


Efficacy of Xpert MTB/RIF Ultra in diagnosing tuberculosis meningitis

A systematic review and meta-analysis

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Abstract

Background: This study aimed to assess whether Xpert MTB/RIF Ultra (Xpert Ultra) can effectively diagnose tuberculosis meningitis (TBM) and to simultaneously compare its effectiveness with Xpert in diagnosing TBM in the same population.

Methods: On August 12, 2020, Wanfang Database, China National Knowledge Infrastructure, Embase, Cochrane Library, and PubMed were searched for studies evaluating the diagnostic accuracy of Xpert Ultra for TBM. Then, we assessed the efficacy of Xpert Ultra against a composite reference standard and culture. If applicable, we also examined the diagnostic efficacy of Xpert in the same population. Heterogeneity was then explored by meta-regression, subgroup, and sensitivity analyses.

Results: Six studies containing 601 specimens reported the diagnostic efficacy of Xpert Ultra for TBM, with a composite reference standard. No study had compared the efficacy between Xpert Ultra and culture. The pooled sensitivity of Xpert Ultra was 64% (95% confidence interval [CI]: 45–80), and the I^2 value was 86% (95% CI: 76–96); its specificity for TBM was consistently 100%. In the same population, 5 studies compared the diagnostic efficacy between Xpert Ultra and Xpert for TBM. The pooled sensitivity of Xpert Ultra and Xpert was 68% (95% CI: 46–84; $I^2=87%$) and 37% (95% CI: 25–50; $I^2=72%$), respectively. The studies were significantly heterogeneous in terms of sensitivity but not heterogeneous in specificity.

Conclusions: Xpert Ultra was more sensitive than Xpert, but both were specific (100%). Therefore, Xpert Ultra had an excellent diagnostic efficacy for TBM, and it could be the preferred initial test for TBM.

Abbreviations: AFB = acid-fast bacilli, CI = confidence interval, CRS = composite reference standard, CSF = cerebrospinal fluid, EPTB = extrapulmonary tuberculosis, FN = false negative, FP = false positive, MTB = *Mycobacterium tuberculosis*, NAAT = nucleic acid amplification tests, TBM = tuberculous meningitis, TN = true negative, TP = true positive.

Keywords: efficacy, meta-analysis, tuberculosis meningitis, Xpert, Xpert Ultra

1. Introduction

Tuberculosis (TB) remains a serious global challenge to public health.^[1] In 2018, TB was found in more than 10 million

individuals, resulting in 1.5 million deaths^[1]; thus, it becomes the leading cause of death among infectious diseases.^[2] According to the presence or absence of lung involvement after *Mycobacterium tuberculosis* (MTB) infection, TB has 2 main categories: pulmonary tuberculosis and extrapulmonary tuberculosis (EPTB).^[3] The most serious type of EPTB is tuberculosis meningitis (TBM); although its incidence is low, accounting for only 1% to 5% of new tuberculosis infections, it causes severe disability or death in nearly half of the infected individuals.^[4] One of the main causes of these serious complications is the lack of early and effective diagnostic tools, leading to delayed diagnosis and consequently, missed treatment.^[5] Therefore, early diagnosis is paramount in TBM management. Classical microbiological assays cannot achieve an early and rapid diagnosis.^[6] The most widely used tool for TBM diagnosis is cerebrospinal fluid (CSF) acid-fast bacilli (AFB) smear with Ziehl-Neelsen staining, owing to its simplicity and user-friendliness. However, AFB is insensitive, especially when professional testers are unavailable.^[7] Although MTB culture is more sensitive than AFB, the culture requires at least 2 weeks to produce the results; thus, early clinical applications are not possible.^[8] Therefore, MTB culture is not effective for early diagnosis.^[9] Hence, a rapid and effective test for TBM is urgently needed.

Meanwhile, nucleic acid amplification tests (NAATs) are gaining prominence in rapid TB diagnosis.^[10] Xpert MTB/RIF (Xpert, Cepheid, Sunnyvale, CA, USA) is the most classical and

Editor: Haider Abdul-Lateef Mousa.

YS and GY contributed equally to this work.

