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REVIEW

The application of sonication in diagnosis of periprosthetic joint infection

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Abstract Periprosthetic joint infection (PJI) is a catastrophic complication after total joint arthroplasty. It has always been difficult to diagnose PJI, which is characterised by existence of biofilm around the implants. The application of sonication has proven advantageous for pathogen detection. This meta-analysis of clinical trials was performed to evaluate the diagnostic value of sonication and to compare it with traditional bacterial culture. We assessed 16 studies that evaluated sonication fluid cultures (SFC) for the diagnosis of PJI. It was shown that sonication may be of great value in PJI diagnosis, with a pooled sensitivity of 0.79 (95 % confidence interval [CI] = 0.76–0.81), specificity of 0.95 (CI = 0.94–0.96), DOR of 71.20 (CI = 31.08–163.10), PLR of 15.25 (CI = 6.44–36.15), and NLR of 0.23 (CI = 0.18–0.30). The AUC value of the SROC was 0.90. The results of this meta-analysis showed that culture of fluid after sonication was of great value for PJI diagnosis. Sonication was more sensitive than traditional tissue culture with lower specificity, especially for patients previously taking antibiotics.

Introduction

Total joint arthroplasty (TJA) is among the most effective and widely performed surgical operations, and this procedure significantly improves quality of life and relieves pain [1]. Given the considerable development and achievement of total joint replacements over the past several decades, the major focus has switched to minimizing surgical complications to further improve long-term outcomes and lower costs [2].

Periprosthetic joint infection (PJI) is the most catastrophic complication seen in TJA [3]. It is reported that the incidence of PJI varied from 1 to 12 % [4, 5]. Meanwhile, PJI requires additional surgeries, antimicrobial therapies, and prolonged hospitalization, with higher risk of disability [6]. According to conservative estimates, the treatment of PJI costs $50,000 [7, 8].

For effective management of PJI, receiving timely treatment is important [9]. The application of anti-bacterial agents has been regarded as playing an important role in treating PJI. The isolation and identification of the pathogen and susceptibility testing are pivotal for appropriate antimicrobial choice, yet this is challenging. Currently, cultures of synovial fluid and intraoperative periprosthetic tissue are considered to be the gold standard for diagnosing PJI. However, its sensitivity and specificity are imperfect, leaving considerable numbers of missed diagnoses [10]. Researchers hypothesized that the forming biofilm protects pathogens around the prosthesis from detection and elimination [11]. Neither specificity nor sensitivity is realised as a result of biofilm and contaminants from skin flora [12].

Several studies have assessed the diagnostic value of sonication techniques for diagnosing PJI, in which long-wave ultrasound was applied before culture to dislodge the bacteria growing within the biofilm and enhance bacterial growth [13]. It has been reported that some cases of aseptic failure are missed cases of PJI [14]. Even in patients receiving antimicrobial therapy within 14 days before surgery, the application of sonication cultures was more sensitive than tissue culture [10]. However, the sensitivities and specificities among studies were inconsistent, and the sample size of any single study was not

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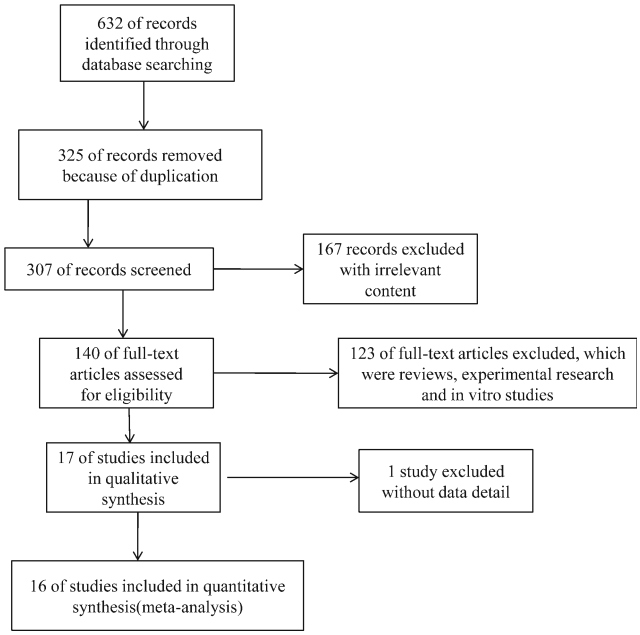


Fig. 1 Flow diagram of the included studies in meta-analysis

sufficiently large [14]. There have been several new clinical studies since the last diagnostic meta-analysis [15]. In addition, we still did not know whether the sensitivity and specificity of sonication is better than tradition tissue culture. Therefore, the aim of our study was to perform an updated meta-analysis to evaluate the detection validity of sonication for PJI to provide further evidence for its clinical use, especially compared with traditional tissue culture.

Material and methods

This study was conducted according to the recommendations of the Cochrane Collaboration's Diagnostic Test Accuracy Group [16]. Electronic and manual search of the literature was performed, and all clinical trials before 2016 related to application of sonication in PJI diagnosis were evaluated.

