RESEARCH ARTICLE

Xpert MTB/RIF Ultra versus Xpert MTB/RIF for diagnosis of tuberculous pleural effusion: A systematic review and comparative meta-analysis

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Abstract

Objective

We compared diagnostic accuracy of pleural fluid Xpert MTB/RIF (Xpert) and Xpert MTB/RIF Ultra (Ultra) assays for diagnosing tuberculous pleural effusion (TPE), through systematic review and comparative meta-analysis.

Methods

We searched PubMed and Embase databases for publications reporting diagnostic accuracy of Xpert or Ultra for TPE. We used bivariate random-effects modeling to summarize diagnostic accuracy information from individual studies using either mycobacterial culture or composite criteria as reference standard. We performed meta-regression through hierarchical summary receiver operating characteristic (HSROC) modeling to evaluate comparative performance of the two tests from studies reporting diagnostic accuracy of both in the same study population.

Results

We retrieved 1097 publications, and included 74 for review. Summary estimates for sensitivity and specificity for Xpert were 0.52 (95% CI 0.43–0.60, I^2 82.1%) and 0.99 (95% CI 0.97–0.99, I^2 85.1%), respectively, using culture-based reference standard; and 0.21 (95% CI 0.17–0.26, I^2 81.5%) and 1.00 (95% CI 0.99–1.00, I^2 37.6%), respectively, using composite reference standard. Summary estimates for sensitivity and specificity for Ultra were 0.68 (95% CI 0.55–0.79, I^2 80.0%) and 0.97 (95% CI 0.97–0.99, I^2 92.1%), respectively, using culture-based reference standard; and 0.47 (95% CI 0.40–0.55, I^2 64.1%) and 0.98 (95% CI 0.95–0.99, I^2 54.8%), respectively, using composite reference standard. HSROC meta-regression yielded relative diagnostic odds ratio of 1.28 (95% CI 0.65–2.50) and 1.80 (95% CI 0.41–7.84) respectively in favor of Ultra, using culture and composite criteria as reference standard.

Conclusion

Ultra provides superior diagnostic accuracy over Xpert for diagnosing TPE, mainly because of its higher sensitivity.

Introduction

Tuberculosis (TB) is an important cause for exudative pleural effusions, especially in high TB burden settings [1]. However, a definite diagnosis of tuberculous pleural effusion (TPE) may often prove difficult. As TPE is a paucibacillary disease, mycobacterial culture positivity from pleural fluid samples is uncommon [1]. Pleural biopsy shows the typical caseating granulomatous inflammation, or even mycobacteria, more frequently in these patients. However, biopsy is an invasive procedure and hence still not routinely performed, especially in resource-constrained situations. Adenosine deaminase and interferon gamma are two commonly used surrogate pleural fluid biomarkers to diagnose TPE. Although both demonstrate good diagnostic accuracy for identifying TPE, there are wide variations in the assay techniques, and a uniform threshold is still not defined for either test [2, 3].

Xpert MTB/RIF (hereafter referred to as Xpert) was developed as a novel automated cartridge-based nucleic acid amplification assay to improve TB diagnosis with a short turnaround test time. Using a hemi-nested real-time polymerase chain reaction to amplify mycobacterial *rpoB* gene, the assay demonstrated improved sensitivity for identifying both pulmonary and extra-pulmonary TB [4, 5]. The most recent version, Xpert MTB/RIF Ultra (hereafter referred to as Ultra), attempts to further improve the limit of mycobacterial DNA detection by amplifying two different insertion sequences (IS*6110* and IS*1081*) in a larger reaction chamber [6]. Both insertion sequences are present in multiple copies only in *Mycobacterium tuberculosis* complex but not in other mycobacteria. Compared to Xpert, Ultra has shown a higher sensitivity, and marginally lower specificity, for diagnosing both pulmonary and extra-pulmonary TB [4, 5].

The World Health Organization (WHO) currently conditionally recommends Xpert as an initial diagnostic test for TPE, with moderate certainty of evidence [7]. Although pleural fluid Xpert assay is a promising tool for diagnosing TPE, its sensitivity is lower than that for some other forms of extra-pulmonary TB [8–10]. It is not clear whether the diagnostic accuracy of Ultra is significantly superior to that of Xpert for TPE. A recent systematic review could not identify enough studies for directly comparing the diagnostic performance of the two tests in pleural fluid [5]. We conducted this systematic review and performed independent meta-analyses to indirectly compare the diagnostic accuracy of both Xpert and Ultra, using both mycobacterial culture and composite clinical criteria as reference standards. We also directly compared the accuracy of the two tests from studies evaluating both tests in the same patients.

Methods

We pre-registered the protocol for this review with PROSPERO registry (registration number CRD42021259421). Prior approval from our Institutional Ethics Committee was not necessary as we acquired summary information from already published articles. We report our findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11, 12].

Search strategy

We queried the PubMed and EMBASE databases for publications indexed till May 31, 2021. We used the following free text search terms: (Tuberculosis, Tuberculous, Tubercular, TB, Mycobacterial, Mycobacterium); (GeneXpert, Xpert, MTB/RIF, Ultra, Cepheid); and (Pleura, Pleural, Pleurisy, Pleuritis, Extra-pulmonary, Extrapulmonary, Non-respiratory, Nonrespiratory) for this purpose. If needed, we contacted investigators of selected publications for additional information. We also examined bibliographies of the included studies, as well as recent review articles, for any additional publications relevant to our analysis.

Study selection and data extraction

After eliminating duplicates, two reviewers (ANA and RA) independently assessed all titles and abstracts identified from our literature search. We excluded animal research, studies on non-tuberculous diseases, publications not primarily reporting on diagnosis of TPE, conference abstracts, case reports, letters to editor not describing original observations, review articles, and editorials. The full texts of publications considered potentially eligible by either reviewer were further retrieved for more detailed evaluation.

We included a study for analysis if it (a) included patients with TPE and at least another cause of exudative pleural effusion, (b) used a microbiologic (mycobacterial culture positivity from pleural fluid or pleural biopsy), pathologic (granulomatous inflammation or presence of acid-fast bacilli on pleural biopsy), and/or clinical (overall clinico-radiological features and pleural fluid investigations suggestive of TPE, or favorable response to empiric anti-tubercular treatment) reference standard for diagnosing TPE, and (c) provided numerical data on sensitivity and specificity of Xpert or Ultra in TPE diagnosis using an appropriate reference standard. If the same patients contributed to diagnostic accuracy estimates in more than one study, only the publication examining the largest dataset was selected. In case of any disagreement, consensus between the two reviewers determined study inclusion.

We extracted the following information from studies finally included: study location, study design, patient inclusion and exclusion criteria, clinical and demographic characteristics of patients studied, human immunodeficiency virus (HIV) status, index tests, reference standard(s) used, number of subjects in each group, and the number of positive and negative test results for each category of subjects.

Statistical analysis

We computed sensitivity and specificity for either index test from each study and calculated their corresponding 95% confidence intervals (95% CI) using the Clopper-Pearson approach [13]. We used 0.5 as continuity correction for publications reporting zero cell frequencies.

Both Xpert and Ultra assays employ uniform manufacturer-recommended positivity criteria for reporting test results. We therefore used hierarchically structured bivariate random-effects modeling to summarize diagnostic accuracy information from individual studies [14]. As a preliminary analysis, we summarized data separately for studies reporting on diagnostic accuracy of Xpert or Ultra, using either mycobacterial culture or composite criteria as reference standard. We used coupled forest plots and summary receiver operating characteristic (SROC) curves for graphical analysis [15]. This provided us broad indicators for differences in diagnostic performance between Xpert and Ultra from different sets of studies. Since direct comparisons of two index tests conducted within each study are superior to indirect comparisons of the same tests from different studies, we then identified publications reporting on the diagnostic accuracy of both Xpert and Ultra in the same study participants [16]. We anticipated only a small number of such publications and attempted a formal comparison only if

three or more studies provided such paired diagnostic accuracy data [16]. For this, we performed meta-regression through a hierarchical summary receiver operating characteristic (HSROC) model that assessed the influence of type of test (Xpert or Ultra) as a covariate while assuming symmetric SROC curves [17].

We assessed methodological quality of all included studies using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies, version 2) tool [18]. We subjectively assessed heterogeneity from visual examination of the confidence limits of individual studies and the width of prediction regions of SROC plots. We also used Higgins' inconsistency index (I^2) as a measure of between-study heterogeneity and considered it high for I^2 values >0.75 [19]. Heterogeneity was further explored through a separate subgroup analysis for each test, if ten or more studies were available for the primary analysis. For this, data was stratified based on pre-specified covariates that included study design, TB burden in country of study, TPE prevalence among study participants, study sample size, nature of non-tuberculous pleural effusions (whether transudates included or not), and nature of pleural fluid specimens (fresh or cryopreserved; whether centrifuged or not). Countries were categorized as high TB burden, or otherwise, based on World Health Organization guidelines [20]. We used Deek's funnel plot to assess the publication bias. We graded the overall quality of evidence using GRADE guidelines [21].

