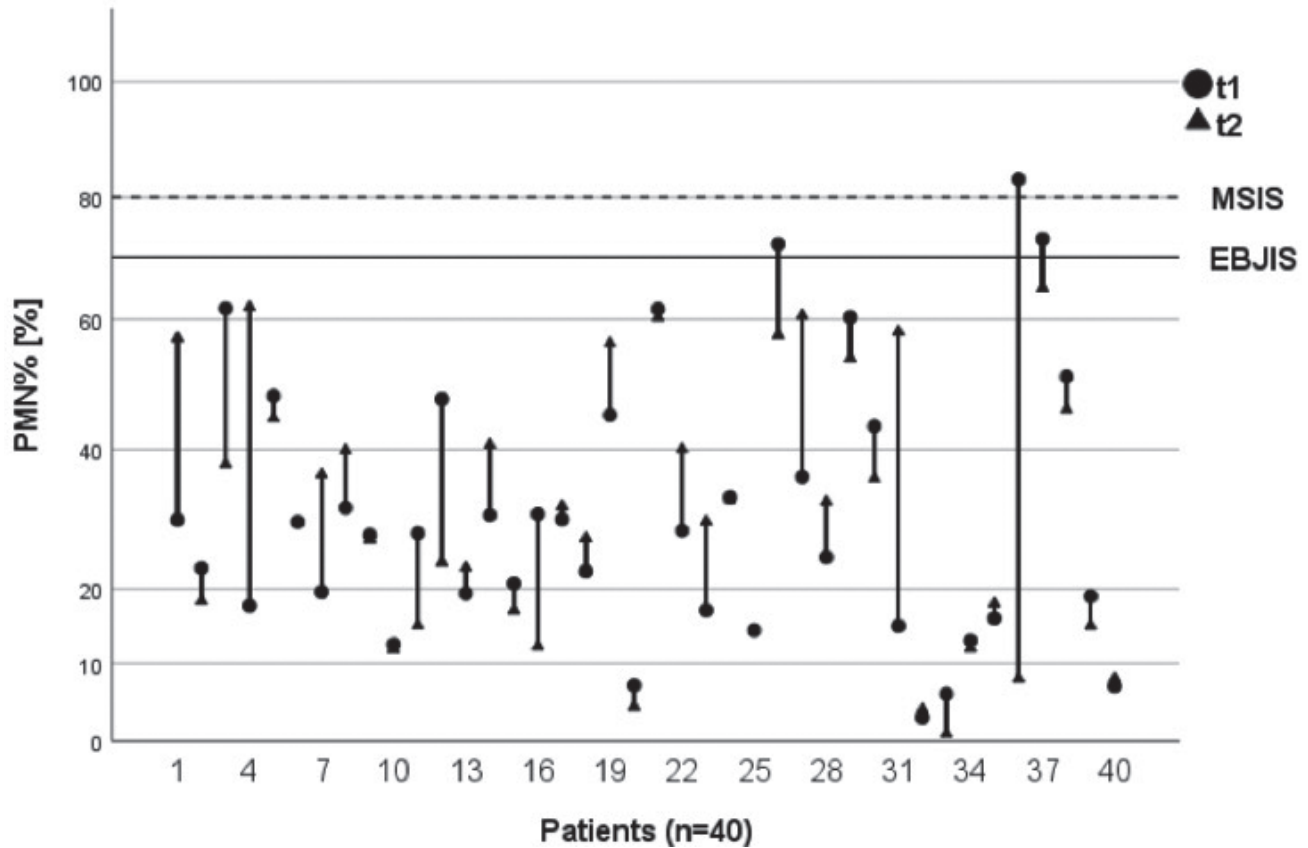


Fig. 2

Variance of polymorphonuclear percentage. Respective polymorphonuclear percentage (PMN%) values per patient at the first (t1) and second (t2) joint aspiration. Displayed lines illustrate the cut-off levels suggestive for periprosthetic joint infection according to the European Bone and Joint Infection Society (EBJIS) (70%) and Musculoskeletal Infection Society (MSIS) (80%) criteria.

31.6% (SD 19.2%). For the average variance of PMN%, a proportion of 11.4% was found (mean 5.8% (SD 15%); 0.04% to 75% (Figure 2). There were no significant differences with respect to the change of PMN% in relation to the time interval between the first and second joint aspiration ( $p = 0.968$ , paired  $t$ -test).

