Advantages of 16S rRNA PCR for the diagnosis of prosthetic joint infection

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Abstract. 16S ribosomal RNA (rRNA) PCR has been reported to be an effective diagnostic means in patients with prosthetic joint infection (PJI). The aim of the present meta-analysis is to establish the overall diagnostic accuracy of the measurement of 16S rRNA PCR for diagnosing PJI. PubMed, Web of Science, Cochrane Library, EMBASE and Wiley Online Library were searched for studies on 16S rRNA PCR in the diagnosis of PJI. The search incorporated all literature published up until December 2018 and the QUADAS-2 checklist were used for quality assessment. The sensitivity, specificity and other measures of accuracy of 16S rRNA PCR in the diagnosis of PJI were pooled. Statistical analysis was performed by employing Meta-Disc 1.4 and Stata 12.0 software. A total of 15 studies met the inclusion criteria. The summary estimates for 16S rRNA PCR in the diagnosis of PJI in these studies were pooled: Sensitivity, 0.70 (95% CI, 0.67-0.73); specificity, 0.93 (95% CI, 0.91-0.94); positive likelihood ratio, 10.93 (95% CI, 5.55-21.51); negative likelihood ratio, 0.33 (95% CI, 0.28-0.40); diagnostic odds ratio, 41.77 (95% CI, 19.90-87.68); and the area under the curve, 0.89. Subgroup analysis showed that the use of sonicate fluid and periprosthetic tissue has higher sensitivity (0.76; 95% CI, 0.69-0.82; and 0.73; 95% CI, 0.68-0.78, respectively), specificity (0.93, 95% CI, 0.90-0.96; and 0.95; 95% CI, 0.90-0.98, respectively) and area under the curve (0.93 and 0.98, respectively). 16S rRNA PCR assay plays an important role in the diagnosis of PJI. The results of 16S rRNA PCR assays should be interpreted in parallel with clinical findings, the results of microbiological, and other laboratory tests.

Introduction

Total joint arthroplasty is a safe and effective method that dramatically improves quality of life and restores the function of the patient with arthritis of the hip and knee (1-4). Although its general success is beyond dispute, postoperative complications still accrue, including prosthetic joint infection (PJI), which is an important cause of implant failure and revision arthroplasty should be carried out in most of the cases (5-9). The financial cost is estimated at U.S. $96,166 per patient requiring revision arthroplasty for infection, which is 4.8 times the cost of a primary arthroplasty (10,11). Due to its insidious onset, early and accurate diagnosis is crucial. Late diagnosis is known to decrease the chance of saving the prosthesis and the joint function, leading to more bone destruction and difficulty in revision surgery (12). Since currently there is no diagnostic gold standard for the identification of PJI, diagnosis is currently based on clinical signs, laboratory and microbiological tests, histopathology and imaging studies (10,13-17). However, aseptic prosthetic loosening may present with similar symptoms as PJI and similar imaging features, which often leads to incorrect diagnosis (18). So, diagnosis of PJI remains a clinical challenge (19).

Laboratory tests including C reactive protein, erythrocyte sedimentation rate, white blood cells count and gram staining are currently recommended but are not specific, particularly for the early stage of infection (20,21). In the past two decades, new molecular techniques have been applied to PJIs to increase the diagnostic yield including utilizing polymerase chain reaction (PCR) (22). Bacterial ribosomal RNA (rRNA) PCR is reported to be a rapid and more sensitive tool for microbiological diagnosis in most studies, while other studies yielded controversial results (20,23). Previous meta-analysis studies have few references and comparatively little evidence (24). In the present study, new contents were added on the basis of previous studies, including the new studies in the past five years, patients and subgroup analysis. Furthermore, the inclusion criteria were reformulated (16S rRNA was selected as the...
target gene for diagnosis of PJI), and studies using other genes were excluded. Therefore, the purpose of the present study was to perform a meta-analysis to establish the overall diagnostic accuracy of 16S rRNA PCR assays for diagnosing PJI.

