RESEARCH

Results of a monocentric field study: value of histology compared to sonication method and conventional tissue culture in the diagnosis of periprosthetic joint infection (PJI)

Alexander Röhrl[1] · Frank Klawonn[2,3] · Bernd Füchtmeier[1] · Christian Wulbrand[1] · Andre Gessner[4] · Jozef Zustin[5,6] · Andreas Ambrosch[7]

Abstract

Background To confirm the diagnosis of periprosthetic joint infection (PJI), the Infectious Diseases Society of America (IDSA) and the International Consensus Meeting (ICM) have defined criteria that include histology as a minor criterion and the sonication method only as an additional criterion. The aim of this monocentric, retrospective study was to investigate the value of histology and whether sonication leads to a more accurate diagnosis.

Materials and methods All revision surgeries for knee and hip arthroplasty between 2017 and 2020 were included. With regard to microbiological diagnostic, conventional culture of periprosthetic biopsies and sonication of explant material were performed. In addition, histology and non-specific inflammatory markers (CRP, leukocytes) were recorded.

Results A total of 78 patients with PJI and 62 aseptic controls were included. From both microbiological methods (conventional culture / sonication), Staphyloccus (S.) epidermidis and *S. aureus* were detected most frequently. However, compared to the conventional microbiology, a higher sensitivity was calculated for sonication, albeit with a lower specificity in relation to a PJI. In two logistic regression models for the significance of all diagnostic parameters in PJI, the AUC was 0.92 and 0.96 with histology in particular making the decisive contribution in both models (p < 0. 001, both models).

Conclusion Since histology showed the highest accuracy in the current study, its importance in the PJI criteria should be reevaluated. Sonication shows a high sensitivity for germ detection with a lower specificity and should only be used in combination with the conventional culture for microbiolgical diagnostics.

Keywords PJI · Histology · Sonication · Minor citeria

✉ Andreas Ambrosch
andreas.ambrosch@barmherzige-regensburg.de

1. Department of Trauma Surgery, Orthopaedics & Sports Medicine, Hospital of Brothers of Mercy, Regensburg, Germany

2. Biostatistics, Helmholtz Centre for Infection Research, Brunswick, Germany

3. Institute for Information Engineering, Ostfalia University, Wolfenbüttel, Germany

4. Institute of Clinical Microbiology and Infection Prevention, University Hospital, Regensburg, Germany

5. Private Histopathology Service, Regensburg, Germany

6. Gerhard Domagk Institute of Pathology, University Medical Center, Münster, Germany

7. Institute of Laboratory Medicine, Microbiology and Infection Prevention, Hospital of Brothers of Mercy, Prüfeninger Straße 86, 93049 Regensburg, Germany

Introduction

Due to demographic changes and longer life expectancy, the number of joint replacements is increasing rapidly. Currently, more than 1 million arthroplasties per year are performed in the USA. A significant increase to up to four million operations per year is expected by 2030 [1, 2]. A corresponding increase in complications and revisions is to be expected.

Periprosthetic joint infection (PJI) is a major problem. Bozic et al. showed that the incidence of revision surgery due to infection after hip replacement is 14.8% [3] and after knee replacement 25.2% [4]. The diagnosis of PJI has far-reaching consequences for patients, as revision surgery, multiple operations and long-term antibiotic treatment are necessary. Long hospitalisation is the result. The economic burden on the healthcare system is correspondingly high.

Vanhegan et al. used the example of total hip arthroplasty to show that septic revisions are almost twice as expensive as periprosthetic fractures and aseptic loosening [5]. Müller et al. point out that the costs of treating a PJI are generally not covered for hospitals in Germany [6].

There are various diagnostic criteria and algorithms for PJI [7–10]. The value of the respective criteria for diagnosing a PJI is the subject of current research due to the lack of a gold standard. However, the definitions of a PJI according to the Infectious Diseases Society of America (IDSA) [7] and the International Consensus Meeting (ICM) [8] are used worldwide. Major criteria for a PJI in both bodies are the detection of the same infectious agent in two tissue samples taken or the presence of a joint fistula (sinus tract communicating with the joint). In addition, there are minor criteria that can be used to diagnose a PJI; this is particularly important when the microbiological examinations have been carried out without detection of germs. Since the diagnosis of a PJI is not based on a single diagnostic marker, but several parameters must be considered (multi-parameter diagnostics) and misinterpretations may occur [11]. None of the commonly used criteria has 100 per cent sensitivity and specificity.

