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Original Article

Diagnostic accuracy of GeneXpert in the diagnosis of spinal tuberculosis: A systematic review and meta-analysis

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Abstract

Tuberculosis remains a significant global health issue, with spinal tuberculosis being a severe form of extrapulmonary tuberculosis. Despite the high morbidity associated with spinal tuberculosis, effective and rapid diagnostic methods are limited. The aim of this study was to evaluate the diagnostic accuracy of the GeneXpert compared to other microbiological methods in diagnosing spinal tuberculosis. A systematic review and meta-analysis were conducted following the PRISMA guidelines. Six databases (PubMed, Scopus, EBSCO, EMBASE, ScienceDirect, and Cochrane Central) were searched for relevant studies as of August 31, 2023. Studies were selected based on predefined inclusion criteria, focusing on patients diagnosed with spinal tuberculosis and comparing GeneXpert to microbiological culture, acid-fast bacilli (AFB) staining, and polymerase chain reaction (PCR). Two authors independently performed data extraction and quality assessment, and the meta-analysis was conducted using Meta-DiSc 2.0. Fourteen studies comprising retrospective cohort, prospective cohort, and cross-sectional designs were included. GeneXpert demonstrated a pooled sensitivity of 92% (85–96%) and specificity of 71% (51–86%) compared to culture. AFB smear had the highest specificity at 80% (70–88%) but the lowest sensitivity at 27% (20–35%). The PCR had sensitivity and specificity of 83% (67–92%) and 58% (31–81%), respectively. Substantial heterogeneity was noted across the studies. This study highlighted that GeneXpert had high sensitivity and moderate specificity in diagnosing spinal tuberculosis, making it an alternative to conventional methods. However, further validation through larger, interventional studies is necessary to standardize its use in clinical practice.

Keywords: Tuberculosis, spinal tuberculosis, GeneXpert, mycobacterial culture, *Mycobacterium tuberculosis*

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, and it remains a common problem worldwide. In 2016, the incidence rate of TB reached 120 cases per 100,000 individuals worldwide, with Indonesia ranking third after China and India [1]. Besides affecting the respiratory system (pulmonary TB), TB can also cause systemic clinical manifestations known as extrapulmonary TB, one of which involves the spine, known as spinal TB [1,2]. The incidence of spinal TB accounts for 1–5% of the overall TB cases, with spinal TB

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comprising 50% of all TB cases affecting the bones and joints [3]. Spinal TB cases are often associated with high morbidity rates, with kyphotic deformity occurring due to vertebral bone damage, leading to sensory and motor deficits in 77.1% of cases, necessitating early detection and appropriate management [2].

To date, global efforts in managing spinal TB have been hindered by the need for accurate, rapid, and simple diagnostic methods. The gold standard microbiological culture method, with high sensitivity and specificity, requires 10 to 14 days to provide results [3]. GeneXpert system is a diagnostic method that utilizes nucleic acid amplification technology (NAAT) to detect the presence of *M. tuberculosis* in clinical specimens, such as sputum, cerebrospinal fluid (CSF), or tissue biopsy. The GeneXpert is based on adapting polymerase chain reaction (PCR) technology, which amplifies specific DNA segments to detectable levels, enabling rapid and accurate identification of *M. tuberculosis* [4].

The GeneXpert has several advantages over conventional TB diagnostic methods, including requiring minimal sample preparation and providing results in less than two hours [5,6]. Its use can help improve the diagnosis and management of the disease, especially in areas where access to conventional diagnostic methods may be limited [5,7]. However, despite the advantages, there is currently no consensus on the basis for using GeneXpert as the standard method for diagnosing spinal TB, and research in this area is still considered very limited. Therefore, the aim of this study was to investigate the sensitivity and specificity of GeneXpert compared to other microbiological methods used in diagnosing spinal TB by using a systematic review and meta-analysis approach.

Methods

Study design and registration

This systematic review and meta-analysis followed the Preferred Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline [8]. The protocol of this systematic review has been registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42024485878.