Materials and methods

Search strategy. A systemic search of the English medical literature of using 16S rRNA PCR in diagnosis of PJI published between January 1980 and December 2018 was performed. The data collection and reporting was in line with the Preferred Reporting Items for Meta-Analyses (PRISMA) Statement (25). Databases including PubMed (www.ncbi.nlm.nih.gov/pubmed), Web of Science (www.webofknowledge.com), Cochrane Central Register (www.cochranelibrary.com), EMBASE (www.embase.com) and Wiley Online Library of Controlled Trials (onlinelibrary.wiley.com) were used. The search strategy was based on the combination of the terms: i) ‘PCR’ or ‘polymerase chain reaction’, ‘reverse transcription-PCR’, ‘real-time PCR’; and ii) ‘prosthesis infection’ or ‘prosthetic joint infection’ or ‘septic loosening’. Searches were limited to human subjects. Moreover, these searches were supplemented with manual searches of references within the interested published articles to identify additional studies. When necessary, the authors were contacted for more information. Initially, there were no restrictions as to the form of publication in order to achieve a highly sensitive search. However, conference abstracts were excluded due to the limited data presented.

Inclusion criteria and exclusion criteria. Only studies meeting the following criteria were included in this meta-analysis: i) Written in English language; ii) 16S rRNA was the targeted gene in the diagnosis of PJI; iii) studies with definite clinical diagnosis of PJI: A sinus tract connected to the prosthesis, purulent fluid visible in the synovial fluid or surgical incision, microbiological cultures positive from at least two samples around the prosthesis and acute inflammation in the histopathological periprosthetic tissue sections; iv) sensitivity and specificity were provided or can be calculated; v) >10 patients or samples were included in the study.

Studies that fell under the following conditions were excluded from the present study: i) Studies presenting non-original data, conference abstracts, editorials, reviews, guidelines and studies conducted in animals were excluded; ii) studies with no definite clinical diagnosis of PJI and sensitivity and specificity cannot be determined; iii) PCR assay with other target genes in diagnosis of PJI.

Data extraction and quality assessment. Two authors (YZ and SFS) independently reviewed the titles and abstracts of the relevant articles in light of the inclusion criteria. When an article’s abstract fulfilled the criteria, the full text was reviewed. Any disagreement in the selection was resolved by a third author. The main elements extracted included the authors’ names, area, study design, clinical sample, study years, sex, blinded status, age, sex and number of patients. In order to evaluate the diagnostic performance, a 2x2 table including true-positive, false-positive, false-negative and true-negative were used for identifying PJIIs. These were derived from the data provided in the studies. The quality assessment was conducted on all of the included studies. The quality of the included studies was assessed using the diagnostic accuracy study quality tool (QUADAS-2) by Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration).

Statistical analysis. Recommended standard methods for diagnostic meta-analysis were used (26,27). Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration) was used for the quality evaluation and Meta-disc software was used for statistical analysis (version 1.4). Various indexes were calculated including sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CIs). A summary of receiver operating characteristic (SROC) curves was obtained to assess the overall performance of the tests by Meta-Disc 1.4. The area under the curve (AUC) displays the trade-off between sensitivity and specificity. An AUC of 1.0 indicates perfect discriminatory ability to distinguish cases from non-cases. The SROC and AUC range between 0 and 1, with higher values indicating a better test performance (28,29). Statistical heterogeneity was determined by chi-square test and F. Meta-regression and subgroup analyses were performed to assess potential heterogeneity and Deeks’ funnel plot was used to evaluate the publication bias analyzed with Meta-Disc 1.4 and Stata 12.0 (StataCorp LLC). All statistical tests were two-sided, P<0.05 was considered to indicate a statistically significant difference.