Statistical significance was assessed at p <0.05. We used the Stata software (Intercooled Edition 12.0, Stata Corp, Texas, USA) for statistical analysis. We also used the MetaDAS macro in SAS environment (SAS University Edition version 9.4, SAS Institute Inc., North Carolina, USA) for meta-regression [22].

Results

Study characteristics

We found 1095 citations through a search of electronic databases and located another two from additional sources (Fig 1). In all we assessed 146 full-text publications in detail against our inclusion criteria, and finally included 74 for our analysis [23–96]. Of these, 64 (86.5%) studies evaluated Xpert alone, five (6.8%) evaluated Ultra alone, and five (6.8%) evaluated both tests concurrently (S1 Table of online supplement). Three (4.1%) of these studies were reported in a language other than English [39, 50, 92]. The number of study subjects varied between 6 and 714. There were five (6.8%) studies with a case-control design [23, 31, 35, 43, 92]. In all, 45 (60.8%) studies reported their data from high TB burden countries (S1 Table of online supplement). One (1.4%) study was conducted exclusively in HIV seropositive patients [43], while seven (9.5%) others included a variable number of such subjects [37, 38, 42, 44, 53, 70, 89]. There were no HIV seropositive patients in thirteen (17.6%) publications [30, 47, 63, 73, 74, 76, 78, 79, 83, 84, 88, 92, 96], while the remaining did not provide any information. Ten investigators thawed cryopreserved fluid samples for their tests [23, 31, 35, 42, 60, 66, 73, 78, 80, 84]. Pleural fluid was concentrated by centrifugation in 32 studies prior to Xpert/Ultra assay [23–25, 27, 30, 33–35, 37, 38, 43, 44, 46, 48–51, 53, 58, 59, 65, 72–74, 76, 78, 85, 88, 89, 91, 94, 95]. Most investigators (51, 68.9%) used mycobacterial culture as reference standard for diagnosing TPE, while 33 used a composite reference standard (S1 Table of online supplement). Ten (13.5%) of these studies provided results by both criteria [25, 33, 35, 46, 62, 71, 73, 74, 84, 88]. A variable and wide range of clinical, laboratory and outcome parameters were used in varying combinations to define the composite reference standards. Four studies reported having included transudative pleural effusions in the non-tuberculous group [42, 45, 63, 66].

1095 records identified through a search of electronic databases

2 records from other sources

315 duplicate citations excluded

782 titles/abstracts screened

636 publications excluded:
    2 Animal studies
    6 Related to non-tuberculous disorders
  231 Not on diagnosis of pleural tuberculosis
  108 Reviews, guidelines, editorials
  193 Conference abstracts
  20 Letters to editor without original data
  76 Case reports and case series

146 full-text publications assessed in detail for eligibility

72 publications excluded:
    8 Not primarily focused on either index test
  12 Not reporting on diagnostic accuracy
  10 Providing sensitivity or specificity alone
   7 Insufficient data to generate 2x2 table
   4 Using inappropriate reference standard
  28 No separate data for pleural effusions
   3 Overlapping/same patient datasets

74 publications for data synthesis

Fig 1. Study selection process.

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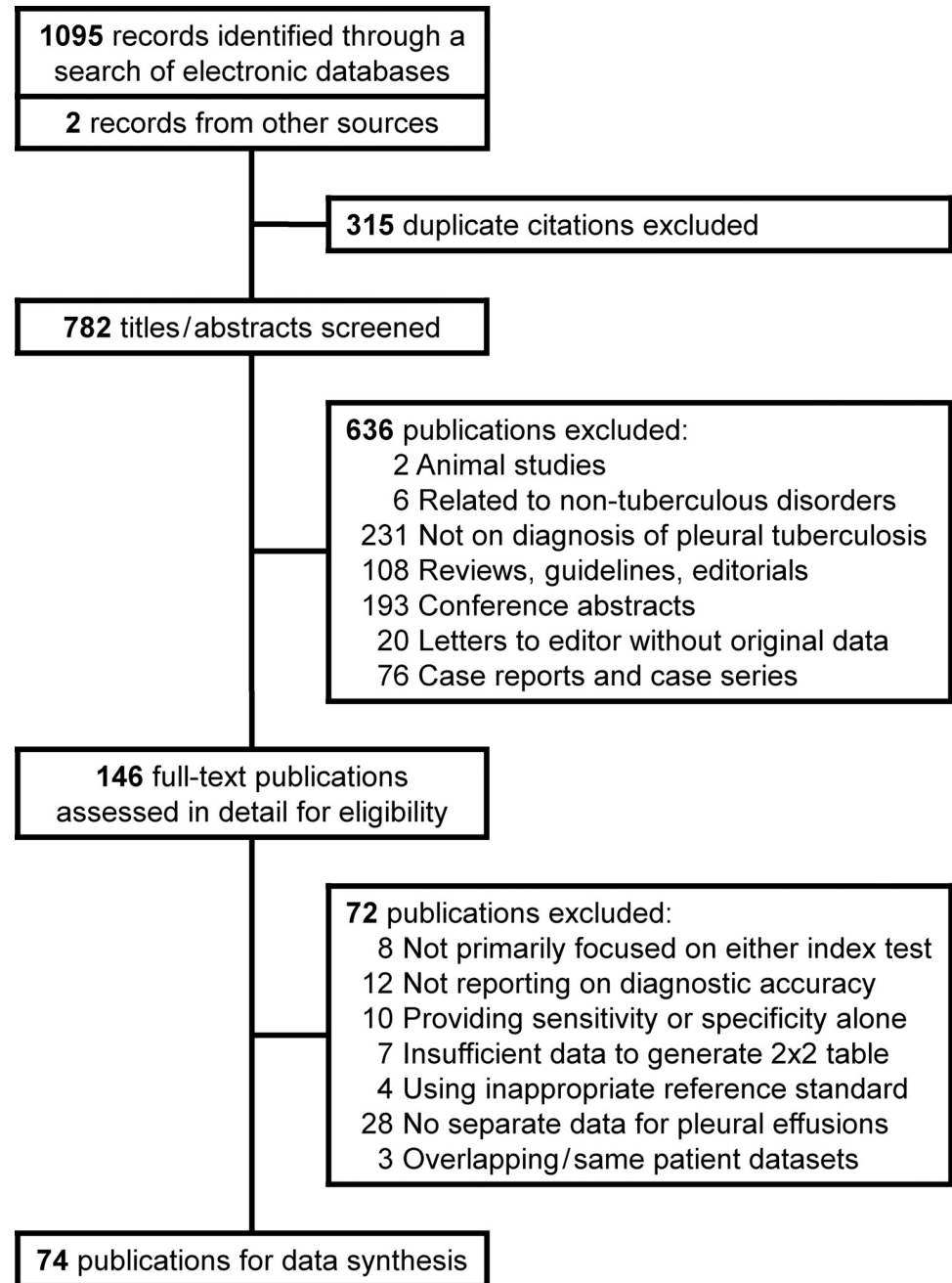
Eleven (14.9%) studies exhibited some risk of bias across one or more QUADAS-2 domains (Fig 2). Thirty (40.5%) studies also showed applicability concerns in one or more QUADAS-2 domains (Fig 2), mostly because the index tests were not conducted strictly as recommended. S2 Table of online supplement summarizes the diagnostic accuracy estimates computed from various studies.
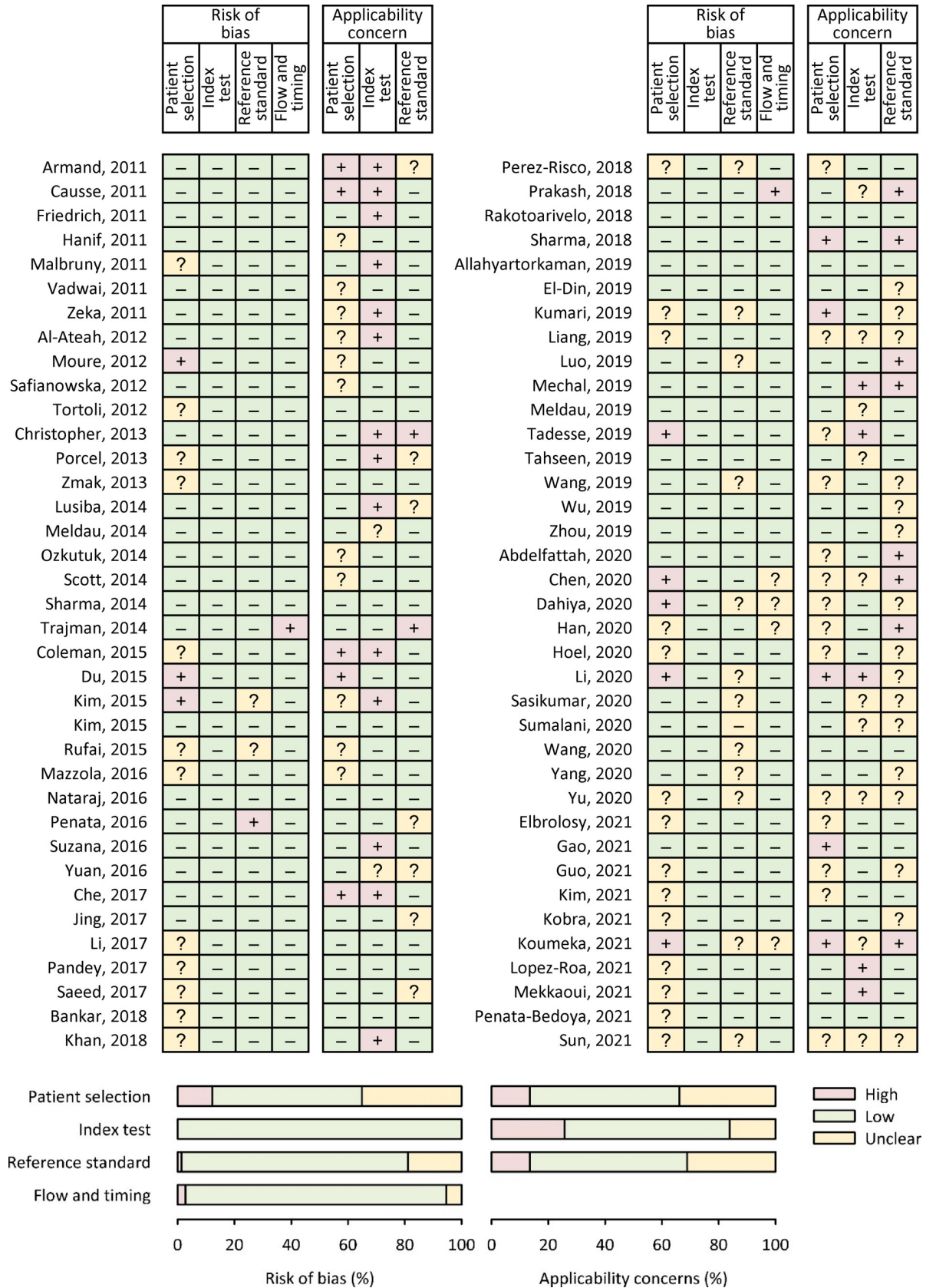
	Risk of bias				Applicability concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Armand, 2011	−	−	−	−	+	+	?
Causse, 2011	−	−	−	−	+	+	−
Friedrich, 2011	−	−	−	−	−	+	−
Hanif, 2011	−	−	−	−	?	−	−
Malbruny, 2011	?	−	−	−	−	+	−
Vadwai, 2011	−	−	−	−	?	−	−
Zeka, 2011	−	−	−	−	?	+	−
Al-Ateah, 2012	−	−	−	−	?	+	−
Moure, 2012	+	−	−	−	?	−	−
Safianowska, 2012	−	−	−	−	?	−	−
Tortoli, 2012	?	−	−	−	−	−	−
Christopher, 2013	−	−	−	−	−	+	+
Porcel, 2013	?	−	−	−	−	+	?
Zmak, 2013	?	−	−	−	−	−	−
Lusiba, 2014	−	−	−	−	−	+	?
Meldau, 2014	−	−	−	−	−	?	−
Ozkutuk, 2014	−	−	−	−	?	−	−
Scott, 2014	−	−	−	−	?	−	−
Sharma, 2014	−	−	−	−	−	−	−
Trajman, 2014	−	−	−	+	−	−	+
Coleman, 2015	?	−	−	−	+	+	−
Du, 2015	+	−	−	−	+	−	−
Kim, 2015	+	−	?	−	?	+	−
Kim, 2015	−	−	−	−	−	−	−
Rufai, 2015	?	−	?	−	?	−	−
Mazzola, 2016	?	−	−	−	?	−	−
Nataraj, 2016	−	−	−	−	−	−	−
Penata, 2016	−	−	+	−	−	−	?
Suzana, 2016	−	−	−	−	−	+	−
Yuan, 2016	−	−	−	−	−	?	?
Che, 2017	−	−	−	−	+	+	−
Jing, 2017	−	−	−	−	−	−	?
Li, 2017	?	−	−	−	−	−	−
Pandey, 2017	?	−	−	−	−	−	−
Saeed, 2017	?	−	−	−	−	−	?
Bankar, 2018	?	−	−	−	−	−	−
Khan, 2018	?	−	−	−	−	+	−

