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MINIREVIEW

Value of Xpert MTB/RIF Using Bronchoalveolar Lavage Fluid for the Diagnosis of Pulmonary Tuberculosis: a Systematic Review and Meta-analysis

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ABSTRACT The performance of Xpert MTB/RIF using bronchoalveolar lavage fluid (BAL) for the diagnosis of pulmonary tuberculosis (PTB) remains unclear. Therefore, a systematic review/meta-analysis was conducted. Studies published before 31 December 2019 were retrieved from the PubMed, Embase, and Web of Science databases using the keywords "pulmonary tuberculosis," "Xpert MTB/RIF," and "BAL." Two independent evaluators extracted the data and assessed the bias risk of the included studies. A random-effects model was used to calculate the overall sensitivity, specificity, positive and negative likelihood ratios (PLR and NLR, respectively), diagnostic odds ratio (DOR), and the area under the curve (AUC), as well as the respective 95% confidence intervals (CIs). Nineteen trials involving 3,019 participants met the inclusion criteria. Compared to the culture method, the pooled sensitivity, specificity, PLR, NLR, DOR, and the AUC with 95% CIs of Xpert MTB/RIF were 0.87 (0.84 to 0.90), 0.92 (0.91 to 0.93), 10.21 (5.78 to 18.02), 0.16 (0.12 to 0.22), 78.95 (38.59 to 161.53), and 0.9467 (0.9462 to 0.9472), respectively. Relative to the composite reference standard, the observed values were 0.69 (0.65 to 0.72), 0.98 (0.98 to 0.99), 37.50 (18.59 to 75.62), 0.30 (0.21 to 0.43), 171.98 (80.82 to 365.96), and 0.9691 (0.9683 to 0.9699), respectively. All subgroups, except children, showed high sensitivity and specificity. In conclusion, the use of Xpert MTB/RIF in the context of BAL samples has a high diagnostic performance for PTB (except for children) and may serve as an alternative rapid diagnostic tool.

KEYWORDS Xpert MTB/RIF, bronchoalveolar lavage fluid, pulmonary tuberculosis, meta-analysis, systematic review

The World Health Organization (WHO) has identified tuberculosis as 1 of the top 10 leading causes of death worldwide (1). The early diagnosis of pulmonary tuberculosis (PTB) is essential to reduce the spread, morbidity, mortality, and escalating costs associated with advanced disease (2). Traditional diagnostic tools, including sputum acid-fast bacillus (AFB) smear and *Mycobacterium* culture, are fraught with challenges. *Mycobacterium tuberculosis* culture based on solid media takes up to 4 to 8 weeks, and the sensitivity of the traditional AFB smear can be as low as 20% (3, 4). Additionally, although the *M. tuberculosis* liquid culture method is faster, it still takes 2 to 4 weeks (4). Moreover, tuberculosis culture methods to support the diagnosis of PTB are not widely available in high-burden settings (5).

In 2011, the WHO recommended the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) for the diagnosis of PTB and the detection of rifampicin resistance. The Xpert MTB/RIF

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assay is an automated, single-cartridge-based nucleic acid amplification test that is able to simultaneously detect *M. tuberculosis* and rifampicin resistance within 2 to 3 h. Currently, Xpert MTB/RIF often uses sputum samples to diagnose PTB. Remarkably, a small clinical validation study of the Xpert MTB/RIF test using 107 clinical sputum samples from suspected tuberculosis cases in Vietnam detected 29/29 (100%) smear-positive culture-positive cases and 33/39 (84.6%) or 38/53 (71.7%) smear-negative culture-positive cases, as determined by growth on solid medium or on both solid and liquid media, respectively (6). Additionally, another large sample study showed that among culture-positive patients, the Xpert MTB/RIF test identified 551 of 561 patients with smear-positive tuberculosis (98.2%) and 124 of 171 with smear-negative tuberculosis (72.5%) (7), suggesting that the sensitivity of the Xpert MTB/RIF test for patients with smear-negative tuberculosis is lower. However, there is a considerable proportion of PTB patients with a negative sputum test, or sputum-scarce PTB, in the clinical practice. Interestingly, fiberoptic bronchoscopy was suggested as a helpful approach for the diagnosis of sputum smear-negative and sputum-scarce PTB, once it provides high-quality biological samples such as bronchoalveolar lavage fluid (BAL) (8). Some evidence has indicated that the performance of the Xpert MTB/RIF method using BAL is superior to that using sputum samples for the diagnosis of PTB, especially for patients with sputum smear-negative PTB (9). However, a systematic review of the Xpert MTB/RIF method using BAL for the diagnosis of PTB was never performed. Thus, the purpose of the present meta-analysis was to clarify the value of the Xpert MTB/RIF test using BAL for the diagnosis of PTB.

