■ ARTHROPLASTY

# Absolute synovial polymorphonuclear neutrophil cell count as a biomarker of periprosthetic joint infection

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## Aims

**The aim of this study was to evaluate the diagnostic accuracy of the absolute synovial polymorphonuclear neutrophil cell (PMN) count for the diagnosis or exclusion of periprosthetic joint infection (PJI) after total hip (THA) or knee arthroplasty (TKA).**

## Methods

**In this retrospective cohort study, 147 consecutive patients with acute or chronic complaints following THA and TKA were included. Diagnosis of PJI was established based on the 2018 International Consensus Meeting criteria. A total of 39 patients diagnosed with PJI (32 chronic and seven acute) and 108 patients with aseptic complications were surgically revised.**

## Results

**Using receiver operating characteristic curves and calculating the area under the curve (AUC), an optimal synovial cut-off value of 2,000 PMN/µl was determined (AUC 0.978 (95% confidence interval (CI) 0.946 to 1)). Using this cut-off, sensitivity and specificity of absolute synovial PMN count for PJI were 97.4% (95% CI 91.2 to 100) and 93.5% (95% CI 88.9 to 98.1). Positive and negative predictive value were 84.4% (95% CI 72.7 to 93.9) and 99.0% (95% CI 96.7 to 100), respectively. Exclusion of 20 patients with acute complications improved specificity to 97.9% (95% CI 94.6 to 100). Different cut-off values for THA (< 3,600 PMN/µl) and TKA (< 2,000 PMN/µl) were identified. Absolute synovial PMN count correlated strongly with synovial alpha-defensin (AD) ($r = 0.759$; $p < 0.001$). With a positive AD result, no additional PJI could be identified in any case.**

## Conclusion

**Absolute synovial PMN count is a widely available, rapid, cost-effective, and accurate marker in PJI diagnostics, whereas synovial AD appears to be a surrogate parameter of absolute synovial PMN count. Despite limitations in the early-postoperative phase, wear, and rheumatic diseases in confirming PJI, an absolute synovial PMN count below 2,000/µl is highly suitable for ruling out PJI, with specific cut-off values for THA and TKA.**

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## Introduction

Periprosthetic joint infection (PJI) represents a serious complication after total hip (THA) and knee arthroplasty (TKA) associated with a substantial burden and high mortality.[1-4] With a five-year cumulative PJI incidence of around 1.0% to 1.5% (greater in revisions),[5,6] and a trend towards increasing number of arthroplasties worldwide, the occurrence of this complication is expected to rise. While there have long been no universally accepted criteria for the diagnosis of PJI, the Musculoskeletal Infection Society (MSIS) and the Infectious Diseases Society of America (IDSA) have previously developed criteria to standardize the definition of PJI.[7,8] The 2013 International Consensus Meeting (ICM) adapted these criteria and adjusted the definition for diagnosis of PJI of the hip and knee in 2018.[9,10] Preoperative diagnostic accuracy is usually achieved by a combination of parameters, including serum CRP,

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**Table I.** Individual pathogens and differentiation into acute and chronic complaints in the periprosthetic joint infection cohort.

| Bacteria | Acute | Chronic |
|---|---|---|
| *Staphylococcus aureus* | 3 | 5 |
| CoNS | 0 | 9 |
| Cutibacteria | 0 | 3 |
| *Enterococci* | 0 | 1 |
| Group B *Streptococci* | 0 | 2 |
| Group C *Streptococci* | 3 | 0 |
| *E. coli* | 0 | 1 |
| *Parvimonas micras* | 1 | 0 |
| Mixed infection | 0 | 6 |
| No growth | 0 | 5 |
| Total | 7 | 32 |

CoNS, coagulase-negative *Staphylococci*.

**Table II.** Individual reasons for aseptic revision.

| Reasons for aseptic revision | n |
|---|---|
| Loosening | 32 |
| Instability, dislocation | 29 |
| Prolonged wound drainage | 4 |
| Wear | 9 |
| Implant failure | 3 |
| Wound reddening | 1 |
| Periprosthetic fracture | 1 |
| Gluteus medius tendon rupture | 1 |
| Others | 28 |
| Total | 108 |

D-dimer level, synovial white blood cell (WBC) count, and differential leucocyte esterase rapid test and microbiological analysis.[11-13] Corresponding synovial WBC count thresholds for PJI diagnosis may be useful for routine clinical practice, but suggestions regarding optimal accuracy range from > 1,100 to > 3,000 cells.[14,15]

Another marker for PJI is synovial alpha-defensin (AD), a peptide released by polymorphonuclear neutrophils (PMN) as part of the host-defense innate immune system.[16] Synovial AD has initially been reported to have a high sensitivity and specificity > 95%,[17-19] but recent studies have shown lower diagnostic accuracy.[20-24] PMN are classically reported as a percentage of WBC in synovial fluid analysis, with optimal thresholds ranging from > 64% PMN to > 80% PMN.[11,14,15] In addition, there are ongoing efforts to improve the diagnosis of PJI. For example, the combined measurement of serum and synovial interleukin 6 showed a high accuracy in the diagnosis of chronic PJI,[25] comparable with synovial WBC count and differential.

The rationale for performing this study was based on both the ICM classification and recent findings. Synovial %PMN, WBC, leucocyte esterase rapid test, and AD are used as 2013 ICM minor criteria.[9] According to 2018 ICM criteria, elevated synovial %PMN is scored as two points and synovial WBC count, positive leucocyte esterase rapid test, or AD are scored as three points.[10] However, these parameters possibly indicate the same condition since AD is released from PMN. Synovial %PMN has been reported to be a more robust parameter compared to synovial WBC count when preoperative PJI evaluation by joint aspiration is performed at different intervals, resulting in fewer false-positive or false-negative test results.[26] The hypothesis of this work was that absolute synovial PMN count has an equivalent diagnostic accuracy, combining synovial %PMN, WBC count, and AD in one parameter. We aimed to determine the optimal cut-off value and diagnostic accuracy of absolute synovial PMN count for the investigation of possible PJI in THA and TKA.