As already mentioned, microbiological diagnostics play an important role in the diagnosis of PJI. However, here too, caution is required when interpreting the results: For example, biofilm-forming microorganisms are not necessarily detectable in the periprosthetic tissue samples (high rate of negative findings). Furthermore, low-grade infections are often problematic in diagnostics, as the causative germs (e.g. coagulase-negative staphylococci, Cutibacterium propioni) are usually part of the skin flora and patients often experience few symptoms [10, 12]. In the case of microbiologically negative findings or in the differentiation of contamination from low-grade infections, histological examination could be of substantial importance [13]. In addition, sonication of explanted prosthesis components has been proposed to improve the sensitivity of microbiological diagnostics [14].

Against the background of the diagnostic problems, the aim of the present field study was to investigate the usefulness of histology in the multiorchestrated diagnosis of PJI including non-specific inflammatory markers, sonication method and conventional microbiological tissue culture from periprosthetic sample material.

Materials and methods

Study design

In this monocentric, retrospective cohort study, all cases of revision surgery for suspected PJI performed in our clinic were included when sonication method of the explant material was performed (e.g. suspicious infections with biofilm producing bacteria, low grade infections / chronic infections). The study period was from 02/2017 to 12/2020. Sonications of antibiotic-containing spacers and sonications of shoulder TEPs were excluded.

The PJI was based on the criteria of the International Consensus Meeting 2018 (ICM) and was used as a reference [8] (Table 1).

The sonication method and conventional microbiology of periprostetic tissue samples were performed independently at different institutes. For the evaluation of inflammatory markers, the results of C-reactive protein (CRP) and leukocytes in the peripheral blood were documented on the day of admission of the patients.

Sonication of removed endoprosthesis material

The explanted prosthesis material (prosthesis components including mobile parts) were packed in the operating theatre in sterile plastic boxes (reusable, disinfected and sterilised at 134° C, double-wrapped) and sent directly to the in-house laboratory. There, the implant boxes were opened under laminar flow and the explants were doused with 60 ml Ringer's solution. The implant box was then gently swirled for approx. 30 s and placed in an ultrasonic bath (Bandelin BactoSonioc 14.2, Germany) at 100% intensity (40 ± 5 kHz) for one minute. The implant boxes were shaken again under laminar flow for 30 s. Next, two Falcon tubes (polypropylene conical tubes, flat top, 50 ml, Falcon, USA) were each loaded with 20 ml sonicate and centrifuged at 2000 rpm for 5 min. The supernatant was carefully pipetted off until approx. 2 ml remained in the tip of the tube. Finally, 100 μL of the centrifugate was spread on semi-solid / liquid culture media (Chocolate Agar, Schaedler Agar (with 5% sheep blood), MacConkey Agar, Kochblut Agar, Thioglycollate Bouillon, Biomerieux, France) using a Drigalski spatula. The agar plates were incubated for 14 days at 37° C (Schaedler agar: anaerobic incubation). All plates exhibiting positive growth were quantified and identified according to the routine established by the laboratory.

Conventional microbiological culture of periprosthetic biopsies

Periprosthetic tissue biopsies (4—6 pieces) were sent immediately to the laboratory in sterile tubes and homogenised there under sterile conditions using tissue homogenisers (tissue homogenisers according to Potter–Elvehjem, VWR International, Germany). The homogenised mixture was then spread on semi-solid / liquid culture media (Chocolate Agar, Schaedler Agar (with 5% sheep blood), MacConkey Agar, Kochblut Agar, Thioglycollate Bouillon, Biomerieux,

Table 1 Definition of a periprosthetic joint infection (PJI) according to the recommendations of the Infectious Disease Society of America (IDSA) [7] and the International Consensus Meeting (ICM) [8]: Major and minor criteria are evaluated in a scoring system, with a score of ≥ 6 points indicating a confirmed PJI and a score of 4–5 indicating a possible PJI