Search strategy

The search for studies was conducted as of August 31, 2023, on six electronic databases (PubMed, Scopus, EBSCO, EMBASE, ScienceDirect, and Cochrane Central). The Cochrane Handbook of Systematic Reviews 2018 search strategy was used, including subject headings (MeSH terms) adopted for other electronic databases. The keywords used were "Spinal tuberculosis," "Pott's disease," "Microbiological culture," "Acid-fast bacilli staining," "PCR," "GeneXpert," "Diagnostic," "Specificity," and "Sensitivity." Eligibility criteria for studies based on PICO were: (1) participant: patients diagnosed with spinal TB; (2) intervention: GeneXpert examination; (3) comparison: microbiological culture examination, AFB staining, and PCR examination; and (4) outcome: sensitivity and specificity of examination methods in diagnosing spinal TB. The inclusion criteria for the study were: (1) studies published in the last 50 years; (2) studies in English and Indonesian languages with human samples; (3) studies with randomized clinical trial (RCT), quasi-RCT, and observational (cohort, case-control, and cross-sectional) designs; and (4) studies comparing the specificity and sensitivity of microbiological culture examination, AFB staining, and PCR with the GeneXpert method in diagnosing spinal TB. Case reports and case series studies with a sample size of less than 10 were excluded.

Study selection and data extraction

Study selection was based on predefined inclusion criteria, screened by two authors (KTB and IGPY). The authors independently screened search results based on the title and abstract. Subsequently, the full text of potential studies was reviewed for inclusion eligibility. The obtained data were input into Review Manager (RevMan) 5, which was then checked for accuracy. The following data were extracted from the selected studies: author names, year of publication, country of study location, sample size, study design, sample type, sensitivity, specificity, true positive (TP), true negative (TN), false positive (FP), and false negative (FN).

Quality assessment

Two authors (KTB and IGPY) independently assessed each study's risk of bias, with any conflicts resolved through discussion. The risk of bias for all included studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist of essential items, modified according to Sanderson *et al.* [9] and Fowkes and Fulton [10]. The modified checklist consists of five criteria: methods for selecting study participants, methods for measuring exposure and outcome variables, methods to control confounding, design-specific sources of bias, and statistical methods. Each study's overall risk of bias was rated as high, moderate/doubtful, or low.

Data synthesis and statistical analysis

The data was analyzed using the extracted information. For each research, a 2×2 contingency table with the number of true positives (TPs), false positives (FPs), false negatives (FNs), and true negatives (TNs) was created. Sensitivity and specificity served as the primary metrics for diagnostic accuracy. Meta-analyses of diagnostic test accuracy (ATD) studies were conducted using Meta-DiSc version 2.0 (Clinical Biostatistics Unit of the Ramon y Cajal Research Institute, Madrid, Spain). When three or fewer papers were included in the analysis, Meta-DiSc 2.0 employed the univariate random effects model for statistical meta-analyses. Otherwise, the bivariate random effects model was used. Pooled accuracy estimates were computed with their 95% confidence intervals (95%CIs), sensitivity and specificity, diagnostic odds ratio, positive and negative predictive likelihood ratios, and false positive rate. The summary receiver operating characteristic (SROC) curves and forest plots were created. The size of the 95% prediction ellipse, the bivariate I^2 index, the logit variances of sensitivity and specificity, and the median odds ratios for each variable were used to measure heterogeneity [11].

Results

Study selection

The searches yielded a total of 1,321 articles, with 347 articles from PubMed, 206 from ScienceDirect, 270 from EBSCO, 149 from EMBASE, 249 from Scopus, and 100 from the Cochrane Central database. After filtering duplicates and excluding irrelevant articles based on title, 30 articles were examined for the availability of full texts and data related to the research objective. Following the assessment of full texts, 14 articles were included for analysis [2-4,12-24]. The study selection steps are presented in **Figure 1**.

