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PCR-Based Diagnosis of Prosthetic Joint Infection

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We performed a meta-analysis to evaluate use of PCR assays for diagnosis of prosthetic joint infection (PJI). The pooled sensitivity and specificity were 0.86 (95% confidence interval [CI], 0.77 to 0.92) and 0.91 (CI, 0.81 to 0.96), respectively. Subgroup analyses showed that use of tissue samples may improve sensitivity, and quantitative PCR and sonication of prostheses fluid may improve specificity. The results showed that PCR is reliable and accurate for detection of PJI.

Prosthetic joint infection (PJI) is one of the most common complications of total joint arthroplasty, with an incidence of 1 to 12%, and it always has catastrophic consequences (1, 2). The distinction between PJI and other causes of joint failure, such as aseptic loosening, is frequently difficult and still challenging. Several studies have assessed the diagnostic value of PCR techniques for diagnosing PJI. However, the true diagnostic capabilities of PCR assays remain controversial. Therefore, the aim of our study was to perform a meta-analysis to evaluate the detection validity of PCR in the diagnosis of PJI.

We searched MEDLINE, EMBASE, and OVID for articles that were published between January 1990 and February 2013, using the following medical subject headings (MeSH) or free text words: (i) joint prosthesis, prosthesis infection, septic loosening, aseptic loosening, replacement, or arthroplasty and (ii) PCR. We also manually searched the reference lists of eligible studies and review articles. Our reviewers independently evaluated the selected studies using the following inclusion criteria: (i) the study reported the accuracy of PCR for the diagnosis of joint infection in comparison with visible purulence of joint aspirate or surgical site, presence of a sinus tract (fistula) communicating with the prosthesis, acute inflammation in histopathology sections of periprosthetic tissue, or simultaneously obtained microbiologic cultures from at least two periprosthetic tissue samples (the reference standard); (ii) sufficient data were reported to allow us to calculate the true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) values; (iii) the study reported evaluations of at least 10 patients, from which data could be extracted using our standardized data collection form (X. Qu and Z. Zhai). Discrepancies were resolved by discussion with other investigators and by consulting the original articles (Huiwu Li and K. Dai). We estimated the sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) of summary receiver operating characteristic (ROC) curves to evaluate the capability of PCR assays for diagnosing PJI. We performed meta-regression and subgroup analyses to assess potential heterogeneity, and we constructed Deeks' funnel plot asymmetry test to evaluate potential publication bias. All of the statistical analyses were undertaken using STATA version 11 (StataCorp, College Station, TX).

Our research yielded 2,024 primary studies. Of these, 1,834 were excluded after reviewing the title and abstract, and 190 were excluded after reviewing the full article. A total of 14 articles (3–16) (that included 1,480 patients in total) fulfilled all of the inclusion criteria and were included in the analysis (Table 1; see also Table S1 in the supplemental material). Twelve studies reported patients with FP results. Eight studies used fresh samples, and five used frozen samples. Nine studies detected PJI of multiple joints, two each detected PJI of the hip and knee, and one detected PJI of the shoulder. Eight studies enrolled patients prospectively. Patient enrollments were consecutive in seven studies and were not documented in another seven. We found significant heterogeneity among all test performances.

The pooled sensitivity, specificity, PLR, NLR, DOR, and AUC estimates for the detection of PJI using PCR were 0.86 (95% confidence interval [CI], 0.77 to 0.92), 0.91 (CI, 0.81 to 0.96), 9.1 (CI, 4.6 to 18.2), 0.16 (CI, 0.10 to 0.25), 59 (CI, 29 to 118), and 0.94 (CI, 0.91 to 0.95), respectively (Fig. 1). The regression test of asymmetry found no evidence of a small-study effect for PCR ($P = 0.64$) (see Fig. S1 in the supplemental material). In subgroup analyses, the test performances varied by study design, sample type, sonication of samples, type of PCR, and reference standards (Fig. 2). The sensitivity and specificity of the tissue samples were 0.95 (CI, 0.91 to 0.99) and 0.81 (CI, 0.66 to 0.90), the sensitivity and specificity of the synovial fluid samples were 0.84 (CI, 0.75 to 0.93) and 0.89 (CI, 0.81 to 0.97), and those of the sonicated prostheses fluid samples were 0.81 (CI, 0.71 to 0.91) and 0.96 (CI, 0.92 to 1.00), respectively. Use of multiple reference standards had the lowest sensitivity, at 0.77 (CI, 0.69 to 0.85), and the highest specificity, at 0.96 (CI, 0.92 to 0.99). Compared with nonquantitative PCR, quantitative PCR had a higher specificity of 0.94 (CI, 0.88 to 1.00) ($P < 0.05$). The sensitivity and specificity of the fresh samples were 0.89 (CI, 0.82 to 0.96) and 0.91 (CI, 0.82 to 0.99), and those of the frozen samples were 0.81 (CI, 0.70 to 0.92) and 0.90 (CI, 0.79 to 1.00), respectively.

