Meta-Analysis of Synovial Fluid Polymerase Chain Reaction for Diagnosing Periprosthetic Hip and Knee Infection

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Research Article

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Abstract

**BACKGROUND AND OBJECTIVE:** The purpose of this study was to estimate the diagnostic performance of synovial fluid polymerase chain reaction (PCR) in periprosthetic hip and knee infection, and whether synovial fluid PCR has greater diagnostic significance than conventional methods.

**METHODS:** The literature databases PubMed, Scopus, and the Web of Science were searched for English articles describing periprosthetic joint infection (PJI) diagnosis by synovial fluid PCR. Articles were limited to the period between January 1990 and December 2019. Subsequently, conventional methods that were used on at least two occasions were included for further analysis. Data analysis was performed using the Meta-DiSc and Stata software.

**RESULTS:** Eleven studies with 1360 cases were included in the meta-analysis. The pooled sensitivity, specificity, and diagnostic odds ratio (DOR) of synovial fluid PCR were 0.70 (95% CI: 0.66–0.74), 0.92 (95% CI: 0.90–0.93), and 37.4 (95% CI: 17.77–78.74), respectively.

**CONCLUSIONS:** Synovial fluid PCR can be used as a diagnostic confirmatory method for PJI in cases of negative synovial fluid culture with highly suspected infection during the early stages.

Background

Periprosthetic joint infection (PJI) is one of the most severe complication following hip or knee arthroplasty, with high morbidity, mortality and costs [1–5]. However, its diagnosis remains a challenge in the management of PJI. To date, there is no test available that rapidly and accurately diagnoses infection with a sensitivity and specificity of 100% [6]. A mixture of several diagnostic methods or diagnostic definition that guide the diagnosis of PJI is currently the most common approach used [7].

Joint aspiration is an invasive diagnostic method and often used as the first step in suspected PJI cases. Currently, various synovial fluid tests have been applied in the clinical diagnosis of PJI [8,9]. Non-microbiological analysis of the synovial fluid white cell count and polymorphonuclear (PMN) leukocytes, alpha-defensin, leukocyte esterase (LE), and C-reactive protein (CRP) were included in the new definition of PJI from the Musculoskeletal Infection Society (MSIS) guideline of 2018 [10]. Although these tests are of high diagnostic value for PJI cases, they are unable to identify the causative pathogen. Conventional synovial fluid culture still appears to be an irreplaceable diagnostic approach for the detection of microorganisms. In recent years, polymerase chain reaction (PCR) was also used in the diagnosis of PJI. A number of reports found that synovial fluid PCR could rapidly detect rare bacterial infections, which is in contrast to conventional synovial fluid culture [11,12]. However, it remains unknown whether better diagnostic results are observed using PCR compared to tissue culture, with several conclusions arguable [13,14]. Although a meta-analysis of PCR for diagnosis of PJI has been previously performed using results combined from synovial fluid, periprosthetic tissue, and sonicate fluid samples [15], the diagnostic value of synovial fluid PCR in the periprosthetic hip and knee remains unclear.

The aim of the present meta-analysis was to assess the diagnostic accuracy of synovial fluid PCR in periprosthetic hip and knee infection. Furthermore, we examined whether synovial fluid PCR has a better diagnostic value compared to conventional methods, especially synovial fluid culture.

Methods

**Search strategy**

A systematic literature search of the electronic databases of Web of Science, PubMed, and Scopus was performed for manuscripts of English language between January 1990 and December 2019. The following medical subject headings (MeSH) or text keywords were used: "arthroplasty or joint prosthesis or joint replacement or periprosthetic joint or prosthetic joint", "infection or infectious or infected", "synovial uid", and "PCR or polymerase chain reaction".

Two authors (LC and LH) independently selected research papers according to the following inclusion criteria: (1) human studies related to synovial fluid PCR in periprosthetic hip or knee infection; (2) clear description of the diagnosis standard of PJI; and (3) values on true-positive (TP), false-positive (FP), true-negative (TN), and false-negative (FN) were provided or could be computed.