Characteristics of studies

Out of the 14 included articles, five were retrospective cohort studies, four were prospective cohort studies, and five were cross-sectional observational studies. The suspected group of spinal TB comprised patients with standard clinical parameters for microbiological testing (microbiological culture, PCR, and AFB staining). Detailed characteristics of the included studies and the results of each study are outlined in **Table 1**.

Risk of bias assessment

The quality of individual studies analysis was conducted according to the study design using STROBE, where this checklist was used to analyze the risk of bias in cohort and cross-sectional studies. The results of the risk of bias assessment are presented in **Table 2**.

Accuracy of GeneXpert and other microbiological examination methods in diagnosing spinal TB compared to microbiological culture

GeneXpert compared to microbiological culture

Four studies consisting of 961 samples were tested with GeneXpert and compared with culture as the reference standard [1,13,18,21]. The sensitivity of GeneXpert ranged from 86% (82–90%) to 97% (83–100%). The pooled sensitivity of GeneXpert was 92% (85–96%), with an I^2=55%. Meanwhile, the specificity ranged from 46% (37–55%) to 90% (55–100%). The pooled specificity of GeneXpert was 71% (51–86%), with an I^2=53%. There was substantial heterogeneity in specificity (**Figures 2A** and **2B**).

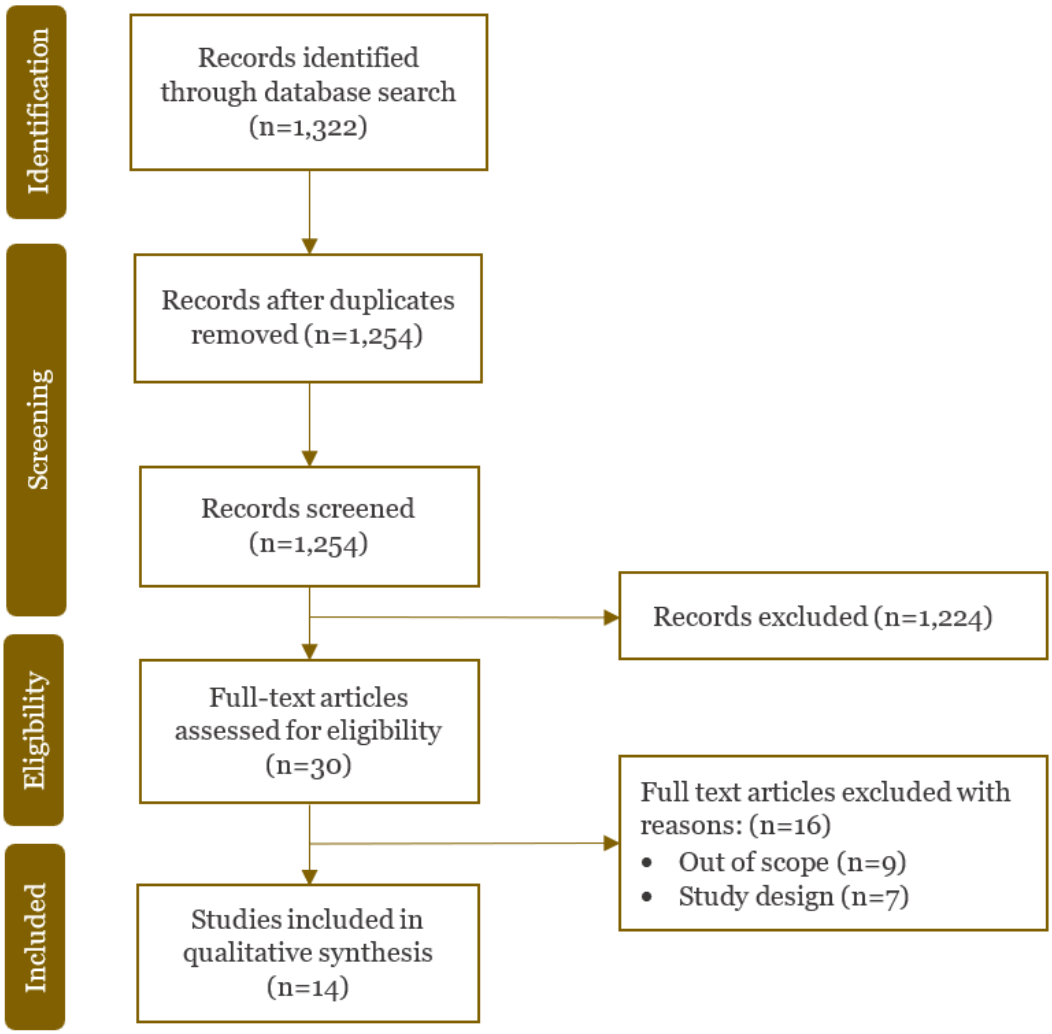

Figure 1. PRISMA flowchart for study selection.

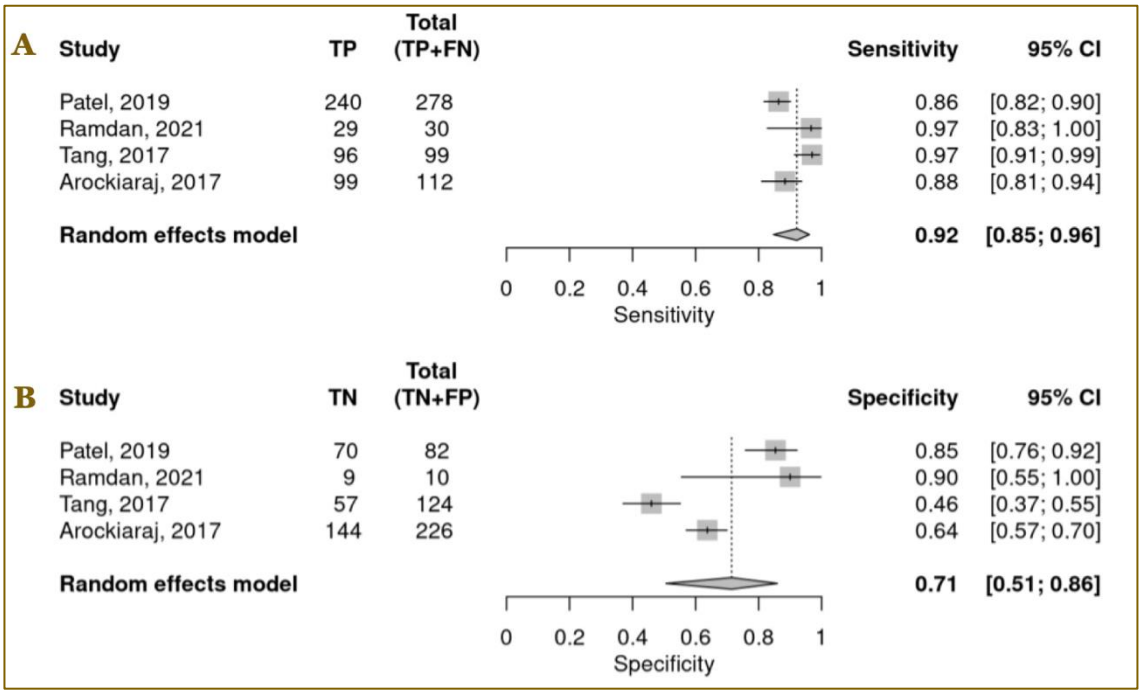

Figure 2. Comparison of accuracy between GeneXpert and microbiological culture. The forest plots showing the sensitivity (A) and specificity (B). CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive.