Of note, there was a significantly higher percentage change in LC compared to PMN% between the first and second joint aspiration (44.1% (SD 28.6%) vs 27.3% (SD 23.7%);  $p = 0.003$ , Mann-Whitney U test).

When applying the EBJIS criteria, elevated LC suggestive for infection were observed in 16 out of 80 joint aspirations (20%), irrespective of the joint aspiration date. Of those, seven (17.5%) of LC values from the first (t1) and nine (22.5%) from the second (t2) aspiration were suggestive for PJI. For PMN%, three (7.5%) events from the first aspiration were beyond the threshold of 70% (Figure 3a). According to both PJI definitions, no suggestive events for PJI with regard to PMN% were obtained for the second joint aspiration. There were significantly more inconclusive results for LC compared to PMN% ( $p = 0.001$ , chi-squared test). According to the MSIS criteria, elevated LC were seen in seven synovial analyses (8.8%).

Of those, four (t1; 10%) and three (t2; 7.5%) events exceeded the defined LC cut-off level. For PMN%, one patient (2.5%) revealed an elevated value at the first aspiration (Figure 3b). Likewise, there were significantly more inconclusive results for LC compared to PMN% ( $p = 0.029$ , chi-squared test). When applying the EBJIS PJI definition criteria, eight synovial analyses (20%) showed discrepant values either below or above the defined LC threshold. For the MSIS criteria, this was evident in seven (17.5%) cases. Notably, this difference between current classifications did not reach statistical significance. For PMN%, discrepant values below or above the determined cut-off levels were found in 7.5% (EBJIS) and 2.5% (MSIS), respectively. In line with LC, there was no significant difference. According to the EBJIS criteria, 14 (17.5%) of synovial LC counts were elevated and suggestive for infection without concomitant PMN% elevation. For MSIS criteria, this was similar in seven cases (8.8%; not significant). PMN% elevation without LC elevation beyond the threshold was observed in one case (1.25%) for EBJIS and MSIS criteria (not significant). Notably, there were significantly more isolated LC count elevations for EBJIS ( $p = 0.0004$ , Mann-Whitney U test) and MSIS

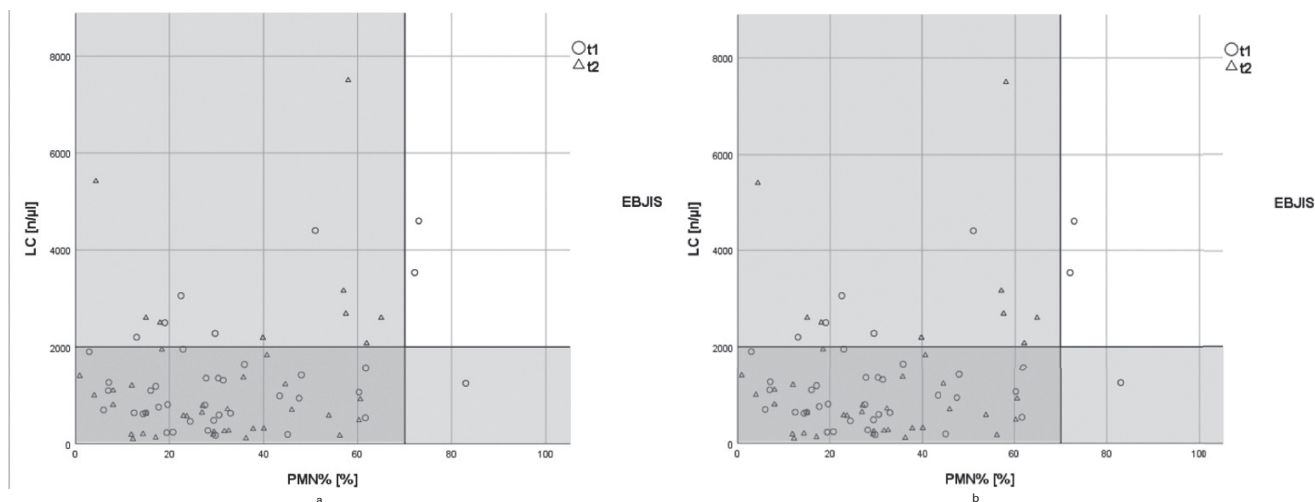


Fig. 3

Different leucocyte cell counts and polymorphonuclear percentage of all patients with displayed European Bone and Joint Infection Society (EBJIS) criteria. a) Leucocyte cell count (LC) (n/µL) and PMN% at the respective time points of the first (t1) and second (t2) joint aspiration. Displayed lines illustrate the cut-off levels suggestive for PJI according to the European Bone and Joint Infection Society (EBJIS) criteria. b) Different leucocyte cell counts and polymorphonuclear percentage (PMN%) at the respective time points of the first (t1) and second (t2) joint aspiration. Displayed lines illustrate the cut-off levels suggestive for PJI according to the Musculoskeletal Infection Society (MSIS) criteria.