The authors have no funding and conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Shen Y, Yu G, Zhao W, Lang Y. Efficacy of Xpert MTB/RIF Ultra in diagnosing tuberculosis meningitis: a systematic review and meta-analysis. *Medicine* 2021;100:29(e26778).

Received: 20 January 2021 / Received in final form: 14 June 2021 / Accepted: 30 June 2021

<http://dx.doi.org/10.1097/MD.00000000000026778>

widely used NAAT.^[11] Xpert can rapidly diagnose TB; hence, it was recommended for the early diagnosis of pulmonary tuberculosis in 2010 and for some types of EPTB in 2013 by the World Health Organization.^[12] However, the test is still flawed, and its sensitivity remains low in EPTB (eg, TBM and tuberculous pleurisy) with low bacterial content.^[13] For TBM, although the World Health Organization recommends Xpert as the initial test, its sensitivity remains unsatisfactory.^[14] A negative Xpert result does not provide enough confidence to rule out TBM.

To improve the diagnostic performance for paucibacillary TB, Cepheid developed Xpert MTB/RIF Ultra (Xpert Ultra), which is the next-generation Xpert; it shares the same equipment platform with Xpert without updating.^[15] Xpert Ultra adds 2 new MTB target genes (IS1081 and IS6110) and provides a larger capacity for DNA amplification reaction chamber.^[16] These improvements greatly enhance the effectiveness of Xpert Ultra in diagnosing TB.^[16,17] The diagnostic efficacy of Xpert Ultra is also beneficial for paucibacillary TB.^[18–20] However, the diagnostic efficacy of Xpert Ultra for TBM in comparison with culture or a composite reference standard (CRS) remains controversial; 1 study showed that Xpert Ultra was more effective than Xpert^[21] but another study demonstrated that the efficacy of Xpert Ultra revealed no statistically significant improvement than that of Xpert.^[22] Hence, this study aimed to conduct a systematic review and meta-analysis to better assess the role of Xpert Ultra in TBM diagnosis in comparison with the CRS and to simultaneously compare its effectiveness with Xpert when diagnosing TBM in the same population.

2. Material and methods

2.1. Design and registration

We designed a systematic review and meta-analysis to assess the efficacy of Xpert Ultra in diagnosing TBM. We registered the protocol on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY, registration number: INPLASY202080045).^[23] The study results were reported in reference to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.^[24] Furthermore, ethical approval was waived for systematic review and meta-analysis.

2.2. Information sources

On August 12, 2020, Wanfang Database, China National Knowledge Infrastructure, Embase, Cochrane Library, and PubMed were searched for studies assessing the diagnostic accuracy of Xpert Ultra in diagnosing TBM. The publication time period of articles was from the database creation to August 12, 2020. Relevant references cited in the review were also screened to find studies that potentially met the criteria.

2.3. Search strategy

YS and GY designed the search strategies for this study. Our search had no language or time limits. The search formula of PubMed is listed as follows:

#1 “Tuberculosis, Meningeal”[Mesh] OR “Meningeal Tuberculoses” OR “Meningeal Tuberculosis” OR “Tuberculoses, Meningeal” OR “TB Meningitis” OR “TB Meningitides” OR

“Tubercular Meningitis” OR “Meningitides, Tubercular” OR “Meningitis, Tubercular” OR “Tubercular Meningitides” OR “Meningitis, Tuberculous” OR “Meningitides, Tuberculous” OR “Tuberculous Meningitides” OR “Tuberculous Meningitis” OR “Tuberculosis Meningitis” OR “Meningitides, Tuberculosis” OR “Meningitis, Tuberculosis” OR “Tuberculosis Meningitides” OR “Tuberculous Hypertrophic Pachymeningitis” OR “Hypertrophic Pachymeningitides, Tuberculous” OR “Hypertrophic Pachymeningitis, Tuberculous” OR “Pachymeningitides, Tuberculous Hypertrophic” OR “Pachymeningitis, Tuberculous Hypertrophic” OR “Tuberculous Hypertrophic Pachymeningitides”

#2 “Extrapulmonary tuberculosis” OR “Extra pulmonary tuberculosis”