Eligibility criteria

Studies considered for inclusion met the following criteria: (1) the study reported the application of sonication in the diagnosis of PJI in comparison with traditional culture; (2) the diagnostic criteria were appropriate, such as visible purulence in the synovial fluid or surrounding the prosthesis, acute inflammation on histopathological examination of permanent tissue sections, a sinus tract communicating with the prosthesis, or positive detection in at least two tissue samples culture; (3) sufficient data of true-positive (TP), false-negative (FN), false-positive (FP), and true-negative (TN) values were reported.

Search strategy

Electronic database searches were conducted using Mesh and text keywords "sonication OR ultrasound", "infection", "joint" and a combination of these terms, in the title, abstract and keyword fields. Only clinical trials were chosen. The major medical databases were covered, which included MEDLINE, EBSCO, COCHRANE library, EMbase and OVID. No language restrictions were set. Chinese databases, CNKI and VIP, were also covered. References from these trials were scrutinized to reveal additional citations using a manual approach. Duplicated articles were deleted in Endnote software.

Quality assessment

Two reviewers independently screened the retrieved clinical studies for inclusion, extracted data from all included studies and conducted the quality assessment. The aggregate quality of the included studies was evaluated according to the modified version of the QUADAS-2 tool [17]. If agreement was not achieved at any stage, a third reviewer adjudicated.

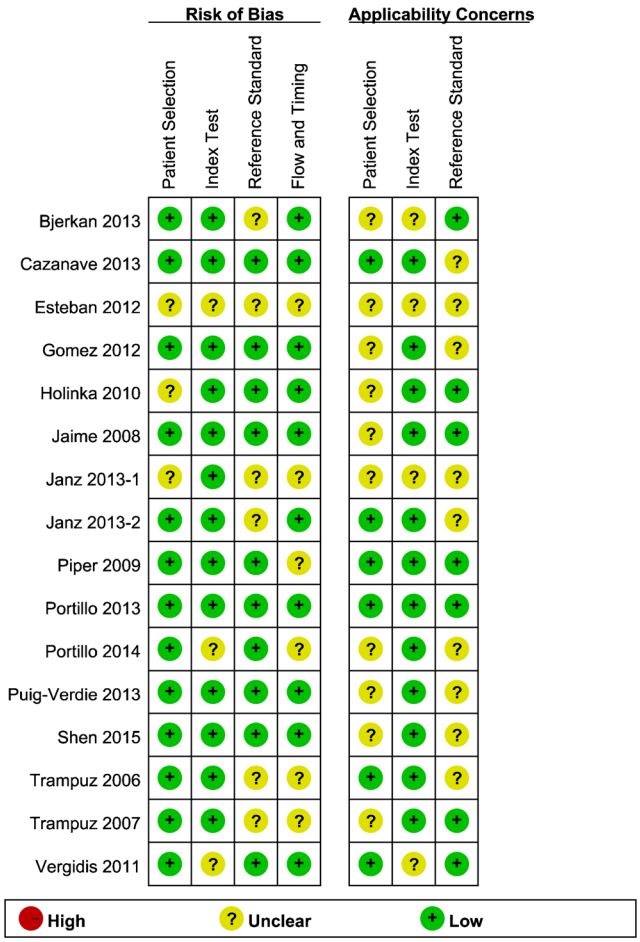


Fig. 2 Methodological quality summary

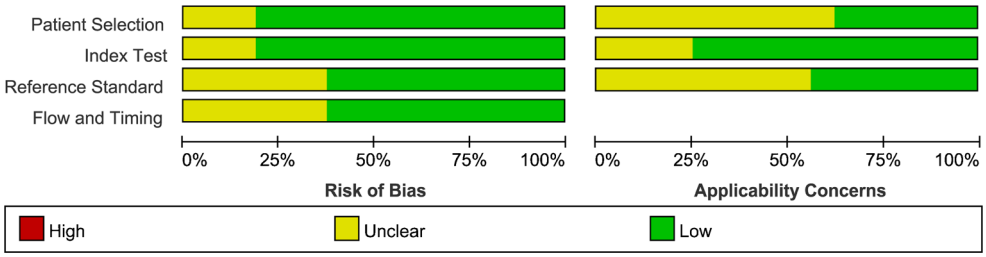


Fig. 3 Methodological quality graph

Data extraction

Data extraction and quality assessment were completed independently by two reviewers according to the inclusion criteria. Information about sample size, diagnostic criteria, ultrasonic conditions, tissue samples and diagnostic outcomes were abstracted independently. If agreement was not achieved at any stage, a third reviewer adjudicated.