	Risk of bias				Applicability concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Perez-Risco, 2018	?	−	?	−	?	−	−
Prakash, 2018	−	−	−	+	−	?	+
Rakotoarivelo, 2018	−	−	−	−	−	−	−
Sharma, 2018	−	−	−	−	+	−	+
Allahyartorkaman, 2019	−	−	−	−	−	−	−
El-Din, 2019	−	−	−	−	−	−	?
Kumari, 2019	?	−	?	−	+	−	?
Liang, 2019	?	−	−	−	?	?	?
Luo, 2019	−	−	?	−	−	−	+
Mechal, 2019	−	−	−	−	−	+	+
Meldau, 2019	−	−	−	−	−	?	−
Tadesse, 2019	+	−	−	−	?	+	−
Tahseen, 2019	−	−	−	−	−	?	−
Wang, 2019	−	−	?	−	?	−	?
Wu, 2019	−	−	−	−	−	−	?
Zhou, 2019	−	−	−	−	−	−	?
Abdelfattah, 2020	−	−	−	−	?	−	+
Chen, 2020	+	−	−	?	?	?	+
Dahiya, 2020	+	−	?	?	?	−	?
Han, 2020	?	−	−	?	?	−	+
Hoel, 2020	?	−	−	−	?	−	?
Li, 2020	+	−	?	−	+	+	?
Sasikumar, 2020	−	−	?	−	−	?	?
Sumalani, 2020	−	−	−	−	−	?	?
Wang, 2020	−	−	?	−	−	−	−
Yang, 2020	−	−	?	−	−	−	?
Yu, 2020	?	−	?	−	?	?	?
Elbrolosy, 2021	?	−	−	−	?	−	−
Gao, 2021	−	−	−	−	+	−	−
Guo, 2021	?	−	−	−	?	−	?
Kim, 2021	?	−	−	−	?	−	−
Kobra, 2021	?	−	−	−	−	−	?
Koumeka, 2021	+	−	?	?	+	?	+
Lopez-Roa, 2021	?	−	−	−	−	+	−
Mekkaoui, 2021	?	−	−	−	−	+	−
Penata-Bedoya, 2021	?	−	−	−	−	−	−
Sun, 2021	?	−	?	−	?	?	?

Patient selection
Index test
Reference standard
Flow and timing

High
Low
Unclear

Risk of bias (%)   Applicability concerns (%)

Fig 2. Risk of bias and applicability concerns summary.

Diagnostic accuracy of individual tests

Forty-five studies, with 1203 TPE patients and 5288 patients of other effusions, evaluated Xpert in pleural fluid using mycobacterial culture as reference standard. Xpert sensitivity for TPE diagnosis ranged widely between zero and 1.00 (I^2 82.1%), and specificity between 0.87 and 1.00 (I^2 85.1%) (S1 Fig of online supplement). The summary sensitivity across studies was 0.52 (95% CI 0.43–0.60), and specificity was 0.99 (95% CI 0.97–0.99). The summary positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) estimates were 39.10 (95% CI 19.96–76.60), 0.49 (95% CI 0.41–0.59), and 79.98 (95% CI 37.82–169.12) respectively. The SROC curve was placed toward the desirable upper left corner of the plot area, and the 95% prediction region was wide, suggesting between-study heterogeneity (S2 Fig of online supplement). Subgroup analysis did not suggest any obvious influence of the prespecified covariates on heterogeneity, except that case-control studies showed considerable homogeneity in specificity estimates, and use of cryopreserved specimens was associated with lesser diagnostic accuracy but better homogeneity (S3 Table of online supplement). There was no publication bias.

Additionally, nine studies, including 194 TPE patients and 747 patients of other effusions, evaluated Ultra in pleural fluid using mycobacterial culture as reference standard. Sensitivity of Ultra for diagnosis of TPE ranged widely between zero and 1.00 (I^2 80.0%), and specificity between 0.68 and 1.00 (I^2 92.1%) (S3 Fig of online supplement). The summary sensitivity across studies was marginally better than Xpert (0.68, 95% CI 0.55–0.79), and specificity was marginally inferior than Xpert (0.97, 95% CI 0.97–0.99) (Table 1). The summary positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) estimates were 27.25 (95% CI 4.56–162.99), 0.33 (95% CI 0.22–0.47), and 83.79 (95% CI 15.53–452.06) respectively. The SROC curve was placed toward the desirable upper left corner of the plot area, and the 95% prediction region was wide, indicating between-study heterogeneity (S2 Fig of online supplement). We did not perform subgroup analysis due to small number of studies. There was no publication bias.

Thirty-five studies, with 2249 TPE patients and 2033 patients of other effusions, assessed Xpert in pleural fluid against a composite reference standard. Xpert sensitivity for detecting TPE ranged widely between zero and 0.71 (I^2 81.5%), and specificity between 0.95 and 1.00 (I^2 37.6%) (S1 Fig of online supplement). The summary sensitivity across studies was 0.21 (95% CI 0.17–0.26), and specificity was 1.00 (95% CI 0.99–1.00). The summary positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) estimates were 110.97 (95% CI 25.70–479.06), 0.79 (95% CI 0.74–0.84), and 140.95 (95% CI 32.32–614.74) respectively. The SROC curve was placed close to the left margin of the plot area, and the 95% prediction region was relatively narrow, suggestive of lesser between-study heterogeneity (S2 Fig of online supplement). Subgroup analysis suggested that retrospective studies, studies with less than 100 patients, studies reporting data only from exudative effusions, and studies assaying pleural fluid without centrifugation showed considerable homogeneity in specificity estimates (S3 Table of online supplement). There was no publication bias.