Overall, in this meta-analysis we found that PCR has adequate diagnostic value for the detection of PJI. It was estimated that, in

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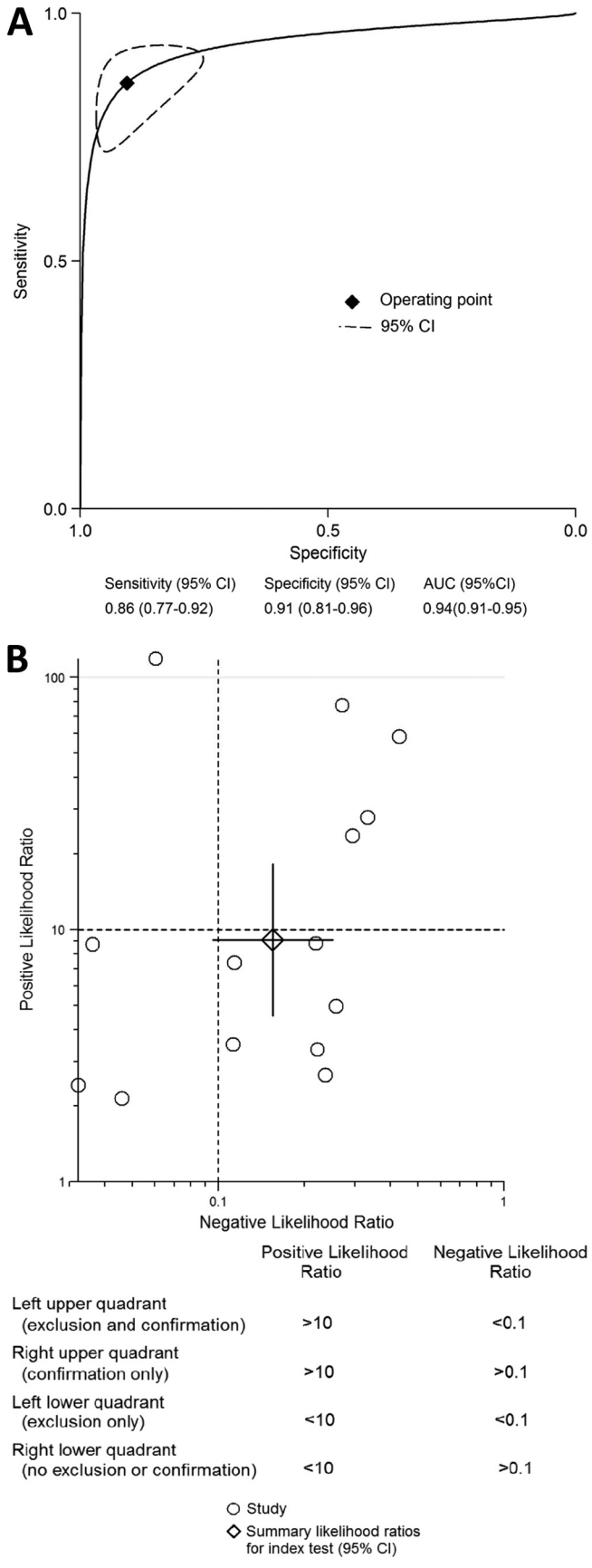
TABLE 1 Characteristics of the 14 reports in our meta-analysis of the diagnosis of PJI based on PCR[a]

