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# The Impact of α-Defensin Test in Diagnosing Periprosthetic Infection After Total Ankle Arthroplasty

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ABSTRACT

Periprosthetic joint infection (PJI) after total ankle arthroplasty (TAA) is a serious complication, and a reliable diagnostic test to identify PJI is needed. The purpose of this study was to investigate the use of synovial α-defensin levels in identifying PJI of the ankle. Data from 33 patients were retrospectively collected between September 2015 and May 2018. Patients who had pain or suspected loosening after TAA and who had undergone joint aspiration were included in the study. Aspiration was performed in a semisterile theatre. Synovial fluid was processed in descending order for microbiological cultures, α-defensin, leukocyte esterase strip test, and cell count. A periprosthetic infection was defined by Musculoskeletal Infection Society criteria. The sensitivity, specificity, and overall accuracy were calculated, and based on a receiver operating characteristic curve, the quality of the α-defensin test was determined. The calculated area under the curve was 0.97 ± 0.32. Two of 33 patients fulfilled the 2014 Musculoskeletal Infection Society criteria and were scheduled for septic revision arthroplasty. Sensitivity, specificity, and overall accuracy of the α-defensin test were 100% (95% confidence interval [CI], 15.8% to 100%), 93.5% (95% CI, 78.6% to 99.2%), and 93.9% (95% CI, 79.8% to 99.3%), respectively. The positive predictive value was 50% (95% CI, 20.7% to 79.3%), and the negative predictive value was 100%. The α-defensin test seems to be the best available synovial test to detect a late-onset PJI after total ankle arthroplasty. Further prospective studies with a larger number of patients are required.



Periprosthetic joint infection (PJI) after total ankle arthroplasty (TAA) is a severe complication that often leads to revision arthroplasty, prolonged antibiotic treatment, fusion of the ankle, or amputation (1–4). As TAA is increasingly used by surgeons and is more accepted by patients, dealing with complications such as PJI is essential.

In general, the prevalence of PJI after TAA varies between 0.8% and 4.6%, but in contrast to total knee arthroplasty (TKA) or total hip arthroplasty (THA), there are limited data regarding a PJI diagnostic algorithm (3,5,6). A reliable diagnostic test to identify PJI so as to avoid recurrent implant failure in false-negative patients is desirable, especially under challenging circumstances at the ankle joint such as a low blood supply and thin soft tissue coverage (4,7). However, making the correct diagnosis of a PJI is demanding because of the great variability in symptoms (8).

Increasing efforts are being made to determine a more rigorous approach to detecting PJIs by using a synovial fluid biomarker such as α-defensin, with promising results (9–15). α-Defensins are small cationic peptides—sometimes called effector molecules—that are produced by various immunoactive cells as part of the innate immune system. They are capable of targeting and destroying the membrane of microorganisms and play a role in the immune response based on their chemotactic activities (16–18). Together with other cytokines such as interleukin-6 or interleukin-1β, the synovial defensin concentration

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level rises in case of PJI (19,20). In a recent meta-analysis by Wyatt et al (15), the pooled diagnostic sensitivity and specificity of α-defensin were 100% and 96%, respectively. However, despite the strong evidence of α-defensin in TKA and THA as the best available test to detect PJI, there is no study reporting on the accuracy of α-defensin immunoassay after TAA.

To overcome these shortcomings, this clinical investigation was performed to answer the following questions: (1) What is the sensitivity, specificity, and negative and positive predictive values for an α-defensin immunoassay in detecting PJI after TAA? (2) Do other diagnostic tests, such as leukocyte esterase (LE), synovial cell count, percentage of polymorphonuclear leukocytes (PMN%), C-reactive protein (CRP), or serum white blood cell count (WBC), have comparable results?

## Materials and Methods

This single-center retrospective cohort study was performed after approval from our institutional review board and was conducted in accordance with the World Medical Association Declaration of Helsinki.

The data were collected between September 2015 and May 2018. Patients who had consecutive pain or loosening of the prosthesis after TAA and who underwent joint aspiration as part of our diagnostic approach introduced in earlier publications were enrolled in the study (9,21). Patients with confirmed metallosis or early infection (prior surgery <4 weeks) were excluded from the study. Additional exclusion criteria were an insufficient amount of synovial fluid to run all necessary tests (n = 6) or antibiotic therapy within the past 2 weeks (n = 2). A PJI was defined based on the 2014 Musculoskeletal Infection Society (MSIS) criteria, which had not yet included α-defensin (22). According to the MSIS criteria, a PJI is present when 1 of the major criteria exists or 3 of the 5 minor criteria exist. The major criteria are 2 positive periprosthetic cultures OR a sinus tract communicating with the joint. The 5 minor criteria are (1) elevated serum CRP *and* ESR, (2) elevated synovial fluid WBC count *or* a change of "++" on the LE test strip, (3) elevated synovial fluid PMN%, (4) positive histological analysis of periprosthetic tissue, and (5) a single positive culture.