## Methods

**Patient cohort and diagnostic procedures.** We conducted a retrospective review of the medical records of all patients with acute or chronic symptoms who were undergoing revision THA or TKA at our institution between August 2018 and June 2021. Inclusion criteria were complete diagnostic parameters as recommended by the ICM 2018, i.e. preoperative serum (CRP, ESR, D-Dimer) and synovial parameters (WBC count, %PMN, AD), collected by blood probe and diagnostic joint aspiration as part of our routine investigations. Additional tissue samples for histological (n = 1) and microbiological analysis (n = 5) were obtained during revision surgery in all cases from the bone-prosthesis interface. If preoperative joint aspirates were missing ("dry tap") or not interpretable (e.g. volume < 0.5 ml), additional intraoperative synovial fluid was obtained through the prepared joint capsule prior to arthrotomy (n = 24). Joints with macroscopically apparent polyethylene and metal wear were documented. Both primary and previously revised arthroplasties were included, and no further exclusion criteria (e.g., chronic inflammatory diseases, wear) were applied (Supplementary Table i). There were no metal-on-metal bearings in our cohort. Retrospective analysis of our study cohort yielded 147 patients (69 male, 78 female) with TKA (n = 76) and THA (n = 71). Median age was 71 years (95% CI 68 to 75). All procedures performed in this study were in accordance with the Declaration of Helsinki and approved by the local ethics committee (2021-300036-WF).[27]

**Analysis of synovial fluid and tissue samples.** Joint aspirates were obtained in separate sterile syringes and stored at room temperature before further processing within a maximum of 24 hours. For microbiological analysis and AD measurement, native aspirate was used. Analysis of synovial WBC count including differential was performed in our institutional facilities after transfer of the aspirate into an EDTA-tube and supplementation of hyaluronidase. Absolute synovial PMN count was calculated from total synovial WBC count and %PMN as an additional parameter. Intraoperatively obtained histological samples were examined by the Department of Pathology at the University Medical Centre Hamburg-Eppendorf, Germany. Microbiological analysis of tissue samples and synovial fluid were carried out in an external laboratory (aescuLabor, Germany). The incubation time of all bacteriological samples was 14 days with daily control of bacterial growth. The synovial AD enzyme-linked immunosorbent assay (ELISA) (CD Diagnostics, USA) was performed in an external laboratory (Fenner und Kollegen, Germany).

**Diagnosis of PJI.** PJI was diagnosed based on the 2018 ICM criteria with at least one fulfilled major criterion (n = 30) or ≥ six points due to fulfilled minor criteria (n = 9), resulting in

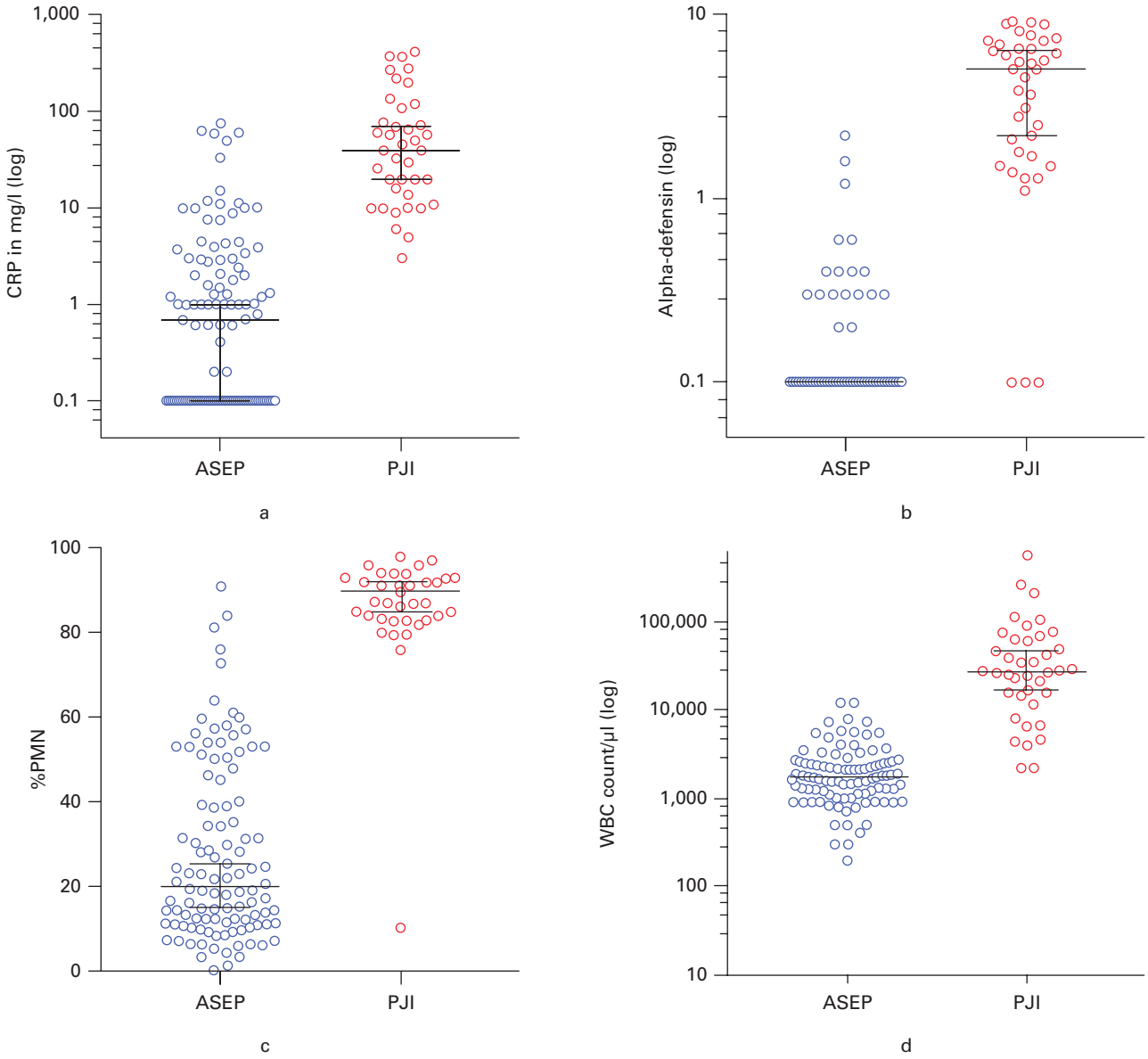


Fig. 1

Comparison of serum CRP, synovial alpha-defensin, percent synovial polymorphonuclear neutrophil (%PMN) cell count, and synovial white blood cell (WBC) count between the aseptic and periprosthetic joint infection (PJI) cohorts. Median and 95% confidence interval are displayed. All $p < 0.001$, Mann-Whitney U test.