METHODS

Trial search. Two researchers independently searched all studies published in the PubMed, EMBASE, and Web of Science databases using the key terms "pulmonary tuberculosis," "Xpert MTB/RIF," and "bronchoalveolar lavage fluid;" all studies published until 31 December 2019 were considered. Two evaluators independently screened the literature, extracted the data, and assessed the bias risk of the included studies. When the opinions of the two researchers did not match, a third researcher was consulted.

Inclusion and exclusion criteria. The inclusion and exclusion criteria for the studies were determined prior to data extraction. The inclusion criteria were as follows: (i) the subjects were suspected PTB patients; (ii) the diagnosis method was the Xpert MTB/RIF assay; (iii) the samples used were BAL; (iv) the reference tests used were *M. tuberculosis* cultures (tuberculosis culture based on solid or liquid media) or the composite reference standard (PTB was defined as a positive culture or clinically diagnosed based on the clinical symptoms of the patients, including cough for more than 2 weeks, fever, or weight loss, pneumonia that did not improve using antibiotics, or contact with an adult who had tuberculosis); and (v) the available data were used for calculating the sensitivity, specificity, and likelihood ratios. The exclusion criteria included the following: (i) republished literature;(ii) letters, abstracts, or conference abstracts; (iii) the use of non-Xpert MTB/RIF methods for the detection of tuberculosis; (iv) incomplete data; and (v) unrelated literature. Based on the above criteria, the researchers used EndNote X7 software (Thomson Corporation, Stamford, CT) to remove duplicated studies.

Data extraction and methodological quality evaluation. The literature selection and data extraction were carried out by two independent researchers. Any inconsistencies were solved through discussion. The extracted data included the following: first author; publication year; age; country; study design; reference test (*M. tuberculosis* culture method); the preanalytic procedure of the BAL samples (using concentrated BAL and/or digested BAL); sputum test (smear-positive; smear-negative or sputum scarce); the number of samples; test results involving true positives, false positives, false negatives, and true negatives; and additional relevant items for bias risk assessment. The risk of bias in each study was evaluated independently by two researchers using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (10). A "yes" (low degree of bias risk or good applicability), "no" (high degree of bias risk or poor applicability), or "unclear" (lack of relevant information or uncertainty of bias risk) designation was attributed to each item to define the quality of each study.