Statistical analysis

For the analysis of diagnostic value of sonication, eligible trials were entered into Meta-DiSc software (version 1.4). Analysis of heterogeneity between studies was conducted using the χ^2 test. If there was no significant heterogeneity between studies ($P > 0.1$, $I^2 \leq 50$ %), the analysis was performed using a fixed-effects model; otherwise, the random-effects model ($P \leq 0.1$, $I^2 > 50$ %) was used. The specificity, sensitivity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and area under the curve (AUC) of summary receiver operating characteristic (SROC) were assessed. Comparison of sonication with traditional culture was analysed in Review Manager 5 software (version 5.1.2). The results were expressed as relative risk (RR) with 95 % confidence intervals (CIs) for dichotomous outcomes. Heterogeneity across trials was assessed via a standard chi-square test with significance being set at $P < 0.10$ and also assessed by means of I^2 statistic with significance being set at $I^2 > 50$ %.

Results

A total of 632 articles were identified by the literature search, and the flow diagram is shown in Fig. 1. After literature review of the title, abstract and full text of the articles, 17 studies were chosen as possible references; however, one did not provide data details and was excluded [1]. Finally, a total of 16 studies were recruited for the diagnostic meta-analysis, all of which were of moderate to high quality (Figs. 2 and 3). Fourteen studies were included that compared sensitivity of sonication with traditional, 13 studies compared specificity and four

Table 1 Baseline of the included studies

Study	Country	Sample size	Mean age (years)	Vortexing	Centrifugation	Culture period (aerobic/anaerobic) (days)	Cut-off (CFU)
Trampuz 2006	USA	331	69	No	No	5/7	NA
Trampuz 2007	USA	78	71	Yes	Yes	5/7	1–50
Esteban 2008	Spain	31	NA	No	Yes	1 or 7 or 15 or 30	NA
Piper 2009	USA	136	65	Yes	Yes	5/7	5 or 20
Holinka 2010	Austria	60	NA	Yes	Yes	5/7	NA
Vergidis 2011	USA	36	60.5	Yes	Yes	2–4/14	20
Esteban 2012	Spain	75	66	No	Yes	NA	100
Gomez 2012	USA	366	66	Yes	Yes	4/14	20
Bjerkan 2013	Norway	54	69	No	Yes	7/7	10
Cazanave 2013	USA	434	67	Yes	Yes	2–4/14	20
Jan. 2013-1	Germany	102	67.7	Yes	No	14	NA
Jan. 2013-2	Germany	59	67	Yes	No	14	NA
Portillo 2013	Spain	135	73	Yes	Yes	7/14	50
Puig-Verdie 2013	Spain	152	62.7	No	No	5/5	5
Portillo 2014	Spain	231	75	Yes	No	5/7	50
Shen 2015	China	110	64.5	Yes	Yes	5/7	NA

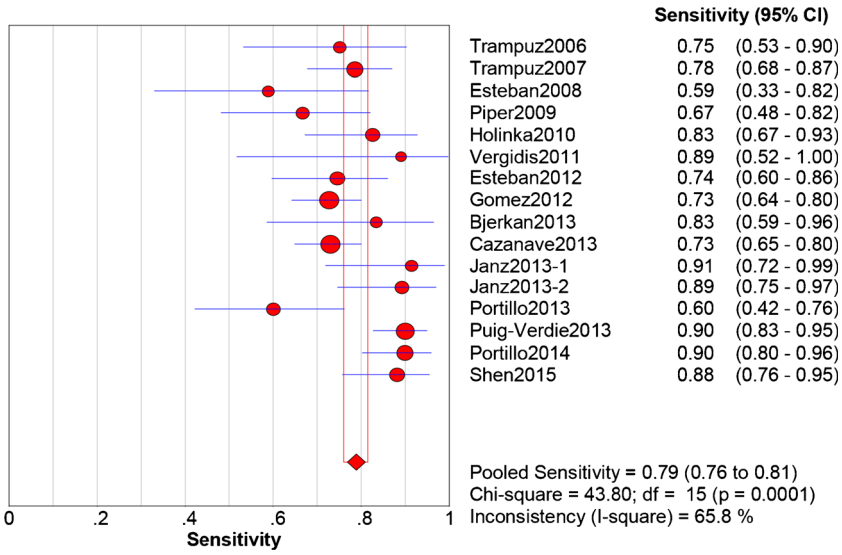


Fig. 4 Forest plots of sensitivity of sonication for PJI diagnosis

studies compared specificity in patients with previous antibiotic treatment. The baseline of the studies is described in Table 1.

Diagnostic value of sonication

No threshold effect existed (Spearman correlation coefficient: 0.065, $P = 0.81$) in the pooled data. Heterogeneity was detected in sensitivity ($I^2 = 65.8$ %), specificity ($I^2 = 91.2$ %), DOR ($I^2 = 81.3$ %), PLR ($I^2 = 93.7$ %), and NLR ($I^2 = 67.2$ %); thus, the random-effects model was used. Pooling the results (Figs. 4, 5, 6, 7 and 8) produced the following summary estimates and 95 % confidence intervals (CIs): sensitivity 0.79 (0.76–0.81), specificity 0.95 (0.94–0.96), DOR 71.20 (31.08–163.10), PLR 15.25 (6.44–36.15), and NLR 0.23 (0.18–0.30). The SROC plot (Fig. 9) showed the summary sensitivity and specificity and the 95 % confidence and prediction regions, with an AUC of 0.90. We used likelihood ratios to simulate low, moderate, and high clinical scenarios using 25, 50, and 75 % pre-test probabilities of PJI and further calculated and plotted post-test probability on Fagan nomograms (Fig. 10–12). Positive sonication fluid cultures resulted in post-test probabilities of 85, 95, and 98 %, and negative sonication fluid cultures resulted in post-test probabilities of 7, 18, and 39 %. Subgroup analysis was performed by dividing the studies into subgroups according to procedures such as vortexing, centrifugation, culture period and cut-off (Table 2).