39 PJI patients. Compared with the 2013 ICM criteria, there was no difference in the diagnosis or exclusion of PJI among the included patients. A different histopathological threshold of at least 23 neutrophil granulocytes in ten consecutive high-power-fields according to Morawietz et al[28] and Bémer et al[29] was used and the periprosthetic membrane was classified according to Krenn-Morawietz type I to IV.[30] ICM classification represented the reference standard against which absolute synovial PMN count was tested. PJI was categorized as acute if ICM criteria were met within four weeks following surgery (early-postoperative PJI) or if the patient presented with acute onset of symptoms for fewer than three weeks more than six months after arthroplasty (acute-haematogenous PJI or direct spread of infection within the affected limb).[31] Chronic PJI was defined by fulfilled ICM criteria more than four weeks after arthroplasty and having symptoms for more than three weeks. Using this definition, PJI patients were classified as acutely infected in seven cases and as chronically infected in 32 cases. A total of six patients presented with a sinus tract. Most chronic PJIs were either due to low-virulence pathogens (e.g. *Staphylococcus epidermidis*, Cutibacteria) and slow bacterial growth or delayed presentation to our clinic with a symptomatic TKA or THA for more than three weeks after a haematogenous spread (Table I). Acute infections were mainly due to *Staphylococcus aureus* and Group C Streptococci.

**Table III.** Diagnostic accuracy for laboratory synovial infection parameters and serum CRP.

| Variable | Serum CRP, % (95% CI) | Alpha-defensin, % (95% CI) | WBC count, % (95% CI) | %PMN, % (95% CI) | Absolute PMN count, % (95% CI) |
|---|---|---|---|---|---|
| Sensitivity | 87.2 (75.6 to 97.2) | 92.3 (82.9 to 100) | 92.3 (82.9 to 100) | 84.6 (71.4 to 94.9) | 97.4 (91.2 to 100) |
| Specificity | 88.9 (82.1 to 94.3) | 97.2 (93.6 to 100) | 84.3 (77.5 to 90.8) | 97.2 (93.8 to 100) | 93.5 (88.9 to 98.1) |
| NPV | 95.0 (90.4 to 99.0) | 97.2 (93.7 to 100) | 96.8 (93.2 to 100) | 94.6 (90.2 to 98.3) | 99.0 (96.7 to 100) |
| PPV | 73.9 (60.9 to 87.5) | 92.3 (82.5 to 100) | 67.9 (54.8 to 80.0) | 91.7 (81.4 to 100) | 84.4 (72.7 to 93.9) |
| AUC | 0.95 (0.92 to 0.98) | 0.95 (0.90 to 1) | 0.97 (0.94 to 0.99) | 0.971 (0.93 to 1) | 0.98 (0.95 to 1) |
| **Acute complications and sinus tracts excluded** | | | | | |
| Sensitivity | 85.2 (70.8 to 96.7) | 96.2 (81.5 to 100) | 92.6 (80.8 to 100) | 85.2 (70.0 to 96.7) | 96.3 (86.4 to 100) |
| Specificity | 93.7 (88.3 to 97.9) | 98.9 (96.4 to 100) | 86.3 (78.9 to 92.9) | 97.9 (94.4 to 100) | 97.9 (94.3 to 100) |
| NPV | 95.7 (91.4 to 99.0) | 97.9 (94.2 to 100) | 97.6 (93.9 to 100) | 95.9 (91.4 to 99.0) | 98.9 (96.6 to 100) |
| PPV | 79.3 (62.5 to 92.6) | 96.2 (86.7 to 100) | 65.8 (48.6 to 80.0) | 92.0 (78.8 to 100) | 92.9 (81.8 to 100) |
| AUC | 0.98 (0.96 to 0.99) | 0.96 (0.90 to 1) | 0.97 (0.93 to 1) | 0.97 (0.91 to 1) | 0.98 (0.93 to 1) |

AUC, area under the receiver operating characteristic curve; CI, confidence interval; NPV, negative predictive value; PMN, polymorphonuclear neutrophils; PPV, positive predictive value; WBC, synovial white blood cell count.

**Table IV.** Differentiation of absolute synovial polymorphonuclear neutrophil cut-off values for total hip and knee arthroplasty.

| Procedure | Absolute synovial PMN/µl cut-off values | | | |
|---|---|---|---|---|
| | Total | Acute complications excluded | Sinus tracts excluded | Both excluded |
| TKA | 2,000 | 2,000 | 2,000 | 2,000 |
| THA | 3,600 | 3,300 | 3,600 | 3,300 |
| TKA/THA | 2,000 | 2,000 | 2,000 | 2,000 |

PMN, polymorphonuclear neutrophil; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Patients without fulfilled ICM criteria were diagnosed as aseptic (n = 108), including patients with acute (recent dislocation, periprosthetic fracture, prolonged wound drainage; n = 13) and chronic complaints (instability, aseptic loosening, implant failure, wear, osteolysis; n = 95) (Table II).

**Statistical analysis.** Statistical analysis and visualization were conducted using SPSS v. 22.0 (IBM, USA) and GraphPad Prism (GraphPad Software, USA). The Kolmogorov-Smirnov-test was used to test for normal distribution within the two study groups (PJI and aseptic). Sensitivity, specificity, positive (PPV) and negative predictive value (NPV), as well as 95% confidence intervals (CIs) were calculated for synovial AD, synovial WBC count and %PMN, as well as absolute synovial PMN count. The diagnostic accuracy was further evaluated using the calculation of the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. Youden's J statistic was used to determine the threshold most appropriate to differentiate between PJI and aseptic complication. Interrelation between synovial AD, serum CRP, synovial WBC, synovial %PMN, and absolute synovial PMN count were tested by Spearman's rank correlation analysis as the data of both groups was not normally distributed. Comparison of synovial AD, synovial WBC count, synovial %PMN, and absolute synovial PMN count between PJI patients and aseptic patients, as well as subgroup analysis, was performed using the Mann-Whitney U test. Unless otherwise, data are presented as median and 95% CIs. Statistical significance was determined by p-values $\leq 0.05$.

## Results

**Established laboratory infection parameters.** Serum CRP, synovial AD, WBC count, and %PMN differed significantly between the PJI and the aseptic group (Figure 1 and Supplementary Table ii). Diagnostic accuracy of synovial AD, synovial WBC count, and synovial %PMN for the diagnosis or exclusion of PJI are displayed in Table III. AD was false-positive and false-negative in three cases each. With a positive AD result, no additional PJI could be identified in any case when applying the 2018 ICM criteria.