Study (reference)	Country	No. of patients	Mean age (yrs)	Study design, enrollment	Sample type	Sample condition	Sample site(s)	PCR type	Target gene	Diagnostic criteria of PJI
Portillo et al., 2012 (15)	Spain	86	73	Prospective, consecutive	Sonicated PF	Fresh	Hip, knee, elbow, and shoulder	RT multiplex PCR	NA	IOF, M
Marín et al., 2012 (11)	Spain	122	72	Prospective, NA	BS or SFS	Fresh	Hip, knee, elbow, and shoulder	PCR	16S rRNA gene	IOF, H
Jacovides et al., 2012 (7)	United States	80	67	Prospective, consecutive	SFS	Frozen	Hip and knee	PCR	16S rRNA gene	IOF, M
Gomez et al., 2012 (6)	United States	366	66	Retrospective, NA	Sonicated PF	Frozen	Hip and knee	RT-qPCR	16S rRNA gene	IOF, H
Esteban et al., 2012 (4)	Spain	75	66	NA, consecutive	Sonicated PF	Frozen	Hip and knee	RT-PCR	16S rRNA gene	M
Bergin et al., 2010 (3)	United States	64	NA	Prospective, consecutive	SFS	NA	Knee	RT-qPCR	16S rRNA gene	IOF, H, M
Piper et al., 2009 (11)	United States	134	65	NA, NA	Sonicated PF	Frozen	Shoulder	RT-qPCR	S probes; P 16S rRNA gene	IOF, H
Kobayashi et al., 2009 (8)	Japan	24	NA	Prospective, consecutive	BS	Fresh	Hip and knee	RT-qPCR	16S rRNA gene	M
Kobayashi et al., 2008 (9)	Japan	54	NA	Prospective, consecutive	BS	Fresh	Hip and knee	RT multiplex qPCR	S and P probes	M
Gallo et al., 2008 (5)	Czech Republic	101	66	Prospective, NA	SFS	Fresh	Hip, knee, and elbow	PCR	16S rRNA gene	IOF, H, M, R
Moojen et al., 2007 (12)	Netherlands	76	NA	Retrospective, NA	BS	Fresh	Hip	qPCR	16S rRNA gene	IOF, H, M, R
Panousis et al., 2005 (13)	United Kingdom	91	66	Prospective, consecutive	SFS	Fresh	Hip and knee	Broad-range PCR	16S rRNA gene	IOF, M
Tunney et al., 1999 (16)	United Kingdom	119	NA	NA, NA	BS	Fresh	Hip	PCR	16S rRNA gene	M
Mariani et al., 1996 (10)	United States	50	NA	NA, NA	SFS	Frozen	Knee	PCR	16S rRNA gene	M

[a] Abbreviations: PF, prosthesis fluid; BS, biopsy sample; SFS, synovial fluid sample; RT, real time; qPCR, quantitative PCR; P, *Propionibacterium*; S, *Staphylococcus*; H, histological examination; IOF, intraoperative finding; M, microbiological or laboratory examination; R, radiological examination; NA, not available.



current practice, the sensitivity and specificity of PCR are approximately 86% and 91%, respectively.

Because of the absence of highly accurate diagnostic methods, the gold standard for diagnosis of PJI is still controversial among clinicians (17). Intraoperative tissue culture has historically been used as the gold standard in most hospitals, although several other tests are available (17). However, the results of culture do not have optimal sensitivity or specificity and are sometimes difficult to interpret, especially when few samples are analyzed (11). The sensitivity of culture ranges from 0.7 to 0.9, and the specificity ranges from 0.75 to 0.95 (3, 11, 17–20). In recent years, PCR methods for the diagnosis of PJI have been investigated and have received much attention. Compared to intraoperative tissue culture, PCR theoretically has higher sensitivity, a faster turnaround time, and is not as affected by treatment (21). Guidelines for PJI by the American Academy of Orthopaedic Surgeons and the Infectious Diseases Society of America recommend further "high evidence"-based studies to assess the diagnostic value of PCR (22, 23).

Our results showed that PCR is another diagnostic method that has an equivalent or better diagnostic value to that of intraoperative tissue culture and may add important insight into the diagnosis of PJI. However, the main problem in the diagnosis of PJI is recovery of bacteria from the samples. Whether relying on intraoperative tissue culture or PCR, the bacterial recovery from the samples is always one of the most important aspects in the diagnosis of PJI. In this meta-analysis, there were three types of samples for PCR: tissue samples, synovial fluid samples, and sonicated prostheses fluid samples. Our subgroup analyses showed that use of tissue samples may improve sensitivity and that sonication of prostheses fluid samples may improve specificity. However, none of the sampling methods can satisfy both increased sensitivity and increased specificity concurrently. Perhaps vortexing of tissue samples by using sonicated prostheses fluid may offer an additional insight into the improvement of sensitivity and specificity concurrently in the diagnosis of PJI.

Moreover, the number of samples taken for PCR may impact the diagnostic sensitivity and specificity of PCR (11). Marín et al. showed that when only considering the number of positive samples, a PCR-positive result in one sample had good specificity and a positive predictive value for PJI (specificity, 0.96; positive predictive value, 0.92). The best combination of results for PCR was observed when 5 samples were studied and the same microorganism was detected in 2 of them (sensitivity, 0.94; specificity, 1.00) (11). In addition, in our meta-analysis, there were 80 false-negative results from 12 studies. Most of the included studies explained that the false-negative resulted from the patient receiving antibiotics previous to sampling (3, 5–8, 11–15).