Results

Following independent reviews of the title, abstract and the full text, a total of 14 English language publications (Fig. 1) of studies on 16S rRNA expression for the diagnosis of PJI were included in the present meta-analysis, based on the aforementioned inclusion and exclusion criteria. A publication
Table I. Details of the 15 studies included in the present meta-analysis.

| Study, author and year (Refs) | Country     | Data collection | Study design | Biological sample | Center         | Blinded status | Age, years | Sex (m/f) | Septic | Aseptic |
|------------------------------|-------------|-----------------|--------------|-------------------|----------------|----------------|------------|-----------|--------|---------|
| Bergin 2010 (48)            | USA         | NR              | Prospective  | Joint fluid       | Single-center | NR             | NR         | 14        | 50     |         |
| De Man 2009 (49)            | Switzerland | 2001-2005       | Retrospective| Joint fluid and   | Single-center | NR             | 53-80      | 13/13     | 12     | 17      |
| Esteban 2012 (35)           | Spain       | 2004-2009       | Retrospective| Sonicate fluid    | Multi-center  | NR             | 23-96      | NR        | 31     | 44      |
| Gallo 2008 (34)             | Czech Republic | 2003-2005     | Prospective  | Joint fluid       | Single-center | NR             | 35-80      | 72/42     | 35     | 66      |
| Gomez 2012 (36)             | USA         | 2006-2011       | Retrospective| Sonicate fluid    | Single-center | Yes            | 24-92      | 183/183   | 135    | 231     |
| Marin 2012 (37)             | Spain       | 2004-2007       | Prospective  | Joint fluid       | Single-center | Yes            | 33-92      | 86/36     | 176    | 321     |
| Panousis 2005 (23)          | UK          | NR              | Prospective  | Joint fluid       | Single-center | NR             | 24-85      | 35/56     | 12     | 80      |
| Vandercam 2008 (50)         | Belgium     | NR              | Prospective  | Intraoperative    | Single-center | Yes            | 41-82      | 21/20     | 34     | 35      |
| Fang 2018 (38)              | China       | 2014-2016       | Prospective  | Joint fluid       | Single-center | Yes            | 47-78      | 20/51     | 38     | 33      |
| Rak-PT 2016 (30)            | Slovenia     | 2011-2016       | Prospective  | Periprosthetic     | Single-center | Yes            | 29-88      | 21/46     | 29     | 58      |
| Rak-SF 2016 (30)            | Slovenia     | 2011-2016       | Prospective  | Sonicate fluid    | Single-center | Yes            | 29-88      | 21/46     | 29     | 58      |
| Fink 2018 (45)              | Germany     | 2016-2017       | Prospective  | Joint fluid       | Single-center | Yes            | 41-91      | 55/61     | 27     | 89      |
| Bemer 2014 (51)             | France       | 2010-2012       | Prospective  | Periprosthetic     | Multi-center  | Yes            | 63-79      | 127/137   | 215    | 49      |
| Stylianakis 2018 (52)       | USA          | 2011-2015       | Prospective  | Joint fluid       | Single-center | Yes            | 49-90      | 32/82     | 27     | 70      |
| Morgenstern 2018 (53)       | Germany      | 2014-2015       | Prospective  | Joint fluid       | Single-center | Yes            | 32-92      | 54/88     | 77     | 65      |

NR, not reported; PT, periprosthetic tissue; SF, sonicate fluid.
by Rak et al (30) used sonication on fluid and tissue samples for the diagnosis of PJI. A total of 15 studies included in the 14 publications enrolled 2,070 patients with an age range of 23-96 years. Table I presents baseline characteristics of these studies including clinical characteristics of the patients. Table II shows true-positive, false-positive, false-negative and true-negative of the 15 studies.

A graphical summary of the methodological assessment based on QUADAS-2 quality assessment for the included studies is illustrated and all the included studies demonstrated a relatively low risk of bias and applicability concern (Fig. 2). Significant heterogeneity among studies was detected by sensitivity (I²=61.1%), specificity (I²=88.6%, Figs. 3 and 4). This indicates significant heterogeneity between studies. The Spearman correlation coefficient was 0.082 (P=0.771), which indicated that the heterogeneity was not caused by threshold effects between the included studies.