The combined database was imported to EndNote X7 (Thomson Reuters, New York, NY, USA, 2013). All relevant publications on the synovial fluid PCR method in detecting periprosthetic hip or knee joint infection and their reference list were reviewed. Furthermore, included studies from two previous meta-analyses of synovial PCR were reviewed [15,16]. In addition, other diagnostic methods that appeared accumulatively on at least two occasions in all studies were collected. Diagnostic classification values of TP, FP, TN, and FN were included and further compared with synovial fluid PCR.

**Data extraction and study quality assessment**

Characteristics of the included studies were collected by two reviewers independently and assessed subsequently by a third reviewer. The following information was extracted: first author, year of publication, country, study design, number of total cases, infection site, acquisition time, diagnostic criteria, type of PCR, target gene, antimicrobial use before specimen collection, and diagnostic sensitivity and specificity. The quality of all identified synovial fluid studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) guidelines.

**Statistical analysis**

To estimate the diagnostic value of synovial fluid PCR for PJI detection, all statistical analyses were performed using Meta-DiSc (version 1.4, Unit of Clinical Biostatistics team, Madrid, Spain) and Stata software (version 14.0, StataCorp, College Station, TX, USA). I² was calculated to evaluate heterogeneity among the studies. If I² > 50%, the random-effects model was used. Meta-regression analyses were performed to further assess the potential source of heterogeneity.
such as type of prosthesis, number of patients, acquisition time, antibiotic use, sample condition, diagnostic standard, and target gene. Deeks’ funnel plot asymmetry test was used to evaluate potential publication bias.

**Results**

**Search results**

Of the identified 145 primary articles, two records were extracted from the reference list of synovial fluid PCR-related studies [17,18]. Fifty-one studies were excluded due to duplication reasons. A further 83 were excluded after further reviewing the title, abstract, and full text. Finally, a total of 11 studies were considered suitable for meta-analysis (Fig. 1) [13,14,17–25]. Characteristics of the studies included are summarized in Table 1. Among these studies, five diagnostic methods could be compared with synovial fluid PCR. The QUADAS-2 quality assessments for the included studies are shown in Fig. 2.

**Diagnostic accuracy**

The random-effects model was used to examine study heterogeneity, which was found for the sensitivity ($I^2 = 73.9\%$), specificity ($I^2 = 86.0\%$), positive likelihood ratio (PLR) ($I^2 = 77.4\%$), negative likelihood ratio (NLR) ($I^2 = 62.2\%$), and diagnostic odds ratio (DOR) ($I^2 = 66.4\%$). The pooled sensitivity, specificity, PLR, NLR, and DOR estimates for the diagnosis of PJI using synovial fluid PCR were 0.70 (95% CI: 0.66–0.74), 0.92 (95% CI: 0.90–0.93), 9.09 (95% CI: 5.28–15.67), 0.32 (95% CI: 0.24–0.42), and 37.4 (95% CI: 17.77–78.74), respectively (Fig. 3–7). The summary receiver operating characteristic (SROC) plot showed the summary sensitivity and specificity and the 95% confidence and prediction regions, with an area under the curve (AUC) of 0.9252 (standard error of 0.0195; Fig. 8).

Synovial fluid PCR was shown to have a better sensitivity and specificity than preoperative examination of CRP and erythrocyte sedimentation rate (ESR). Similar sensitivities were observed for conventional synovial fluid culture (70%) and PCR (69%). However, the specificity of synovial fluid PCR was lower than that of synovial fluid culture (91% vs. 98%, respectively). Intraoperative histology, periprosthetic tissue culture, and sonicate fluid demonstrated better sensitivity and specificity than synovial fluid PCR. Details of the diagnostic values of synovial fluid PCR and other preoperative and intraoperative examination are shown in Table 2.