#3 “Meningitis”[Mesh] OR Meningitides OR Pachymeningitis OR Pachymeningitides

#4 “Cerebrospinal Fluid”[Mesh] OR “Cerebrospinal Fluids” OR “Fluid, Cerebrospinal” OR “Fluids, Cerebrospinal” OR “Cerebro Spinal Fluid” OR “Cerebro Spinal Fluids” OR “Fluid, Cerebro Spinal” OR “Fluids, Cerebro Spinal” OR “Spinal Fluid, Cerebro” OR “Spinal Fluids, Cerebro”

#5 #1 OR #2 OR #3 OR #4

#6 “Xpert Ultra” OR “GeneXpert Ultra”

#7 “Xpert” OR “GeneXpert”

#8 #5 AND #6 AND #7

Similar search formulae were used for Wanfang databases, China National Knowledge Infrastructure, Embase, and the Cochrane Library.

2.4. Eligibility criteria

2.4.1. Type of study. Any type of study that had evaluated the accuracy of Xpert Ultra for TBM.

2.4.2. Participants. TBM participants diagnosed using Xpert Ultra without any limitations on age, gender, or nationality.

2.4.3. Index test. Xpert Ultra was considered as the index test.

2.4.4. Comparator test. A comparator test was optional. A study with satisfied participants, intervention, and outcomes can be enrolled even if it was a single-arm study.

2.4.5. Target conditions. Full-text original studies evaluating the Xpert Ultra assay in TBM diagnosis, with clear reference standards and comprehensive data to extract or calculate true positive (TP), false positive (FP), false negative (FN), and true negative (TN) values, were considered eligible, thereby included in the study. However, studies published in languages other than English and Chinese, abstracts and conference reports without full text, case reports, and studies with <10 specimens did not meet the criteria; thus, they were excluded.

2.4.6. Outcomes. The main outcomes were the sensitivity and specificity of the Xpert Ultra system for TBM. Sensitivity refers to the probability that the index test result will be positive in an infected case, the calculation formula is $TP/(TP+FN) \times 100\%$. Specificity refers to the probability that the index test result will be negative in a non-infected case, the calculation formula is $TN/(FP+TN) \times 100\%$.

2.4.7. Reference standards. Culture or a CRS was used as the reference standard. A CRS comprised clinical symptoms, imaging features, CSF biochemical analysis, MTB smears, culture, and effectiveness to anti-TB therapy.

2.5. Literature screening and selection

The collected works of literature were managed by the ENDNOTE X9.2 literature management software (Clarivate Corporation, Stanford, USA), where all search records were imported. In selecting eligible articles, YS and GY independently assessed all imported articles by reviewing their titles and abstracts and then the full text according to the inclusion criteria. Any dispute that occurred between the 2 researchers was discussed with another researcher (YL). First, we gave the controversial literature to a third researcher for independent evaluation, then the 3 researchers discussed and reported the reasons for inclusion or exclusion, respectively, and then the literature was included or excluded according to the inclusion and exclusion criteria after obtaining agreement.

2.6. Data extraction

For each included article, the following were extracted: first author's name; publication year; country; TP, FP, FN, and TN values for the assay; research type; patient selection method; sample type; sample condition; decontamination method; and homogenization along with other parameters. If an article compared the diagnostic efficacy of the Xpert Ultra and Xpert in the same population, the relevant data of the Xpert were similarly extracted. The same 2 researchers individually extracted the aforementioned relevant data from each included article and then cross-checked them, with the disputed data being resolved by discussing with the third researcher.

2.7. Quality evaluation

The quality of the included literature was assessed by the same 2 researchers using a revised tool for the Quality Assessment of Diagnostic Accuracy Studies independently.^[25] Any disagreement between researchers was resolved via a discussion with the third researcher (YL). According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Diagnostic Test Accuracy guideline, publication bias did not need to be assessed.^[26]

2.8. Data synthesis and statistical analysis

Initially, we determined the TP, FP, FN, and TN values for each study. Then, the pooled sensitivity and specificity with 95% confidence interval (CI) of the Xpert Ultra or Xpert for TBM diagnosis in comparison with the CRS were calculated using the bivariate random-effects models. The forest plots of the sensitivity and specificity for each study were generated using RevMan version 5.3 (Cochrane Collaboration, Oxford, United Kingdom). Meanwhile, heterogeneity between the studies was assessed using the I^2 statistics. A value of 0% indicated no heterogeneity, whereas a value >50% indicated substantial heterogeneity.^[27] Heterogeneity sources were explored by meta-regression, subgroup, and sensitivity analyses. Potential sources of heterogeneity included the patient selection method, sample condition, decontaminate method, and homogenization. Meta-analyses and meta-regression analyses were conducted using Stata version 15.0 (Stata Corp., College Station, TX, the USA) and *midas*. At least 4 studies were required for meta-analysis to obtain the combined effect values for each preset parameter using Stata.