Comparison with traditional tissue culture

Six studies provided the data for both sonication and tissue culture. Analysis of the synthesized data, shown in Fig. 13, revealed that the application of sonication was more sensitive

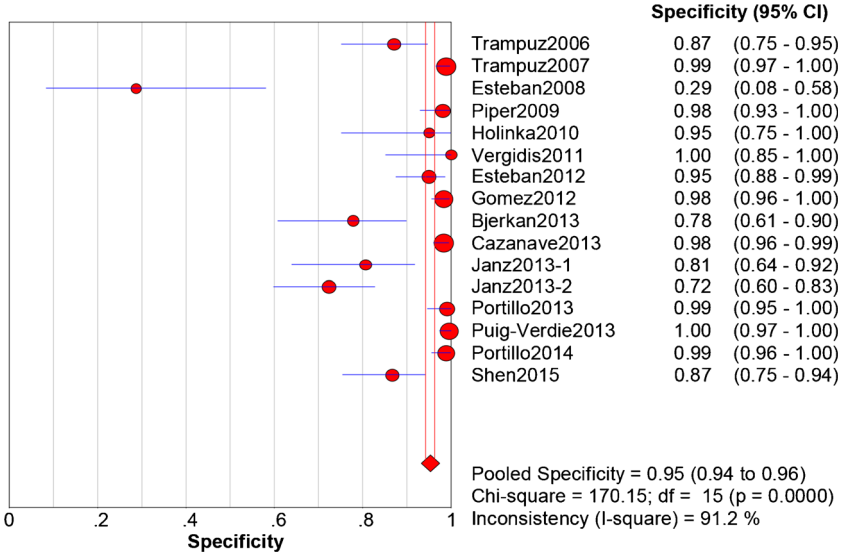


Fig. 5 Forest plots of specificity of sonication for PJI diagnosis

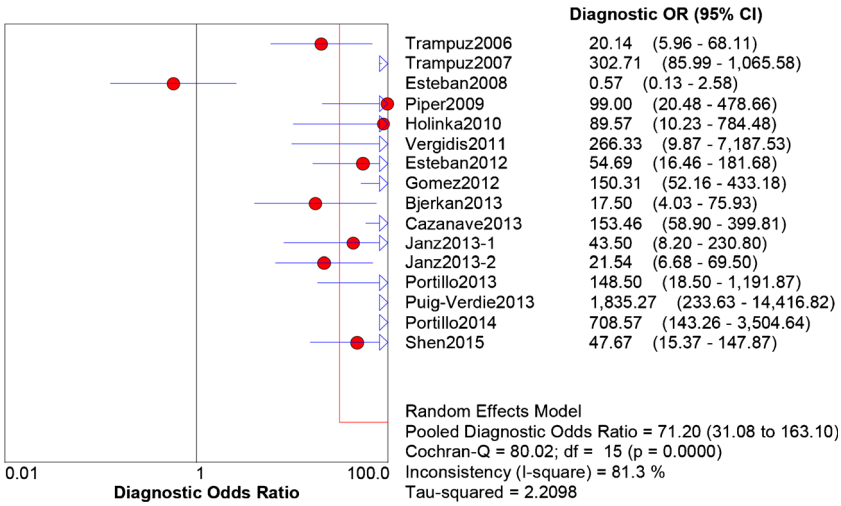


Fig. 6 Forest plots of diagnostic odds ratio of sonication for PJI diagnosis

than traditional tissue culture ($P < 0.0001$) without heterogeneity among the studies ($P = 0.74$, $I^2 = 0$ %). However, there was no significant difference with regard to specificity between the two options ($P = 0.44$), with between-study heterogeneity ($P = 0.48$, $I^2 = 0$ %) analysed from five included studies using a random effects model (Fig. 13).

For patients who received antibiotic therapy within 14 days in four studies (Fig. 14), sonication performed better than traditional tissue culture ($P = 0.00$), with no heterogeneity ($P = 0.98$, $I^2 = 0$ %).

Discussion

Currently, the only effective treatment for biofilm infection is to remove the implant, fight the infection with antibiotics, and replace the implant, which is a costly and stressful procedure. PJI can result in a disaster, not only for the patient but also for society because of expensive treatments, multiple required surgeries and long hospital stays [4]. Although considerable effort has already been expended, the incidence of PJI had not been significantly reduced. It was reported that PJI occurred in approximately 1 % of the joints after primary hip or shoulder arthroplasty, 2 % after knee arthroplasty, and up to 9 % after elbow arthroplasty [18].

