Is Procalcitonin (PCT) a reliable biomarker for preoperative diagnosing of low grade Periprosthetic Joint Infection? A Prospective Study

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Abstract

Background: Since a „gold-standard“ is missing, diagnosing periprosthetic joint infection (PJI) remains a challenge in orthopedic surgery. The purpose of this study was to evaluate the accuracy of serum and synovial fluid Procalcitonin (S-PCT and SF-PCT) as a diagnostic parameter and to compare it to the biomarkers recommended in the 2018 Definition of periprosthetic hip and knee infection. Methods: Between August 2018 and July 2019, a prospective cohort study was conducted in 70 patients with painful hip, shoulder and knee arthroplasty. Besides medical history, clinical and laboratory data was gathered. PJI was diagnosed based on the 2018 Definition of periprosthetic hip and knee infection. Preoperative blood and synovial joint fluid were taken for PCT measurement. S-PCT levels were quantified under the use of immunoassay (Centaur, Siemens, Germany). SF- PCT levels were measured using a standard quantitative PCT enzyme immunoassay kit, according to the manufacturers' instructions (Anti-Procalcitonin antibody ab166963, ABCAM, Cambridge,UK). Results: Twenty three patients (33%) were classified as the PJI group and fourty seven patient (67%) as the aseptic group. The mean levels of S-PCT were significantly ($p<0.001$) higher than those in the aseptic group (PJI 0.05 ng/mL (0.0-1.03) vs. aseptic 0.02 ng/mL (0.0-0.18)). In synovial fluid, the mean PCT values in the aseptic group were significantly higher ($p<0.001$) than those of PJI group (PJI 2.7 ng/mL (0.53-9.7) vs. aseptic 8.7 ng/mL (0.25-87.9)). S- PCT, with a cut-off level of 0.5 ng/mL, had a sensitivity of 13.0% and a specifity of 91.0%. SF-PCT, with a cut-off level of 5.0 ng/mL, had a sensitivity of 13.0% and a specifity of 52.0%. Conclusion: S-PCT and SF-PCT appeared to be no reliable biomarkers in the differential diagnosis of PJI from aseptic loosening in total joint arthroplasty.

Background

Periprosthetic joint infection (PJI) is a severe complication after total joint arthroplasty. It is one of most common reasons for revision surgery in arthroplasty 1. The 5- year incidence exceeds one percent after primary arthroplasty 2. The differentiation between aseptic and septic failure is crucial for surgical planning3. According to the current Consensus Definition for PJI, a minimum of two positive cultures of periprosthetic tissue or the presence of a sinus tract with evidence of communication to the joint or visualization of the implant are major crtiteria in diagnosis 4. However, microbiological diagnostic is occasionally false negative or positive5. Conventional serum biomarkers such as white cell count (WCC) and C-reactive protein (CRP) have limited diagnostic accuracy6 7. Other serum biomarkers such as Interleukin-6 (Il-6) which are often used in inflammation diagnostics reveal also shortcommings in sensitivity and specifity8. A wide spectrum of synovial fluid biomarkers (SF-alpha-1-Defensin, SF-CRP, SF-Il-6) have been utilized with the goal to diagnose PJI 9. Yet, there is no “gold standard” for definite diagnosis of PJI 10.

Procalcitonin (PCT) has been utilized as a serum marker in detecting bacterial infection for several years. 11 12 13. Besides CRP serum PCT seems to be the most promising biomarker to differentiate between aseptic and septic processes 14. PCT, the precursor of calcitonin, is a 116-amino-acid protein produced by the neuroendocrine and the parafollicular cells of the thyroid15. In healthy patients, serum PCT level is in

general very low16, but markedly increased in severe bacterial and fungal infections17. It has been demonstrated that the injection of bacterial endotoxin in normal subjects induces the release of PCT systemically18 19.

The purpose of our study was to investigate the diagnostic value of serum and synovial PCT in Periprosthetic Infection. The hypothesis to be tested was: Due to its properties as a reliable biomarker in bacterial infection, serum and synovial PCT is significantly increased in patients with PJI.

Methods

Study design:

After approval of the institutional review board (18-8042-BO), a prospective study was performed of data gathered from Department of Orthopedics and Trauma Surgery from University of Duisburg-Essen, Germany, in patients with persisting pain20 after hip, knee and shoulder arthroplasty. All patients signed informed consent forms prior to being enrolled.

The study was conducted in accordance with the declaration of Helsinki.

Medical history, clinical examinations, laboratory values including C-reactive protein (CRP) and joint aspiration fluid were gathered preoperatively as routine diagnostic procedures. Based on the findings of the preoperative diagnostic tests, the patients were considered as aseptic or septic according to the 2018 Definition of periprosthetic hip and knee infection21. In order to determine the impact of renal dysfunction on serum and synovial values of PCT, serum creatinin concentrations were gathered at the time of joint puncture.

Inclusion criteria were a sufficient amount of synovial fluid for all determinations, and full clinical and laboratory data to allow for diagnosis of periprosthetic infection (PJI). Patients were further excluded, if they showed signs of early postoperative PJI (8 weeks) due to lack of reliability of synovial and serologic markers shortly after surgery 22 23. Metallosis, other inflammatory comorbidities (HIV, rheumatic diseases), and previous or concomitant antibiotic therapy were considered as exclusion criteria.