ICM				Decision
Major criteria	A sinus tract communication with the joint			infected
	Two positive periprosthetic cultures with phenotypically identical organisms			
Minor criteria				
Institution	Threshold		Score	Decision
	Acute	chronic		Combined pre-& postoperative score:
Serum CRP (mg/l)	≥ 100	≥ 10	2	
or	unknown	≥ 860		≥ 6 = infected
D-Dimer (µg/l)				4–5 = Inoclusive
Elevated Erythrocye sedimentation rate (ESR) SD (mm /h)	No role	≥ 30	1	≤ 3 = Not infected
Elevated Synovial WBC (cells/µl)	≥ 10,000	≥ 3,000	3	
or	+ +	+ +		
Leucocyte esterase	1.0	1.0		
or				
positive Alpha Defensin (signal/cutoff)				
Positive Histology	+	+	3	
Single Positive Culture	+	+	2	
Positive Intraoperative Purulence	+	+	3	
elevated polymorph nuclei cells in peripheral blood (%)	≥ 90	≥ 70	2	

IDSA	Definitive Infection	Suspicious infection
The presence of a sinus tract that communicates with the prosthesis	x	
The presence of purulence surrounding the prosthesis	x	
Two or more intraoperative cultures or combination of preoperative aspiration and intraoperative cultures that yield the same organism	x	
Growth of a virulent microorganism (e.g., *Staphylococcus aureus*) in a single specimen of a tissue biopsy or synovial fluid may also represent PJI		x
The presence of acute inflammation based on histopathologic examination of periprosthetic tissue at the time of surgical debridement or prosthesis removal		x
One of multiple tissue cultures or a single aspiration culture that yields an organism that is a common contaminant (eg, coagulase-negative staphylococci, *Propionibacterium acnes*)		x
The presence of PJI is possible even if the above criteria are not met; the clinician should use his/her clinical judgment to determine if this is the case after reviewing all the available preoperative and intraoperative information		x

France). The agar plates were incubated for 14 days at 37° C (Schaedler agar: anaerobic incubation). All plates exhibiting positive growth were quantified and identified according to the routine established by the laboratory.

Routine germ identification and resistance testing

Germ identification was carried out using MALDI-Tof analysis (Matrix assisted laser desorbtion ionization time of flight analysis; Vitek MS, Biomerieux, France). In this technology, bacterial proteins are mixed with matrices, typically organic acids (α-Cyano-4-hydroxycinnamic acid (HCCA)), which can adsorb the laser energy to assist sample desorption and transfer protons for sample ionization. Mostly single charged ions or ions with low charge number are produced. The charged ions are accelerated in an electric field to gain kinetic energy, and then pass a field-free flight tube for separation, wherein the ions with larger mass-to-charge (m/z) ratio arrive at the end of the flight tube with a longer flight time whereas the ones with smaller m/z with a shorter flight time. The mass spectrum of the bacterial proteins is compared with a database. MALDI technique is a very precise and rapid technology to identify bacterial species. Resistance testing was performed using automated microdilution technology (Vitek 2, Biomerieux, France).

Histological examination (according to [15])

Three to seven tissue samples taken from the respective joint during the procedure were fixed in buffered formalin immediately after excision and sent to the histopathological laboratory. The bone tissue was decalcified with EDTA solution. The samples were embedded in paraffin, sectioned with a microtome and stained with haematoxylin & eosin and Prussian blue. Periprosthetic joint infection was considered to be present if either three neutrophils were found in a high power field (HPF) or five or more neutrophils were found in 5 HPF (magnification × 400). Cases with three and four neutrophils in 5 HPF were considered suspicious for periprosthetic joint infection. Neutrophils located within the superficial fibrin exudate or intravascularly were not considered.

Statistics

Analysis of possible differences between groups were performed using the Fishers exact test or the student's t-test. Logistic regression was evaluated using leave-one-out cross-validation. For this purpose, one patient was removed from the data set, the coefficients for the logistic regression were determined with the remaining data set and the logistic regression model was then applied to the previously removed patient. The AUC analysis was performed on this basis. Logistic regression was calculated with forward selection on the one hand and with all variables (histology, sonicate or microbiology, CRP and leukocytes) on the other. The stated coefficients for the logistic regression models with all variables are based on the entire data set (without leave-one-out cross-validation). The difference in AUCs in the logistic regression models was calculated using a two-sided DeLong's test. Statistical analysis was performed with the statistics software R version 4.2.3 or with SPSS version 29.0.1.0.