In addition, five studies, with 498 TPE patients and 245 patients of other effusions, assessed Ultra in pleural fluid against a composite reference standard. Sensitivity of Ultra for TPE identification ranged widely between 0.38 and 0.71 (I^2 64.1%), and specificity between 0.90 and 1.00 (I^2 54.8%) (S3 Fig of online supplement). The summary sensitivity across studies was better than Xpert (0.47, 95% CI 0.40–0.55), and specificity was marginally lower than Xpert (0.98, 95% CI 0.95–0.99) (Table 1). The summary positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) estimates were 21.88 (95% CI 8.81–54.33), 0.54 (95% CI 0.47–0.62), and 40.68 (95% CI 16.15–102.46) respectively. The SROC curve was

Table 1. Summary diagnostic accuracy parameters and their comparison.

	Xpert MTB/RIF Ultra	Xpert MTB/RIF
Independent analysis for each index test		
1. Mycobacterial culture as reference standard		
• Number of included studies	9	45
• Summary sensitivity (95% CI)	0.68 (0.55–0.79)	0.52 (0.43–0.60)
• Summary specificity (95% CI)	0.97 (0.85–1.00)	0.99 (0.97–0.99)
2. Composite reference standard		
• Number of included studies	5	35
• Summary sensitivity (95% CI)	0.47 (0.40–0.55)	0.21 (0.17–0.26)
• Summary specificity (95% CI)	0.98 (0.95–0.99)	1.00 (0.99–1.00)
Direct head-to-head comparison of both tests		
1. Mycobacterial culture as reference standard		
• Number of included studies	4	4
• Summary sensitivity (95% CI)	0.78 (0.63–0.87)	0.42 (0.28–0.59)
• Summary specificity (95% CI)	0.88 (0.56–0.98)	0.96 (0.82–0.99)
• Relative diagnostic odds ratio (95% CI)*	1.28 (0.65–2.50)	
• Relative sensitivity (95% CI)*	1.83 (1.37–2.46)	
• Relative specificity (95% CI)*	0.91 (0.78–1.06)	
2. Composite reference standard		
• Number of included studies	5	5
• Summary sensitivity (95% CI)	0.47 (0.40–0.55)	0.23 (0.18–0.29)
• Summary specificity (95% CI)	0.98 (0.95–0.99)	0.99 (0.96–1.00)
• Relative diagnostic odds ratio (95% CI)*	1.80 (0.41–7.84)	
• Relative sensitivity (95% CI)*	2.07 (1.70–2.51)	
• Relative specificity (95% CI)*	0.99 (0.97–1.02)	

* Xpert MTB/RIF Ultra in comparison to Xpert MTB/RIF

CI confidence interval

https://doi.org/10.1371/journal.pone.0268483.t001

placed close to the left margin of the plot area, and the 95% prediction region was relatively narrow, suggestive of moderate between-study heterogeneity (S2 Fig of online supplement). Subgroup analysis was not performed due to small number of studies. There was no publication bias.

Comparative diagnostic accuracy of both tests

Only five studies, all from high TB burden countries, evaluated diagnostic accuracy of both Xpert and Ultra in pleural fluid in the same study population [70, 73, 74, 84, 88]. None had a case-control design. The number of study subjects ranged from 61 to 292. Four of these publications from China provided information for both mycobacterial culture and composite criteria as reference standards [73, 74, 84, 88], and one from South Africa used only composite reference standard [70]. One study used previously archived pleural fluid samples from a biobank [73]. None of the Chinese studies had any HIV seropositive patient, but the South African study reported 14.2% HIV seropositivity rate [70]. No study reported evaluation of any transudative pleural effusion. There was no apparent risk of bias in any study, but the risk of bias in the reference standard domain was not clear for two studies [73, 84].

Four studies, with 155 TPE patients and 458 patients of other effusions, evaluated both Xpert and Ultra in pleural fluid using mycobacterial culture as reference standard [73, 74, 84,
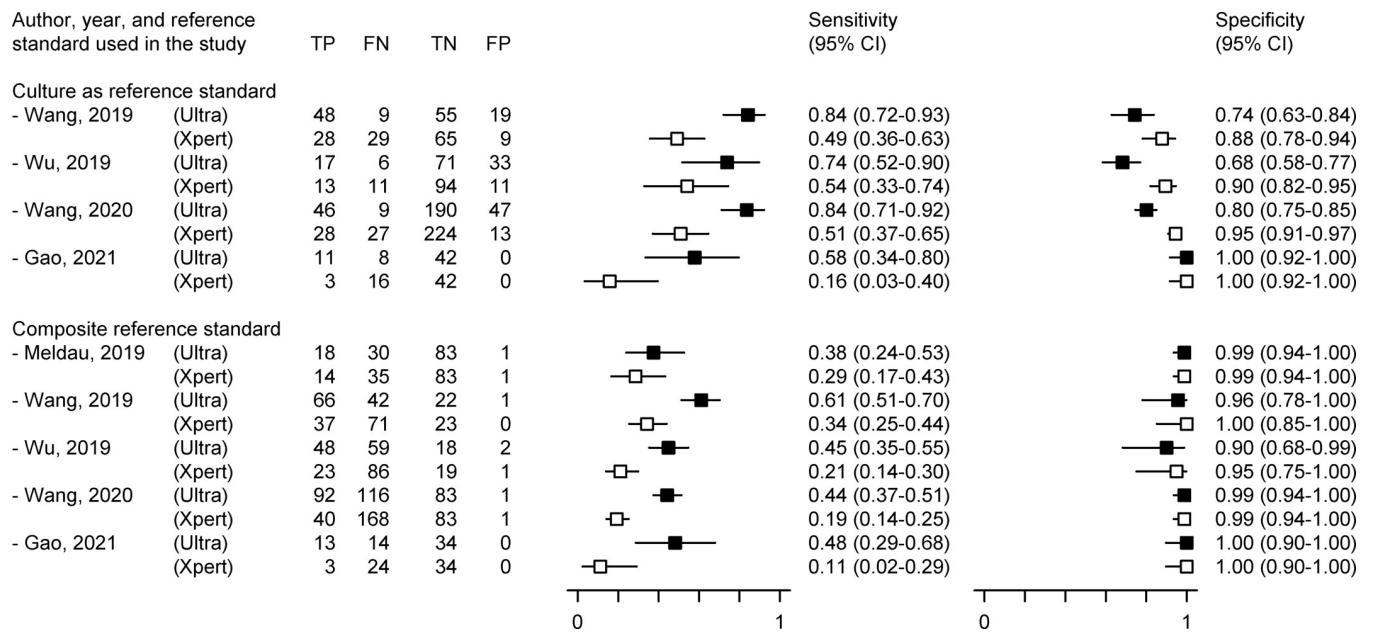
Author, year, and reference standard used in the study		TP	FN	TN	FP	Sensitivity (95% CI)	Specificity (95% CI)
Culture as reference standard							
- Wang, 2019	(Ultra)	48	9	55	19	0.84 (0.72-0.93)	0.74 (0.63-0.84)
	(Xpert)	28	29	65	9	0.49 (0.36-0.63)	0.88 (0.78-0.94)
- Wu, 2019	(Ultra)	17	6	71	33	0.74 (0.52-0.90)	0.68 (0.58-0.77)
	(Xpert)	13	11	94	11	0.54 (0.33-0.74)	0.90 (0.82-0.95)
- Wang, 2020	(Ultra)	46	9	190	47	0.84 (0.71-0.92)	0.80 (0.75-0.85)
	(Xpert)	28	27	224	13	0.51 (0.37-0.65)	0.95 (0.91-0.97)
- Gao, 2021	(Ultra)	11	8	42	0	0.58 (0.34-0.80)	1.00 (0.92-1.00)
	(Xpert)	3	16	42	0	0.16 (0.03-0.40)	1.00 (0.92-1.00)
Composite reference standard							
- Meldau, 2019	(Ultra)	18	30	83	1	0.38 (0.24-0.53)	0.99 (0.94-1.00)
	(Xpert)	14	35	83	1	0.29 (0.17-0.43)	0.99 (0.94-1.00)
- Wang, 2019	(Ultra)	66	42	22	1	0.61 (0.51-0.70)	0.96 (0.78-1.00)
	(Xpert)	37	71	23	0	0.34 (0.25-0.44)	1.00 (0.85-1.00)
- Wu, 2019	(Ultra)	48	59	18	2	0.45 (0.35-0.55)	0.90 (0.68-0.99)
	(Xpert)	23	86	19	1	0.21 (0.14-0.30)	0.95 (0.75-1.00)
- Wang, 2020	(Ultra)	92	116	83	1	0.44 (0.37-0.51)	0.99 (0.94-1.00)
	(Xpert)	40	168	83	1	0.19 (0.14-0.25)	0.99 (0.94-1.00)
- Gao, 2021	(Ultra)	13	14	34	0	0.48 (0.29-0.68)	1.00 (0.90-1.00)
	(Xpert)	3	24	34	0	0.11 (0.02-0.29)	1.00 (0.90-1.00)

Fig 3. Coupled forest plot from studies on diagnostic accuracy of pleural fluid Xpert MTB/RIF and Xpert MTB/RIF Ultra in the same patient population. Individual sensitivity and specificity estimates for diagnosing tuberculous pleural effusion are derived from data on true positives (TP), false negatives (FN), true negatives (TN), and false positives (FP), and are represented by solid and hollow squares for Xpert MTB/RIF Ultra and Xpert MTB/RIF respectively. Horizontal lines depict 95% confidence interval.