**Absolute synovial PMN count as a new PJI marker.** After the calculation of ROC curves for synovial PMN count and the AUC (0.978 (95% CI 0.946 to 1)), an optimal absolute synovial cut-off value of 2,000 PMN/µl (exact value: 1,942 PMN/µl) was determined using Youden's J statistic. With this cut-off, sensitivity and specificity of absolute synovial PMN count for PJI were 97.4% (95% CI 91.2 to 100) and 93.5% (95% CI 88.9 to 98.1). PPV and NPV were 84.4% (95% CI 72.7 to 93.9) and 99.0% (95% CI 96.7 to 100) (Table III). Absolute synovial PMN count was > 2,000 cells/µl in 45 joints and < 2,000 cells/µl in 112 joints. A false-negative result was found in one patient with a low-virulent pathogen and seven false-positive results were associated with aseptic early-postoperative revisions (e.g. stem subsidence, dislocation) and wear-related extensive osteolysis in rheumatoid arthritis (Supplementary Table iii).

Absolute synovial PMN count correlated moderately with serum CRP ($r = 0.663$; $p < 0.001$, Spearman's rank correlation) and strongly with synovial AD levels ($r = 0.759$; $p < 0.001$, Spearman's rank correlation) for the whole cohort (Figure 2). A significant positive correlation with absolute synovial PMN count was found for aseptic patients ($r = 0.401$; $p < 0.001$, Spearman's rank correlation) and PJI patients ($r = 0.595$; $p < 0.001$, Spearman's rank correlation) (Figure 3). Exclusion of 20 patients with acute complications, possibly impairing the interpretation of test results, improved specificity of absolute synovial PMN count to 97.9% (95% CI 94.6 to 100). Sensitivity, PPV, and NPV were 96.9% (95% CI 89.7 to 100), 93.9% (95% CI 84.8 to 100) and 98.9% (95% CI 96.6 to 100) (Table III).

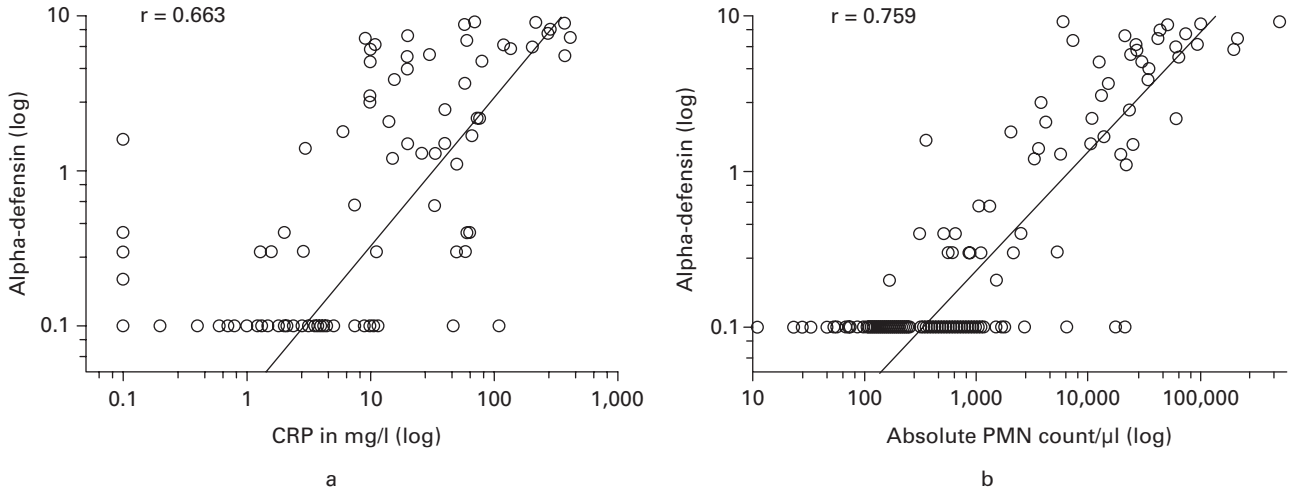


Fig. 2

Correlation of serum CRP as well as absolute synovial polymorphonuclear neutrophil cell (PMN) count with synovial alpha-defensin levels for the whole study cohort. Both $p < 0.001$, Spearman's rank correlation analysis.

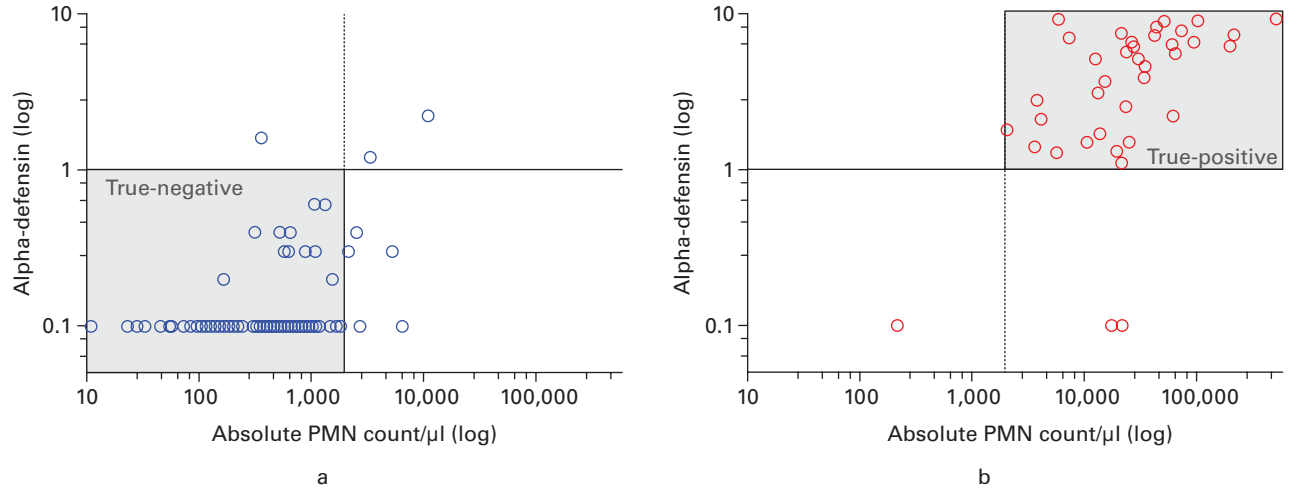


Fig. 3

Correlation of absolute synovial polymorphonuclear neutrophil cell (PMN) count and synovial alpha-defensin levels for a) aseptic and b) periprosthetic joint infection (PJI) patients. The grey highlighted area shows the true-negative aseptic and the true-positive PJI cases.