Detection of pathogens from PJI patients in a rapid, convenient, and economic method is still challenging for researchers and surgeons. It was always a consensus that the diagnosis of PJI was challenging because the diagnostic tests were inaccurate [19]. Currently, periprosthetic tissue culture was regarded as the "gold standard" for microbiological diagnosis of PJI, yet this method yielded considerable false positives and false negatives [3]. Recovery of the pathogens is essential to bacterial culture and selection of antibiotics [6]. However, the biofilm protected the bacteria from being detected and attacked by antibiotics, which prevented recovery.

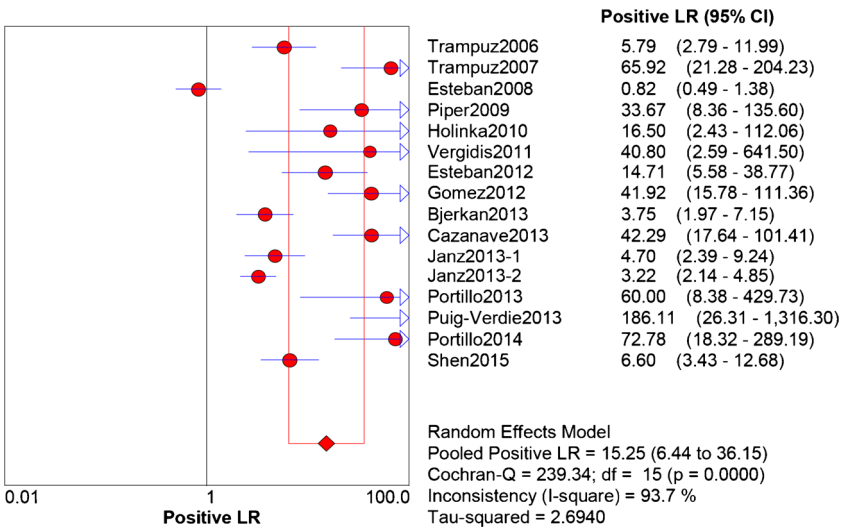


Fig. 7 Forest plots of positive likelihood ratio of sonication for PJI diagnosis

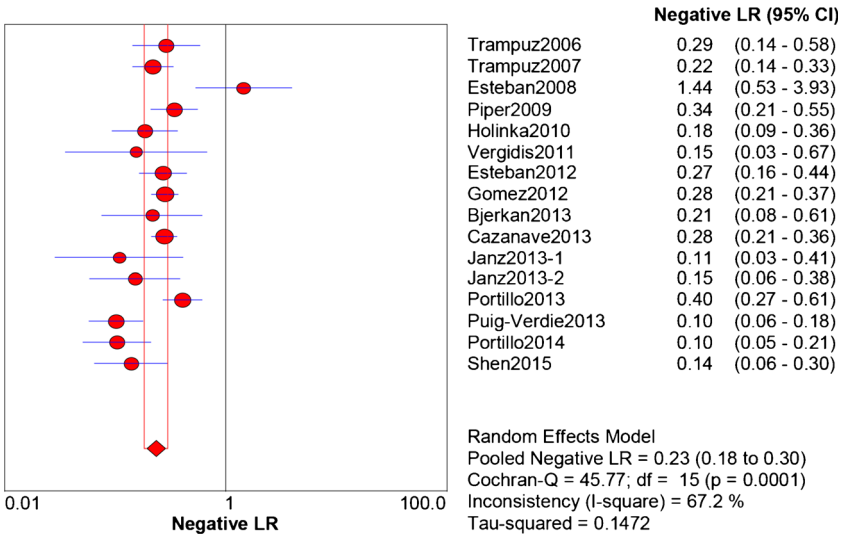


Fig. 8 Forest plots of negative likelihood ratio of sonication for PJI diagnosis

A series of new technologies was applied to promote diagnosis of PJI, including sonication. It was reported that long-wave ultrasound would dislodge the bacteria growing within the biofilm and enhance bacterial growth [13]. Although sonication presented improved detection in diagnosing urinary tract infection [20] and contamination of electrophysiological cardiac devices [21], the efficacy of sonication for detection in PJI was controversial. Our results showed that the application of sonication may be of great value in PJI diagnosis with a pooled sensitivity of 0.79 (95 % confidence interval [CI] = 0.76–0.81), specificity of 0.95 (CI = 0.94–0.96), DOR of 71.20 (CI = 31.08–163.10), PLR of 15.25 (CI = 6.44–36.15), and NLR of 0.23 (CI = 0.18–0.30). The AUC value of the SROC curve was 0.90. According to the above data, sonication should be regarded as a reliable method to diagnose PJI with the meta-analysis pooled sensitivity and specificity aspiration culture as 72 and 95 %, respectively. Furthermore, the last meta-analysis of 12 studies reported the pooled sensitivity of 0.80 (0.74–0.84) and specificity of 0.95 (0.90–0.98). The results were similar to our analysis, which included four additional clinical studies.