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88]. All studies showed a higher sensitivity, and lower or equal specificity, for Ultra (Fig 3). On meta-regression, when compared to Xpert, testing with Ultra resulted in higher summary sensitivity (0.78, 95% CI 0.63–0.87 vs. 0.42, 95% CI 0.28–0.59) but lower summary specificity (0.88, 95% CI 0.56–0.98 vs. 0.96, 95% CI 0.82–0.99). The corresponding SROC plots for the two assays did not overlap, and the curve for Ultra was located more towards the upper left corner of SROC space (Fig 4), implying that Ultra was consistently better than Xpert in diagnosing TPE across the whole range of data from the studies analyzed. However, the 95% confidence and prediction ellipses around both the summary estimates were wide and overlapping (Fig 4), implying significant heterogeneity. The relative diagnostic odds ratio (RDOR, a summary measure of relative accuracy) for Ultra was 1.28 (95% CI 0.65–2.50), suggestive of no significant difference in summary diagnostic accuracy between the two tests. However, Ultra showed significantly better sensitivity (relative sensitivity 1.83, 95% CI 1.37–2.46), but a similar specificity (Table 1).

Five studies, with 501 TPE patients and 245 patients of other effusions, evaluated both Xpert and Ultra in pleural fluid using a composite reference standard [70, 73, 74, 84, 88]. All studies showed a higher sensitivity, and lower or equal specificity, for Ultra (Fig 3). On meta-regression, when compared to Xpert, testing with Ultra resulted in higher summary sensitivity (0.47, 95% CI 0.40–0.55 vs. 0.23, 95% CI 0.18–0.29) but lower summary specificity (0.98, 95% CI 0.95–0.99 vs. 0.99, 95% CI 0.96–1.00). The corresponding SROC plots for the two assays were positioned close to each other but did not overlap, and the curve for Ultra was located more towards the upper left corner of SROC space (Fig 4), implying that Ultra was marginally better than Xpert in diagnosing TPE across the whole range of data from the studies analyzed. However, the 95% confidence and prediction ellipses around both the summary estimates were medium-sized and overlapping (Fig 4), implying moderate heterogeneity. The RDOR for Ultra was 1.80 (95% CI 0.41–7.84), suggestive of no significant difference in summary
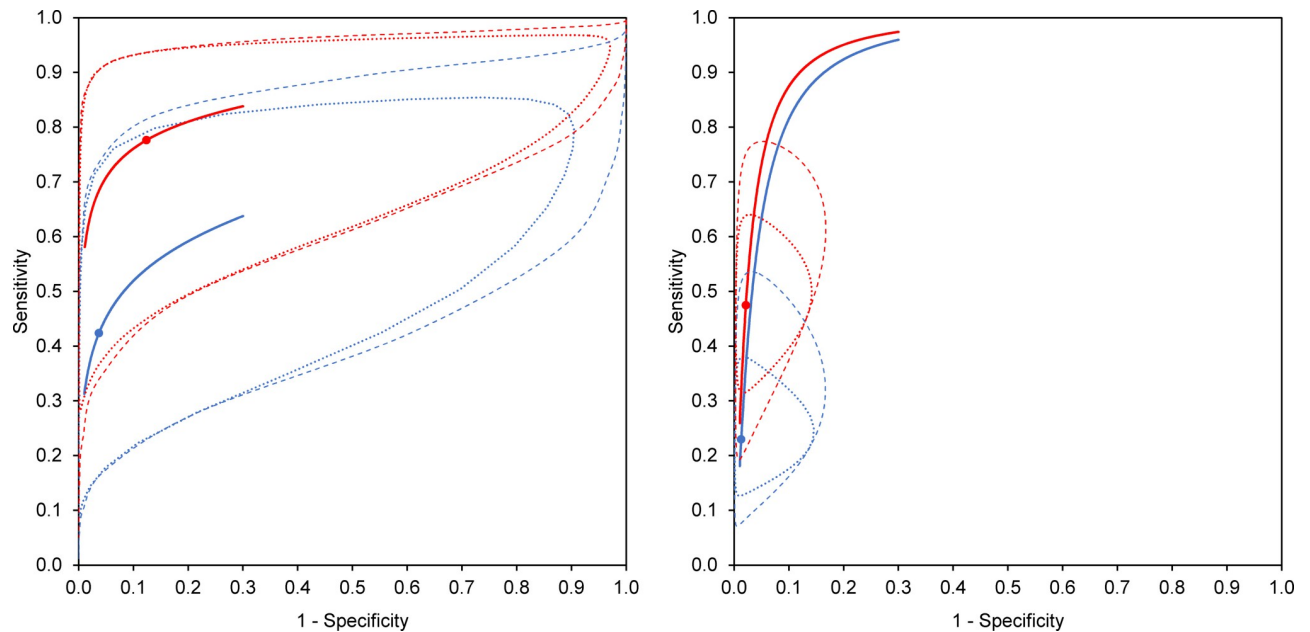
Fig 4. Comparison of summary points and hierarchical summary receiver operating characteristic plots for studies evaluating both pleural fluid Xpert MTB/RIF (blue) and Xpert MTB/RIF Ultra (red), using mycobacterial culture (left panel) and composite criteria (right panel) as reference standard for diagnosing tuberculous pleural effusion. Summary diagnostic accuracy points are depicted by solid circles. The dotted ellipses characterize the 95% confidence region around these summary estimates, while the dashed ellipses represent the 95% prediction region (area within which one is 95% certain the results of a new study will lie).

diagnostic accuracy between the two tests. However, Ultra showed significantly better sensitivity (relative sensitivity 2.07, 95% CI 1.70–2.51), but a similar specificity (Table 1).

Grading of evidence

Based on the summary diagnostic accuracy estimates derived from comparative studies, we projected the relative yield of the two index tests at low (5%), and high (50%) pre-test probability of TPE (Table 2). When using mycobacterial culture as reference standard in a low prevalence setting, the extra TPE patients identified through Ultra were overshadowed by a far greater number of false positive test results. Such disagreement was, however, not noted in a high TPE prevalence setting, or with comparisons using a composite reference standard (Table 2). This discrepancy was considered to suggest imprecision in relative specificity estimates among studies using mycobacterial culture as the reference standard. In view of this, and the wide confidence intervals for true negative and false positive estimates, we downgraded the level of certainty of evidence to 'moderate' for specificity comparisons using culture as reference standard. Other comparisons were considered to provide high certainty of evidence (Table 2).

Discussion

We reviewed 74 publications reporting on the diagnostic accuracy of pleural fluid Xpert or Ultra in TPE. In independent analyses, both tests showed low-to-moderate summary sensitivity and high summary specificity. Ultra had higher summary sensitivity than Xpert, both when mycobacterial culture (0.68 from nine studies vs. 0.52 from 45 studies) and composite criteria (0.47 from five studies vs. 0.21 from 35 studies) were used as the reference standard. Summary specificity was marginally lower for Ultra. On direct comparative analysis through HSROC

Table 2. Summary of findings from studies comparing both pleural fluid Xpert and Ultra assays for diagnosing tuberculous pleural effusion in the same patient population.

Test result	Number of subjects (number of studies)	Number of results per 1000 patients tested (95% confidence interval)				Risk of bias Inconsistency Indirectness Publication bias	Imprecision	Certainty of the evidence
		5% prevalence of tuberculosis		50% prevalence of tuberculosis				
		Ultra	Xpert	Ultra	Xpert			
Mycobacterial culture as reference standard								
True positives	155 (4)	39 (32 to 44)	21 (14 to 29)	388 (317 to 437)	212 (138 to 294)	Not serious	Not serious	HIGH
		18 more with Ultra		176 more with Ultra				
False negatives		11 (6 to 18)	29 (21 to 36)	112 (63 to 183)	288 (206 to 362)			
		18 fewer with Ultra		176 fewer with Ultra				
True negatives	458 (4)	833 (529 to 927)	915 (778 to 944)	438 (278 to 488)	482 (409 to 497)	Not serious	Serious [a]	MODERATE
		82 fewer with Ultra		44 fewer with Ultra				
False positives		117 (23 to 421)	35 (6 to 172)	62 (12 to 222)	18 (3 to 91)			
		82 more with Ultra		44 more with Ultra				
Composite reference standard								
True positives	501 (5)	24 (20 to 28)	11 (9 to 15)	237 (200 to 275)	115 (89 to 146)	Not serious	Not serious	HIGH
		13 more with Ultra		122 more with Ultra				
False negatives		26 (22 to 30)	39 (35 to 41)	263 (225 to 300)	385 (354 to 411)			
		13 fewer with Ultra		122 fewer with Ultra				
True negatives	245 (5)	930 (902 to 942)	938 (913 to 946)	489 (475 to 496)	494 (480 to 498)	Not serious	Not serious	HIGH
		8 fewer with Ultra		5 fewer with Ultra				
False positives		20 (8 to 48)	12 (4 to 37)	11 (4 to 25)	6 (2 to 20)			
		8 more with Ultra		5 more with Ultra				

[a] Wide confidence limits for estimates, and a disproportionally large increase in number of false positives, more so in a low tuberculosis prevalence setting

meta-regression from studies with paired datasets, Ultra had a RDOR of 1.28 and 1.80 respectively when compared to Xpert, using culture (four studies) and composite criteria (five studies) as reference standard. Our results suggest Ultra to be the better diagnostic investigation for TPE.