**Subgroup analysis of patients with acute or chronic complaints.** Aseptic patients with acute complications showed a significantly higher serum CRP, synovial AD, synovial %PMN, and absolute synovial PMN count compared to patients with chronic complaints (all $p < 0.001$, Mann-Whitney U test) (Figure 4 and Supplementary Table iv). Although synovial WBC count was larger in acute complications, the comparison with chronic complaints failed to reach statistical significance ($p = 0.178$, Mann-Whitney U test). In PJI patients, serum CRP, synovial AD (both $p < 0.001$, Mann-Whitney U test), synovial WBC count, and absolute synovial PMN count (both $p = 0.006$, Mann-Whitney U test) differed significantly between acute and chronic infections, but synovial %PMN did not ($p = 0.484$, Mann-Whitney U test) (Figure 5).

**Different cut-off values for PJI diagnosis in TKA and THA patients.** After the exclusion of patients with acute complications and sinus tracts, ROC curves were recalculated and optimal cut-off values for hip or knee joints (or both) were determined. This resulted in a change of absolute synovial PMN count to 3,300 to 3,600 cells/µl (exact values: 3,271 to 3,573 cells/µl) for hip joints (Table IV). For the knee joints and the whole cohort, the optimal cut-off value of 2,000 cells/µl did not vary and diagnostic accuracy of absolute synovial PMN count remained the same. Using the optimal cut-off for hip joints only, a synovial PMN count of 3,300 cells/µl revealed a sensitivity and specificity of 94.1% (95% CI 78.6 to 100) and 97.5% (95% CI 91.4 to 100) if acute complications and sinus tracts were excluded. Using these criteria, a PPV and NPV of 94.1% (95% CI 79.0 to

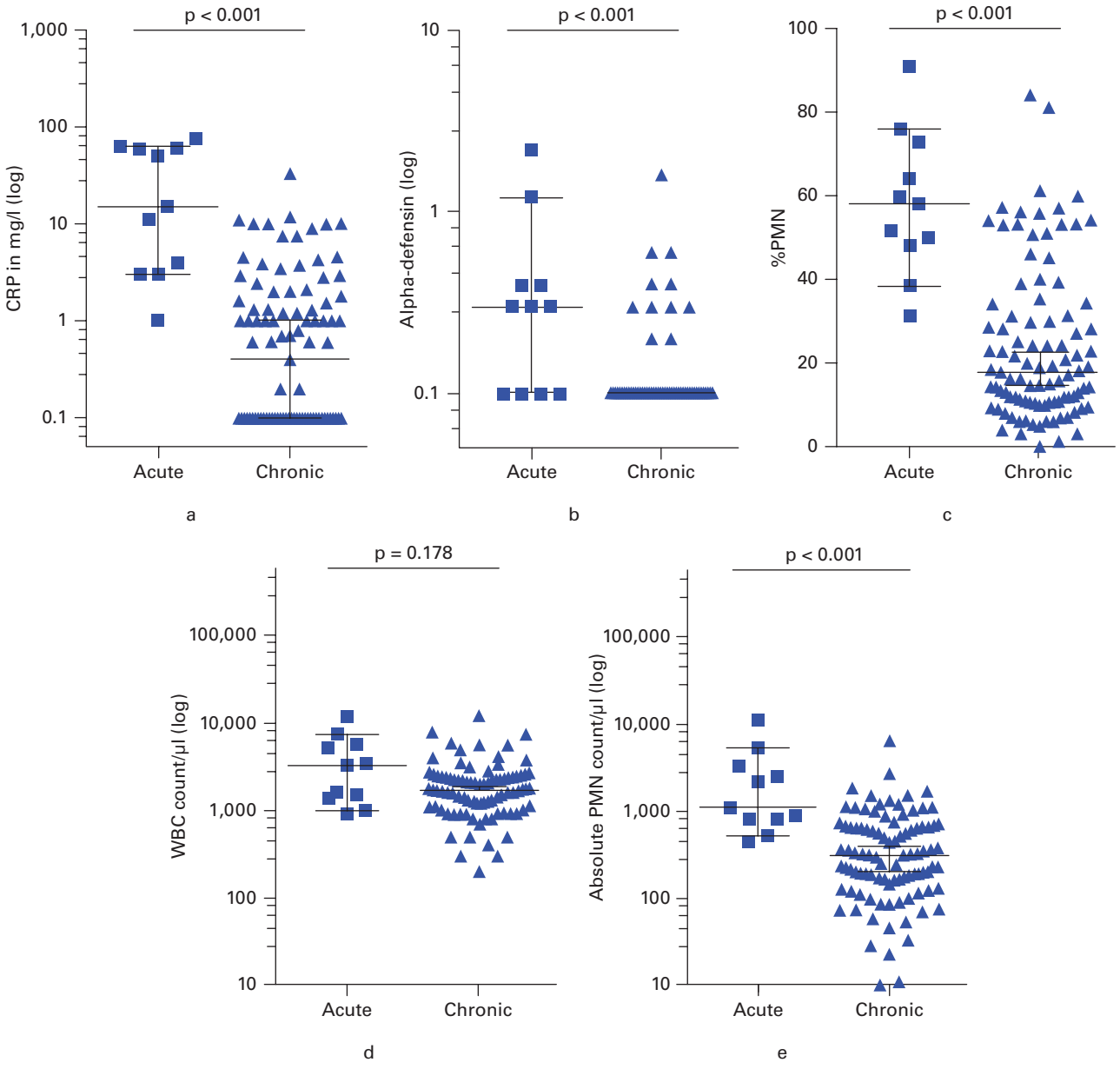


Fig. 4

Comparison of a) serum CRP, b) synovial alpha-defensin, c) percent synovial polymorphonuclear neutrophil (%PMN) cell count, d) synovial white blood cell (WBC) count, and e) absolute synovial PMN count in aseptic patients with acute and chronic complaints. Median and 95% confidence interval are displayed. p-values calculated with Mann-Whitney U tests.