Results

Patient characteristics

A total of 140 patients with suspected PJI were included in the study. Of these patients, 78 cases were defined as PJI / or possible PJI according to the consensus recommendation, with 42 patients fulfilling the major criteria (Table 2). Of these infections, 11 were defined as early infections (within four weeks after joint replacement surgery); 34 patients were receiving antibiotic therapy on admission. The remaining patients (n = 62) were defined as aseptic controls.

The age structure of patients with aseptic or septic revisions was comparable (p = 0.97), the mean age was

Table 2 Demographic data, risk factors, laboratory parameters and clinical course in patients with PJI and aseptic controls

Parameters	Aseptic controls n = 62	PJI n = 78	p
Age, years (range) gender n (%)	72.4 (49 – 91)	72.5 (48 – 88)	0.97
male	29 (47)	39 (50)	0.62
Female	33 (53)	39 (50)	
Riskfactor, n (%)			
Diabetes	23 (37)	19 (24)	0.72
Adipositas	22 (36)	16 (21)	0.45
Renal insufficiency	16 (26)	7 (9)	0.07
Nicotin abuse	4 (7)	2 (3)	0.68
At least one risk factor	26 (42)	46 (59)	0.07
Hospital stay, days (range)	17.0 (4 – 75)	33.4 (8 – 137)	0.01
Hospital mortality, n	0	0	1.00
Antibiotics (on admission)	4 (6)	34 (44)	0.01
Major criteria (rate)	n.r	42 (54)	
joint n (%)			
hip	30 (48)	39 (50)	
knee	32 (52)	39 (50)	
CRP mg/l (range)	11.4 (1 – 72)	104.6 (1 – 484)	< 0.001
Leukocytes /nl (range)	7.8 (3.9 – 12.7)	9.5 (4.6 – 23)	0.01

72.5 years (Table 2). There is no difference in the gender distribution (p = 0.62). The mean length of stay for PJI was almost twice as long (33.4 d) as for aseptic changes (17 d; p = 0.01).

Influence of risk factors on the detection of a PJI

When analysing the risk factors for a PJI, diabetes (p = 0.72, 95%CI 0.53—2.57), obesity (defined with a body mass index > 25) (p = 0.45, 95%CI 0.61—3.14), renal insufficiency (p = 0.07, 95%CI 0.85—7.40) and nicotine abuse (p = 0.68, 95%CI 0.26—21.39) showed no significant influence. In the PJI group, at least one risk factor was found in 59% of the patients compared to 42% in the control group (p = 0.07).

Microbiological identification and microbes spectrum after using sonication of removed endoprosthetic material and conventional culture from tissue samples (Fig. 1)

In the PJI group, the most common microorganisms detected by sonication were Staphylococcus (S.) epidermidis (n = 20 (25.6%)), followed by S. aureus (14 (17.9)) and Streptococci (Str.) (11 (14.1)). The most common germs in the conventional culture of tissue samples were S. aureus (15 (19%))