3. Results

3.1. Characteristics of the studies

By searching the relevant databases using our designed search strategies, we acquired 153 candidate articles. Ultimately, we found 6 articles that met the inclusion criteria for the final quantitative analysis^[21,22,28–31] (Fig. 1). The study type of all 6 included articles was a prospective study. The kappa value of agreement between the 2 researchers at the literature screening and data extraction stages was 0.736 (95% CI: 0.489–0.983). All studies were conducted in developing countries with TB epidemic, with English as the language of publication. In addition, CSF is the selected specimen type for all articles. All studies used CRS as the reference standard, and no studies used culture as the reference standard. Five articles simultaneously compared the diagnostic efficacy of Xpert Ultra and Xpert in TBM against CRS in the same population.^[21,22,28,30,31] The range of study specimen volume for Xpert Ultra was 21 to 204, with a median specimen volume of 93.5 and a total specimen volume of 601. For Xpert, the range of study specimen volume was 21 to 166, with a median specimen volume of 102 and a total specimen volume of 478. Table 1 lists the characteristics of the included studies. However, 2 articles were excluded because 1 article only reported sensitivity^[32] and the other 1 analyzed the same data as 1 of the included articles.^[33] We also excluded 2 articles that did not separately report data related to Xpert Ultra for TBM diagnosis.^[34,35]

3.2. Study quality

The results of the overall methodological quality assessment of the included studies are displayed in Figure 2, with the CRS as the reference standard. The risk of bias emerged primarily from patient selection and the reference standard; nonetheless, its flow and timing from the index test were relatively low.

3.3. Diagnostic efficacy of Xpert Ultra and Xpert for TBM

Six studies containing 601 specimens reported the efficacy of Xpert Ultra, with a CRS, in diagnosing TBM. The sensitivity of Xpert Ultra ranged from 44% (95% CI: 29–60) to 95% (95% CI: 77–100), whereas its pooled sensitivity in diagnosing TBM was 64% (95% CI: 45–80), with the I^2 value of 86% (95% CI: 76–96); its specificity for TBM was consistent (all 100%) (Fig. 3). The studies were significantly heterogeneous in terms of sensitivity but not heterogeneous in specificity.

Meanwhile, 5 studies containing 478 specimens reported the diagnostic efficacy of Xpert, with a CRS, for TBM. The sensitivity of Xpert ranged from 19% (95% CI: 8–33) to 56% (95% CI: 40–70), whereas its pooled sensitivity in diagnosing TBM was 37% (95% CI: 25–50), with the I^2 value of 72% (95% CI: 46–98). The specificity of the Xpert for TBM was also consistent (all 100%) (Fig. 3). The studies were significantly heterogeneous in terms of sensitivity.

For all studies, Xpert Ultra had a higher pooled sensitivity than Xpert, but the specificity of both was consistent. For the same population, 5 studies compared the efficacy of Xpert Ultra and Xpert in diagnosing TBM. The pooled sensitivity of Xpert Ultra and Xpert was 68% (95% CI: 46–84; $I^2=87%$) and 37% (95% CI: 25–50; $I^2=72%$), respectively (Fig. 4). In each study, Xpert Ultra had higher sensitivity and pooled sensitivity than Xpert.