The joint aspirations were performed as described by Gehrke et al (9) in a semisterile theatre. After a 4-time skin disinfection with alcohol and application of sterile drapes around the ankle joint, the aspiration was performed without admixing of local anesthetic agents or saline solution. The obtained synovial liquid was then divided for diagnostic testing in descending order: (1) a separate sterile tube for microbiology cultures, (2) 1 mL for α-defensin immunoassay, (3) a dipstick (Combur10 Test; Roche Diagnostics) to test LE activity, and (4) at least 500 μL in an EDTA tube to perform cell count. Samples 1 and 4 were sent to an independent laboratory at the University Hospital Schleswig-Holstein, Kiel, Germany. The Laboratory of Clinical Chemistry in Kiel performed the automated cell counting; setting up of the microbiological cultures was done at the Department of Microbiology. The cultures were incubated for 14 days. The aspirated synovial fluid in sample 2 was sent to independent Laboratory Fenner, Hamburg, Germany, where the enzyme-linked immunosorbent essay (ELISA) was conducted.

Patient data regarding blood samples (WBC, CRP), LE strip test, ELISA of α-defensin, and intraoperative findings including bacterial cultures and clinical symptoms were gathered.

### *Statistics*

To statistically evaluate the performance of the α-defensin immunoassay, the specificity, sensitivity, positive and negative predictive values, and overall accuracy were calculated. In addition, we calculated the receiver operating characteristic and established a cutoff value and calculated the area under the curve.

Patients were divided into 2 groups—the PJI group and the non-PJI group—according to the MSIS criteria (22). Mean and standard deviation values for the synovial α-defensin concentration, synovial cell count, PMN%, and serum CRP and WBC levels were determined. The statistical analysis was performed by using SPSS 25.1 (IBM Corp., Armonk, NY), and the graphics were produced with the use of STATA/IC 13.1 for Windows (StataCorp, College Station, TX).

## Results

The study group consisted of 33 patients (23 females and 10 males) with a mean ± SD age of 63.4 ± 12.4 (range 32 to 83) years. The mean CRP was 8.8 ± 12.8 (range 0.3 to 47) mg/L, and the WBC in serum was 7.4 ± 1.95 (range 5.05 to 14.0)/nL. The mean synovial cell count was 3556 ± 1432 (range 208 to 13,500)/μL. Two of 33 patients fulfilled the MSIS criteria and were scheduled for septic revision arthroplasty. The remaining 31 patients were in the non-PJI group. The microbiological cultures showed a growth of *Staphylococcus aureus* and *Candida albicans*. The prevalence of PJI after TAA in our cohort of patients with consecutive pain or loosening of the prosthesis was 6.1%. Demographic data and mean values of the diagnostic tests are given in Table 1.

After statistical analyses, the overall sensitivity of the α-defensin ELISA test was 100% (95% confidence interval [CI], 15.8% to 100%), the specificity was 93.5% (95% CI, 78.6% to 99.2%), the positive predictive value was 50% (95% CI, 20.7% to 79.3%), and the negative predictive value was 100%. The overall accuracy of the α-defensin ELISA test was 93.9% (95% CI, 79.8% to 99.3%); see also Table 2.

The 2 patients with false-positive α-defensin tests both had an α-defensin concentration of 1.4 ng/mL; 1 patient fulfilled 2 minor criteria of the MSIS definition: elevated CRP and a positive synovial leukocyte count. The second false-positive case did not meet the MSIS criteria. In 1 patient, there was a positive bacterial culture after joint aspiration with *S aureus* without fulfilling other MSIS criteria. In that case, the α-defensin concentration was 0.4 ng/mL and intraoperatively no signs of infection were seen; there were no signs of infection in histological and microbiological workup.

The specificity for the ELISA of synovial α-defensin concentration was 93.5% to rule out a PJI. The specificity for the LE strip test, CRP, clinical signs, WBC, and synovial PMN% was 81.8%, 77.4%, 0.1%, 96.7%, and 77.8%, respectively (Table 2).

The LE strip test could not be used in 8 patients because of hemorrhagic contamination and in 14 patients because of a lack of synovial fluid. Therefore, the LE strip test could be performed in only 12 (36%) of 33 patients. Similar findings were seen for PMN%, with 11 and 9 successfully performed tests, respectively. However, in 23 patients, the PMN% could not be used because of the lack of synovial fluid.