Fig. 1. Bacterial spectrum in PJI after performing sonication or conventional culture of biopsies for microbiological diagnostics. High rates of microbial cultures without growth between 21.8 and 32% were obtained (no growth).
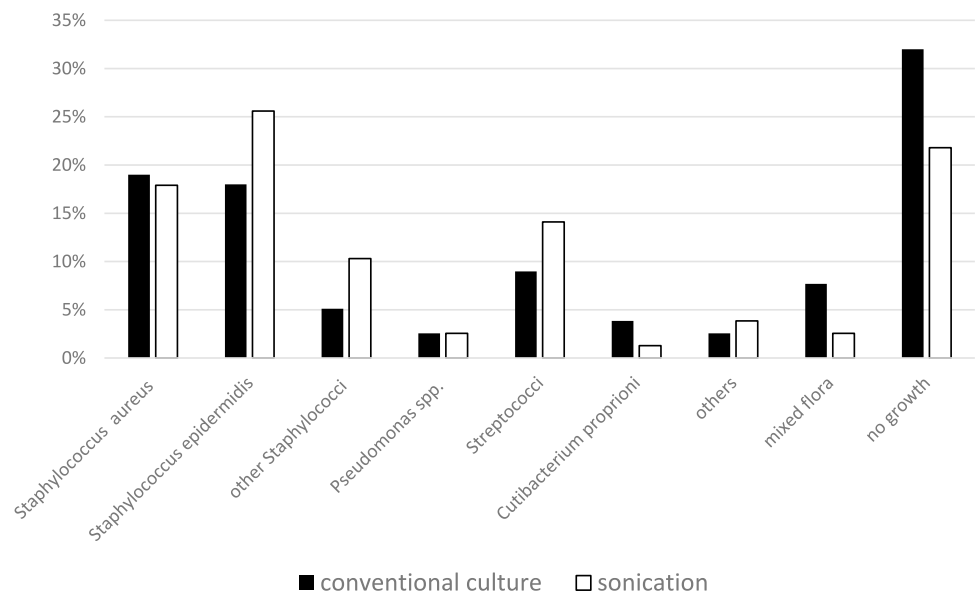
and S. epidermidis (14 (18), followed by streptococci (7 (8.9)). Overall, 21.8% of the cases remained undetected after sonication and 32% after conventional culture of biopsy material.

In the aseptic control group, 75.8% of the sonicates and 91.9% of cultured biopsies have shown no growth after cultivation. So, most common germ particular found after sonication was Cutibacterium cutis (n = 7 (11.3%)).

Results of non-specific inflammatory markers (CRP and leukocytes) in PJI and controls

The concentrations of CRP and the leukocyte count in the peripheral blood of patients with PJI were significantly higher than in the controls (CRP: $p < 0.001$, leukocytes $p = 0.010$) (Table 2).

Significance of histology, sonication method, conventional culture from tissue samples and non-specific inflammatory markers (CRP, leukocytes) in PJI

To clarify the question of the importance of histology compared to sonication and culture from tissue samples, logistic regression (leave-one-out method) was calculated (Fig. 2): in one model, the diagnostic criteria histology, sonication, leukocytes, CRP were used for the calculation; in the other model, the results of conventional culture from biopsies were included instead of sonication. The first model resulted in an Area Under the Curve (AUC) of 0.92, 95% CI 0.87—0.97, whereby only histology ($p < 0.001$) was a significant parameter in the diagnosis of PJI (sonication $p = 0.78$, CRP $p = 0.35$, leukocytes $p = 0.21$). The model with conventional

culture instead of sonication showed an AUC of 0.96, 95% CI 0.92—0.99. Here, histology ($p < 0.001$) and the conventional culture method ($p = 0.01$) were significantly associated with the diagnosis of PJI (for CRP $p = 0.25$, leukocytes $p = 0.12$ were calculated). The difference between the AUCs was significant ($p = 0.0544$).

The statistical indices sensitivity / specificity, negative predictive value (NPV) and positive predictive value (PPV) for the presence of a PJI for the parameters histology, conventional culture from biopsies, sonication method, CRP (calculated for the cut off concentrations 5 / 100 mg/L) and leukocytes (cut off 10 / nL) can be found in Table 3. Histology method defined as minor parameter has been found the most sensitive and specific parameter for diagnosing PJI. Sonication of explanted endoprothetic material compared to the conventional culture of biopsies has a higher sensitivity albeit with a lower specificity in diagnosing PJI.

Discussion

The diagnosis of PJI is a multiparameter diagnosis in everyday clinical practice. The present study on the value of the individual diagnostic criteria for PJI showed that histology was superior to conventional culture of biopsies and sonication method in terms of significance, sensitivity and specificity; the inflammatory parameters CRP and leukocytes in peripheral blood were only diagnostic parameters of second choice, depending on the cut-off. The ICM and IDSA criteria used to diagnose PJI did not show any differences in the present study, nor did the evaluation of individual risk factors such as diabetes mellitus, obesity, renal insufficiency and nicotine abuse

Fig. 2. Performance of two logistic regression models and calculation of the AUC to evaluate the significance of the individual diagnostic parameters in the context of multi-parameter diagnostics of PJI: in the first model (**A**), the parameters histology, conventional cultures of biopsies, leucocytes and CRP were taken into account, in the second model (**B**), sonication was used in place of the conventional culture. In both models, a high AUC of 0.96 (**A**) and 0.92 (**B**) was achieved, which differed significantly (p = 0.054). In principle, both multiparameter models are suitable for the diagnosis of PJI. The highly significant importance of histology in the diagnosis compared to all other parameters is also evident here.