**Meta-regression analysis**

Meta-regression analysis was performed in the group of diagnostic standards, acquisition time, number of patients, antibiotic use, and target gene (Table 3). Results showed that the most likely sources of heterogeneity were acquisition time and antibiotic treatment ($P < 0.001$). Compared with the diagnostic standards of MSIS, International Consensus Meeting (ICM), or European Bone and Joint Infection Society (EBJIS), other diagnostic criteria had a higher sensitivity of 0.85 (95% CI, 0.72–0.98; $P < 0.05$). A small sample size ($<100$) was observed to have a higher sensitivity of 0.81 (95% CI, 0.71–0.90) compared to studies including more than 100 patients with a sensitivity of 0.71 (95% CI, 0.59–0.83) ($P = 0.01$).

**Assessment of publication bias**

Deeks’ funnel plot analysis did not identify a potential publication bias for synovial fluid PCR ($P = 0.41$; Fig. 9).

**Discussion**

The present meta-analysis showed that the pooled sensitivity and specificity of synovial fluid PCR are 70% and 92%, respectively. The AUC value of the SROC was 0.9252. These results suggest that synovial fluid PCR could be used for the diagnosis of infection after hip and knee arthroplasty. The first meta-analysis of the use of PCR in the diagnosis of PJI presented the sensitivity and specificity of synovial fluid (84% and 89%, respectively), tissue samples (95% and 81%, respectively), and sonicate fluid (81% and 96%, respectively) [16], with moderate sensitivity and specificity levels observed for the three sample types. Interestingly, similar results were also reported by the retrospective study performed by Huang and colleagues [17]. In 2018, Jun et al. [15] performed a diagnostic meta-analysis of PCR in PJI, reporting a sensitivity of 0.76 (95% CI: 0.65–0.85) and specificity of 0.94 (95% CI: 0.92–0.95). Unfortunately, the pooled result combines samples from synovial fluid, sonicate fluid, and intraoperative tissue. Hence, the diagnostic value of synovial fluid PCR in periprosthetic hip and knee by meta-analysis remained unexplored. The present study is the first meta-analysis evaluating the diagnostic value of synovial fluid PCR for diagnosing infection after hip and knee replacement.

In recent years, the use of joint fluid for diagnosing PJI was a topic of considerable interest. Multiple synovial fluid tests were applied in clinical practice, with several valuable tests incorporated into the new definition of MSIS [10]. Through a literature review of the published meta-analysis of these synovial fluid methods from the MSIS guideline [26–30], the pooled sensitivity of these tests is superior to that of synovial fluid PCR. The specificity of synovial fluid PCR exceeded that of synovial fluid interleukin-6 (IL-6), CRP, WBC, and PMN, but was lower than synovial fluid culture, alpha-defensins, and LE. Based on the AUC value of meta-analysis of synovial fluid [31], only LE demonstrated excellent accuracy in the diagnosis of PJI, followed by alpha-defensins, IL-6, CRP, and PMN. Furthermore, synovial fluid WBC as well as PCR showed good accuracy (Table 4). Although the results of most synovial fluid biomarkers were superior to that of the synovial fluid PCR [26–30], synovial fluid culture and some PCR tests can detect bacteria and could provide a more valuable reference for further comparisons with intraoperative diagnostic results. However, the diagnostic value between synovial fluid culture and PCR for PJI detection is controversial.