The pooled analysis revealed: Sensitivity, 0.70 (95% CI 0.67-0.73); specificity, 0.93 (95% CI 0.91-0.94); PLR, 10.93 (95% CI 5.55-21.51); NLR, 0.33 (95% CI 0.28-0.40); and DOR, 41.77 (95% CI 19.90-87.68) (Figs. 3 and 4; Table III). The corresponding SROC (Fig. 5) shows an AUC of 0.89, and the pooled diagnostic accuracy is 0.82 with a standard error of 0.037, which indicates high overall accuracy of 16S rRNA PCR for PJI.

Due to the heterogeneity caused by the non-threshold effects between the included studies, a subgroup analysis was conducted to explore the possible sources of heterogeneity. Subgroup analysis was conducted according to the clinical sample, study design, center, blinded status and country (Table III). In the subgroup of the clinical sample, both sonicated fluids and periprosthetic tissues showed higher sensitivity (0.76, 95% CI 0.69-0.82; and 0.73, 95% CI 0.68-0.78, respectively).

Table II. Data showing true-positives, false-positives, false-negatives and true-negatives, the sensitivities, specificities and the DOR of the 15 studies.

| Study, author and year (Refs) | Tp | Fp | Fn | Tn | Sensitivity | Specificity | DOR |
|------------------------------|----|----|----|----|-------------|------------|-----|
| Bergin 2010 (48)             | 10 | 0  | 4  | 50 | 0.71        | 1          | 235.67 |
| De Man 2009 (49)             | 6  | 1  | 6  | 16 | 0.50        | 0.94       | 16   |
| Esteban 2012 (35)            | 26 | 14 | 5  | 30 | 0.84        | 0.68       | 11.14 |
| Gallo 2008 (34)              | 25 | 2  | 10 | 64 | 0.71        | 0.97       | 80   |
| Gomez 2012 (36)              | 95 | 5  | 40 | 226| 0.70        | 0.98       | 107.35 |
| Marin 2012 (37)              | 119| 4  | 57 | 317| 0.68        | 0.99       | 165.45|
| Panousis 2005 (23)           | 11 | 2  | 1  | 59 | 0.92        | 0.74       | 30.9 |
| Vandercam 2008 (50)          | 31 | 1  | 3  | 34 | 0.91        | 0.97       | 351.33|
| Fang 2018 (38)               | 28 | 0  | 10 | 33 | 0.74        | 1          | 30.90 |
| Rak-PT 2016 (30)             | 22 | 4  | 7  | 54 | 0.76        | 0.93       | 42.43 |
| Rak-SF 2016 (30)             | 27 | 4  | 2  | 54 | 0.93        | 0.93       | 182.25|
| Fink 2018 (45)               | 15 | 16 | 7  | 73 | 0.55        | 0.82       | 5.70  |
| Bemer 2014 (51)              | 151| 2  | 64 | 47 | 0.7         | 0.96       | 55.45 |
| Stylianakis 2018 (52)        | 16 | 11 | 11 | 59 | 0.59        | 0.84       | 7.80  |
| Morgenstern 2018 (53)        | 46 | 7  | 31 | 58 | 0.6         | 0.89       | 12.29 |

Tp, true positive; Fp, false positive; Fn, false negative; Tn, true negative; Se, sensitivity; Sp, specificity; DOR, diagnostic odds ratios; PT, periprosthetic tissue; SF, sonicate fluid.

Figure 2. Methodological quality assessment of included studies. PT, periprosthetic tissue. SF, sonicate fluid. High and low represent high and low risk of bias or applicability concern.
respectively) and specificity (0.93, 95% CI 0.90-0.96; 0.95, 95% CI 0.90-0.98) compared with joint fluid (sensitivity, 0.67, 95% CI 0.62-0.71; specificity, 0.92, 95%; CI 0.90-0.94). For studies using the blind method, analysis showed a higher specificity and lower sensitivity compared with the studies using the non-blind method (Table III). The analysis results of the
remaining subgroups showed no significant difference in diagnostic value. The results are shown in Table III. Deeks' funnel chart analysis revealed that there were no notable publication biases in the included studies (P=0.14; Fig. 6). Studies 2 and 10 had the highest observed specificity, which was indicative of a high test threshold and the highest DOR.