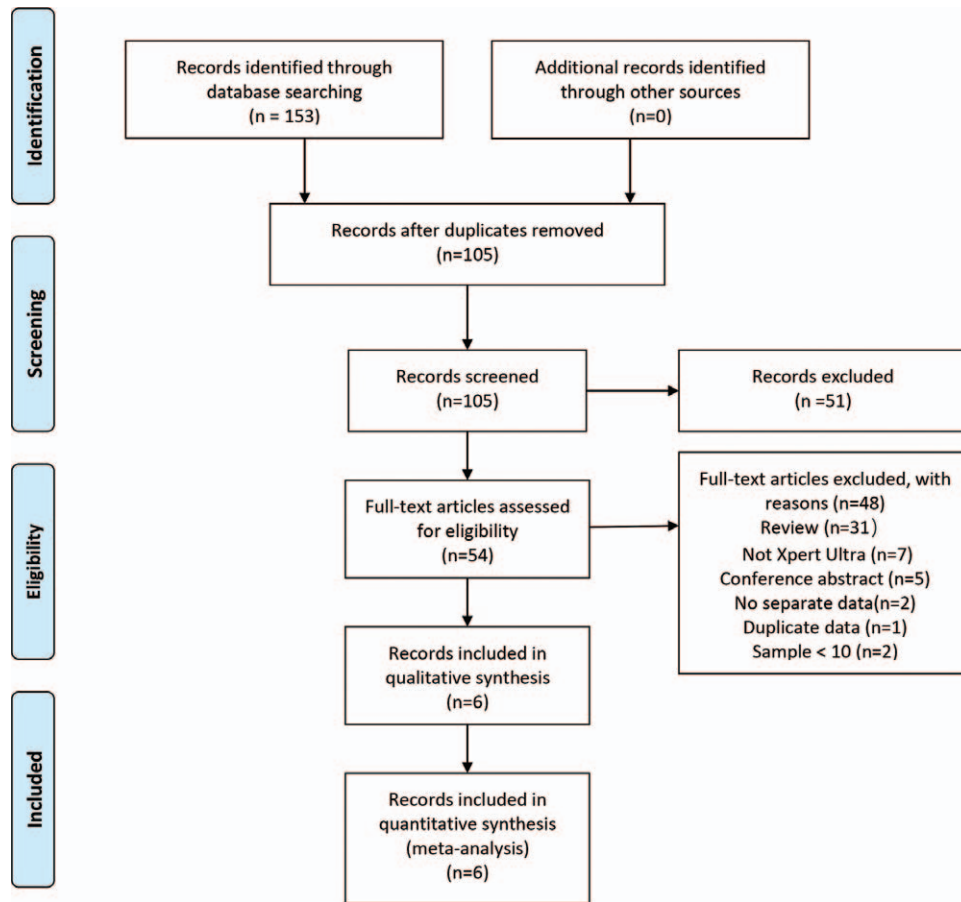


Figure 1. Flow chart of literature retrieval. In total, 3, 96, 10, 10, and 34 articles were found in Wanfang Database, China National Knowledge Infrastructure, Embase, Cochrane Library, and PubMed, respectively.

The heterogeneity between studies in terms of sensitivity was determined by meta-regression, subgroup, and sensitivity analyses. The patient selection method, sample condition, decontamination method, and homogenization method used in the assay of the predefined subgroups were assessed by meta-regression and subgroup analyses. Meta-regression analysis demonstrated that the patient selection method, sample condi-

tion, decontamination method, and homogenization method did not affect the sensitivity of Xpert Ultra and Xpert for TBM diagnosis in comparison with the CRS (meta-regression $P > .05$). In the subgroup analyses performed on the subgroups of the consecutive patient selection method, decontamination without *N*-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH), and mechanical homogenization method of Xpert Ultra, the

Table 1
Characteristics of the included studies.