Synovial fluid PCR was compared with preoperative and intraoperative tests from the included studies. The PCR test was found to have better sensitivity and specificity than that of serum CRP and ESR. In contrast, lower sensitivity and specificity were observed in comparison to all intraoperative methods. Compared with synovial fluid culture, synovial fluid PCR had an almost identical level of sensitivity with synovial fluid culture (69% vs. 70%, respectively) and a lower specificity level (91% vs. 98%, respectively). Synovial fluid PCR and culture were also observed to have similar results in comparison to the previous meta-
analysis of synovial fluid culture, with a sensitivity of 70% and 72%, respectively, and a specificity of 92% and 95%, respectively [30]. Although the current meta-analysis and our subgroup results showed that the sensitivity and specificity of synovial fluid PCR were lower than that of synovial fluid, PCR has several advantages in regard to the detection of bacteria. Synovial fluid PCR has been reported to rapidly provide results within 3–72 h [14,23,25], and could also detect culture-negative bacteria [11,12,21,22,25]. Sujee and co-workers reported that the sensitivity of 16S rRNA PCR and synovial fluid culture was 68.1% and 70.2%, respectively [22]. PJI was detected by PCR in five cases that were negative by synovial fluid culture. Synovial fluid multiplex PCR identified 12 cases of negative by synovial fluid culture, with 10 cases caused by low-virulence bacteria (coagulase-negative staphylococci and Cutibacterium acnes) [25]. The author also found that more cases of polymicrobial infections were detected by synovial PCR than synovial fluid culture (four vs. two cases), with similar results also reported by Melendez and colleagues [18,21]. Due to rare cases of mixed infection in these studies, further research is required. However, in cases treated with antibiotics before specimen collection, the testability of synovial fluid PCR was lower than synovial fluid culture. A comparison of the PCR panel and synovial fluid culture in patients that received antibiotics within 30 days before joint aspiration revealed the sensitivity of the PCR panel and synovial culture to be 64.5% and 85.4%, respectively [21]. In another study, PCR-ESI/MS detected eight of nine PJI cases that had received antibiotics within 30 days, whereas synovial fluid culture detected all nine cases [18]. The use of antibiotics before PCR analysis most likely impacts culture results. Meta-regression analysis results from the current study show that the sensitivity level of cases receiving antibiotic therapy were less than cases without antibiotic therapy (73% vs. 80%). Moreover, meta-regression was also analyzed in the preoperative and intraoperative aspiration groups, with slightly higher sensitivity and lower specificity observed for the intraoperative test compared to the preoperative test (sensitivity: 77% vs. 75%, respectively; specificity: 93% vs. 96%). In contrast, the meta-analysis of synovial fluid white cell count performed by Qu and co-workers [32] found that preoperative collection had a higher sensitivity than intraoperative samples (91% vs. 77%, respectively), and lower specificity than that of intraoperative samples (89% vs. 97%). However, due to the limited data of the studies included in our intraoperative study (two studies) and different tests performed in these two meta-analyses, whether intraoperative and preoperative collection infers with the diagnostic accuracy remains an avenue for further exploration.

Although various types of synovial fluid PCR have been tested in the clinical diagnosis of PJI, the diagnostic ability has most likely been disregarded. The most frequently described disadvantage of PCR is FP results, with the potential impacting factors, including the use of different target genes, PCR type, laboratory technician skills, and laboratory conditions [13,19,22,24]. The use of 16S/28S rRNA RT-PCR with high-quality control standards demonstrated excellent results, with a sensitivity of 100% and specificity of 99.5% [13]. Sebastian and colleagues [22] found that DNase treatment could reduce exogenous bacterial contamination, with no FP results observed in synovial fluid PCR: however, the sensitivity was affected. Further studies are required to determine the most suitable type of PCR for PJI diagnosis and the standard procedure required.

The present study has several limitations. First, the identified studies used different types of PCR; therefore, the overall result may impact the estimates of diagnostic accuracy. Second, meta-regression analysis was not performed in regard to the prosthesis type or sample condition to further explore sources of heterogeneity. The type of prosthesis described in the included studies were the knee or both the hip and knee; however, studies focusing only on the periprosthetic hip were not found. Therefore, further analysis of differences between the hip and knee could not be performed in meta-regression analysis. Regarding the sample condition, frozen specimens were used in the studies; however, there was ambiguity in terms of the use of fresh samples. Third, the diagnostic accuracy of synovial fluid PCR may be affected by the standard definition of PJI [33].

**Conclusions**

The diagnostic capability of synovial fluid PCR is not superior to that of synovial fluid culture. However, in cases of negative synovial fluid culture with highly suspected early-stage infection, synovial fluid PCR can be used as a rapid, diagnostic confirmatory tool.