Sample Preparation

All patients gave their written informed consent that surplus material of their blood and synovial samples which is not needed for standard diagnostics is used for research studies.

Blood was taken from the cubital vein the day before surgery. Synovial aspiration was executed avoiding an admixture of blood with an 18-gauge needle. Synovial fluid was aseptically aliquoted into sterile tubes and centrifuged for 8 minutes at 4°C with 2000 g. The synovial fluid samples were put on ice and transported within 60 minutes to Laboratory of Institute of Medical Psychology and Behavior Science University of Duisburg-Essen and frozen at −80°

Determination of the Levels of Serum and Synovial Fluid biomarkers:

Serum PCT levels were quantified under the use of immunoassay (Centaur, Siemens,Germany) with lower limit of detection of 0.02 ng/mL (normal < 0.5 ng/mL). Serum CRP was analyzed by immune turbidimetry (Centaur, Siemens, Germany) (normal < 0.5 mg/dl). Synovial leukocyte level and percentage of polymorphic neutrophils was measured by flow cytometry with EDTA plasma (normal range, <3000/µl and <80%). Synovial PCT levels were measured using a standard quantitative PCT enzyme immunoassay kit, according to the manufacturer´s instructions (Anti-Procalcitonin antibody ab166963, ABCAM, Cambridge,UK). Synovial alpha-1-Defensin was analyzed using a standard quantitative enzyme immunoassay kit (Human α-Defensin 1 Antibody, R&D Systems Bio-Techne, Minneapolis, USA)(cut-off level 4800 ng/mL). The results were given as standardized signal relative to a tolerance limit value (interpretation values: < 0.9 aseptic, 0.9–0.99 unspecific, ≥ 1.0 septic). Synovial CRP was analyzed under use of a quantitative enzyme-linked immunoassay (CRP ELISA (EU59131), IBL International GmbH, Hamburg, Germany)(cut-off level (> 6,9 mg / l)).

Statistical Analysis:

The data were processed with the statistical software package SPSS. Basic descriptive statistics were used to analyze clinical and laboratory values. Normally distributed continuous data were shown as mean ± standard deviation (SD) and compared using student's t-test. Non-normally distributed continuous data were shown as mean and compared using the Mann–Whitney U test. A p value < 0.05 was considered statistically Sensitivity, specificity, AUC and their 95% confidence interval (CI) for any cut-off level were calculated via ROC analysis.

Results

Patients:

From July 2018 to June 2019, 78 patients introduced themselves with persisting pain 20 after hip, knee and shoulder arthroplasty in the consultation hour. 70 patients could be included in the study. Three patients were excluded due to insufficient amount of synovial fluid via preoperative puncture. Two patients each were excluded due to inflammatory comorbidities and early postoperative PJI. One patient was excluded because antibiotic therapy was already started prior to the puncture. All 78 patients who introduced themselves in consultation hour were operatively treated. In all 78 cases histological specimens were taken according to the current recommendations in the 2018 Definition of periprosthetic hip and knee infection 21.

From the 70 included patients, 47 patients were identified as having an aseptic joint effusion according to the Definition of Parvizi et al. (2018) were included into the study. The group included 27 women and 20 men with a mean age of 66 ± 12.5 (38-88) years. There were 18 knees, 27 hips and 2 shoulders. The

group consisted of 45 patients with polyethylene wear debris induced osteolysis and 2 hips with corrosion of modular head-neck junction. The mean BMI (Body Mass Index) was 26.7 ± 3.1 (22-37).

In the same period, 23 patients were classified as having a PJI according to the Definition of Parvizi et al. (2018). The group consisted of 15 women and 8 men with a mean age of 72 ± 3 (47-89) years. There were 3 knees, 17 hips and 3 shoulders. The mean BMI was 27.1 ± 3 (19-45). In 16 aspirations joint fluid was tested positive in microbiological culture. Bacteria were identified in 16 (70%) of 23 patients of the infection group. Staphylococci were found in 11 (69%), Propioni bacteria and and Enterococci in each two (13%) and Serratia marcescens were found in one (6%). In 7 patients (29%) in the infection group with positive histologic specimens for infection, no bacteria could be isolated after 14 days The patients who were identified as having PJI were operatively revised via two-stage revision with implantation of an intermittent antimicrobial-impregnated There were no significant differences in age (p=0.32) sex (p=0.53) and age at time of surgery (p=0.70) between the two groups. The distribution of site of joint arthroplasty was significantly different between the two groups (p=0.01) with higher rates of hip arthroplasties in the PJI group.