100) and 97.5% (95% CI 91.4 to 100) were calculated. Without exclusion criteria, a synovial PMN count of 3,600 cells/µl appeared to be the optimal cut-off for hip joints, resulting in a sensitivity and specificity of 95.2% (95% CI 84.2 to 100) and 94.0% (95% CI 86.5 to 100). PPV and NPV then were 87.0% (95% CI 70.6 to 100) and 97.9% (95% CI 92.9 to 100).

## Discussion

Although PJI criteria have been standardized through the efforts of bodies such as MSIS and ICM, preoperative diagnosis of PJI remains one of the major challenges in orthopaedic surgery. Diagnosis is usually made by a combination of clinical and laboratory parameters, as there is still no single haematological or synovial marker with sufficient diagnostic power. Here, we demonstrate in a comparably large cohort of patients scheduled for revision TKA and THA due to septic (i.e. PJI) or aseptic complications that a threshold of absolute synovial PMN count > 2,000 cells/µl has a high diagnostic accuracy for the investigation of PJI, being equivalent or even surpassing that of synovial %PMN and synovial AD regarding most criteria. Being rapid, affordable, and widely available, we conclude that

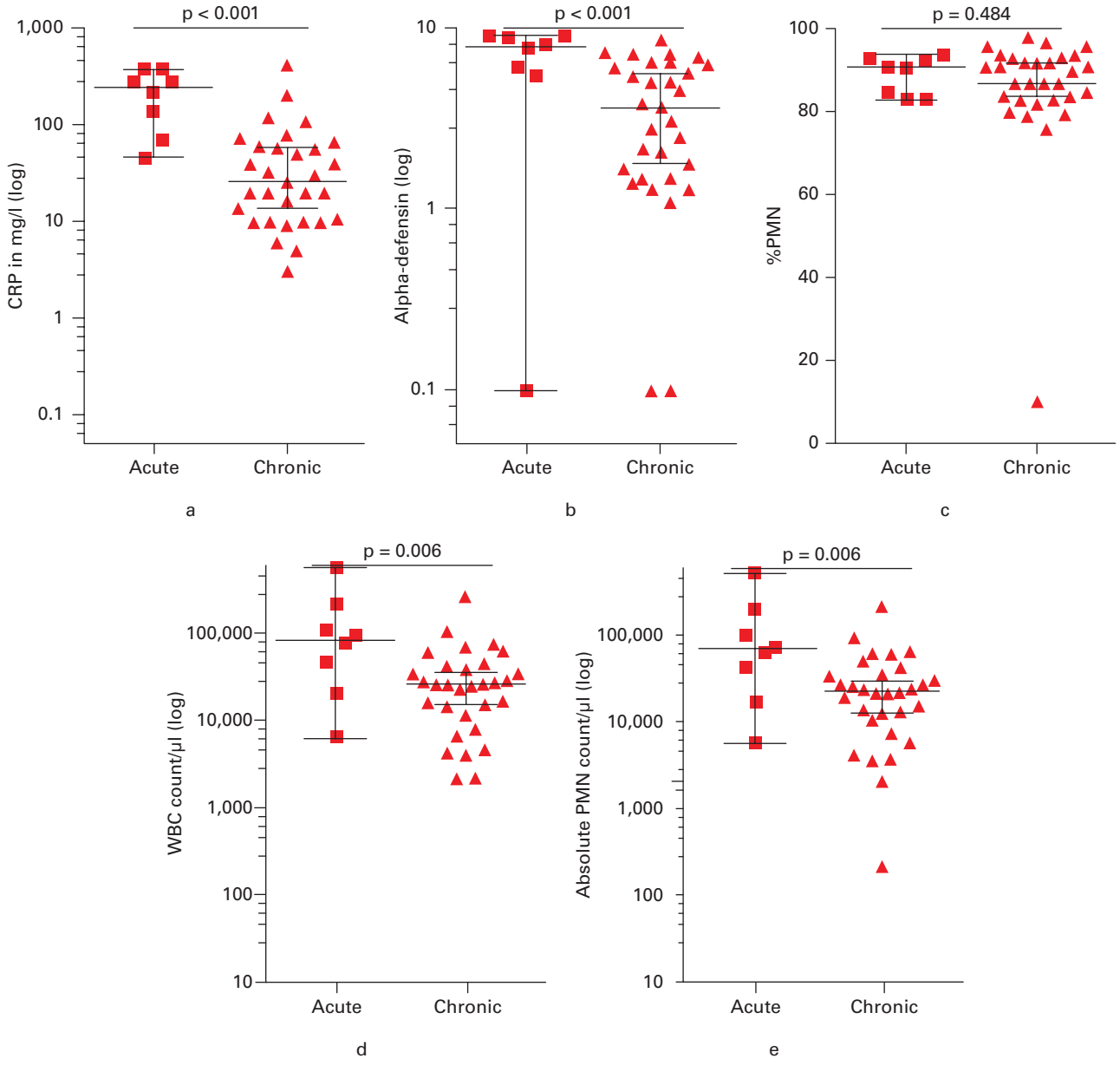


Fig. 5

Comparison of a) serum CRP, b) synovial alpha-defensin, c) percent synovial polymorphonuclear neutrophil (%PMN) cell count, d) synovial white blood cell (WBC) count, and e) absolute synovial PMN count in periprosthetic joint infection (PJI) patients with acute (squares) and chronic infections (triangles). Median and 95% confidence intervals are displayed. p-values calculated with Mann-Whitney U tests.

absolute synovial PMN count is a useful marker for establishing the likelihood of PJI.

That absolute synovial PMN count performed at least as well as AD when investigating for PJI was unexpected, but seems plausible given that AD is produced by PMN cells. This is underscored by a strong association of synovial AD and absolute synovial PMN count reported elsewhere and our work. However, previous studies have frequently used synovial %PMN as a cut-off for PJI.[15,24] Here, the use of a cut-off value for absolute synovial PMN count of 2,000 cells/µl showed even better diagnostic performance than synovial AD or synovial %PMN, suggesting this parameter as a new marker in PJI diagnostics. Converting the previously defined cut-off value of 80% PMN at 3,000 cells/µl synovial WBC count to absolute synovial PMN count yields a level of 2,400 PMN/µl.[11] As this value is only slightly higher than our threshold, it underpins that synovial %PMN and WBC count are well summarized by the single parameter of absolute synovial PMN count.