Discussion

The diagnosis of PJI represents a notable clinical challenge. In recent years, several guidelines have been released for the correct diagnostic approach to this disease (31-38). In the latest guidelines released in 2011, the authors claimed that the diagnosis of PJI is established when one of the following criteria have been fulfilled (32): i) Sinus tract communicating with the prosthesis; ii) a microorganism isolated by culture from at least two separate tissue or fluid samples of affected prosthetic joint; iii) four of the following six criteria exist: iiia) Elevated serum erythrocyte sedimentation rate and elevated serum C-reactive protein concentration; iiib) elevated synovial leukocyte count; iiic) elevated synovial neutrophil percentage; iiid) presence of purulence in the affected joint; iii) isolation of a microorganism in one culture of periprosthetic tissue or fluid; and iiiif) more than five neutrophils per high-power field observed from histologic analysis of periprosthetic tissue at x400 magnification. Although molecular methods are not included in these criteria and PCR assay is not extensively tested in the routine of a clinical practice, PCR can meet the demanding expectations of the orthopedic community because it is helpful in making an early diagnosis of infection (39-42).

After an extensive evaluation of the literature, fifteen papers were identified on the usefulness of 16S rRNA in diagnosing PJIs. These 15 studies involved 862 PJIs and 1,208 aseptic prostheses. The analysis of these studies shows the sensitivities of 0.70 (range, 0.50-0.93). The false positive PCR results may be due to contamination in the surgery process by skin, vials used for collection of samples or by the presence of 16S rRNA from nonviable bacteria present in sterilized medical devices (23,30,43). Contaminants can also be introduced during the PCR reaction by reagents and equipment (44,45). The heterogeneity found by the present meta-analysis was likely due to clinical sample, study design, center, blinded status and the country used for PCR diagnosis. In the clinical sample subgroup, joint fluid samples had a lower sensitivity and specificity compared with all the other groups. Sonicated fluid samples had a higher sensitivity (0.76/0.73) and lower specificity (0.93/0.95) compared with the periprosthetic tissue subgroup. A comparison among the different studies showed that significantly heterogeneous specificity values were found in spite of a limited range of pooled specificity value (0.91-0.94). In other subgroups, the sensitivity and specificity were not significantly different. The DOR is the ratio of the odds of a positive test result in patients with the disease relative to the patients without disease; which is a single indicator of test accuracy that combines the data from sensitivity and specificity into a single number. A higher value DOR indicates a better discriminatory test performance. In the present meta-analysis, the present study has found that the mean DOR was 41.77 and this value was 68.15 in periprosthetic tissue sample, which indicated that there was a high level of overall accuracy. But in joint fluid sample, this value was 32.89 which was lower than the mean DOR. In the present study, PLR and NLR were also used for the measurement of diagnostic accuracy. A PLR value of 10.93 suggested that patients with PJIs have a 10-fold greater chance of having a positive 16S rRNA PCR test compared with the controls. NLR is found to be 0.33 in the present meta-analysis, which indicates that if the 16S rRNA PCR result is negative for an individual, the probability of this individual having PJI is 33%, which is not low enough to rule out PJI. The SROC approach shows a good overview of the pooled results from several studies. The SROC curve and its AUC demonstrate the tradeoff between sensitivity and
Table III. Subgroup analyses.

A, Clinical sample

| Subgroup analyses | Studies, n | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | DOR (95% CI) | AUC (SE) |
|-------------------|------------|----------------------|----------------------|--------------|--------------|--------------|----------|
| Overall studies   | 15         | 0.70 (0.67-0.73)     | 0.93 (0.91-0.94)     | 10.93 (5.55-21.51) | 0.33 (0.28-0.40) | 41.77 (19.90-87.68) | 0.89 (0.0375) |
| Joint fluid       | 8          | 0.67 (0.62-0.71)     | 0.92 (0.90-0.94)     | 10.09 (3.83-26.61) | 0.38 (0.31-0.64) | 32.89 (10.73-100.76) | 0.8128 (0.0794) |
| Sonicate fluid    | 3          | 0.76 (0.69-0.82)     | 0.93 (0.90-0.96)     | 10.25 (1.45-72.45) | 0.22 (0.11-0.43) | 56.78 (10.44-308.89) | 0.9310 (0.0505) |
| Periprosthetic tissue | 3       | 0.73 (0.68-0.78)     | 0.95 (0.90-0.98)     | 14.56 (7.02-30.23) | 0.22 (0.11-0.44) | 68.15 (24.43-190.08) | 0.9860 (0.0304) |