Compared to intraoperative tissue culture, PCR is expensive and involves complex techniques. To assess the value of PCR, cost-effectiveness studies should be conducted. Furthermore, we must highlight that PCR can serve as a valuable additional tool for diagnosing PJI, but it cannot replace intraoperative tissue culture, since the antibiotic susceptibility testing included in the tissue culture method is highly important for adequate treatment.

FIG 1 Summary ROC curves (A) and likelihood ratio scattergram (B) for PCR. Curves include a summary operating point for sensitivity and specificity on the curve and a 95% confidence contour ellipsoid. The likelihood ratio profile shows that PCR is a potent tool for ruling out PJI in this patient population.

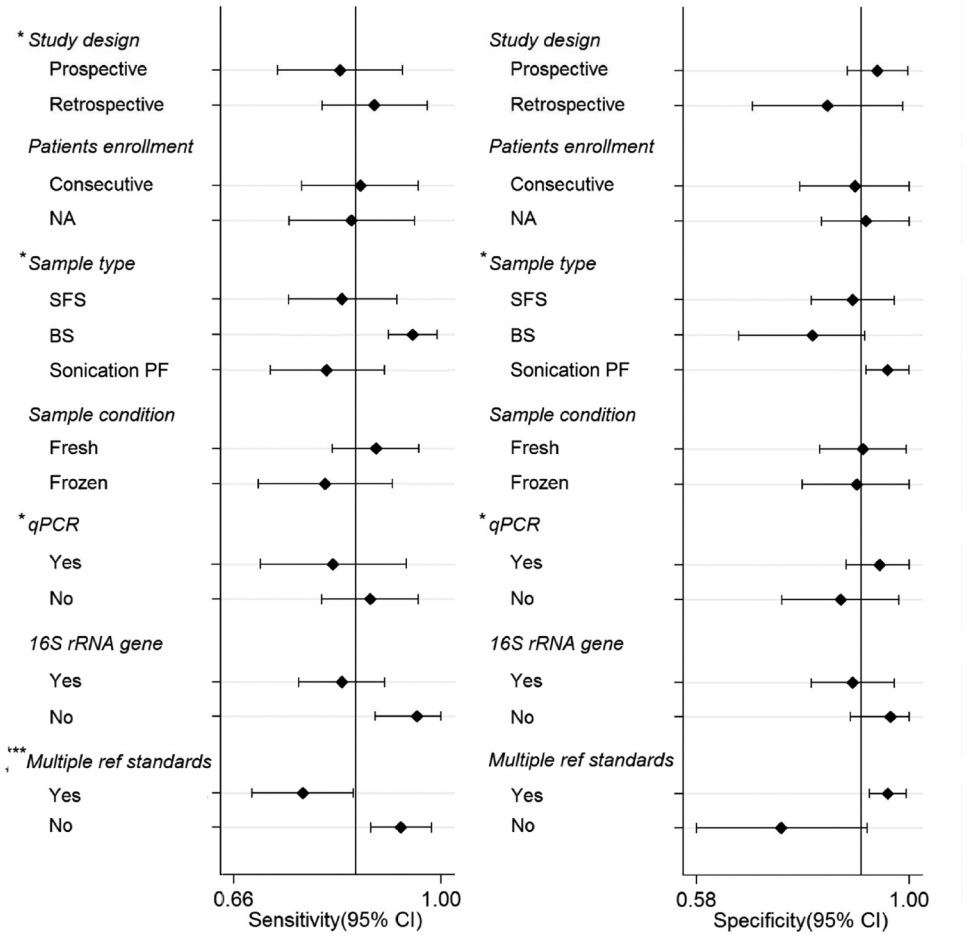


FIG 2 Forest plots of subgroup analyses of sensitivity and specificity. BS, biopsy sample; SFS, synovial fluid sample.

Our study had some limitations. First, there was no established gold standard, which is a universal drawback to all studies assessing PCR procedures for diagnostic accuracy in the detection of PJI. In this meta-analysis, the reference standards of the included studies varied. We performed subgroup analysis and examined reference standards as possible sources of heterogeneity. Second, not all studies explicitly stated whether they were performed in a prospective manner. Subgroup analysis showed that a prospective study design as a covariate in the bivariate statistical model may have significantly influenced the sensitivity. Third, the summary results of this meta-analysis had high statistical heterogeneity. The heterogeneity had multiple sources, including study design, sample type, sonication of samples, type of PCR, and reference standards, which may have led to an overestimation of the true diagnostic performance.

In summary, this meta-analysis of diagnostic accuracy demonstrated that PCR has an adequate diagnostic value for the detection of PJI, with a sensitivity of 86% and specificity of 91%, which is acceptable for clinical practice. Future studies should assess the cost-effectiveness of this test.

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We have no conflicts of interest to declare.

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