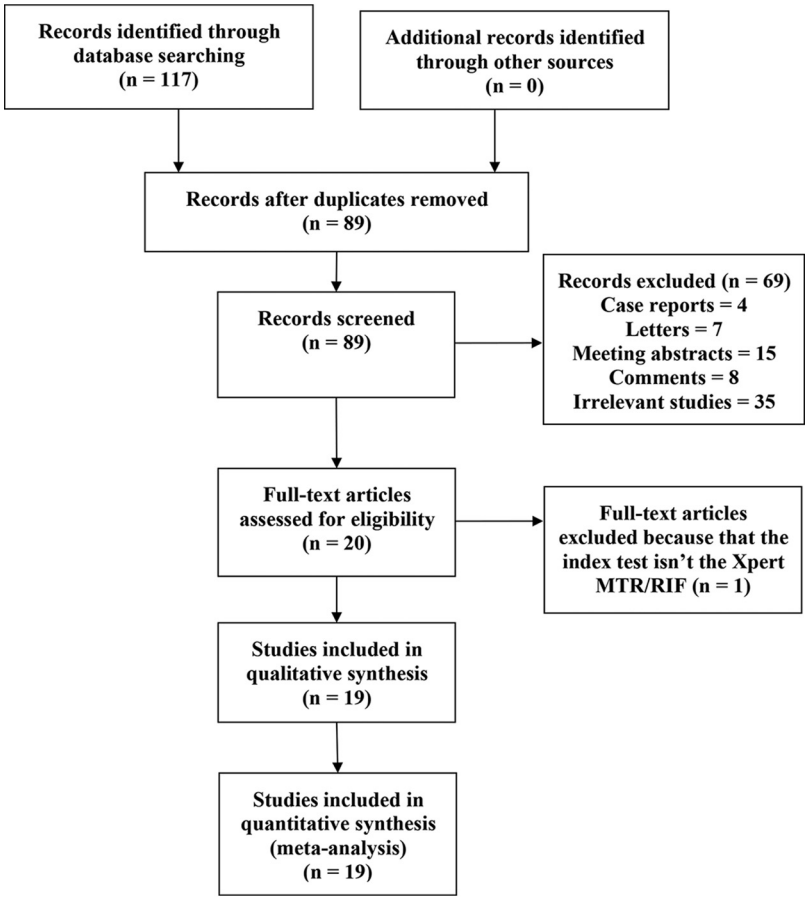

FIG 1 Literature search and screening process.

Statistical analysis. The Stata 15.1 (StataCorp, College Station, TX), Meta-Disc 1.4 (Clinical Biostatistics Unit, Madrid, Spain), and Review Manager 5.2 (Cochrane Collaboration, Oxford, UK) software tools were used for this meta-analysis. The overall sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% confidence interval (CI) and the area under the curve (AUC) in the context of the Xpert MTB/RIF test were calculated. Heterogeneity was evaluated using I^2 statistics. The I^2 was interpreted as follows: 0% to 25%, no significant heterogeneity; 26 to 50%, low heterogeneity; 51% to 75%, moderate heterogeneity; and >75%, high heterogeneity. Spearman correlation was employed to determine the presence of a threshold effect (a strong correlation indicated a threshold effect). Meta-regression and subgroup analyses were conducted using six independent variables, including age (children or adults), country (developed or developing country), study design (retrospective or prospective), sputum test (smear positive or smear negative/sputum scarce), culture method of the reference test (liquid culture or other culture methods) and the preanalytic procedure of BAL (yes or no). Using DOR as the dependent variable and the reciprocal of the square root of the effective sample size as the independent variable, a Deeks funnel plot was generated to evaluate the publication bias. *P* values lower than 0.05 were considered statistically significant.

RESULTS

Literature screening and inclusion. A total of 117 documents were obtained from the initial examination. After removal of duplicates and irrelevant records, 19 studies met the inclusion criteria (Fig. 1).

TABLE 1 Characteristics of the included studies and their respective participants