It was reported that ultrasound could release more bacteria from protection of the biofilm without decreasing its activity. Compared with traditional tissue culture, sonication was less specific, but more sensitive in patients with and without previous antibiotics. The results of this meta-

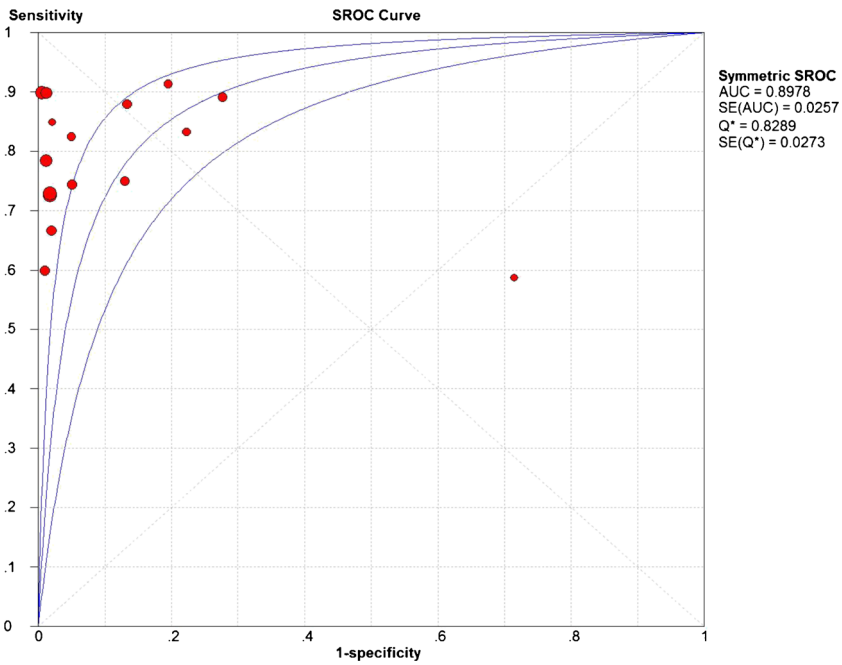
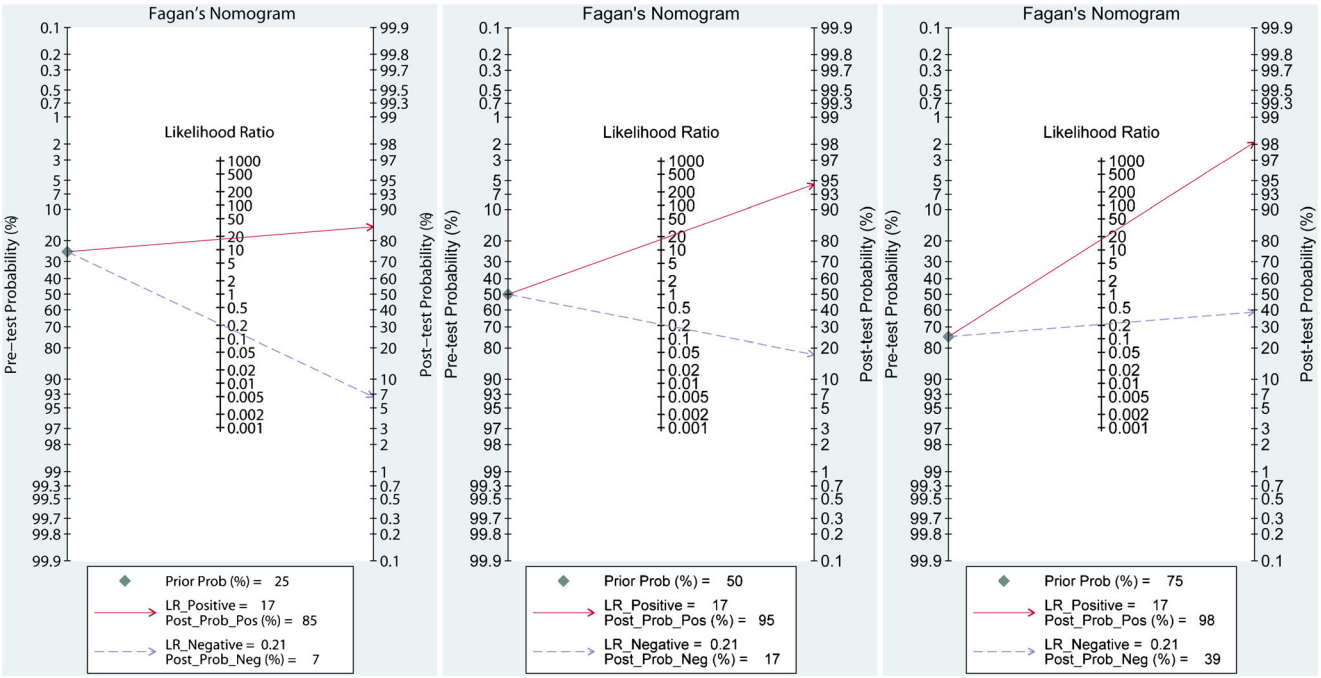