Table 1. Characteristics of included studies

Authors, year	Sample size	Country	Study design	Sample type	DNA extraction	Comparison	GeneXpert	
							Sensitivity (%)	Specificity (%)
Shetty *et al.*, 2022 [16]	150	India	Retrospective cohort study	Tissue lesion	No centrifuge	Microbiological culture, AFB smear, PCR	100.0	80.0
Jagiasi *et al.*, 2020 [17]	31	India	Retrospective cohort study	Tissue lesion	No centrifuge	Microbiological culture, PCR	77.0	88.0
Held *et al.*, 2014 [3]	71	South Africa	Prospective cohort study	Tissue lesion/pus swab	Centrifuge	CRS, microbiological culture, PCR	96.0	96.0
Solanki *et al.*, 2019 [4]	68	India	Prospective cohort study	Tissue lesion	Centrifuge	CRS	91.0	100.0
Patel *et al.*, 2019 [18]	360	India	Cross-sectional study	Tissue lesion	Centrifuge	Microbiological culture, AFB Smear	86.0	85.0
Salim *et al.*, 2021 [1]	40	Indonesia	Cross-sectional study	Tissue lesion	Centrifuge	Microbiological culture, PCR	97.0	90.0
Qi *et al.*, 2022 [20]	519	China	Prospective cohort study	Tissue lesion	Centrifuge	NA	51.0	99.0
Tang *et al.*, 2017 [21]	223	China	Cross-sectional study	Pus, granulation tissue, and caseous necrotic tissue specimen	Centrifuge	Microbiological culture	96.0	96.0
Yu *et al.*, 2020 [22]	128	China	Prospective cohort study	Tissue lesion	Centrifuge	Histopathology	86.7	60.0
Karthek *et al.*, 2021 [2]	125	India	Retrospective cohort study	Tissue samples and pus samples	Centrifuge	CRS	65.1	100.0
Massi *et al.*, 2017 [12]	70	Indonesia	Cross-sectional study	Tissue specimen from bone	Centrifuge	Microbiological culture	100.0	16.6
Arockiaraj *et al.*, 2017 [13]	338	India	Retrospective cohort study	Tissue/pus	No centrifuge	CRS	88.4	63.7
Li *et al.*, 2023 [14]	41	China	Retrospective cohort study	Serum, pus, and pathological tissues	Centrifuge	CRS	54.0	100.0
Wang *et al.*, 2018 [15]	319	China	Cross-sectional study	Tissue bone and joint	No centrifuge	Microbiological culture, AFB smear, CRS	85.0	100.0

AFB: acid-fast bacilli; CRS: composite reference standard; NA: not applicable; PCR: polymerase chain reaction

Table 2. Risk of bias assessment summary

Authors, year	Methods for selecting study participants	Methods for measuring exposure and outcome variables	Methods to control confounding	Design-specific sources of bias	Statistical methods	Overall risk of bias
Shetty *et al.*, 2022 [16]	+	+	+	+	+	+
Jagiasi *et al.*, 2020 [17]	+	+	+	+	+	+
Held *et al.*, 2014 [3]	+	+	-	+	+	-
Solanki *et al.*, 2019 [4]	+	+	X	+	+	-
Patel *et al.*, 2019 [18]	+	+	+	+	+	+
Salim *et al.*, 2021 [1]	+	-	X	+	+	-
Qi *et al.*, 2022 [20]	+	+	+	+	+	+
Tang *et al.*, 2017 [21]	+	+	+	+	+	+
Yu *et al.*, 2020 [22]	+	+	+	+	+	+
Karthek *et al.*, 2021 [2]	+	+	+	+	+	+
Massi *et al.*, 2017 [12]	+	+	+	+	+	+
Arockiaraj *et al.*, 2017 [13]	+	+	+	+	+	+
Li *et al.*, 2023 [14]	+	+	+	+	+	+
Wang *et al.*, 2018[15]	+	+	+	+	+	+

+ : low

- : some concerns

X : high

Acid-fast bacilli (AFB) smear compared to microbiological culture

Three studies consisting of 824 samples were tested with AFB smear and compared with culture as reference standard [15,16,18]. The sensitivity of AFB smear ranged from 23% (15–31%) to 36% (29–44%). The pooled sensitivity of AFB smear was 27% (20–35%), with an I^2=71%. Meanwhile, the AFB specificity ranged from 71% (53–85%) to 88% (82–93%). The pooled specificity of AFB smear against culture was 80% (70–88%), with an I^2=68%. There was substantial heterogeneity in sensitivity (**Figures 3A** and **3B**).