The serum PCT measurement was positive in 1 joint and negative in 69 (see figure 1). The mean serum PCT level in the PJI and aseptic groups was 0.05 ng/ml (0.00 to 1.03) and 02 ng/ml (0.00 to 0.18), respectively (p < 0.001). Comparing these data with the diagnosis criteria of PJI according to the Definition of Parvizi et al (2018), it was found that the PCT- assay was false-positive in 0 and false-negative in 22 cases. The mean SF-PCT in the PJI and aseptic groups was 2.7 ng/ml (0.53 to 9.7) and 8.7 ng/ml (0.25 to 87.9), respectively (p < 001) (See figure 2). The mean serum CRP values in the PJI and aseptic groups was 2.3 mg/dl (0.0 to 8.6) and 0.35 mg/dl (0.0-1.9) respectively (p < 0.001) (See figure 3). The mean SF-CRP in the PJI and aseptic groups was 19.6 µg/ml (0.6 to 339) and 1.4 µg/ml (0.4 to 3), respectively (p < 0.001) (See figure 4). The mean synovial fluid alpha-1-defensin levels were significantly higher (p=0.006) in PJI group with 3.6 µg/ml (0.2-5.7) than in aseptic group with 0 µg/ml (0.2-5.7). The data of statistical analysis are presented in table 2.

There were no significant differences (p=0.98) in the creatinin values between the aseptic and the PJI group. There was no significant correlation between PCT and creatinin values (p=0.68).

Discussion

A periprosthetic joint infection (PJI) is a serious complication after total joint Despite the existence of an international consensus for the definition of PJI, there is no “gold standard” for definite diagnosis of PJI 10 10. The differentiation between aseptic and septic failure remains a key challenge in orthopedic surgery as the treatment of aseptic failure is completely different to the treatment of PJI 24.

In recent years, several studies reported on the determination of synovial and serum biomarkers for diagnosing periprosthetic infection25 26 27 28 29. CRP is a protein that is synthesized in the liver in response to acute inflammation when there are increased macrophages30. Several studies have endorsed the role of synovial CRP in diagnosing patients with PJI. Most studies reported that synovial

CRP is a parameter with high sensitivity and specifity in diagnosing chronic periprosthetic hip infection and favorable to serum CRP 31 32 33. In contrast, Tetreault et al (2014) found no advantage to the use of synovial-fluid CRP over serum CRP in the diagnosis of PJI34. In our study, as expected the additional determination of synovial CRP increases the specifity , but not the sensitivity.

Alpha-Defensins are microbicidal peptides that are active against many Gram-negative and Gram-positive bacteria, fungi, and enveloped viruses35. Bingham et al (2014) concluded that the sensitivity and specificity of the synovial fluid α-defensin assay is superior to other currently available clinical tests 36 37. However, there are also reports about low sensitivity values (64%) of synovial alpha-1-defensin 38. In our study, synovial alpha-1-defensin was presented as very specific, but less sensitive biomarker to distinguish between aseptic and septic loosening.

The reports about PCT as a diagnostic biomarker for periprposthetic infection are inconsistent (see table 3). Randau et al (2014) and Bottner et al (2007) demonstrated that serum PCT is a very specific, but a less sensitive biomarker for diagnosis of PJI 15 39 40. In contrast, Glehr et al (2013) classified serum PCT as a sensitive, but not specific biomarker for PJI detection8. In a systematic review and meta-analysis, Yoon et al (2018) concluded that serum PCT is not recommended for use as a rule-out diagnostic tool for PJI 29. Sa-Ngasoongsong et al (2019) reported on synovial fluid PCT as a reliable test for PJI diagnostic with high specifity and sensitivity 15. The results of the current study show that serum PCT is a specific, but less sensitive marker for PJI diagnostic. Interestingly, the aseptic group presented significantly higher synovial PCT values than septic patients.

We could not confirm the initially described hypothesis. We believe that there is no solid evidence to recommend a single determination of serum PCT to rule out PJI. Also, the use of synovial PCT as a parameter in PJI diagnostic´s does not appear to be expedient. The lower PCT values in synovial fluid in PJI in comparison with aseptic patients may base on different Firstly, since not all patients suffering from PJI show bacteremia41, there is no trigger for release of PCT into the blood. It is conceivable that low grade infects such as the majority of PJI do not have the virulence to trigger PCT release. Secondly, in healthy patients transient bacteremia, even after tooth brushing, is a frequent phenomenon that may induce low-grade PCT release 42 43 44 .Thirdly, it is well known, that in patients with chronic kidney disease PCT levels are increased due to reduced renal elimination 45 46. Thus, the retention of PCT in patients with kidney diseases could results in false higher PCT values. In our cohort, we could not find any correlation between PCT and creatinin values. Finally, the penetration of PCT into the joint fluid has been infrequently studied. The penetration of PCT into synovial fluid is maybe different in each patient.

Another reason which may have an influence on the results of this study is the possible high rate of false-negatives despite the measurement of serum and synovial fluid biomarkers in addition to conventional microbiological diagnostics. Kheir et al (2018) pointed out that surgeons should be aware of the high rate of false-negatives associated with low-virulence organisms and culture-negative cases due to low sensitivity rates. The sensitivity of the serum and synovial biomarkers appears to be related to organism type 47.

In comparison to serum and synovial CRP as well as synovial AD-1, serum and synovial PCT show a lack of specifity (synovial) and sensitivity (serum) and thus cannot be counted as reliable biomarkers for the differentiation between aspetic processes and PJI (see table 1 and figure 6).