Fig. 9 SROC of sonication for PJI diagnosis



Figs. 10–12 Pre-test probabilities and likelihood ratios (LR) for sonication fluid cultures

analysis suggested that sonication before culture improves microbial recovery in comparison to conventional periprosthetic tissue culture, making it a valid approach and adding important insight into the diagnosis of PJI. Additionally, it could be concluded from the subgroup analysis that the application of vortexing and centrifugation could improve specificity for detecting PJI. Intuitively, sonication would not lead to additional costs or complexity. To assess the value of sonication, cost-effectiveness studies should be conducted. Furthermore, it should be highlighted that sonication can serve as a valuable additional tool for diagnosing PJI, as antibiotic susceptibility testing could be performed more efficiently for adequate treatment.

Preoperative administration of antimicrobial therapy can significantly affect the diagnosis of PJI. Even after stopping antibiotic therapy 14 days before tissue culture, which was usually chosen in clinical practice, the sensitivity was not ideal [22]. It was speculated that this was because planktonic bacteria present in tissue were more susceptible to antimicrobial agents and were killed upon antibiotic therapy. However, bacteria within the biofilm were difficult to kill and be cultured. On this occasion, the application of sonication demonstrated an advantage in dislodging the bacteria out of the biofilm and enhancing its growth, leading to higher sensitivity.

The use of sonication to detect the pathogens is promising. Ultrasound had been used in multiple applications, is well accepted, and has few if any side effects. Using ultrasound, the biofilm-infected device can be specifically targeted. The disadvantages of sonication lay in its false-positive determinations coming from contamination, frequently caused by coagulase-negative Propioni bacterium

Table 2 Subgroup analysis of different clinical procedures

Procedures		Sensitivity	Specificity	PLR	NLR	DOR
Vortexing	Yes	0.778 (0.744–0.810)	0.962 (0.950–0.972)	21.387 (8.305–55.077)	0.231 (0.182–0.294)	111.37 (60.323–205.63)
	No	0.819 (0.760–0.868)	0.923 (0.892–0.948)	7.647 (1.286–45.468)	0.284 (0.132–0.611)	27.091 (3.251–225.79)
Centrifugation	Yes	0.746 (0.710–0.780)	0.962 (0.949–0.972)	16.262 (5.015–52.736)	0.280 (0.223–0.351)	59.941 (21.913–163.96)
	No	0.885 (0.841–0.921)	0.933 (0.908–0.953)	13.671 (3.160–59.146)	0.138 (0.089–0.216)	107.45 (19.102–604.40)
Culture period (days)	≤7	0.827 (0.784–0.865)	0.959 (0.942–0.972)	16.614 (5.589–49.388)	0.200 (0.141–0.283)	87.823 (28.804–267.77)
	>7	0.763 (0.722–0.801)	0.949 (0.933–0.962)	14.237 (3.338–60.725)	0.260 (0.175–0.387)	61.411 (14.119–267.10)
Cutoff (CFU)	<20	0.890 (0.822–0.938)	0.963 (0.931–0.983)	25.316 (0.049–13084.3)	0.129 (0.065–0.258)	169.66 (1.521–18923.0)
	≥20	0.750 (0.711–0.785)	0.983 (0.974–0.989)	38.474 (25.244–58.638)	0.265 (0.212–0.332)	160.59 (96.094–268.36)