Our results also demonstrate that synovial AD has no additional value for diagnosing PJI. Sensitivity (92.3% vs 97.4%), specificity (97.2% vs 93.5%), NPV (97.2% vs 99.0%), and PPV (92.3% vs 84.4%) were comparable between synovial AD

and absolute synovial PMN count. While initial studies have shown promising results with a high sensitivity and specificity of > 95% for synovial AD,[17-19] more recent studies by our group and others have demonstrated a lower diagnostic accuracy.[22,24] Consistent with our findings, recent studies also failed to find any additional benefit of synovial AD over conventional synovial fluid analysis or leucocyte esterase.[13,24] However, Ivy et al[24] could include only 18 arthroplasties fulfilling the criteria of PJI, preventing subgroup analyses, and limiting overall transferability. Notably, the AUC for %PMN to diagnose PJI was even higher in our study compared to Ivy et al[24] (0.971 vs 0.886). Furthermore, when applying the 2018 ICM criteria, no additional PJI could be detected in any case with a positive synovial AD result.

The number of PJI cases included allowed us to differentiate between TKA and THA cases. We found remarkable differences in the cut-off values of absolute synovial PMN count for PJI in THA and TKA. Importantly, 2,000 PMN/µl was the optimal cut-off for the TKA cohort, while a cut-off of 3,600 PMN/µl showed the highest diagnostic accuracy in the THA cohort. This is in line with a study comparing synovial WBC count between THA and TKA in PJI investigation.[32] A reason for different cut-off values could be the different size and synovial fluid volume of hip and knee joints. Dilution effects due to serous effusion may be more pronounced in knee joints, lowering cut-off values for synovial WBC and absolute PMN count. Thus, this individualized approach provides a rapid and inexpensive source of information with which to confirm or exclude the presence of PJI of the knee or hip joint.

It is noteworthy that absolute synovial PMN count had lower specificity than synovial AD and %PMN in the total cohort. Seven false-positive results were associated with aseptic early-postoperative revisions (e.g. stem subsidence, dislocation) and wear-related extensive osteolysis in rheumatoid arthritis. Exclusion of patients with acute complications markedly improved the specificity of absolute synovial PMN count to 97.9%. These clinical constellations are also known to cause false-positive findings for synovial AD and PJI criteria in general.[11,22]

Our study has some limitations. Although matching preoperative markers with ICM criteria (including pre- and intraoperative criteria) was the best option, even these benchmark criteria do not have 100% diagnostic accuracy, and therefore PJI may not have been correctly determined in all cases. Furthermore, it is known that the tested markers sometimes also have strong dependence on each other and on other ICM criteria, accounting for a large part of their accuracy. In this context, it is also worth mentioning that our histological threshold for PJI may have been too conservative compared to a recent study,[33] which may have resulted in a high NPV but an increased number of false-positive histological results. Finally, additional diagnostic methods, including sonication and leucocyte esterase rapid test, could not be performed.

In conclusion, this study found that absolute synovial PMN count is an accurate marker for PJI, whereas synovial AD (a surrogate parameter of PMN count) provided no additional value for the diagnosis of PJI. Our data also indicate that individual thresholds for THA (3,600/µl) and TKA (2,000/µl) may be beneficial. Knowledge of the limited accuracy in the early-postoperative period allows the use of absolute synovial PMN as a valuable marker in the challenging diagnosis of PJI.

### Take home message

- Absolute synovial polymorphonuclear neutrophil cell (PMN) count is a widely available, rapid, cost-effective, and accurate marker in periprosthetic joint infection (PJI) diagnostics with specific values to exclude PJI in total hip and knee arthroplasty.
- Synovial alpha-defensin (AD) appears to be a surrogate parameter of absolute synovial PMN count.
- With a positive AD result, no additional PJI could be identified when the other infection parameters recommended by the International Consensus Meeting in 2018 were determined.

## Supplementary material

Tables showing detailed synovial infection parameters and serum CRP in the aseptic and periprosthetic joint infection cohorts, with further subdivision into patients acute and chronic complaints. Furthermore, patient characteristics regarding rheumatic disease, wear and sinus tract are given as well as a detailed description of variables in cases of false-positive and false-negative synovial alpha-defensin and absolute synovial polymorphonuclear neutrophil cell count.

## References


1. **Kamath AF**, **Ong KL**, **Lau E**, **et al**. Quantifying the burden of revision total joint arthroplasty for periprosthetic infection. *J Arthroplasty*. 2015;30(9):1492–1497.
2. **Natsuhara KM**, **Shelton TJ**, **Meehan JP**, **Lum ZC**. Mortality during total hip periprosthetic joint infection. *J Arthroplasty*. 2019;34(7S):S337–S342.
3. **Lum ZC**, **Natsuhara KM**, **Shelton TJ**, **Giordani M**, **Pereira GC**, **Meehan JP**. Mortality during total knee periprosthetic joint infection. *J Arthroplasty*. 2018;33(12):3783–3788.
4. **Yapp LZ**, **Clement ND**, **Moran M**, **Clarke JV**, **Simpson A**, **Scott CEH**. Long-term mortality rates and associated risk factors following primary and revision knee arthroplasty: 107,121 patients from the Scottish Arthroplasty Project. *Bone Joint J*. 2022;104-B(1):45–52.
5. **Gundtoft PH**, **Overgaard S**, **Schønheyder HC**, **Møller JK**, **Kjærsgaard-Andersen P**, **Pedersen AB**. The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties: a prospective cohort study. *Acta Orthop*. 2015;86(3):326–334.
6. **Koh CK**, **Zeng I**, **Ravi S**, **Zhu M**, **Vince KG**, **Young SW**. Periprosthetic joint infection is the main cause of failure for modern knee arthroplasty: an analysis of 11,134 knees. *Clin Orthop Relat Res*. 2017;475(9):2194–2201.
7. **Parvizi J**, **Zmistowski B**, **Berbari EF**, **et al**. New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res*. 2011;469(11):2992–2994.
8. **Osmon DR**, **Berbari EF**, **Berendt AR**, **et al**. Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2013;56(1):1–10.
9. **Parvizi J**, **Gehrke T**, **International Consensus Group on Periprosthetic Joint Infection**. Definition of periprosthetic joint infection. *J Arthroplasty*. 2014;29(7):1331.
10. **Shohat N**, **Bauer T**, **Buttaro M**, **et al**. Hip and Knee Section, What is the definition of a periprosthetic joint infection (PJI) of the knee and the hip? Can the same criteria be used for both joints?: Proceedings of International Consensus on Orthopedic Infections. *J Arthroplasty*. 2019;34(2S):S325–S327.
11. **Parvizi J**, **Tan TL**, **Goswami K**, **et al**. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. *J Arthroplasty*. 2018;33(5):1309–1314.
12. **Zagra L**, **Villa F**, **Cappelletti L**, **Gallazzi E**, **Materazzi G**, **De Vecchi E**. Can leucocyte esterase replace frozen sections in the intraoperative diagnosis of prosthetic hip infection? *Bone Joint J*. 2019;101-B(4):372–377.
13. **Shohat N**, **Yacovelli S**, **Chisari E**, **Clarkson S**, **Mann D**, **Parvizi J**. Alpha-defensin does not provide additional benefit over leukocyte esterase in the diagnosis of periprosthetic joint infection. *Expert Rev Mol Diagn*. 2021;21(8):845–849.
14. **Ghanem E**, **Parvizi J**, **Burnett RSJ**, **et al**. Cell count and differential of aspirated fluid in the diagnosis of infection at the site of total knee arthroplasty. *J Bone Joint Surg Am*. 2008;90(8):1637–1643.