Test	Author	Year	County	Sample type	Reference	Research type	N	TP	FP	FN	TN	Decontaminate method	Sample condition	Homogenisation	patient selection method
Xpert Ultra	Bahr et al ^a	2018	Uganda	CSF	CRS	Prospective	129	21	0	1	107	No	Frozen	Mechanical	Consecutive
	Wang et al ^a	2019	China	CSF	CRS	Prospective	60	19	0	24	17	NALC-NaOH	Frozen	Mechanical	Consecutive
	Zhang et al ^a	2019	China	CSF	CRS	Prospective	21	10	0	5	6	NALC-NaOH	Fresh	Mechanical	Convenience
	Cresswell et al ^a	2020	Uganda	CSF	CRS	Prospective	204	39	0	12	153	No	Fresh	No	Consecutive
	Donovan et al ^a	2020	Vietnam	CSF	CRS	Prospective	103	25	0	28	50	No	Fresh	Mechanical	Convenience
	Shao et al	2020	China	CSF	CRS	Prospective	84	28	0	32	24	No	Frozen	No	Consecutive
Xpert	Bahr et al ^b	2018	Uganda	CSF	CRS	Prospective	129	10	0	12	107	No	Frozen	Mechanical	Consecutive
	Wang et al. ^b	2019	China	CSF	CRS	Prospective	60	8	0	35	17	NALC-NaOH	Frozen	Mechanical	Consecutive
	Zhang et al ^b	2019	China	CSF	CRS	Prospective	21	4	0	11	6	NALC-NaOH	Fresh	Mechanical	Convenience
	Cresswell et al ^b	2020	Uganda	CSF	CRS	Prospective	166	25	0	20	121	No	Fresh	No	Consecutive
	Donovan et al ^b	2020	Vietnam	CSF	CRS	Prospective	102	21	0	32	49	No	Fresh	Mechanical	Convenience

CRS = composite reference standard, CSF = cerebrospinal fluid, FN = false negative, FP = false positive, TN = true negative, TP = true positive.

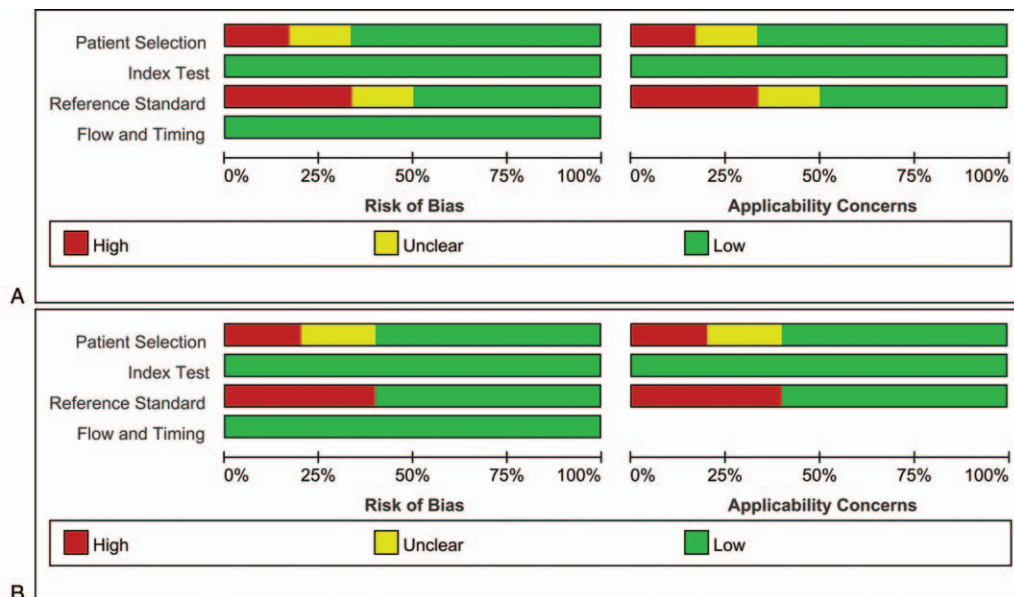


Figure 2. Methodological quality graphs of risk of bias and applicability concerns, presented as percentages across the included studies against the composite reference standard. (A) Xpert Ultra. (B) Xpert.

heterogeneity between studies in the subgroups remained highly significant ($I^2 > 50\%$). For the Xpert, the heterogeneity also remained highly significant ($I^2 > 50\%$) according to the subgroup analyses that were performed on the subgroup of mechanical homogenization method. However, the studies included in other subgroups of Xpert were limited; thus, subgroup analysis could not be conducted. In sensitivity analyses, a particular study was either included or excluded to reanalyze whether the conclusions had changed. Unfortunately, sensitivity analysis did not identify studies that resulted in significant heterogeneity.