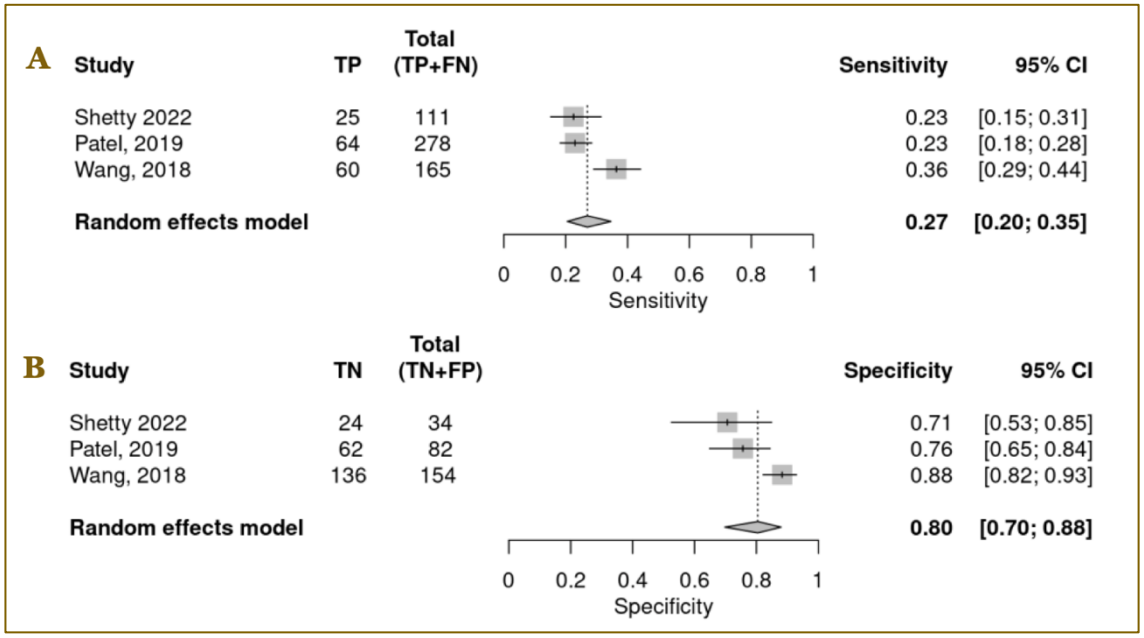

Figure 3. Comparison of accuracy between AFB smear and microbiological culture. The forest plots show sensitivity (A) and specificity (B). CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive.

PCR compared to microbiological culture

Four studies consisting of 292 samples used PCR and compared with culture as the reference standard [1,3,16,17]. The sensitivity of PCR ranged from 65% (47–80%) to 97% (83–100%). The pooled sensitivity of PCR was 83% (67–92%), with an I^2=52%. Meanwhile, the specificity ranged from 20% (6–44%) to 90% (55–100%). The pooled specificity of PCR against culture was 58% (31–81%), with an I^2=68%. There was substantial heterogeneity in sensitivity and specificity (**Figures 4A** and **4B**).

The summary of each assay's combined sensitivity and specificity results compared to the gold standard microbiological culture are presented in **Table 3**. Among all assays compared to culture, GeneXpert had the highest sensitivity, 92% (85–96%). Meanwhile, the assay with the highest specificity compared to culture was the AFB smear, with a specificity of 80% (70–88%).