A.

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-5.780	1.795	-3.219	0.001
Histology	4.342	0.791	5.488	< 0.001
Conventional culture	2.006	0.808	2.480	0.013
CRP	0.009	0.008	1.145	0.252
Leukocyte	0.300	0.190	1.575	0.115

AUC: 0.96, 95% CI: [0.92,0.99]
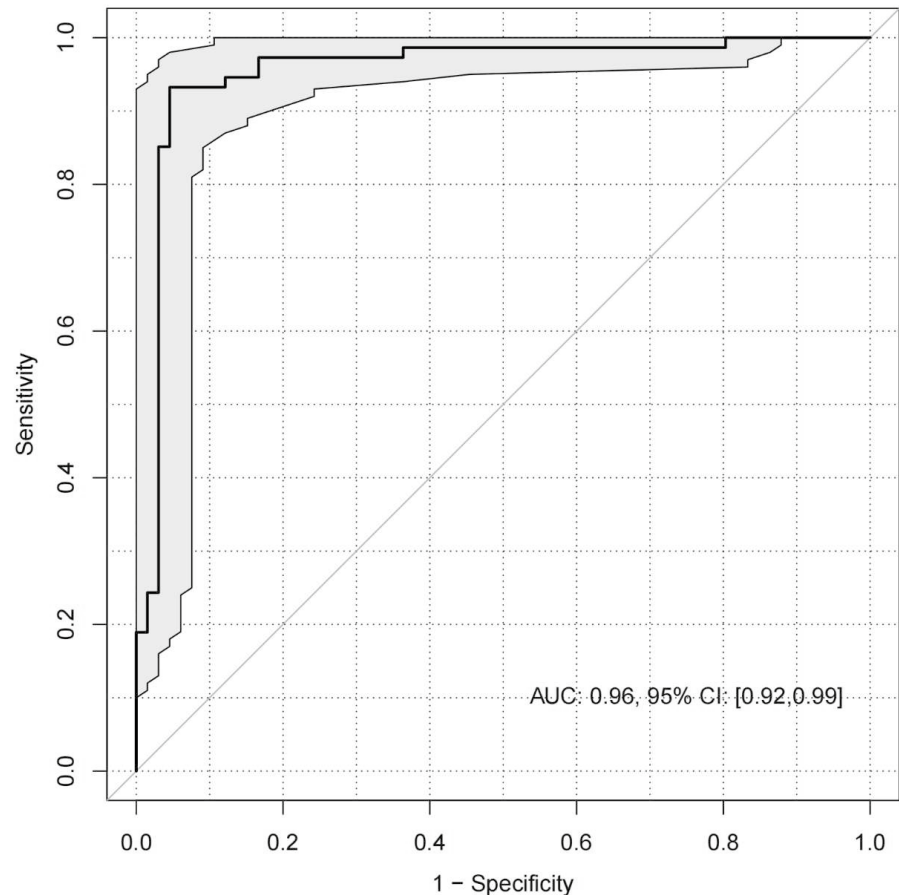
reveal any particular risk constellations for PJI. The bacterial spectrum we determined (11 early, 67 late infections) largely corresponded to the bacterial spectrum known from the literature with frequent detection of coagulase-negative staphylococci and *Staphylococcus aureus* [16–20].

The identification of germs from periprosthetic biopsies or from sonicates with consecutive resistance testing is the basis for the optimal treatment of a PJI. Whether one of the two methods is superior in terms of sensitivity and specificity for the diagnosis of a PJI is the subject of a number of studies with controversial results [14, 16, 21–27: the studies by Dudareva et al. [28] and Ribeiro et al. [24] with a design comparable to our study showed comparable sensitivities of sonication and microbiology; however, the

authors recommended sonication only as a supplement to microbiology due to its significantly poorer specificity. In the authors' opinion, sonication could have added value in special infection constellations with a lower bioburden (patients who have been pre-treated with antibiotics, late infections > 24 months after implantation). The study by Ribeiro also made it clear that the sensitivity and specificity of the microbiological examination methods were significantly dependent on the respective diagnostic criteria used for a PJI (IDSA [7], ICM [8] or EBJIS [29]). In the work by Rothenberg [17], sonication showed a comparable specificity compared to classical microbiology with high sensitivity; the high specificity was achieved here in particular in samples with a high bioburden of > 5 CFU/

Fig. 2. (continued)

B.