Study no.	Authors (reference)	Yr	Country	Age category	Sputum smear	Study design	Reference standard	Preanalytic procedure	Sample size	TP	FP	FN	TN
1	Theron et al. (9)	2013	South Africa	Adults	Negative	Prospective	Culture (liquid)	Yes	152	25	5	2	120
2	Barnard et al. (11)	2015	South Africa	Adults	Negative	Retrospective	Culture (liquid)	No	112	36	9	3	64
							CRS[a]		112	39	6	5	62
3	Feliciano et al. (12)	2019	Brazil	Adults	Positive	Retrospective	Culture (liquid)	Unclear	348	19	8	1	320
							CRS		348	22	5	1	320
4	Gowda et al. (13)	2018	India	Adults	Negative	Prospective	Culture (liquid)	No	56	13	11	3	29
							CRS		60	24	0	28	8
5	Khalia and Butt (14)	2014	Pakistan	Adults	Negative	Prospective	Culture (liquid)	Unclear	93	79	2	7	5
6	Kilaru et al. (15)	2019	India	Adults	Negative	Prospective	Culture (liquid)	No	56	9	22	1	24
7	To et al. (16)	2018	Hong Kong	Adults	Positive	Prospective	Culture (uncertain)	Unclear	223	32	7	6	178
							CRS		223	36	3	9	175
8	Lee et al. (17)	2018	Korea	Adults	Negative	Retrospective	Culture (both)	No	132	31	0	7	94
9	Lu et al. (18)	2018	China	Adults	Positive	Retrospective	Culture (both)	Unclear	238	49	2	9	178
							CRS		238	62	2	23	151
10	Mok et al. (19)	2016	Singapore	Adults	Negative	Retrospective	Culture (liquid)	Unclear	158	30	0	14	112
11	Le Palud et al. (20)	2014	France	Adults	Negative	Retrospective	Culture (liquid)	Yes	162	16	2	4	140
							CRS		162	18	0	12	132
12	Pan et al. (21)	2018	China	Adults	Positive	Prospective	Culture (liquid)	Yes	190	64	18	13	95
							CRS		190	80	2	51	57
13	Saini et al. (22)	2018	India	Children	Positive	Prospective	Culture (liquid)	Unclear	41	9	15	2	15
14	Silva et al. (23)	2018	Brazil	Adults	Positive	Retrospective	Culture (solid)	Unclear	199	19	9	0	171
15	Ullah et al. (24)	2017	Pakistan	Adults	Positive	Prospective	Culture (uncertain)	Yes	88	32	6	8	42
16	Walters et al. (25)	2013	South Africa	Children	Positive	Prospective	Culture (liquid)	No	14	7	2	2	3
17	Xu et al. (26)	2019	China	Adults	Positive	Prospective	Culture (uncertain)	Yes	182	75	3	2	102
18	Yin et al. (27)	2014	China	Children	Positive	Prospective	CRS	Unclear	251	44	0	39	168
19	Jo et al. (28)	2016	Korea	Adults	Positive	Retrospective	Culture (uncertain)	Unclear	320	59	47	5	209
							CRS		320	104	2	26	188

[a]CRS, composite reference standard.

Characteristics and quality assessment of the included studies. Altogether, 3,019 samples from the 19 studies were included in this meta-analysis (11–29). There were 7 prospective studies and 12 retrospective studies. The *M. tuberculosis* culture method was used as the reference standard in 18 studies, whereas the clinical composite diagnosis method was used as the reference standard in 9 studies. Among the studies, 16 involved adults and the other 3 focused on children. The characteristics of the included trials and participants are summarized in Table 1.

Figure 2 shows the quality and applicability evaluations of the 19 included studies. With respect to patient selection, 14 studies had a low risk of bias, whereas the remaining 5 were rated as "unclear" owing to unclear recruitment procedures. Regarding the inclusion of patients in the applicability analysis, 12 studies were rated as "of high concern" because their patient populations were assessed in a tertiary hospital center rather than the local community or primary hospital, and 7 studies were defined as "of unknown concern." Concerning index testing and reference standards, all bias risks in the studies as well as their applicability were rated as "of low concern."

Meta-analysis results of Xpert MTB/RIF. When *M. tuberculosis* culture was used as the gold standard for diagnosis, the pooled sensitivity, specificity, PLR, NLR, DOR, and AUC with 95% CIs of Xpert MTB/RIF using BAL for the diagnosis of PTB were 0.87 (0.84 to 0.90), 0.92 (0.91 to 0.93), 10.21 (5.78 to 18.02), 0.16 (0.12 to 0.22), 78.95 (38.59 to 161.53), and 0.9467 (0.9462 to 0.9472), respectively (Fig. 3 and 4; Fig. S1). When the composite reference standard (CRS) was the reference method, the pooled sensitivity, specificity, PLR, NLR, DOR, and AUC with 95% CIs of Xpert MTB/RIF using BAL for the diagnosis of *M. tuberculosis* were 0.69 (0.65 to 0.72), 0.98 (0.98 to 0.99), 37.50 (18.59 to 75.62), 0.30 (0.21 to 0.43), 171.98 (80.82 to 365.96), and 0.9691 (0.968 to 0.9699), respectively (Fig. 5 and 6; Fig. S2). Of note, there was a significant heterogeneity ($I^2 >$ 75%) in the pooled sensitivity and specificity among the studies.