Table 3. Summary of sensitivity and specificity of each GeneXpert, acid-fast bacilli smear and polymerase chain reaction (PCR) compared to microbiological culture

Type of assay vs bacterial culture	Sensitivity (%)	Specificity (%)
GeneXpert	92 (85–96)	71 (51–86)
Acid-fast bacilli (AFB)	27 (20–35)	80 (70–88)
Polymerase chain reaction (PCR)	83 (67–92)	58 (31–81)

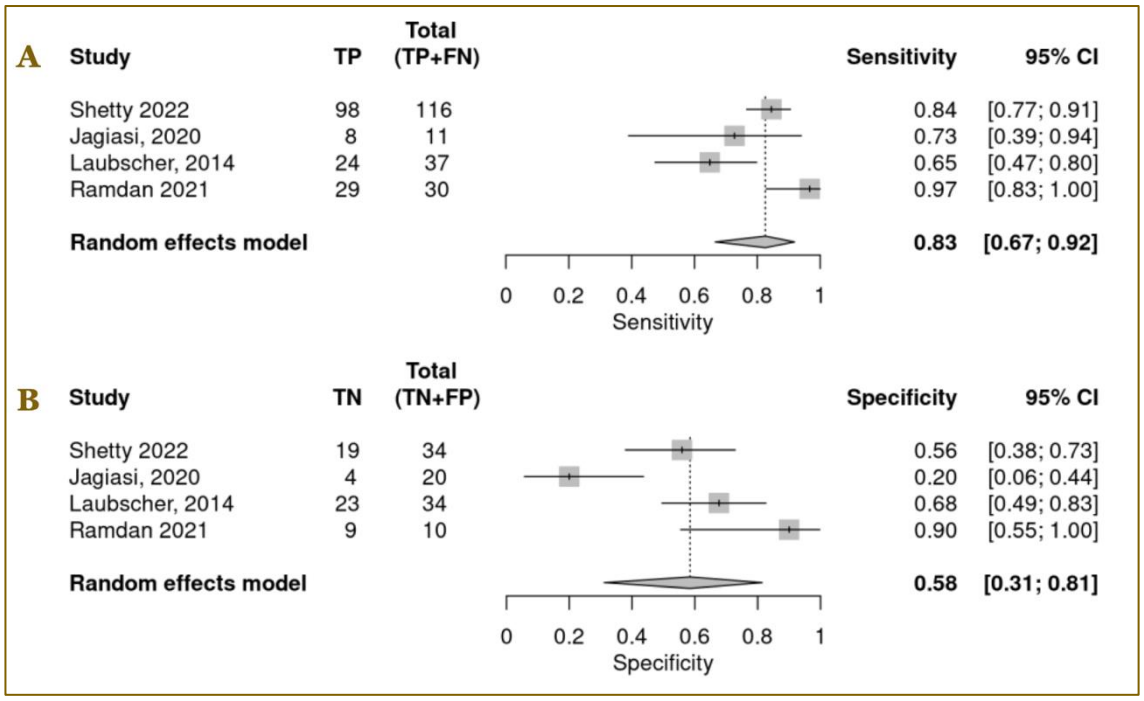

Figure 4. Comparison of accuracy between PCR and microbiological culture. The forest plots showing the sensitivity (A) and specificity (B). CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive.

Discussion

In this study, the sensitivity and specificity of GeneXpert and other microbiological examinations (AFB smear and PCR) were compared to microbial culture examination as the gold standard in diagnosing spinal TB. Among the three examinations, GeneXpert had the highest sensitivity rate (92%) compared to microbiological culture. In addition to having the highest sensitivity rate, GeneXpert ranked second for specificity (71%). Referring to these results, the GeneXpert could be an alternative diagnostic method for diagnosing spinal TB. Besides having a relatively high level of diagnostic accuracy, GeneXpert also shows various advantages, including faster results with diagnostic accuracy similar to the gold standard microbiological culture and the ability to detect rifampicin resistance in a population [25-27].