The summary diagnostic accuracy estimates computed by us, individually for both pleural fluid Xpert and Ultra, are largely similar to those reported by recent meta-analyses [5, 9]. A direct comparative analysis of studies reporting paired diagnostic accuracy data is preferred to deriving indirect inferences from different meta-analyses on individual tests, as the former removes confounding due to differences in study methodology and patient characteristics [97]. A recent Cochrane review did not perform a direct comparative analysis due to paucity of studies providing concurrent information on both pleural fluid Xpert and Ultra for the same patients [5]. Another review identified four studies providing paired data on pleural fluid Xpert and Ultra, but reported only the individual summary diagnostic accuracy estimates separately for each test without specifying the reference standard [98].

What are the clinical implications of our study? The positioning of HSROC plots, as well as the numerical information for summary estimates from studies providing paired data, suggests

pleural fluid Ultra to be a better diagnostic marker for TPE than pleural fluid Xpert. This information is likely to influence current algorithms for evaluating patients with pleural effusion in whom TB is considered as one of the possible etiologies, especially once the Ultra kits become more widely available. Our estimates suggest that using Ultra might paradoxically increase false positive rates in low TB prevalence settings if mycobacterial culture is considered as the reference standard. This is not the case if composite criteria are employed as the reference standard. Notably, all studies included for our comparative meta-analyses were conducted in high TB burden countries. Neither mycobacterial culture nor composite criteria can be considered an ideal reference standard. Since culture requires a much higher viable mycobacterial load than nucleic acid amplification assays, it may be possible that some of the extra cases identified by Ultra (and categorized as false positives) actually represent those patients whose diagnosis was missed by the definitive reference standard. The lower limit of detecting mycobacterial genetic material in pleural fluid is further approximately ten-fold lower for Ultra as compared to Xpert [70]. This might be advantageous for diagnosing TPE, a paucibacillary condition. On the other hand, using composite criteria lowers the precision in picking up true TPE, and the problem is further compounded by the fact that different investigators used variable composite criteria to define TPE without providing additional information on treatment outcomes stratified by culture or Xpert/Ultra results or by pleural fluid characteristics. From a purely medical perspective, physicians tend to consider several clinical and laboratory parameters while assigning a presumptive diagnosis of TPE. Moreover, culture reporting takes time, and results are often not available while deciding on initiation of anti-tubercular treatment.

The main strengths of our analysis are a larger sample size of paired data on the two index tests, and the use of hierarchical models for formal test comparison, allowing us to generate robust comparative diagnostic accuracy estimates. Our evaluation also has few limitations. The studies reviewed herein showed substantial heterogeneity. Only a few studies enrolled patients with exudative pleural effusions only. As TPE is not a diagnostic consideration in transudative effusions, several studies may have reported a spuriously higher specificity. We summarized and compared the diagnostic accuracy of Xpert and Ultra as isolated investigations, but cannot judge if their concurrent use with results of other diagnostic tests can further expand their role in routine clinical decision-making. Nearly all studies describing role of both Ultra and Xpert on the same patient dataset were performed in a single country, precluding the generalizability of our findings to other locations.

Conclusion

In summary, the results from our meta-analysis suggest that pleural fluid Ultra assay provides superior diagnostic accuracy over Xpert assay for diagnosing TPE, mainly because of its higher sensitivity. We propose that pleural fluid Ultra should be used as a primary diagnostic biomarker while evaluating patients with suspected TPE, especially in high TB prevalence settings. More information, especially on Ultra's positioning in any diagnostic algorithm evaluating pleural effusions and it utility when combined with other clinical and laboratory data, is needed to fully characterize the added advantage of Ultra in different countries and settings.

Supporting information

S1 Checklist. PRISMA-DTA checklist.
(PDF)

S1 Table. Characteristics of studies included in data synthesis.
(PDF)

S2 Table. Diagnostic accuracy estimates from included studies.
(PDF)

S3 Table. Evaluation of factors affecting individual summary diagnostic accuracy estimates from studies on pleural fluid Xpert MTB/RIF assay.
(PDF)

S1 Fig. Forest plots of studies evaluating sensitivity and specificity of pleural fluid Xpert MTB/RIF assay in diagnosing tuberculous pleural effusion. Solid squares indicate individual study estimates, and horizontal lines represent corresponding 95% confidence limits.
(PDF)

S2 Fig. Summary receiver operating characteristic (SROC) curves from bivariate models summarizing diagnostic performance of pleural fluid Xpert MTB/RIF using culture (top left) or composite criteria (top right) as reference standard, and pleural fluid Xpert MTB/RIF Ultra using culture (bottom left) or composite criteria (bottom right) as reference standard. Each individual study on diagnosis of tuberculous pleural effusion is represented by an open circle, whose size is proportional to the inverse standard error of sensitivity and specificity. The square represents the summary estimate of test accuracy, with the surrounding dashed zone outline denoting the 95% confidence region around this estimate. The outer dotted zone represents the 95% prediction region (area within which one is 95% certain the results of a new study will lie).
(PDF)

S3 Fig. Forest plots of studies evaluating sensitivity and specificity of pleural fluid Xpert MTB/RIF Ultra in diagnosing tuberculous pleural effusion. Solid squares indicate individual study estimates, and horizontal lines represent corresponding 95% confidence limits.
(PDF)

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References

1. Shaw JA, Ahmed L, Koegelenberg CFN. Effusions related to TB. ERS Monograph. 2020; 2020 (9781849841160):172–92. https://doi.org/10.1183/2312508X.10023819

2. Aggarwal AN, Agarwal R, Sehgal IS, Dhooria S. Adenosine deaminase for diagnosis of tuberculous pleural effusion: A systematic review and meta-analysis. PLoS One. 2019; 14(3):e0213728. Epub 2019/03/27. https://doi.org/10.1371/journal.pone.0213728 PMID: 30913213

3. Aggarwal AN, Agarwal R, Dhooria S, Prasad KT, Sehgal IS, Muthu V. Unstimulated pleural fluid interferon gamma for diagnosis of tuberculous pleural effusion: a systematic review and meta-analysis. J Clin Microbiol. 2021; 59(5):e02112–20. Epub 2020/11/20. https://doi.org/10.1128/JCM.02112-20 PMID: 33208475

4. Horne DJ, Kohli M, Zifodya JS, Schiller I, Dendukuri N, Tollefson D, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019; 6(6):CD009593. Epub 2019/06/08. https://doi.org/10.1002/14651858.CD009593.pub4 PMID: 31173647

5. Kohli M, Schiller I, Dendukuri N, Yao M, Dheda K, Denkinger CM, et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2021; 1(1):CD012768. Epub 2021/01/16. https://doi.org/10.1002/14651858.CD012768.pub3 PMID: 33448348

6. Chakravorty S, Simmons AM, Rowneki M, Parmar H, Cao Y, Ryan J, et al. The new Xpert MTB/RIF Ultra: Improving detection of Mycobacterium tuberculosis and resistance to rifampin in an assay suitable for point-of-care testing. mBio. 2017; 8(4):e00812–17. Epub 2017/08/31. https://doi.org/10.1128/mBio.00812-17 PMID: 28851844

7. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 3: diagnosis—rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization; 2021.

8. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2014; 44(2):435–46. Epub 2014/04/04. https://doi.org/10.1183/09031936.00007814 PMID: 24696113

9. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Diagnostic performance of Xpert MTB/RIF in tuberculous pleural effusion: Systematic review and meta-analysis. J Clin Microbiol. 2016; 54 (4):1133–6. Epub 2016/01/29. https://doi.org/10.1128/JCM.03205-15 PMID: 26818675

10. Huo ZY, Peng L. Is Xpert MTB/RIF appropriate for diagnosing tuberculous pleurisy with pleural fluid samples? A systematic review. BMC Infect Dis. 2018; 18(1):284. Epub 2018/06/27. https://doi.org/10.1186/s12879-018-3196-4 PMID: 29940951

11. Salameh JP, Bossuyt PM, McGrath TA, Thombs BD, Hyde CJ, Macaskill P, et al. Preferred reporting items for systematic review and meta-analysis of diagnostic test accuracy studies (PRISMA-DTA): explanation, elaboration, and checklist. BMJ. 2020; 370:m2632. Epub 2020/08/21. https://doi.org/10.1136/bmj.m2632 PMID: 32816740

12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009; 151(4):W65–94. Epub 2009/07/23. https://doi.org/10.7326/0003-4819-151-4-200908180-00136 PMID: 19622512

13. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934; 26(4):404–13.

14. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. J Clin Epidemiol. 2005; 58(10):982–90. Epub 2005/09/20. https://doi.org/10.1016/j.jclinepi.2005.02.022 PMID: 16168343

15. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, editors. Handbook for Systematic Reviews of Diagnostic Test Accuracy, version 10: The Cochrane Collaboration; 2010.

16. Takwoingi Y, Leeflang MM, Deeks JJ. Empirical evidence of the importance of comparative studies of diagnostic test accuracy. Ann Intern Med. 2013; 158(7):544–54. Epub 2013/04/03. https://doi.org/10.7326/0003-4819-158-7-201304020-00006 PMID: 23546566

17. Takwoingi Y, Guo B, Riley RD, Deeks JJ. Performance of methods for meta-analysis of diagnostic test accuracy with few studies or sparse data. Stat Methods Med Res. 2017; 26(4):1896–911. Epub 2015/06/28. https://doi.org/10.1177/0962280215592269 PMID: 26116616

18. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011; 155(8):529–36. https://doi.org/10.7326/0003-4819-155-8-201110180-00009 PMID: 22007046

19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414):557–60. Epub 2003/09/06. https://doi.org/10.1136/bmj.327.7414.557 PMID: 12958120

20. World Health Organization. WHO global lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025. Geneva: World Health Organization; 2021.

21. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from: https://gdt.guidelinedevelopment.org/app/handbook/handbook.html.

22. Takwoingi Y, Deeks JJ. MetaDAS: A SAS macro for meta-analysis of diagnostic accuracy studies (version 1.3, July 2010) [July 1, 2021]. Available from: https://methods.cochrane.org/sdt/software-meta-analysis-dta-studies.

23. Armand S, Vanhuls P, Delcroix G, Courcol R, Lemaître N. Comparison of the Xpert MTB/RIF test with an IS6110-TaqMan real-time PCR assay for direct detection of Mycobacterium tuberculosis in respiratory and nonrespiratory specimens. J Clin Microbiol. 2011; 49(5):1772–6. Epub 2011/03/18. https://doi.org/10.1128/JCM.02157-10 PMID: 21411592

24. Causse M, Ruiz P, Gutiérrez-Aroca JB, Casal M. Comparison of two molecular methods for rapid diagnosis of extrapulmonary tuberculosis. J Clin Microbiol. 2011; 49(8):3065–7. Epub 2011/06/10. https://doi.org/10.1128/JCM.00491-11 PMID: 21653775

25. Friedrich SO, von Groote-Bidlingmaier F, Diacon AH. Xpert MTB/RIF assay for diagnosis of pleural tuberculosis. J Clin Microbiol. 2011; 49(12):4341–2. Epub 2011/10/15. https://doi.org/10.1128/JCM.05454-11 PMID: 21998430

26. Hanif SN, Eldeen HS, Ahmad S, Mokaddas E. GeneXpert® MTB/RIF for rapid detection of Mycobacterium tuberculosis in pulmonary and extra-pulmonary samples. Int J Tuberc Lung Dis. 2011; 15(9):1274–5. Epub 2011/09/29. https://doi.org/10.5588/ijtld.11.0394 PMID: 21943862

27. Malbruny B, Le Marrec G, Courageux K, Leclercq R, Cattoir V. Rapid and efficient detection of Mycobacterium tuberculosis in respiratory and non-respiratory samples. Int J Tuberc Lung Dis. 2011; 15(4):553–5. Epub 2011/03/15. https://doi.org/10.5588/ijtld.10.0497 PMID: 21396219

28. Vadwai V, Boehme C, Nabeta P, Shetty A, Alland D, Rodrigues C. Xpert MTB/RIF: a new pillar in diagnosis of extrapulmonary tuberculosis? J Clin Microbiol. 2011; 49(7):2540–5. Epub 2011/05/20. https://doi.org/10.1128/JCM.02319-10 PMID: 21593262

29. Zeka AN, Tasbakan S, Cavusoglu C. Evaluation of the GeneXpert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampin resistance in pulmonary and extrapulmonary specimens. J Clin Microbiol. 2011; 49(12):4138–41. Epub 2011/10/01. https://doi.org/10.1128/JCM.05434-11 PMID: 21956978

30. Al-Ateah SM, Al-Dowaidi MM, El-Khizzi NA. Evaluation of direct detection of Mycobacterium tuberculosis complex in respiratory and non-respiratory clinical specimens using the Cepheid Gene Xpert® system. Saudi Med J. 2012; 33(10):1100–5. Epub 2012/10/11. PMID: 23047207

31. Moure R, Martín R, Alcaide F. Effectiveness of an integrated real-time PCR method for detection of the Mycobacterium tuberculosis complex in smear-negative extrapulmonary samples in an area of low tuberculosis prevalence. J Clin Microbiol. 2012; 50(2):513–5. Epub 2011/12/14. https://doi.org/10.1128/JCM.06467-11 PMID: 22162564

32. Safianowska A, Walkiewicz R, Nejman-Gryz P, Grubek-Jaworska H. [Two selected commercially based nucleic acid amplification tests for the diagnosis of tuberculosis]. Pneumonol Alergol Pol. 2012; 80(1):6–12. Epub 2011/12/22. PMID: 22187175

33. Tortoli E, Russo C, Piersimoni C, Mazzola E, Dal Monte P, Pascarella M, et al. Clinical validation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis. Eur Respir J. 2012; 40(2):442–7. Epub 2012/01/14. https://doi.org/10.1183/09031936.00176311 PMID: 22241741

34. Christopher DJ, Schumacher SG, Michael JS, Luo R, Balamugesh T, Duraikannan P, et al. Performance of Xpert MTB/RIF on pleural tissue for the diagnosis of pleural tuberculosis. Eur Respir J. 2013; 42(5):1427–9. Epub 2013/08/01. https://doi.org/10.1183/09031936.00103213 PMID: 23900990

35. Porcel JM, Palma R, Valdés L, Bielsa S, San-José E, Esquerda A. Xpert® MTB/RIF in pleural fluid for the diagnosis of tuberculosis. Int J Tuberc Lung Dis. 2013; 17(9):1217–9. Epub 2013/07/06. https://doi.org/10.5588/ijtld.13.0178 PMID: 23827859

36. Zmak L, Jankovic M, Jankovic VK. Evaluation of Xpert MTB/RIF assay for rapid molecular diagnosis of tuberculosis in a two-year period in Croatia. Int J Mycobacteriol. 2013; 2(3):179–82. Epub 2013/09/01. https://doi.org/10.1016/j.ijmyco.2013.05.003 PMID: 26785988

37. Lusiba JK, Nakiyingi L, Kirenga BJ, Kiragga A, Lukande R, Nsereko M, et al. Evaluation of Cepheid's Xpert MTB/Rif test on pleural fluid in the diagnosis of pleural tuberculosis in a high prevalence HIV/TB setting. PLoS One. 2014; 9(7):e102702. Epub 2014/07/23. https://doi.org/10.1371/journal.pone.0102702 PMID: 25051491

38. Meldau R, Peter J, Theron G, Calligaro G, Allwood B, Symons G, et al. Comparison of same day diagnostic tools including Gene Xpert and unstimulated IFN-γ for the evaluation of pleural tuberculosis: a prospective cohort study. BMC Pulm Med. 2014; 14:58. Epub 2014/04/09. https://doi.org/10.1186/1471-2466-14-58 PMID: 24708530

39. Ozkutuk N, Surucüoglu S. Evaluation of the Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary tuberculosis in an intermediate-prevalence setting. Mikrobiyol Bul. 2014; 48(2):223–32. Epub 2014/05/14. https://doi.org/10.5578/mb.7456 PMID: 24819260

40. Scott LE, Beylis N, Nicol M, Nkuna G, Molapo S, Berrie L, et al. Diagnostic accuracy of Xpert MTB/RIF for extrapulmonary tuberculosis specimens: establishing a laboratory testing algorithm for South Africa. J Clin Microbiol. 2014; 52(6):1818–23. Epub 2014/03/14. https://doi.org/10.1128/JCM.03553-13 PMID: 24622091

41. Sharma SK, Kohli M, Chaubey J, Yadav RN, Sharma R, Singh BK, et al. Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. Eur Respir J. 2014; 44(4):1090–3. Epub 2014/07/27. https://doi.org/10.1183/09031936.00059014 PMID: 25063241

42. Trajman A, da Silva Santos Kleiz de Oliveira EF, Bastos ML, Belo Neto E, Silva EM, da Silva Lourenço MC, et al. Accuracy of polimerase chain reaction for the diagnosis of pleural tuberculosis. Respir Med. 2014; 108(6):918–23. Epub 2014/05/08. https://doi.org/10.1016/j.rmed.2014.04.007 PMID: 24803060