( $O = 0.029$ , Mann-Whitney U test) compared to isolated PNM% elevations. In two cases (2.5%), synovial analysis revealed elevated LC and PMN%, according to the EBJIS criteria. This concordance was not seen under application of the MSIS criteria. Taken the defined cut-off levels of the EBJIS and MSIS criteria together, four events (5%) showed elevated LC constellations at both evaluated time points.

## Discussion

The main finding of this study was that synovial fluid biomarkers exhibit substantial individual variations at different time points in patients scheduled for aseptic knee arthroplasty revision surgery. More precisely, LC showed a significantly higher percentage change compared to PMN%. As a consequence, there were significantly more results in need of clarification in LC than for PMN%. Even though PMN% also revealed distinct interindividual changes, the consequences of this variation were proven to bear less impact on diagnostics, as these changes were mostly below the threshold of common PJI definition criteria (EBJIS 92.5%; MSIS 97.5%). In contrast, LC partly were found to skip back and forth between the evaluated time points. Notably, the findings of the current results may have important clinical implications. In all, 20% of leucocyte counts according to the EBJIS and 17.5% according to the MSIS criteria would qualify for septic as well as for aseptic revision surgery, depending on the evaluated time point. Accordingly, those affected may potentially undergo two-stage revision surgery, long-term antibiotics and an impaired clinical outcome. To the best of our knowledge, this is the first study highlighting individual variations of synovial fluid biomarkers

over time. From the authors' point of view, two main reasons for the observed variations are conceivable. First, we presume that the homeostasis of replaced knee joints is subject to constant pro- and anti-inflammatory signaling pathways leading to a changing degree of cytokine and cell-mediated immunological responses. For native joints, a constant modulation of endogenous pro- and anti-inflammatory signalling has previously been described.<sup>20-22</sup> In this context, a certain degree of LC and PMN% variation over time is compelling.

Second, we hypothesize that beneath biological circumstances, physical facts interact with time-dependent deviations of marker molecules. Given this thought, leucocytes and neutrophils are subject to gravitation and sedimentation due to their cell mass. We assume that the individual joint-related range of motion, as well as the physical activity prior to joint aspiration, may interact with the subsequent quantitative analyses. With regard to the current literature, an interesting issue is reflected by the fact that all studies evaluate marker molecules at a single time point. Taking the results of the present study into account, there is a growing body of evidence that there is need for further research illuminating the variability of biomarkers at different time points. In line with Bottner et al,<sup>23</sup> the question arises if there is need for more sophisticated LC and PMN% thresholds, dependent on the indication for aseptic TKA revision. Interestingly, previous studies already suggested different cut-off levels for the diagnosis of PJI with respect to the anatomical location of joint arthroplasty. Zahar et al<sup>24</sup> conducted an analysis of 337 cases with aseptic or septic hip and knee arthroplasty revision surgery. The authors reported about an optimal cut-off

value of 1,630 leucocytes  $\mu\text{l}$  for TKA and 3,063 leucocytes  $\mu\text{l}$  for total hip arthroplasty (THA). Of note, PMN% levels were similar between the evaluated anatomical locations (TKA 60.5%; THA 66.1%). The distinct differences of LC values could not be traced back to a specific reason. By analyzing synovial fluid specimens of 391 patients, Gallo et al<sup>25</sup> also stated different cut-off values for PJI of the hip and knee. The authors reported about a LC threshold of 4,100 leucocytes  $\mu\text{l}$  for THA and 3,200 leucocytes  $\mu\text{l}$  for TKA, respectively.