One major strengths of our study is the design as a prospective trial. To our knowledge, this is one of the first reports about PCT determination in synovial fluid. In addition, patients with chronic diseases (HIV, rheumatic diseases) which could affect the laboratory values were excluded.

Conclusion

Serum and SF-PCT appeared to be no reliable alternative biomarker in the differential diagnosis of PJI from aseptic loosening in total joint arthroplasty. The frequently described high sensitivity of alpha-1-Defensin in PJI diagnosis could not be confirmed with our In future studies, the detection of direct parameters for a periprosthetic infection should probably play a more prominent role .

List Of Abbreviations

PJI = Periprosthetic joint infection

WCC = white cell count

CRP = C-reactive protein

IL–6 = Interleukin–6

SF = synovial fluid

PCT = Procalcitonin

BMI = body mass index

SD = standard deviation

CI = confidence interval

HIV = Human immunodeficiency virus

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: All patient-related data were collected by file research from the archives of the participating centers

Consent to publish: All patients consented to publish personal data in an anonymized form.

Ethics approval and consent to participate: The study was approved by the ethics committee University of Duisburg-Essen (18–8042-BO).

Competing Interests: None of the authors had competing interests.

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Authors contribution: All authors ensured that they had furnished a substantial contribution to the article and that they are in agreement with form and contents of the manuscript.

MJ analyzed and interpreted the patient data regarding the scientific relevance and supervised the study as chairman of the department.

AB and AW conceived the study and wrote the article.

CB and HE were responsible for sample analysis.

MH and SL as senior surgeons were responsible for sample collection.

References

1 Otto-Lambertz C, Yagdiran A, Wallscheid F, Eysel P, Jung N. Dtsch Arztebl Int. 2017 May 26;114(20):347-353. doi: 10.3238/arztebl.2017.0347. Periprosthetic Infection in Joint Replacement.

2 Gundtoft PH, Overgaard S, Schonheyder HC, Moller JK, Kjaersgaard-Andersen P, Pedersen AB. The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties. Acta Orthop 2015. January 30:1–9.

3 Parvizi J, Jacovides C, Antoci V, Ghanem E. Diagnosis of periprosthetic joint infection: the utility of a simple yet unappreciated enzyme. J Bone Joint Surg Am. 2011;93:2242–2248. doi: 10.2106/JBJS.J.01413.

4 Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 Definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplast 2018. doi:10.1016/j.arth.2018.02.078..

5 Bjerke-Kroll B.T., Christ A.B., McLawhorn A.S., Sculco P.K., Jules-Elysée K.M., Sculco T.P. Periprosthetic joint infections treated with two-stage revision over 14 years: an evolving microbiology profile. J. Arthroplasty. 2014;29(5):877–882. doi: 10.1016/j.arth.2013.09.053.

6 Yuan K, Chen HL, Cui ZM. Diagnostic accuracy of C-reactive protein for periprosthetic joint infection: a meta-analysis. Surg Infect (Larchmt) 2014;15:548–559. doi: 10.1089/sur.2013.066.

7 Kheir MM, Tan TL, Shohat N, Foltz C, Parvizi J. Routine Diagnostic Tests for Periprosthetic Joint Infection Demonstrate a High False-Negative Rate and Are Influenced by the Infecting Organism. J Bone Joint Surg Am. 2018 Dec 5;100(23):2057-2065. doi: 10.2106/JBJS.17.01429.

8 Glehr M, Friesenbichler J, Hofmann G, Bernhardt GA, Zacherl M, Avian A, Windhager R, Leithner A. Novel biomarkers to detect infection in revision hip and knee arthroplasties. Clin Orthop Relat Res. 2013 Aug;471(8):2621-8. doi: 10.1007/s11999-013-2998-3. Epub 2013 Apr 23

9 Deirmengian C, Kardos K, Kilmartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? Clin Orthop Relat Res. 2014 Nov;472(11):3254-62. doi: 10.1007/s11999-014-3543-8

10 Patel R, Alijanipour P, Parvizi J., Advancements in Diagnosing Periprosthetic Joint Infections after Total Hip and Knee Arthroplasty., Open Orthop J. 2016 Nov 30;10:654-661. doi: 10.2174/1874325001610010654. eCollection 2016.

11 Simon L, Gauvin F, Amre DK, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004;39(2):206–217.

12 Whicher J, Bienvenu J, Monneret G. Procalcitonin as an acute phase marker. Ann Clin Biochem. 2001;38(Pt 5):483–493.

13 Arkader R, Troster EJ, Lopes MR, Junior RR, Carcillo JA, Leone C, Okay TS. Procalcitonin does discriminate between sepsis and systemic inflammatory response syndrome. Arch Dis Child. 2006;91(2):117–120.

14 Pontrelli G, De Crescenzo F, Buzzetti R, Jenkner A, Balduzzi S, Calò Carducci F, Amodio D, De Luca M, Chiurchiù S, Davies EH, Copponi G, Simonetti A, Ferretti E, Di Franco V, Rasi V, Della Corte M, Gramatica L, Ciabattini M, Livadiotti S, Rossi P. Accuracy of serum procalcitonin for the diagnosis of sepsis in neonates and children with systemic inflammatory syndrome: a meta-analysis. BMC Infect Dis. 2017 Apr 24;17(1):302. doi: 10.1186/s12879-017-2396-7.