	Estimate	Std. Error	z value	Pr(>|z|)
(Intercept)	-4.743	1.632	-2.906	0.003
Histology	4.826	0.906	5.323	< 0.001
Conventional culture	0.234	0.848	0.276	0.782
CRP	0.007	0.008	0.931	0.351
Leukocyte	0.223	0.177	1.261	0.207
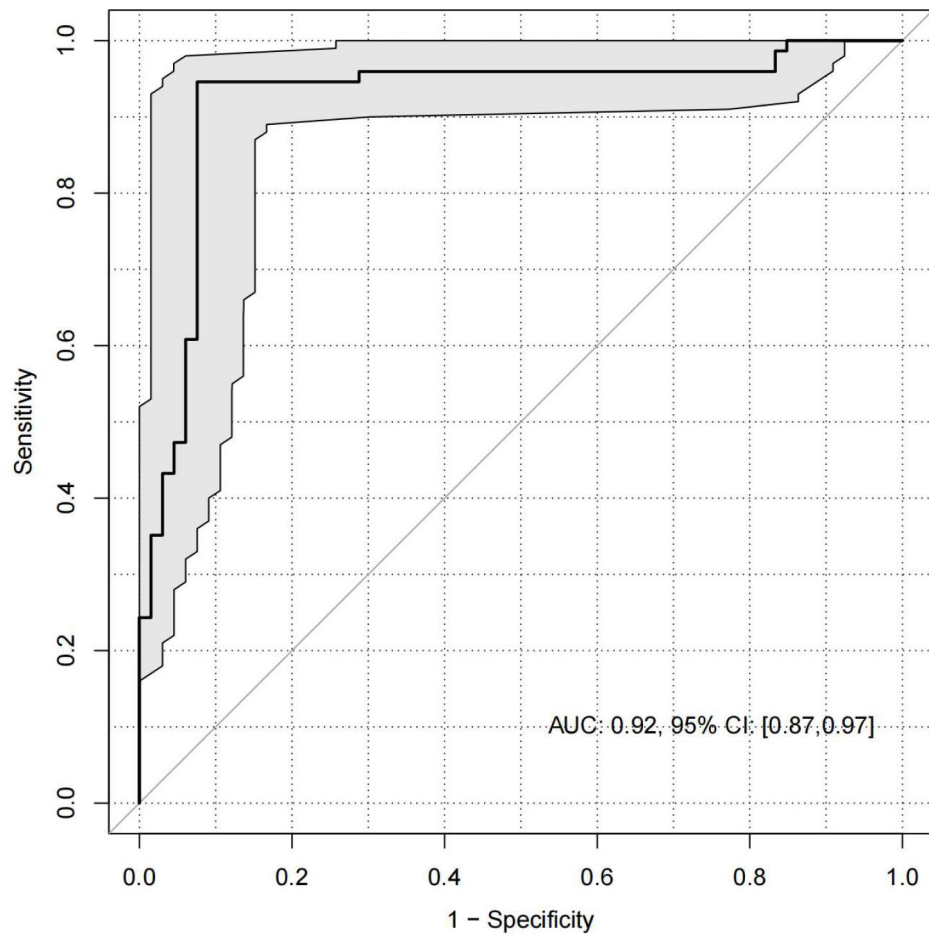
ml. In our opinion, the question of evaluating sonication by including a threshold value—as in Rothenberg's work—has not yet been sufficiently investigated. For these reasons, no threshold value was considered in the evaluation of the results in our study either. The definition of a threshold value could lead to an improvement in specificity, as sonication is more susceptible to contamination due to several diagnostic steps. The differences in sensitivity and specificity between microbiology and sonication are certainly also due to the fact that both procedures are not standardised.