15. **Zmistowski B**, **Restrepo C**, **Huang R**, **Hozack WJ**, **Parvizi J**. Periprosthetic joint infection diagnosis: a complete understanding of white blood cell count and differential. *J Arthroplasty*. 2012;27(9):1589–1593.
16. **Lehrer RI**, **Lu W**. $\alpha$-defensins in human innate immunity. *Immunol Rev*. 2012;245(1):84–112.
17. **Deirmengian C**, **Kardos K**, **Kilmartin P**, **Cameron A**, **Schiller K**, **Parvizi J**. Combined measurement of synovial fluid $\alpha$-Defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. *J Bone Joint Surg Am*. 2014;96-A(17):1439–1445.
18. **Bonanzinga T**, **Zahar A**, **Dütsch M**, **Lausmann C**, **Kendoff D**, **Gehrke T**. How reliable is the alpha-defensin immunoassay test for diagnosing periprosthetic joint infection? A prospective study. *Clin Orthop Relat Res*. 2017;475(2):408–415.
19. **Suen K**, **Keeka M**, **Ailabouni R**, **Tran P**. Synovasure "quick test" is not as accurate as the laboratory-based $\alpha$-defensin immunoassay: a systematic review and meta-analysis. *Bone Joint J*. 2018;100-B(1):66–72.
20. **Stone WZ**, **Gray CF**, **Parvataneni HK**, **et al**. Clinical evaluation of synovial alpha defensin and synovial C-reactive protein in the diagnosis of periprosthetic joint infection. *J Bone Joint Surg Am*. 2018;100-A(14):1184–1190.
21. **Kelly MP**, **Darrith B**, **Hannon CP**, **Nam D**, **Courtney PM**, **Della Valle CJ**. Synovial fluid alpha-defensin is an adjunctive tool in the equivocal diagnosis of periprosthetic joint infection. *J Arthroplasty*. 2018;33(11):3537–3540.
22. **Kleiss S**, **Jandl NM**, **Novo de Oliveira A**, **Rüther W**, **Niemeier A**. Diagnostic accuracy of alpha-defensin enzyme-linked immunosorbent assay in the clinical evaluation of painful hip and knee arthroplasty with possible prosthetic joint infection: a prospective study of 202 cases. *Bone Joint J*. 2019;101-B(8):970–977.
23. **Kleeman-Forsthuber LT**, **Johnson RM**, **Brady AC**, **Pollet AK**, **Dennis DA**, **Jennings JM**. Alpha-defensin offers limited utility in routine workup of periprosthetic joint infection. *J Arthroplasty*. 2021;36(5):1746–1752.
24. **Ivy MI**, **Sharma K**, **Greenwood-Quaintance KE**, **et al**. Synovial fluid $\alpha$ defensin has comparable accuracy to synovial fluid white blood cell count and polymorphonuclear percentage for periprosthetic joint infection diagnosis. *Bone Joint J*. 2021;103-B(6):1119–1126.
25. **Qin L**, **Li X**, **Wang J**, **Gong X**, **Hu N**, **Huang W**. Improved diagnosis of chronic hip and knee prosthetic joint infection using combined serum and synovial IL-6 tests. *Bone Joint Res*. 2020;9(9):587–592.
26. **Fuchs M**, **Kirchhoff F**, **Reichel H**, **Perka C**, **Faschingbauer M**, **Gwinner C**. Variation of synovial fluid leucocyte cell count and polymorphonuclear percentage in patients with aseptic revision total knee arthroplasty. *Bone Jt Open*. 2021;2(8):566–572.
27. **World Medical Association**. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194.
28. **Morawietz L**, **Tiddens O**, **Mueller M**, **et al**. Twenty-three neutrophil granulocytes in 10 high-power fields is the best histopathological threshold to differentiate between aseptic and septic endoprosthesis loosening. *Histopathology*. 2009;54(7):847–853.
29. **Bémer P**, **Léger J**, **Milin S**, **et al**. Histopathological diagnosis of prosthetic joint infection: does a threshold of 23 neutrophils do better than classification of the periprosthetic membrane in a prospective multicenter study? *J Clin Microbiol*. 2018;56(9):e00536-18.
30. **Morawietz L**, **Classen R-A**, **Schröder JH**, **et al**. Proposal for a histopathological consensus classification of the periprosthetic interface membrane. *J Clin Pathol*. 2006;59(6):591–597.
31. **Konigsberg BS**, **Della Valle CJ**, **Ting NT**, **Qiu F**, **Sporer SM**. Acute hematogenous infection following total hip and knee arthroplasty. *J Arthroplasty*. 2014;29(3):469–472.
32. **Zahar A**, **Lausmann C**, **Cavalheiro C**, **et al**. How reliable is the cell count analysis in the diagnosis of prosthetic joint infection? *J Arthroplasty*. 2018;33(10):3257–3262.
33. **Sigmund IK**, **McNally MA**, **Luger M**, **Böhler C**, **Windhager R**, **Sulzbacher I**. Diagnostic accuracy of neutrophil counts in histopathological tissue analysis in periprosthetic joint infection using the ICM, IDSA, and EBJIS criteria. *Bone Joint Res*. 2021;10(8):536–547.



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