15 Sa-Ngasoongsong P, Wongsak S, Jarungvittayakon C, Limsamutpetch K, Channoom T, Kawinwonggowit V. Comparison of Synovial Fluid and Serum Procalcitonin for Diagnosis of Periprosthetic Joint Infection: A Pilot Study in 32 Patients. Biomed Res Int. 2018 Oct 1;2018:8351308. doi: 10.1155/2018/8351308. eCollection 2018.

16 Morgenthaler N. G., Struck J., Fischer-Schulz C., Seidel-Mueller E., Beier W., Bergmann A. Detection of procalcitonin (PCT) in healthy controls and patients with local infection by a sensitive ILMA. Clinical Laboratory. 2002;48(5-6):263–270.

17 Ferriere F. Procalcitonin, a new marker for bacterial infections. Annales de Biologie Clinique. 2000;58(1):49–59.

18 Dandona P, Nix D, Wilson MF, Aljada A, Love J, Assicot M, Bohuon C. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab. 1994;79(6):1605–1608.

19 Wegner, A., S. Elsenbruch, J. Maluck, J.S. Grigoleit, H. Engler, M. Jager, I. Spreitzer, M. Schedlowski Benson S. Inflammation-induced hyperalgesia: effects of timing, dosage, and negative affect on somatic pain sensitivity in human experimental endotoxemia. Brain Behav Immun, 2014. 41: p. 46-54.

20 Cats-Baril W, Gehrke T, Huff K, Kendoff D, Maltenfort M, Parvizi J. International consensus on periprosthetic joint infection: description of the consensus process. Clin Orthop Relat Res. 2013;471:4065–4075. doi: 10.1007/s11999-013-3329-4.

21 Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 Definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplast 2018. doi:10.1016/j.arth.2018.02.078.

22 Bilgen O, Atici T, Durak K. Karaeminoğullari, Bilgen MS. C-reactive protein values and erythrocyte sedimentation rates after total hip and total knee arthroplasty. J Int Med Res. 2001;29:7–12. doi: 10.1177/147323000102900102.

23 Larsson S, Thelander U, Friberg S. C-reactive protein (CRP) levels after elective orthopedic surgery. Clin Orthop Relat Res. 1992;275:237–242.

24 Ellenrieder M, Lenz R, Haenle M, Bader R, Mittelmeier W. Two-stage revision of implant-associated infections after total hip and knee arthroplasty. GMS Krankenhhyg Interdiszip. 2011;6(1):Doc17. doi: 10.3205/dgkh000174. Epub 2011 Dec 15.

25 Lee Y. S., Koo K., Kim H. J., et al. Synovial Fluid Biomarkers for the Diagnosis of Periprosthetic Joint Infection. The Journal of Bone & Joint Surgery. 2017;99(24):2077–2084. doi: 10.2106/JBJS.17.00123.

26 Vicenti G, Bizzoca D, Nappi V, Pesce V, Solarino G, Carrozzo M, Moretti F, Dicuonzo F, Moretti B. Serum biomarkers in the diagnosis of periprosthetic joint infection: consolidated evidence and recent developments. Eur Rev Med Pharmacol Sci. 2019 Apr;23(2 Suppl):43-50. doi: 10.26355/eurrev_201904_17473.

27 Xie K., Dai K., Qu X., Yan M. Serum and Synovial Fluid Interleukin-6 for the Diagnosis of Periprosthetic Joint Infection. Scientific Reports. 2017;7(1) doi: 10.1038/s41598-017-01713-4.

28 Yuan K, Li WD, Qiang Y, Cui ZM. Comparison of procalcitonin and C-reactive protein for the diagnosis of periprosthetic joint infection before revision total hip arthroplasty. Surg Infect (Larchmt). 2015 Apr;16(2):146-50. doi: 10.1089/sur.2014.034. Epub 2015 Feb 6.

29 Yoon JR, Yang SH, Shin YS. Diagnostic accuracy of interleukin-6 and procalcitonin in patients with periprosthetic joint infection: a systematic review and meta-analysis. Int Orthop. 2018 Jun;42(6):1213-1226. doi: 10.1007/s00264-017-3744-3. Epub 2018 Jan 2.

30 Parvizi J, Jacovides C, Adeli B, Jung KA, Hozack WJ Mark B. Coventry Award: synovial C-reactive protein: a prospective evaluation of a molecular marker for periprosthetic knee joint infection. Clin Orthop Relat Res. 2012 Jan; 470(1):54-60.

31 Ghanem E, Antoci V Jr, Pulido L, Joshi A, Hozack W, Parvizi J The use of receiver operating characteristics analysis in determining erythrocyte sedimentation rate and C-reactive protein levels in diagnosing periprosthetic infection prior to revision total hip arthroplasty. Int J Infect Dis. 2009 Nov; 13(6):e444-9.