The synovial α-defensin level revealed a good diagnostic value for predicting PJI after TAA with an area under the curve of 0.97 ± 0.32. An ideal cutoff value, with a sensitivity of 100% and a specificity of 93.5%, would be a concentration of 0.9 ng/mL of α-defensin in the synovial fluid (see also Fig.).

**Table 1**
Demographic and clinical characteristics of cohort patients who underwent joint aspiration of the ankle joint divided by group

| Variable | N = 33 | PJI Group, n = 2 | Non-PJI Group, n =31 |
|---|---|---|---|
| Age, mean ± SD y | 63.4 ± 12.4 | 79 ± 3.6 | 61.9 ± 12.4 |
| Female, n (%) | 23 (67.6) | 1 (50) | 21 (67.7) |
| Positive microbiological culture, n (%) | 3 (9) | 2 (100)<br>*S epidermidis*, n = 1<br>*Candida albicans, n = 1* | 1 (3)<br>*Staphylococcus aureus*, n = 1 |
| Patients undergoing revision surgery, n (%) | 26 (76.5) | 2(100) | 24 (74) |
| CRP in serum, mean ± SD mg/L | 8.8 ± 12.8 | 39 ± 5.2 | 6.8 ± 10.3 |
| WBC count serum, mean ± SD/nL | 7.3 ± 1.9 | 10.7 ± 3.46 | 7.1 ± 1.6 |
| Synovial α-defensin, mean ± SD ng/mL | 0.12 ± 0.33 | 3.5 ± 1.7 | 0.26 ± 0.37 |
| WBC synovial count, mean ± SD/μL (range) | 3556 ± 1432 (208 to 13,500) | 13,500 | 2313 ± 795 (208 to 6550) |

Abbreviations: CRP, C-reactive protein; PJI, periprosthetic joint infection; SD, standard deviation; WBC, white blood cell.

**Table 2**
Sensitivity, specificity, positive and negative predictive values, and the overall accuracy of clinical tests in detecting periprosthetic joint infection

| Test | n | Sensitivity, % | Specificity, % | Positive Predictive Value, % | Negative Predictive Value, % | Overall Accuracy, % |
|---|---|---|---|---|---|---|
| α-Defensin | 33 | 100 | 93.5 | 50 | 100 | 93.9 |
| Leukocyte esterase | 13 | 100 | 81.8 | 40 | 100 | 84.6 |
| CRP in serum | 33 | 100 | 77.4 | 22.2 | 100 | 78.8 |
| Clinical signs | 33 | 66.7 | 0 | 3 | 0 | 6 |
| WBCs in serum | 33 | 50 | 96.7 | 50 | 93.5 | 93.9 |
| Percentage of polymorphonuclear leukocytes | 11 | 100 | 77.8 | 50 | 100 | 81.8 |
| WBC synovial count | 9 | 100 | 37.5 | 16.67 | 100 | 44.4 |

Abbreviations: CRP, C-reactive protein; WBC, white blood cell.

## Discussion

This is the first study to analyze the quality of the α-defensin ELISA in detecting PJI after TAA, to the authors' best knowledge. We were able to show that the quantitative α-defensin test was, together with the serum WBC level, the most accurate of the tested laboratory parameters with an overall accuracy of 93.9%. Similar results have been already presented for the use of α-defensin in THA and TKA (10,15,23). However, the α-defensin test showed less sensitivity in detecting PJI after total shoulder arthroplasty. The authors concluded that the lower accuracy in total shoulder arthroplasty might be associated with the high number of *Propionibacterium acnes* infections, which was not detected in our cohort.

In our study cohort, no false-negative results were reported, but 2 false-positive test results were revealed, leaving 29 true-negative and 2 true-positive α-defensin results. The reason for our false-positive results was not apparent. First, none of the included patients had a draining sinus. Second, metallosis was an exclusion criterion of our study. Those 2 factors might influence the α-defensin results as reported in previous studies (9,14). Surprisingly, the WBC serum level showed the same diagnostic accuracy as the synovial α-defensin test with a value of 93.9%. Although the WBC of the serum is known as an uncertain parameter regarding PJI of TKA and THA with a sensitivity of 21% to 70% and a specificity of 60% to 94% in previous studies (24,25), its accuracy was excellent in our cohort, possibly because of the low number of true infections and thus an error-prone statistical calculation. Because the synovial α-defensin showed the same accuracy but did not fail to reveal both true-positive infections, the serum WBC missed 1 true infection and therefore seems to be inferior.