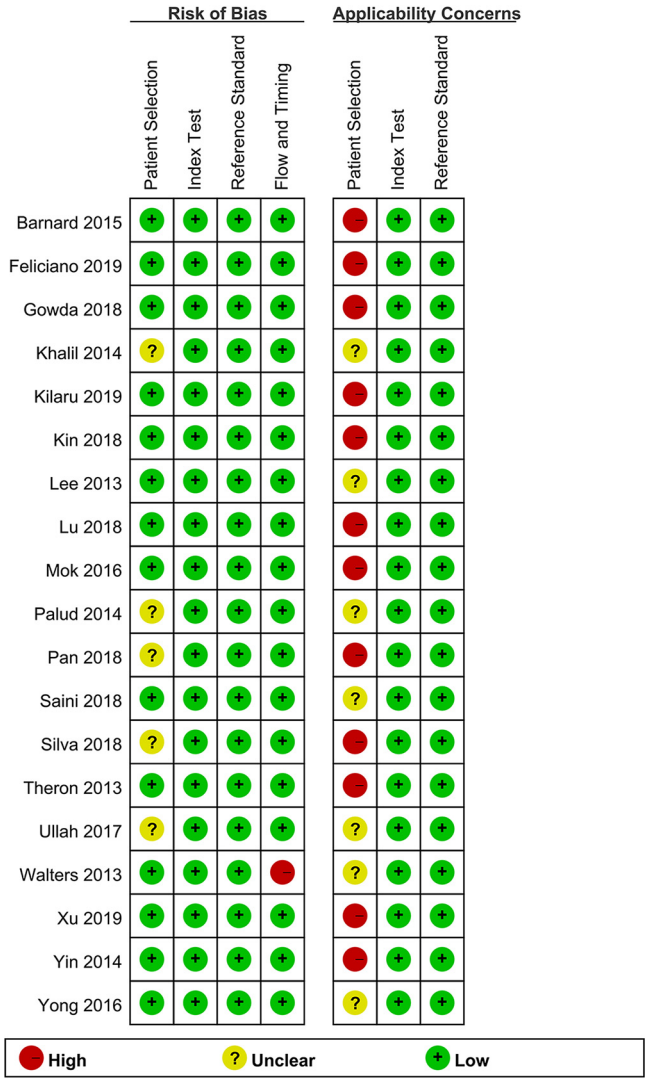

FIG 2 Bias risks and applicability concerns.

Meta-regression and subgroup analyses of the sensitivity and specificity. The meta-regression analyses showed that the sensitivity values were consistent between subgroups based on different countries, age, study designs, sputum test, culture method of the reference test, and preanalytic procedure ($P > 0.05$). The specificity values were also consistent between subgroups based on different countries, study designs, sputum test, culture method of the reference test, and preanalytic procedure ($P > 0.05$); however the specificity (0.92 [0.90 to 0.95]) in adults was higher than that (0.51 [0.35 to 0.68]) in children ($P < 0.05$) (Table 2). Of note, subgroup analyses revealed that the sensitivity and specificity of the Xpert MTB/RIF test using BAL for sputum smear-negative patients with PTB were 0.86 (0.80 to 0.92) and 0.93 (0.86 to 1.00), respectively (Table 2). Together, our data showed slight fluctuations in the sensitivity and specificity between subgroups; however, all subgroups showed high sensitivity and specificity except for children (Table 2).

Threshold analysis. When *M. tuberculosis* culture and CRS were each considered the reference standard for diagnosis, the Spearman correlation coefficients were −0.011 and 0.243, respectively ($P > 0.05$). No threshold effects were observed.

Publication bias. No publication bias was found as per the Deeks funnel plot with a *P* value of 0.1 (Fig. S3).