**Abbreviations**

AUC: Area under the curve

C: Clinical signs of infection

CI: Confidence interval

CRP: C-reactive protein

DOR: Diagnostic odds ratio

EBJIS: European Bone and Joint Infection Society

ESI/MS: Electrospray ionization mass spectrometry

ESR: Erythrocyte sedimentation rate

FN: False-negative

FP: False-positive

H: Histological examination

IDSA: Infectious Diseases Society of America
ICM: International Consensus Meeting
IL-6: Interleukin-6
LE: Leukocyte esterase
M: Microbiological or laboratory examination
MeSH: Medical subject headings
MSIS: Musculoskeletal Infection Society
NLR: Negative likelihood ratio
N: No
NA: Not available
P: Presence sinus tract or purulence around the prosthesis
PCR: Polymerase chain reaction
PJ: Periprosthetic joint infection
PLR: Positive likelihood ratio
PMN: Polymorphonuclear
QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies - 2
qPCR: Quantitative PCR
R: Radiographic images
RT: Real-time
SROC: Summary receiver operating characteristic
SE: Standard error
Sen: Sensitivity
Spe: Specificity
TN: True negative
TP: True positive
WBC: White blood cell count
Y: Yes

Declarations

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Competing interests

The authors declare that they have no competing interests.

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Tables
Due to technical limitations, table 1-4 is only available as a download in the Supplemental Files section.

Figures

Figure 1
Flow diagram of the selection process for eligible studies.
Figure 2
Methodological quality assessment of the included studies.

Figure 3
Forest plots of sensitivity of synovial fluid PCR for PJI diagnosis.
Figure 4
Forest plots of specificity of synovial fluid PCR for PJI diagnosis.

Figure 5
Forest plots of positive likelihood ratio of synovial fluid PCR for PJI diagnosis.
Figure 6

Forest plots of negative likelihood ratio of synovial fluid PCR for PJI diagnosis.

| Study     | Negative LR (95% CI) |
|-----------|----------------------|
| Bergin    | 0.36 (0.13 - 0.97)   |
| Fink      | 0.54 (0.35 - 0.84)   |
| Larsen    | 0.29 (0.17 - 0.49)   |
| Melendez  | 0.48 (0.38 - 0.61)   |
| Melendez  | 0.21 (0.07 - 0.59)   |
| Sebastian | 0.33 (0.22 - 0.49)   |
| Janz      | 0.18 (0.04 - 0.76)   |
| Janz      | 0.20 (0.08 - 0.50)   |
| Morgenstern | 0.45 (0.34 - 0.60)   |
| Pancousis | 0.11 (0.02 - 0.74)   |
| Kuo       | 0.02 (0.00 - 0.30)   |
| Melendez  | 0.20 (0.08 - 0.48)   |
| Huang     | 0.20 (0.11 - 0.37)   |

Random Effects Model
Pooled Negative LR = 0.32 (0.24 to 0.42)
Cochran-Q = 31.73; df = 12 (p = 0.0015)
Inconsistency (I-square) = 62.2 %
Tau-squared = 0.1215

Figure 7

Forest plots of diagnostic odds ratio of synovial fluid PCR for PJI diagnosis.

| Study     | Diagnostic OR (95% CI) |
|-----------|------------------------|
| Bergin    | 210.60 (8.72 - 5,085.37) |
| Fink      | 5.70 (2.25 - 14.49)     |
| Larsen    | 162.50 (19.77 - 1,335.99) |
| Melendez  | 14.13 (7.29 - 27.40)    |
| Melendez  | 25.33 (5.74 - 111.83)   |
| Sebastian | 168.84 (9.79 - 2,947.15) |
| Janz      | 3.60 (0.80 - 161.57)    |
| Janz      | 12.29 (4.96 - 30.45)    |
| Morgenstern | 3.90 (3.76 - 254.10)   |
| Kuo       | 6,409.00 (254.23 - 161,568.28) |
| Melendez  | 82.88 (18.83 - 364.75)  |
| Huang     | 29.33 (5.58 - 154.25)   |

Random Effects Model
Pooled Diagnostic Odds Ratio = 37.40 (17.77 to 78.74)
Cochran-Q = 35.74; df = 12 (p = 0.0004)
Inconsistency (I-square) = 66.4 %
Tau-squared = 1.0318
Figure 8

Summary of SROC of synovial fluid PCR for PJI diagnosis.
Figure 9

Deeks’ funnel plot for evaluation of publication bias.

Supplementary Files

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