4. Discussion

Similar to other paucibacillary EPTB, the MTB content of the test specimen was low, making the early diagnosis of TBM extremely difficult.^[36] Delays in early diagnosis allow for treatment deficits,

preventing patients to receive optimal treatments and leading to serious consequences, such as severe disability and death. As a result, the patient’s prognosis worsens, and the burden on the patient’s family increases.^[22] In patients with suspected TBM, a lumbar puncture to obtain a CSF sample for correlation testing is the most common and critical step. However, the MTB content in CSF is extremely low, and the probability of obtaining a positive result by AFB and culture is also very low^[37]; therefore, diagnosing TBM using these 2 methods alone still does not meet the clinical needs.^[37] In the studies included in this meta-analysis, no study had compared the sensitivity and specificity between Xpert Ultra and culture; thus, the current study used CRS as the reference standard for correlation analysis. However, larger clinical studies are required to confirm the relevant diagnostic efficacy of Xpert Ultra in comparison with that of culture.

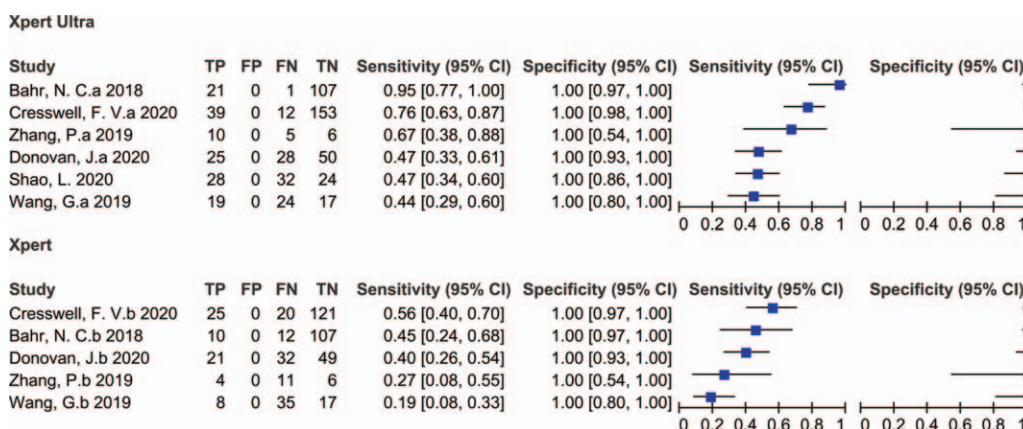


Figure 3. Forest plot for the sensitivity and specificity of Xpert Ultra and Xpert for the diagnosis of tuberculosis meningitis diagnosis against a composite reference standard.

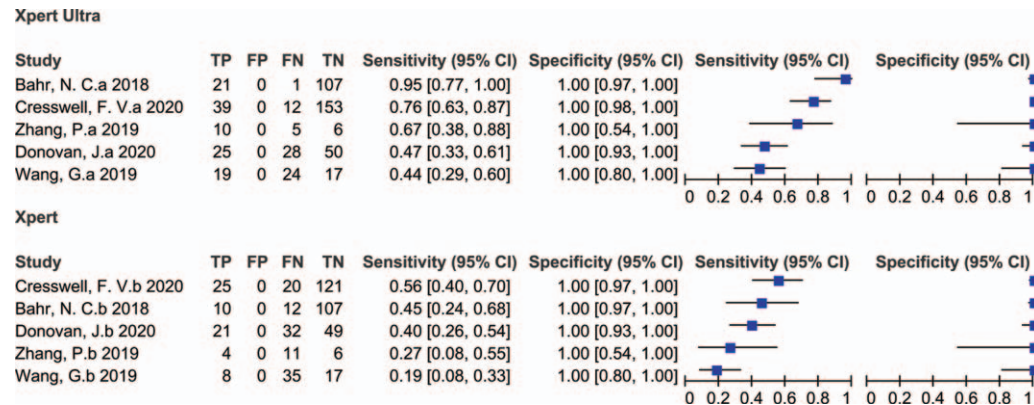


Figure 4. Forest plot for the sensitivity and specificity of Xpert Ultra and Xpert for the diagnosis of tuberculosis meningitis diagnosis against a composite reference standard in the same population.