B, Study design

| Subgroup analyses | Studies, n | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | DOR (95% CI) | AUC (SE) |
|-------------------|------------|----------------------|----------------------|--------------|--------------|--------------|----------|
| Prospective       | 12         | 0.70 (0.67-0.74)     | 0.93 (0.91-0.94)     | 11.55 (5.47-24.39) | 0.33 (0.26-0.40) | 46.64 (19.44-111.87) | 0.9044 (0.0437) |
| Retrospective     | 3          | 0.71 (0.64-0.78)     | 0.93 (0.90-0.96)     | 8.89 (0.86-91.97) | 0.34 (0.23-0.51) | 29.32 (5.36-160.51) | 0.8766 (0.0359) |

C, Center

| Subgroup analyses | Studies, n | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | DOR (95% CI) | AUC (SE) |
|-------------------|------------|----------------------|----------------------|--------------|--------------|--------------|----------|
| Single-center     | 13         | 0.70 (0.66-0.73)     | 0.94 (0.92-0.95)     | 12.21 (5.76-25.87) | 0.33 (0.27-0.41) | 46.73 (20.11-108.61) | 0.9032 (0.0436) |
| Multi-center      | 2          | 0.72 (0.66-0.77)     | 0.83 (0.74-0.90)     | 6.38 (0.44-92.65) | 0.31 (0.25-0.38) | 23.68 (4.56-120.92) | NA |

D, Blinded status

| Subgroup analyses | Studies, n | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | DOR (95% CI) | AUC (SE) |
|-------------------|------------|----------------------|----------------------|--------------|--------------|--------------|----------|
| NR                | 5          | 0.75 (0.66-0.83)     | 0.85 (0.80-0.89)     | 6.62 (2.62-16.75) | 0.32 (0.22-0.48) | 30.81 (10.81-87.81) | 0.8894 (0.0293) |
| Yes               | 10         | 0.70 (0.67-0.73)     | 0.95 (0.93-0.96)     | 12.79 (5.74-28.48) | 0.33 (0.27-0.46) | 46.55 (17.88-121.20) | 0.8899 (0.0695) |

E, Area

| Subgroup analyses | Studies, n | Sensitivity (95% CI) | Specificity (95% CI) | PLR (95% CI) | NLR (95% CI) | DOR (95% CI) | AUC (SE) |
|-------------------|------------|----------------------|----------------------|--------------|--------------|--------------|----------|
| USA and Asia      | 4          | 0.70 (0.63-0.76)     | 0.96 (0.93-0.98)     | 20.90 (3.12-139.86) | 0.33 (0.26-0.42) | 60.50 (9.19-398.40) | 0.5076 (0.1565) |
| Europe            | 11         | 0.71 (0.67-0.74)     | 0.91 (0.89-0.93)     | 9.32 (4.46-19.50) | 0.32 (0.25-0.41) | 38.36 (16.47-89.32) | 0.9072 (0.0344) |

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the curve; NR, not reported.
Finally, during the statistical analysis the Meta-disc software should be interpreted with caution. To obtain more accurate estimates, and consequently, the findings of this meta-analysis should be interpreted in parallel with clinical findings and the results of microbiological and other laboratory tests.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YZ, ZHC and SFS conceptualized and designed this study. YZ and QCZ analyzed and processed the data. YZ, XYC and SFS conceptualized and designed this study. YZ, XYC and SFS performed the technical assistance and support.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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