32 Greidanus NV, Masri BA, Garbuz DS, Wilson SD, McAlinden MG, Xu M, Duncan CP. Use of erythrocyte sedimentation rate and C-reactive protein level to diagnose infection before revision total knee arthroplasty: a prospective evaluation. J Bone Joint Surg Am. 2007;89:1409–1416. doi: 10.2106/JBJS.D.02602.

33 Omar M, Ettinger M, Reichling M, Petri M, Guenther D, Gehrke T, Krettek C, Mommsen P. Synovial C-reactive protein as a marker for chronic periprosthetic infection in total hip arthroplasty. Bone Joint J. 2015 Feb;97-B(2):173-6. doi: 10.1302/0301-620X.97B2.34550.

34 Tetreault MW, Wetters NG, Moric M, Gross CE, Della Valle CJ. Is synovial C-reactive protein a useful marker for periprosthetic joint infection? Clin Orthop Relat Res. 2014 Dec;472(12):3997-4003. doi: 10.1007/s11999-014-3828-y. Epub 2014 Jul 29.

35 White SH, Wimley WC, Selsted ME Structure, function, and membrane integration of defensins. Curr Opin Struct Biol. 1995 Aug; 5(4):521-7.

36 Bingham J, Clarke H, Spangehl M, Schwartz A, Beauchamp C, Goldberg B The alpha defensin-1 biomarker assay can be used to evaluate the potentially infected total joint arthroplasty. Clin Orthop Relat Res. 2014 Dec; 472(12):4006-9.

37 Shahi A, Parvizi J. The role of biomarkers in the diagnosis of periprosthetic joint infection. EFORT Open Rev. 2017 Mar 13;1(7):275-278. doi: 10.1302/2058-5241.1.160019. eCollection 2016 Jul.

38 Frangiamore SJ, Saleh A, Grosso MJ, Kovac MF, Higuera CA, Iannotti JP, Ricchetti ET. α-Defensin as a predictor of periprosthetic shoulder infection. J Shoulder Elbow Surg. 2015 Jul;24(7):1021-7. doi: 10.1016/j.jse.2014.12.021. Epub 2015 Feb 8.

39 Randau TM, Friedrich MJ, Wimmer MD, Reichert B, Kuberra D, Stoffel-Wagner B, Limmer A, Wirtz DC, Gravius S. Interleukin-6 in serum and in synovial fluid enhances the differentiation between periprosthetic

joint infection and aseptic loosening. PLoS One. 2014 Feb 21;9(2):e89045. doi: 10.1371/journal.pone.0089045. eCollection 2014.

40 Bottner F, Wegner A, Winkelmann W, Becker K, Erren M, Götze C. Interleukin-6, procalcitonin and TNF-alpha: markers of peri-prosthetic infection following total joint replacement. J Bone Joint Surg Br. 2007 Jan;89(1):94-9.

41 Klement MR, Siddiqi A, Rock JM, Chen AF, Bolognesi MP, Seyler TM. Positive Blood Cultures in Periprosthetic Joint Infection Decrease Rate of Treatment Success. J Arthroplasty. 2018 Jan;33(1):200-204.e1. doi: 10.1016/j.arth.2017.08.034. Epub 2017 Sep 4.

42 Lucas VS, Gafan G, Dewhurst S, Roberts GJ. Prevalence, intensity and nature of bacteraemia after toothbrushing. J Dent. 2008;36(7):481–487.

43 Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. Circulation. 2008;117(24):3118–3125

44 Schlein RA, Kudlick EM, Reindorf CA, Gregory J, Royal GC. Toothbrushing and transient bacteremia in patients undergoing orthodontic treatment. Am J Orthod Dentofacial Orthop. 1991;99(5):466–472.

45 Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. PLoS One. 2018 Nov 14;13(11):e0206527. doi: 10.1371/journal.pone.0206527. eCollection 2018.

46 Herget-Rosenthal S, Klein T, Marggraf G, Hirsch T, Jakob HG, Philipp T, Kribben A. Modulation and source of procalcitonin in reduced renal function and renal replacement therapy. Scand J Immunol. 2005 Feb;61(2):180-6.

47 Kheir MM, Tan TL, Shohat N, Foltz C, Parvizi J. Routine Diagnostic Tests for Periprosthetic Joint Infection Demonstrate a High False-Negative Rate and Are Influenced by the Infecting Organism. J Bone Joint Surg Am. 2018 Dec 5;100(23):2057-2065. doi: 10.2106/JBJS.17.01429.

48 Scemama C., Anract P., Dumaine V., Babinet A., Courpied J.P., Hamadouche M. Does vitamin E-blended polyethylene reduce wear in primary total hip arthroplasty: a blinded randomised clinical trial. Int Orthop. 2017 Jun;41(6):1113-1118. doi: 10.1007/s00264-016-3320-2. Epub 2016 Nov 4.