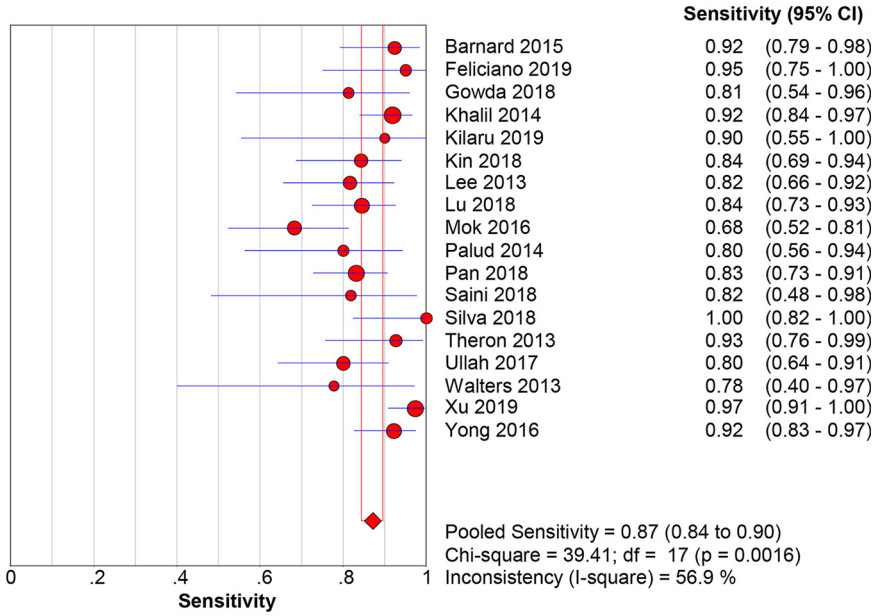

FIG 3 The pooled sensitivity of Xpert MTB/RIF using bronchoalveolar lavage fluid for the diagnosis of PTB (versus the culture method). The diamond represents the pooled sensitivity; lines represent the respective 95% confidence intervals (CI).

DISCUSSION

At present, *M. tuberculosis* culture methods and sputum smears are often used in the laboratory diagnosis of PTB (29–31). However, diagnosis using sputum smear is not a good option for PTB. In addition, the specificity of the sputum smear is limited because acid-fast staining is unable to distinguish between *M. tuberculosis* and non-*M. tuberculosis* specimens (31, 32). *M. tuberculosis* culture is generally considered the gold standard for the diagnosis of tuberculosis, but this method tends to be time-consuming (report period, 2 to 8 weeks) (31, 32), which is less than ideal for the diagnosis of PTB.

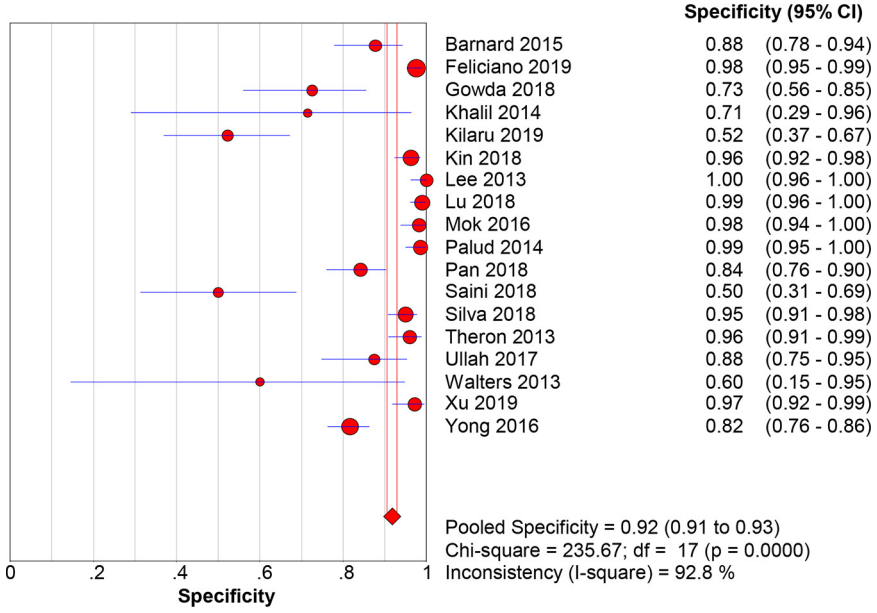

FIG 4 The pooled specificity of Xpert MTB/RIF using bronchoalveolar lavage fluid for the diagnosis of PTB (versus the culture method). The diamond represents the pooled sensitivity; lines represent the respective 95% CI.