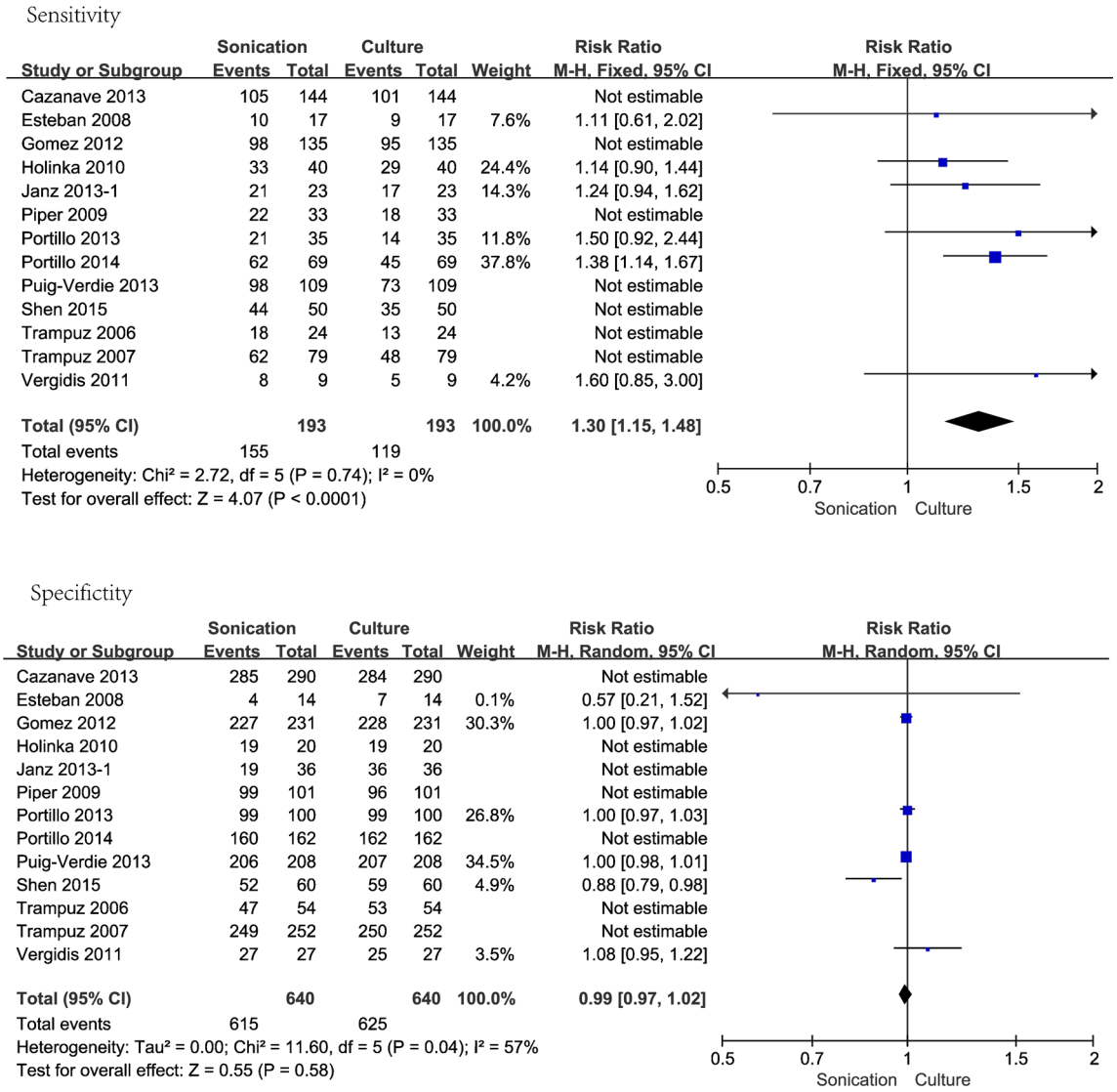


Fig. 13 Comparison of sensitivity and specificity between sonication and traditional culture

or Staphylococcus (CNS). Contamination was thought to occur in transportation to the diagnostic unit, especially due to leakages in plastic transport bags. Interestingly, Esteban [23] reported that organisms isolated as contributing to false positives were all non-fermenter, gram-negative rods or uncommon isolates (environmental mycobacteria and fungi) with a low pathogenic potential for humans, and none of these patients had clinical symptoms. Compared to the high number of colonies detected at the surface of the implants, with the absence of these organisms in control cultures from the sonicator, the authors believed that these organisms could have contributed to the "aseptic loosening" of the implants without causing clinical infection.

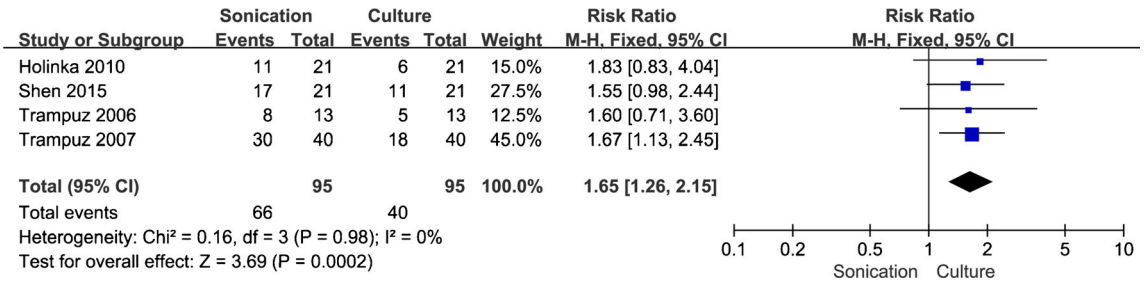


Fig. 14 Comparison of sensitivity in patients with previous antibiotic therapy between sonication and traditional culture

Conclusions

The results of meta-analysis showed that culture of fluid after sonication was of great value for PJI diagnosis. This technique was more sensitive than traditional tissue culture with lower specificity, especially for patients with previous antibiotic treatment. Sonication was simple and could be performed in most microbiology laboratories. Further study should focus on the optimal sonication working parameters, and situations with high isolate colony counts but without clinical symptoms need to be better distinguished as contaminants or pathogens [23].

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The ethics approval was not needed.

Informed consent Informed consent was obtained from all individual participants included in the study.

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