Few studies on multiparameter diagnostics of PJI have so far included the significance of histology in the diagnosis of PJI [30, 31, 32]: our data show better sensitivity (0.95) and specificity (0.92) of histology in the diagnosis of PJI compared to sonication and microbiology. Also, our two logistic regression models including all investigated diagnostic parameters show that histology is a highly significant diagnostic parameter, regardless of whether conventional culture of biopsies was introduced as a major criterion or whether sonication was included in the model. In his publications [30, 31], Müller et al. also described a comparably high sensitivity and specificity for histology, which correlated well with the results of intraoperative bacterial detection (however, sonication of endoprosthesis material was not

Table 3 The sensitivity / specificity, the negative predictive value (NPV) and the positive predictive value (PPV) were calculated for the parameters histology, sonication, conventional culture from biopsy, CRP and leucocytes for the presence of a PJI. For the unspecific inflammatory marker CRP, a cut-off of 5 mg/L (elevated level) or 100 mg/L (indication of a PJI) and for leukocytes 10 / nl (elevated level) were used as the basis for calculation

	Sensitivity	Specificity	NPV	PPV
Histology	0.95	0.92	0.94	0.93
Conventional culture	0.70	0.88	0.72	0.86
Sonication	0.80	0.74	0.77	0.78
CRP				
> 5 mg/L	0.92	0.44	0.83	0.65
> 100 mg/l	0.35	0.97	0.57	0.93
Leukocytes	0.30	0.86	0.55	0.68
> 10 / nl				

performed in the studies by Müller et al.) In the study by Tani et al. [32], the sensitivity of histopathological examination was comparable to that of sonication (72 vs. 77%), but significantly better than that of conventional culture from biopsy material (55%). Based on the current study and the studies described above, it could be concluded that the histological examination of periprosthetic biopsies should be given greater importance in the diagnosis of PJI. Particularly in view of the high rate of negative microbiological evidence, histology appears to be a reliable instrument in the multi-parameter diagnosis of PJI and clearly superior to the non-specific inflammatory parameters CRP and leukocytes.

The use of CRP and leukocytes from peripheral blood in the diagnosis of PJI would only play a subordinate role due to the sensitivities and specificities we have determined: Although both parameters are inexpensive in routine diagnostics and easy to determine due to their low invasiveness, they are very susceptible to interference in antibiotic-pretreated patients (44% of our patients were on antibiotics on admission) [33], depending on the type of infectious agent [34] and due to non-specific increases caused by co-morbidities such as autoimmune diseases or other acute/chronic inflammations. Leukocyte / CRP detection from synovial fluid [35, 36] or the use of new inflammatory parameters such as calprotectin [37] may be more suitable here.

Several studies have shown that patients with certain underlying diseases or risk factors (diabetes, obesity, renal insufficiency, nicotine) develop a higher risk of PJI after joint replacement surgery [38–43]. We were unable to determine this for individual risk factors in our study, but our patients with PJI also tended to have a more critical risk profile.

The added value of the present study certainly lies in the fact that the significance of histology was reassessed. One limitation for the interpretation of the data is certainly the limited number of patients analysed and the monocentric design. When evaluating the statistics, it must also be taken into account that parameters relating to the diagnosis of a PJI were included that are themselves part of the PJI definition. Our slightly modified criteria for histopathological diagnosis of the periprosthetic infection might represent further limitation of the current study. Although we use a more conservative citeria for the diagnosis of PJI in our institution (3 or more neutrophils/1 HPF or 5 and more neutrophils/5 HPF) when compared with the EBJIS 2021 criteria (5 or more neutrophils/1 HPF or 5 and more neutrophils/5 HPF [29] for routine diagnostics, we believe our data are comparable with other European groups. Even though there is some uncertainty about the exact number and localization of the histopathological specimens, we analyzed comparable numbers of specimens with other researchers [44] and believe that our data might help to better understanding of the pathogenesis and diagnostics of PJI.

Concluding from our data, histology seems to have the most significant role among the multiparameter diagnostic of PJI and should be reevaluated particularly in view of the high rate of negative microbiological finding. Sonication lacks standardization, is labor-intensive and in our study showed no advantage over the microbiological culture of biopsies. It should therefore by no means replace conventional microbiology, but in individual cases it may represent a supplementary diagnostic method. In our view, CRP and leukocytes in peripheral blood as criteria are dispensable when histology is available.

Declarations

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