Tables

Major criteria (at least one of the following	Decision
Two positive cultures of the same organism	Infected
Sinus tract with evidence of the communication to the joint or visualization of the prosthesis	

Minor criteria	Score	Decision
Elevated serum CRP or D-Dimere	2	≥6 Infected
Elevated serum ESR	1	
Elevated synovial WBC or LE (++)	3	2-5 Possibly Infected
Positive Alpha-Defensin	3	
Elevated synovial PMN	2	0-1 Not Infected
Elevated synovial CRP	1	

Inconclusive pre-op Score or dry tap	Score	Decision
Preoperative Score	-	≥6 Infected
Positive Histology	3	
Positive Purulence	3	4-5 Inconclusive
Positive Single Culture	2	≤3 Not Infected

Table 1: 2018 Definition of periprosthetic hip and knee infection

Parameter	PJI (n=23)	Aseptic (n=47)	Cut-Off	Sensitivity (%)	Specifity (%)	AUC	p-value
Serum CRP (mg/dl)	2.3 (0.0-8.6)	0.35 (0.0-1.9)	0.5	57	81	0.70 (0.59-0.87)	<0.001
Synovial CRP (mg/ml)	19.6 (0.6-339)	1.4 (0.4-5.3)	6.9	26	100	0.79 (0.65-0.91)	<0.001
Serum PCT (ng/ml)	0.05 (0.0-1.03)	0.02 (0.0-0.18)	0.1 0.3 0.5	26 17 13	81 84 91	0.53 (0.39-0.68)	<0.001
Synovial PCT (ng/ml)	2.7 (0.53-9.7)	8.7 (0.25-87.9)	1.0 5.0	87 13	0 52	0.26 (0.13-0.38)	<0.001
Synovial AD-1 (µg/ml)	3.6 (0.2-5.7)	2.0 (0.2-5.7)	4.8	52	88	0.67 (0.52-0.82)	0.006

Table 2: Diagnostic accuracy of PJI diagnosis using serum or synovial fluid biomarkers

Author	Parameter	Cut-Off	Sensitivity	Specifity	p-value
Current study	Serum PCT	0.5 ng/ml	13	91	<0.001
		1.0 ng/mL	87	0	
	Synovial fluid PCT	5.0 ng/mL	13	52	
Glenn et al (2013)	Serum PCT	0.055 ng/mL	81	54	0.038
		0.36 ng/mL	90	33	
Randau et al (2014)	Serum PCT	46 ng/mL	13	100	
Sa-Ngasoong-song P et al (2019)	Serum PCT	0.1 ng/mL	65	92	< 0.001
		0.3 ng/mL	50	100	
		0.5 ng/mL	40	100	
	Synovial fluid PCT	0.08 ng/mL	90	83	< 0.001
		0.12 ng/mL	80	92	
		0.16 ng/mL	55	91	
Bottner et al (2007)	Serum PCT	0.3 ng/mL	33	98	n.a.

Table 3: Procalcitonin: Overview of sensitivity and specificity values in different studies

Figures

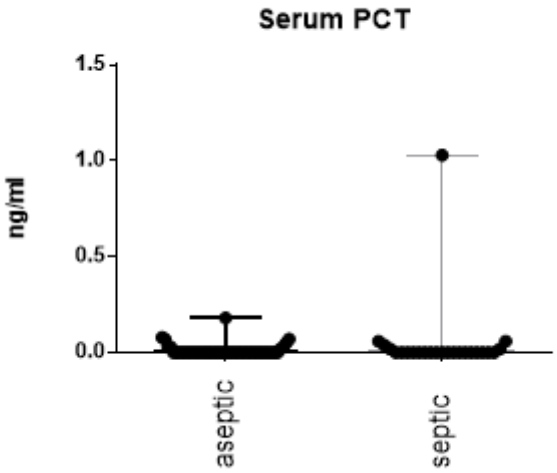

Figure 1

Serum PCT: Log-scale dot plots demonstrate the diagnostic separation of study groups

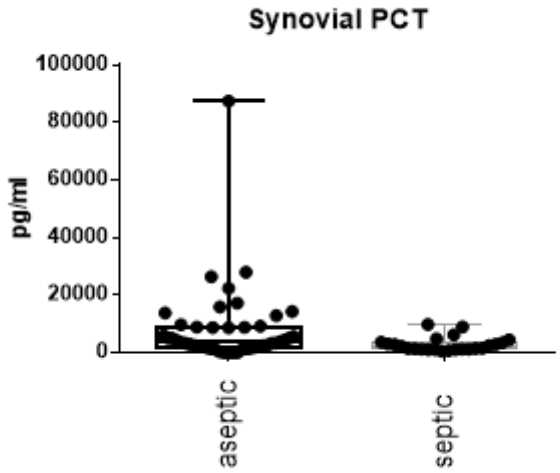

Figure 2

Synovial PCT: Log-scale dot plots demonstrate the diagnostic separation of study groups

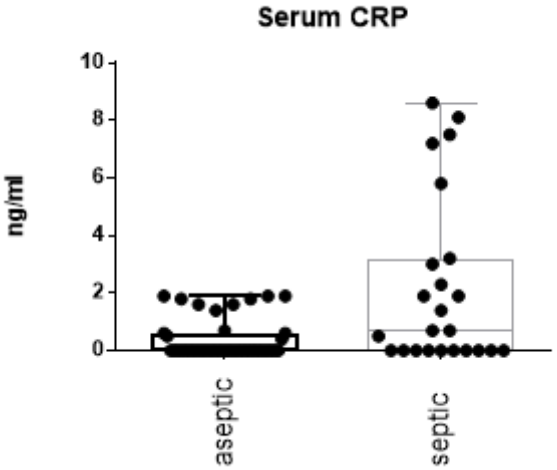

Figure 3

Serum CRP: Log-scale dot plots demonstrate the diagnostic separation of study groups