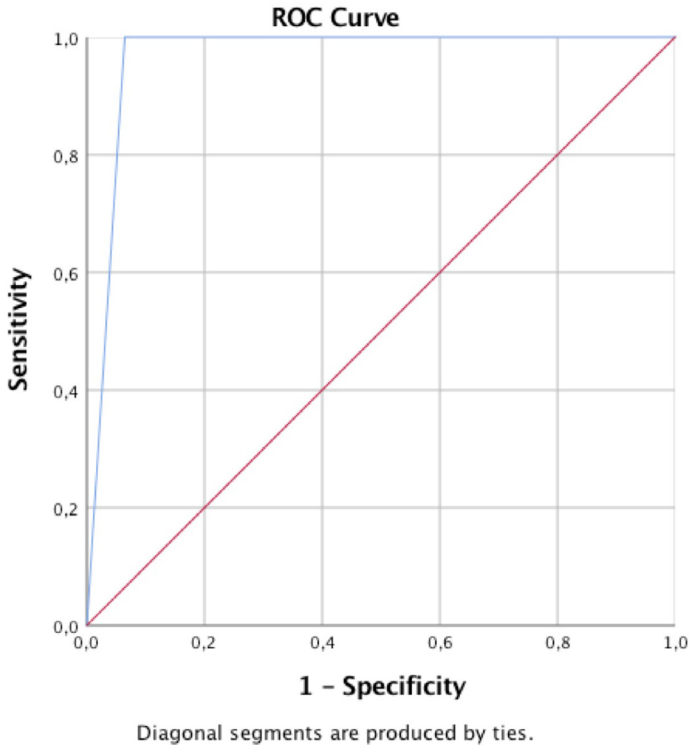


**Fig.** Showing the receiver operating characteristics (ROC) for prediction of periprosthetic joint infection after total ankle arthroplasty based on synovial α-defensin. The relationship between sensitivity and 1 – specificity is depicted by the blue curved line. The area under the (blue) curve indicates the strength of a test, whereas 1.0 is the maximum value achievable, which would indicate a 100% sensitivity and specificity. A value of 0.5 indicates no discrimination. The area calculated was 0.97 ± 0.32 (95% confidence interval).

The overall accuracy of the LE strip test was 84.6%, considerably lower than that of the α-defensin test. The accuracy of the LE test in TAA was also less in comparison with previous studies reporting on TKA and THA cases (10,26–29). Almost all aspirated joints in these studies were artificial knee and hip joints; only 1 study included a single native ankle joint and therefore makes a direct comparison blurred (29). However, our results might suggest a lower specificity for the LE strip test in the ankle joint compared with in the knee or hip joint.

As presented in our study, clinical signs as a predictor are not reliable to detect a PJI, which can lead to delay or misdiagnosis. For instance, in a study by Patton et al (4), the diagnosis of PJI was made after 18 months when signs like wound dehiscence or acute wound infection were absent. These results underline the difficulties in finding the correct diagnosis if an acute complication is missing and highlights the possible usefulness of a reliable test. Laboratory parameters such as WBC or CRP are helpful tools and broadly available. However, these diagnostic tests could also misdiagnose a PJI as shown in the current and prior studies, especially in cases with low-virulent germs (7,30–32).

Therefore, the excellent ability of the α-defensin test to rule out a PJI (93.5% specificity) might help to avoid unnecessary surgery such as open biopsy, which could be of importance in case of the known elevated risk of wound healing complications, even after minor surgery like open biopsy, compared with knee or hip cases (33,34). The MSIS criteria have recently been changed to include synovial α-defensin as one of the most influential minor criteria in a point system, underlining the importance of α-defensin immunoassays for the diagnosis of PJI after TKA and THA, which may be transferred to the ankle joint (35). Yet, neither of the 2 false-positive cases would have changed after adaptation to the new guideline.

In general, our study adds valuable new information to the current literature, although we had some clear limitations. First, the study results are based on retrospective data. Second, the small sample size and the fact that only 2 patients had a PJI are major limitations of the study and carry the risk of a β error. Third, there is no clear explanation for the 2 false-positive results. Fourth, there are inconsistent data regarding the LE test and cell count, which are also weaknesses of the study.

In conclusion, the α-defensin test appears to be the best synovial test for the detection of a PJI after TAA. However, it should not be considered as a single test but rather as one of many components for diagnosing a PJI. The α-defensin test might lead to a better approach regarding

revision surgery and is a meaningful aid in patients with no prior obvious signs of inflammation.

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