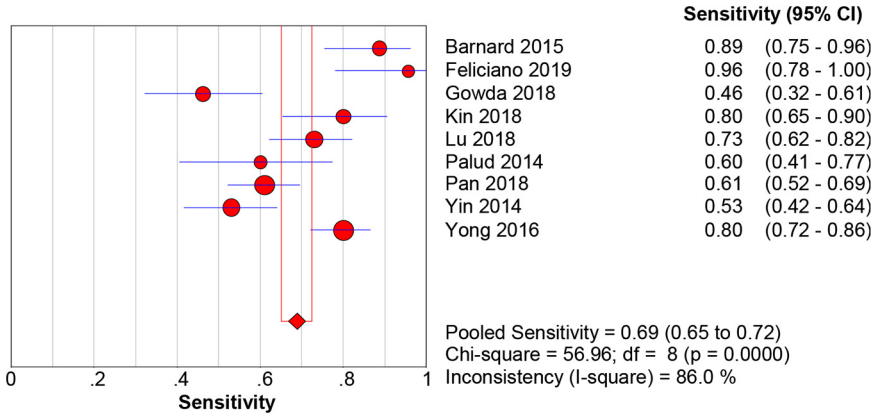

FIG 5 The pooled sensitivity of Xpert MTB/RIF using bronchoalveolar lavage fluid for the diagnosis of PTB (versus the composite reference standard method). The diamond represents the pooled sensitivity; lines represent the respective 95% CI.

As a fast and automatic molecular testing tool, Xpert MTB/RIF has been reported to display potential value using sputum samples for the diagnosis of PTB. This said, in clinical practice (29–33), using BAL samples may be necessary and valuable in the context of sputum smear-negative or sputum-scarce patients. However, the performance of Xpert MTB/RIF in the context of the diagnosis of PTB using BAL samples remains unclear.

According to the results of this meta-analysis, the use of Xpert MTB/RIF for the diagnosis of PTB using BAL samples had higher sensitivity and specificity. The high AUCs (>0.9) indicated that the Xpert MTB/RIF method using BAL has a high diagnostic value in PTB. However, the PLRs (>10) and NLR (>0.1) revealed that the advantage of Xpert MTB/RIF was in terms of confirmation rather than of exclusion. Therefore, a negative result in the context of the Xpert MTB/RIF method cannot completely rule out *M. tuberculosis* infection and should be interpreted with caution.

In this study, neither threshold effects nor publication bias was observed. However, there was substantial heterogeneity in the sensitivity and specificity among studies. Of note, heterogeneity can affect the accuracy of meta-analysis results, impacting their validity. Importantly, most of the individual studies revealed higher diagnostic performance based on the overall results of sensitivity and specificity.

According to the results of our meta-regression, the sensitivities and the specificities of Xpert MTB/RIF were consistent between subgroups based on different countries, study designs, sputum smear results, culture method of the reference test, and

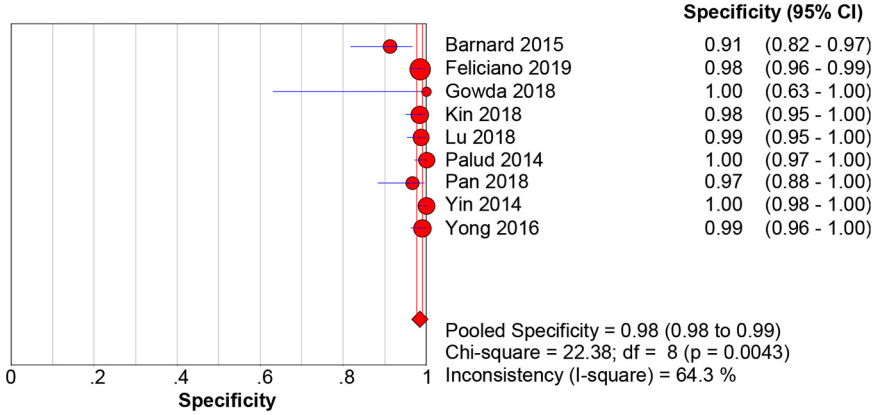

FIG 6 The pooled specificity of Xpert MTB/RIF using bronchoalveolar lavage fluid for the diagnosis of PTB (versus the composite reference standard). The diamond represents the pooled sensitivity; lines represent the respective 95% CI.