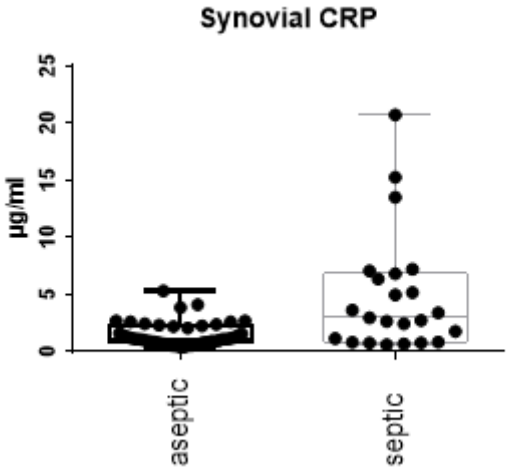

Figure 4

Synovial CRP: Log-scale dot plots demonstrate the diagnostic separation of study groups

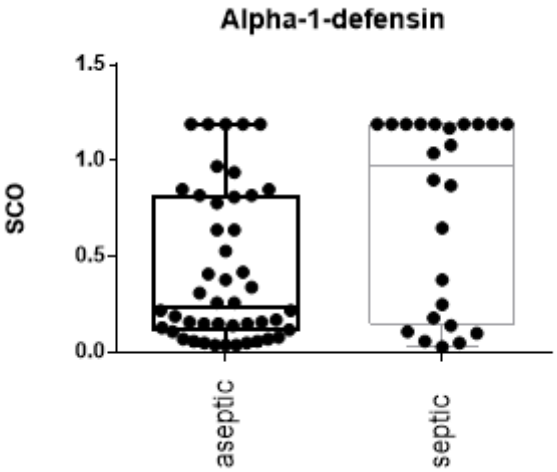

Figure 5

Synovial Alpha-1-Defensin: Log-scale dot plots demonstrate the diagnostic separation of study groups

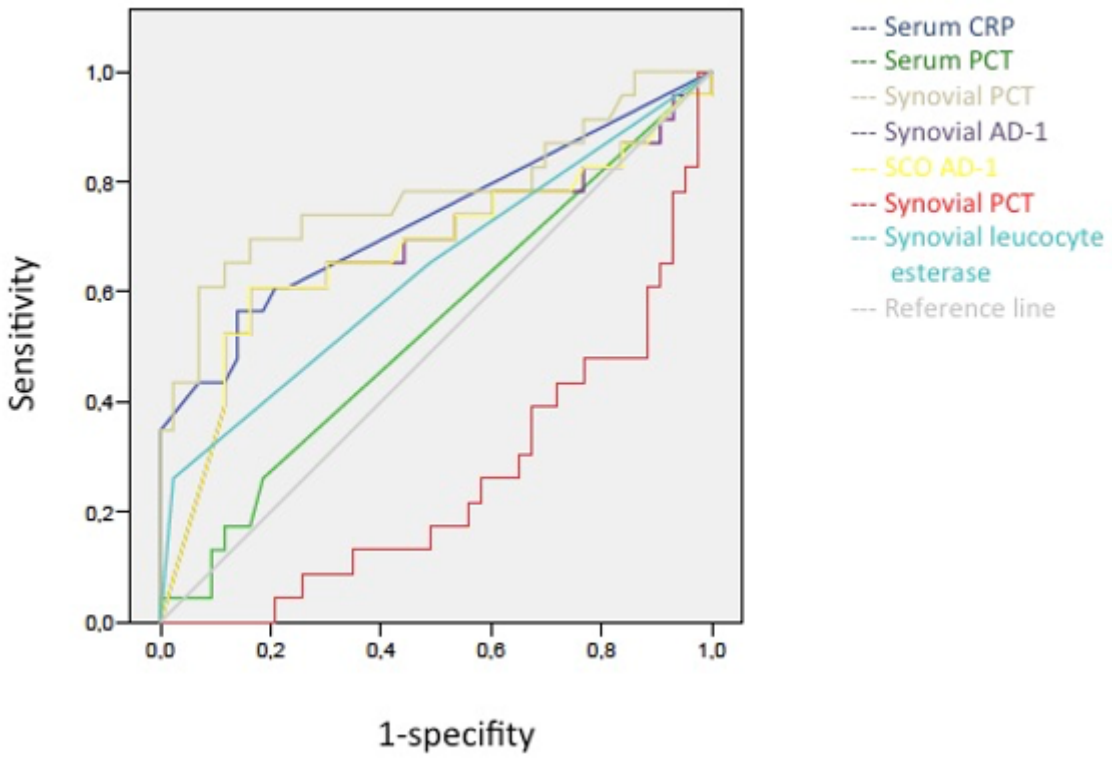

Figure 6

ROC analysis of all parameters

Supplementary Files

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