Aside from AFB and culture, other valid tests have also been explored for TBM diagnosis. Owing to molecular biology advancement, rapid microbiological testing was made possible, with NAAT as the crucial step. Xpert is the leading NAAT in TB diagnostics and is widely used. This test has led to a significant increase in the diagnostic efficacy of TB because it shortens the diagnosis time and allows a considerably earlier therapeutic window, thereby beneficial for TB control.^[11] However, Xpert still seems impractical for paucibacillary EPTB such as TBM. Xpert's diagnostic performance in TBM remains unsatisfactory. Therefore, more efficient detection methods are still being developed. Based on the Xpert, the second-generation Xpert Ultra was developed by Cepheid. According to numerous reported improvements, the Xpert Ultra is considerably more sensitive than the Xpert. However, the diagnostic performance of the Xpert Ultra for TBM remains unclear. Most of the studies agreed that the Xpert Ultra is more sensitive than the Xpert statistically,^[21,28,29] but another study reported otherwise.^[22] Although a meta-analysis mentioned the role of Xpert Ultra in TBM,^[38] the study included only 2 papers on TBM, an extremely limited number, and our study included more studies, and the results might be more informative. To the best of our knowledge, no independent systematic review and meta-analysis on the efficacy of Xpert Ultra in TBM diagnosis are available; hence, we conducted the present study.

Six studies using CRS as the gold standard were included in this study; they demonstrated that Xpert Ultra had a pooled sensitivity of 64% and a specificity of 100% for TBM diagnosis, indicating that Xpert Ultra has good diagnostic efficacy for TBM. The sensitivity results across independent studies were strikingly different, and a substantial level of heterogeneity was observed. Moreover, 5 studies compared the efficacy between Xpert Ultra and Xpert for TBM diagnosis in the same population. The pooled sensitivity of Xpert Ultra and Xpert was 68% and 37%, respectively, and the specificity of both tests was tremendously high (100%). In the same population, the sensitivity of Xpert Ultra was significantly better than that of Xpert. The sensitivity of Xpert in this population was low, possibly related to the low number of specimens included in the study. A recent meta-analysis on Xpert for TBM diagnosis showed that the Xpert had a pooled sensitivity of 63% and a pooled specificity of 98.1%.^[39] Although the Xpert sensitivity of that study was higher than ours, it was still lower than the sensitivity of Xpert Ultra in this study. Meanwhile, the present study did not compare the sensitivity and

specificity between the 2 tests and culture examination. As a composite standard with multiple factors, CRS might lead to sensitivity decrement and specificity increment. Therefore, for TBM confirmed by a positive CSF culture, the sensitivity of Xpert Ultra should be higher than that observed in the current study.

Moreover, we observed significant heterogeneity in the sensitivity of Xpert Ultra and Xpert. The patient selection method, sample condition, decontamination method, and homogenization method were different among the studies. The sources of heterogeneity were explored in these terms. However, according to the meta-regression and subgroup analyses, these factors did not affect the sensitivity. Similarly, the sensitivity analysis did not reveal particularly heterogeneous articles. In addition, CRS might be different in each independent study (eg, some studies had not included treatment response), which itself might be a source of heterogeneity.

This meta-analysis had several limitations. Some studies might be missed during literature screening, although we had tried to expand the search the best that we could. In addition, some studies did not report TBM data separately; hence, the final results might be biased. The CRS might also differ across individual studies. The sensitivity between the studies was clearly heterogeneous; therefore, the pooled estimates of sensitivity must be treated prudently.

5. Conclusions

This was the first independent systematic review and meta-analysis on the efficacy of Xpert Ultra in TBM diagnosis. The pooled sensitivity and specificity of Xpert Ultra for TBM diagnosis were 64% and 100%, respectively. Xpert Ultra was more sensitive than Xpert, and both were identical in terms of specificity (100%). Therefore, Xpert Ultra is highly effective in diagnosing TBM, and it could be the preferred initial test for TBM.

Acknowledgments

We thank the patients and their families who were included in this study, and our colleagues in the department.

Author contributions

Data curation: Yanqin Shen, Guocan Yu, Yazhen Lang.

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Validation: Wuchen Zhao.

Visualization: Yazhen Lang.

Writing – original draft: Yanqin Shen, Guocan Yu.

Writing – review & editing: Yanqin Shen, Guocan Yu, Yazhen Lang.

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