Currently, there are two methods of PCR that are commonly used in the diagnosis of TB: PCR with GenXpert method and conventional PCR. Our study found that GeneXpert had higher sensitivity and specificity rates (92% and 71%) compared to microbiological culture as the gold standard, while PCR had 83% and 58% rates. These numbers again demonstrate the GeneXpert method's superiority in diagnosing spinal TB. GeneXpert itself uses the β-subunit of RNA polymerase gene (*rpoB*) as the target, while conventional PCR widely uses insertion sequence (IS) 6110 segments in the *M. tuberculosis* genome as its target [28-30]. In addition to having advantages in terms of diagnostic accuracy, the GeneXpert also has the advantage of faster examination processing time (around two hours) compared to PCR, with a processing time of 4–5 hours. GeneXpert is semi-automated and more accessible to perform so that it can be operated by human resources trained in simple ways, and it has a shorter hands-on time (2–3 minutes per sample), thus reducing the risk of sample cross-contamination [31-33].

Among the three examinations compared to microbiological culture as the gold standard, the AFB smear examination was found to have the highest specificity rate, around 80%, but with a low sensitivity rate (27%). Therefore, the AFB smear examination is considered more suitable for use as a screening method than a diagnostic confirmation method; this method can be chosen considering that this examination is available in almost every primary health care center in Indonesia with relatively more affordable operational costs than other examination methods [34,35]. The high specificity of AFB in detecting *M. tuberculosis* can also provide an alternative

to supporting diagnostic accuracy through its combination with GeneXpert so that examination results and diagnoses can be more accurate.

The sensitivity and specificity of GeneXpert as a diagnostic method for pulmonary and extrapulmonary TB are essential metrics in assessing its clinical utility. In one study, GeneXpert showed extraordinary sensitivity and specificity for pulmonary TB, with sensitivity and specificity values of 100% and 99%, respectively [36]. This underscores the efficacy of GeneXpert as a reliable diagnostic tool for detecting *M. tuberculosis* in sputum samples, facilitating rapid treatment initiation and disease containment. Two systematic reviews found that GeneXpert showed slightly lower sensitivity, 87%, which may be related to the lower bacterial load in samples other than sputum (respiratory tract) but maintained a relatively high specificity of 99% [37,38]. A previous study also found that GeneXpert had advantages over PCR with a sensitivity of 80% [39]. Another study proved that GeneXpert was superior to PCR in detecting TB in terms of higher sensitivity in detecting extrapulmonary TB, where in addition to diagnostic accuracy, GeneXpert is also very fast in providing output and can identify resistance to rifampicin drugs so that it can be used as the primary choice for the diagnosis of extrapulmonary TB [40]. Although it needs to be reviewed, low sensitivity in extrapulmonary TB cases indicates difficulties in diagnosing TB with non-respiratory sample collection locations, where the bacterial load and sample quality are very different. Nevertheless, the high specificity of GeneXpert indicates its potential as a diagnostic examination method that can be useful for confirming extrapulmonary TB cases with a combination of clinical and radiological findings to ensure accurate diagnosis and treatment decisions [41-43].

This study has some limitations. First, it has a relatively small sample size. Second, it has a relatively high level of heterogeneity in the results of each comparison of examination methods. The substantial heterogeneity variation in the sensitivity and specificity highlighted the uncertainty in diagnostic research, reflecting various patient groups and laboratory techniques, including the sample preparations used in multiple contexts. These differences highlight the importance of critically evaluating research findings based on specific demographics, procedures, and sample forms.

Conclusion

GeneXpert demonstrated moderate to high sensitivity and specificity in diagnosing spinal TB, with PCR being the most sensitive and specific method compared to other microbiological examinations. These findings suggest that GeneXpert can be a reliable alternative for diagnosing spinal TB, especially in settings with limited access to conventional diagnostic methods. However, further research is needed to validate these findings and establish standardized protocols for using GeneXpert to diagnose spinal TB.

Ethics approval

Not required.

Acknowledgments

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Data supporting the findings of this study are available in the article.

How to cite

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