In line with the results of Zahar et al,<sup>24</sup> Gallo et al<sup>25</sup> did not find substantial differences in the amount of PMN% variation with respect to the anatomical location (TKA 72.8%; THA 76.5%). These findings are linked to another key message of the current work: while leucocyte cell count analysis might inconsistently comply with contemporary PJI thresholds, the percentage of neutrophils showed a significantly higher consistency throughout both time points. By implication, the latter might enable a higher diagnostic reliability. This hypothesis is, in part, supported by the findings of a study by Heckmann et al,<sup>26</sup> who analyzed synovial fluid biomarkers in 78 patients with suspected PJI of the hip and knee. The authors evaluated the diagnostic potential of LC and PMN% in patients with intraarticular saline lavage. Interestingly, particularly in patients with a LC > 3,000, PMN% remained similar pre- and post-lavage, while significantly lowered leucocyte counts were observed between the respective time points. Taken together, this study underlines our findings suggesting a higher diagnostic potential of PMN% compared to LC.<sup>26</sup>

This study has several limitations. We conducted a retrospective analysis of prospectively collected data, being inherently prone to several shortcomings associated with a retrospective evaluation. Moreover, patients underwent joint aspiration at two different time points. Against this background, the authors decided to exclude samples with a time period of greater than 120 days between the joint punctures. Furthermore, aseptic revision surgery was performed due to different indications. It is conceivable that knee joints of patients with aseptic implant loosening may be subject to an elevated proinflammatory signalling compared to patients who were revised due to instability. A reason for this might be reflected by the fact that monocytes respond to polyethylene (PE) particles by producing IL-6.<sup>23</sup> As a consequence, this could lead to higher LC and PMN% counts. With respect to the diagnostic value of synovial IL-6 measurements, Mihalic et al could demonstrate that the latter are not superior in detecting PJI compared to LC and PMN%.<sup>27</sup>

Another important perspective relies on the fact that there is a certain degree of natural variation in the result of any laboratory test.<sup>28,29</sup> Against this background, it is crucial to be aware of these technical challenges with

regard to the interpretation of slight differences, as the latter might be within the limitations of the test method.

In conclusion, the results of the current study indicate that synovial fluid biomarkers are subject to considerable variation, which complicates a stringent clinical work-up in the setting of suspected PJI. In comparison to LC, PMN% showed a significantly lower percentage change and a significantly lower chance of false positive results in regard to the thresholds of current guidelines. Thus, our findings emphasize particularly the importance of PMN% compared to LC, which brings the current hierarchy of biomarker-based PJI diagnosis into question. New diagnostic tools, such as reverse transcription-quantitative polymerase chain reaction and metagenomic next-generation sequencing of synovial fluid, might be the future, and already offer promising results that contribute to a substantial progress of PJI detection.<sup>30,31</sup>



### Take home message

- Leucocyte cell count (LC) and polymorphonuclear percentage (PMN%) exhibit substantial individual variations at different time points, presumably due to biological, physical, and time-dependent alterations.
- LC showed a significantly higher percentage change compared to PMN%.
- With regard to the different diagnostic parameters to exclude periprosthetic joint infection, PMN% might be of greater significance than LC.

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#### Author information:

- M. Fuchs, MD, Orthopaedic Surgeon
- F. Kirchoff, cand. med, Medical Student
- H. Reichel, MD, Professor, Orthopaedic Surgeon, Head of the RKU University Department of Orthopaedics
- M. Faschingbauer, MD, Orthopaedic Surgeon, Senior Physician RKU Department of Orthopaedic Surgery, University Ulm Medical Centre, Ulm, Baden-Württemberg, Germany.
- C. Perka, MD, Professor, Orthopaedic Surgeon, Head of the Center for Musculoskeletal Surgery
- C. Gwinner, MD, Senior Orthopaedic Surgeon Department of Orthopaedic Surgery, Charite Universitätsmedizin Berlin, Berlin, Berlin, Germany.

#### Author contributions:

- M. Fuchs: Developed the study design, Collected and analyzed the data, Wrote the manuscript.
- F. Kirchoff: Collected the data, Undertook the statistical the analysis.
- H. Reichel: Provided administrative support, Proofread and approved the manuscript.
- C. Perka: Analyzed the data, Reviewed and approved the manuscript.
- M. Faschingbauer: Developed the study design, Analyzed the data, Reviewed the manuscript.
- C. Gwinner: Conceptualized the study, Collected the data, Undertook the statistical analysis, Edited the manuscript.

- M. Faschingbauer and C. Gwinner contributed equally to this work.

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