TABLE 2 Sensitivity and specificity subgroup analyses: different regions, economic statuses, study designs, sputum smear statuses, and ages

Parameter (no. of studies)	Sensitivity (95% CI)	*P*	Specificity (95% CI)	*P*
Age				
Adult (16)	0.88 (0.84–0.92)	>0.05	0.92 (0.90–0.95)	<0.05
Children (2)	0.81 (0.60–1.00)		0.51 (0.35–0.68)	
Country				
Developed countries (5)	0.83 (0.75–0.90)	>0.05	0.97 (0.94–1.00)	>0.05
Developing countries (13)	0.90 (0.86–0.93)		0.89 (0.81–0.96)	
Study design				
Retrospective studies (8)	0.86 (0.79–0.92)	>0.05	0.96 (0.92–1.00)	>0.05
Prospective studies (10)	0.89 (0.85–0.94)		0.88 (0.78–0.98)	
Sputum test				
Sputum smear negative/sputum scarce (8)	0.86 (0.80–0.92)	>0.05	0.93 (0.86–1.00)	>0.05
Sputum smear positive (10)	0.89 (0.85–0.94)		0.92 (0.85–0.99)	
Culture method				
Liquid or both media (14)	0.87 (0.82–0.91)	>0.05	0.91 (0.85–0.98)	>0.05
Solid media or uncertain (4)	0.91 (0.85–0.97)		0.95 (0.88–1.00)	
Preanalytic procedure				
Yes (5)	0.88 (0.82–0.95)	>0.05	0.95 (0.89–1.00)	>0.05
No or uncertain (13)	0.88 (0.83–0.92)		0.91 (0.84–0.98)	

preanalytic procedure; however, the specificity in adults was higher than that in children.

Emphatically, the subgroup analysis revealed that the sensitivity and specificity of the Xpert MTB/RIF method using BAL has a high diagnostic value for smear-negative patients with PTB. Meanwhile, low specificity was observed for diagnosis in children. However, this conclusion may not be completely reliable owing to the small number of included studies and of their high heterogeneity. Data from a previous meta-analysis reported that the positive rate of detection from sputum smears in children is low, ranging from 0.5% in children 0 to 4 years old to 14% in children 5 to 14 years old (34). However, Xpert MTB/RIF was reported to have increased clinical value for the rapid and accurate diagnosis of PTB in children when fiber-optic bronchoscopy was recommended based on a chest radiograph (35).

In clinical practice, Xpert MTB/RIF using BAL has obvious advantages. For sputum smear-negative patients with clinical radiologic features of active PTB, the Xpert MTB/RIF assay using BAL displays high sensitivity (13). Moreover, Xpert MTB/RIF using BAL could achieve an early diagnosis of PTB, contributing to early patient treatment (32).

However, Xpert MTB/RIF relies on the availability of complex instruments and has a high cost; moreover, the collection of BAL requires invasive procedures, especially in children with poor compliance. Therefore, its clinical application is limited to hospitals. At present, the tool is mainly used in tertiary hospitals. Although we included 19 studies and conducted a large sample meta-analysis, this review still has the following limitations: (i) the methodological quality of the included studies was not high owing to constraints on the level of study design; (ii) some subgroups, such as children, were included only in a small number of studies; (iii) substantial heterogeneity with an unknown source was observed; and (iv) this study did not include unpublished literature. Therefore, systematic research should be continued in the future.

In conclusion, this systematic review and meta-analysis showed that the Xpert MTB/RIF test using BAL has a high diagnostic performance for PTB and may serve as an alternative rapid diagnostic tool, especially for suspected PTB patients with a negative sputum test or sputum-scarce PTB. However, for children, the specificity of this method is low.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

SUPPLEMENTAL FILE 2, PDF file, 0.1 MB.

SUPPLEMENTAL FILE 3, PDF file, 0.1 MB.

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We have no conflicts of interest to declare.

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Study design, C.-T.Z., H.-C.L., Y.-Q.P., and Y.-L.G.; literature search, data collection, and analysis, H.-C.L., C.-T.Z., Y.-L.G., D.-F.L., and X.-Y.Z.; manuscript writing and editing, H.-C.L., C.-T.Z., Y.-Q.P., and Y.-L.G.

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