43. Coleman M, Finney LJ, Komrower D, Chitani A, Bates J, Chipungu GA, et al. Markers to differentiate between Kaposi's sarcoma and tuberculous pleural effusions in HIV-positive patients. Int J Tuberc Lung Dis. 2015; 19(2):144–50. Epub 2015/01/13. https://doi.org/10.5588/ijtld.14.0289 PMID: 25574911

44. Du J, Huang Z, Luo Q, Xiong G, Xu X, Li W, et al. Rapid diagnosis of pleural tuberculosis by Xpert MTB/RIF assay using pleural biopsy and pleural fluid specimens. J Res Med Sci. 2015; 20(1):26–31. Epub 2015/03/15. PMID: 25767518

45. Kim CH, Hyun IG, Hwang YI, Kim DG, Lee CY, Lee MG, et al. Identification of Mycobacterium tuberculosis and rifampin resistance in clinical specimens using the Xpert MTB/RIF assay. Ann Clin Lab Sci. 2015; 45(1):32–8. Epub 2015/02/20. PMID: 25696008

46. Kim YW, Kwak N, Seong MW, Kim EC, Yoo CG, Kim YW, et al. Accuracy of the Xpert® MTB/RIF assay for the diagnosis of extra-pulmonary tuberculosis in South Korea. Int J Tuberc Lung Dis. 2015; 19(1):81–6. Epub 2014/12/19. https://doi.org/10.5588/ijtld.14.0500 PMID: 25519795

47. Rufai SB, Singh A, Kumar P, Singh J, Singh S. Performance of Xpert MTB/RIF assay in diagnosis of pleural tuberculosis by use of pleural fluid samples. J Clin Microbiol. 2015; 53(11):3636–8. Epub 2015/08/28. https://doi.org/10.1128/JCM.02182-15 PMID: 26311855

48. Mazzola E, Arosio M, Nava A, Fanti D, Gesu G, Farina C. Performance of real-time PCR Xpert ®MTB/RIF in diagnosing extrapulmonary tuberculosis. Infez Med. 2016; 24(4):304–9. Epub 2016/12/25. PMID: 28011966

49. Nataraj G, Kanade S, Mehta P. Xpert(®) MTB/RIF for improved case detection of extra-pulmonary TB in a tertiary care setting in urban India. Int J Tuberc Lung Dis. 2016; 20(7):890–4. Epub 2016/06/12. https://doi.org/10.5588/ijtld.15.0849 PMID: 27287640

50. Penata A, Salazar R, Castano T, Bustamante J, Ospina S. Molecular diagnosis of extrapulmonary tuberculosis and sensitivity to rifampicin with an automated real-time method. Biomedica. 2016; 36(0):78–89. Epub 2016/09/14. https://doi.org/10.7705/biomedica.v36i3.3088 PMID: 27622628

51. Suzana S, Ninan MM, Gowri M, Venkatesh K, Rupali P, Michael JS. Xpert MTB/Rif for the diagnosis of extrapulmonary tuberculosis—an experience from a tertiary care centre in South India. Trop Med Int Health. 2016; 21(3):385–92. Epub 2015/12/17. https://doi.org/10.1111/tmi.12655 PMID: 26671654

52. Yuan M, Lyu Y, Chen ST, Cai C, Li Y, Zhang ZG, et al. Evaluation of Xpert MTB/RIF for the diagnosis of extrapulmonary tuberculosis in China. Biomed Environ Sci. 2016; 29(8):599–602. Epub 2016/09/24. https://doi.org/10.3967/bes2016.080 PMID: 27660225

53. Che N, Yang X, Liu Z, Li K, Chen X. Rapid detection of cell-free Mycobacterium tuberculosis DNA in tuberculous pleural effusion. J Clin Microbiol. 2017; 55(5):1526–32. Epub 2017/03/10. https://doi.org/10.1128/JCM.02473-16 PMID: 28275073

54. Jing H, Lu Z, Deng Y, Gao D, Liang L, Graviss EA, et al. Evaluation of Xpert MTB/RIF in detection of pulmonary and extrapulmonary tuberculosis cases in China. Int J Clin Exp Pathol. 2017; 10(4):4847–51.

55. Li Y, Pang Y, Zhang T, Xian X, Wang X, Yang J, et al. Rapid diagnosis of extrapulmonary tuberculosis with Xpert Mycobacterium tuberculosis/rifampicin assay. J Med Microbiol. 2017; 66(7):910–4. Epub 2017/07/15. https://doi.org/10.1099/jmm.0.000522 PMID: 28708053

56. Pandey S, Congdon J, McInnes B, Pop A, Coulter C. Evaluation of the GeneXpert MTB/RIF assay on extrapulmonary and respiratory samples other than sputum: a low burden country experience. Pathology. 2017; 49(1):70–4. Epub 2016/12/04. https://doi.org/10.1016/j.pathol.2016.10.004 PMID: 27913043

57. Saeed M, Ahmad M, Iram S, Riaz S, Akhtar M, Aslam M. GeneXpert technology. A breakthrough for the diagnosis of tuberculous pericarditis and pleuritis in less than 2 hours. Saudi Med J. 2017; 38(7):699–705. Epub 2017/07/05. https://doi.org/10.15537/smj.2017.7.17694 PMID: 28674714

58. Bankar S, Set R, Sharma D, Shah D, Shastri J. Diagnostic accuracy of Xpert MTB/RIF assay in extrapulmonary tuberculosis. Indian J Med Microbiol. 2018; 36(3):357–63. Epub 2018/11/16. https://doi.org/10.4103/ijmm.IJMM_18_173 PMID: 30429387

59. Khan AS, Ali S, Khan MT, Ahmed S, Khattak Y, Abduljabbar, et al. Comparison of GeneXpert MTB/RIF assay and LED-FM microscopy for the diagnosis of extra pulmonary tuberculosis in Khyber Pakhtunkhwa, Pakistan. Braz J Microbiol. 2018; 49(4):909–13. Epub 2018/05/13. https://doi.org/10.1016/j.bjm.2018.02.011 PMID: 29752010

60. Perez-Risco D, Rodriguez-Temporal D, Valledor-Sanchez I, Alcaide F. Evaluation of the Xpert MTB/RIF Ultra assay for direct detection of Mycobacterium tuberculosis complex in smear-negative extrapulmonary samples. J Clin Microbiol. 2018; 56(9):e00659–18. Epub 2018/06/29. https://doi.org/10.1128/JCM.00659-18 PMID: 29950333

61. Prakash AK, Datta B, Tripathy JP, Kumar N, Chatterjee P, Jaiswal A. The clinical utility of cycle of threshold value of GeneXpert MTB/RIF (CBNAAT) and its diagnostic accuracy in pulmonary and extrapulmonary samples at a tertiary care center in India. Indian J Tuberc. 2018; 65(4):296–302. Epub 2018/12/14. https://doi.org/10.1016/j.ijtb.2018.05.021 PMID: 30522616

62. Rakotoarivelo R, Ambrosioni J, Rasolofo V, Raberahona M, Rakotosamimanana N, Andrianasolo R, et al. Evaluation of the Xpert MTB/RIF assay for the diagnosis of smear-negative pulmonary and extrapulmonary tuberculosis in Madagascar. Int J Infect Dis. 2018; 69:20–5. Epub 2018/02/07. https://doi.org/10.1016/j.ijid.2018.01.017 PMID: 29408360

63. Sharma S, Dahiya B, Sreenivas V, Singh N, Raj A, Sheoran A, et al. Comparative evaluation of GeneXpert MTB/RIF and multiplex PCR targeting mpb64 and IS6110 for the diagnosis of pleural TB. Future Microbiol. 2018; 13:407–13. Epub 2018/02/22. https://doi.org/10.2217/fmb-2017-0147 PMID: 29464970

64. Allahyartorkaman M, Mirsaeidi M, Hamzehloo G, Amini S, Zakiloo M, Nasiri MJ. Low diagnostic accuracy of Xpert MTB/RIF assay for extrapulmonary tuberculosis: A multicenter surveillance. Sci Rep. 2019; 9(1):18515. Epub 2019/12/08. https://doi.org/10.1038/s41598-019-55112-y PMID: 31811239

65. El-Din MG, Sobh E, Adawy Z, Farghaly N. Diagnostic utility of gene X-pert in the diagnosis of tuberculous pleural effusion. Infect Dis (Lond). 2019; 51(3):227–9. Epub 2018/10/30. https://doi.org/10.1080/23744235.2018.1532105 PMID: 30371120

66. Kumari P, Lavania S, Tyagi S, Dhiman A, Rath D, Anthwal D, et al. A novel aptamer-based test for the rapid and accurate diagnosis of pleural tuberculosis. Anal Biochem. 2019;564–565:80–7. Epub 2018/10/24. https://doi.org/10.1016/j.ab.2018.10.019 PMID: 30352198

67. Liang Q, Pang Y, Yang Y, Li H, Guo C, Yang X, et al. An improved algorithm for rapid diagnosis of pleural tuberculosis from pleural effusion by combined testing with GeneXpert MTB/RIF and an anti-LAM antibody-based assay. BMC Infect Dis. 2019; 19(1):548. Epub 2019/06/23. https://doi.org/10.1186/s12879-019-4166-1 PMID: 31226940

68. Luo Y, Tan Y, Yu J, Lin Q, Hou H, Mao L, et al. The performance of pleural fluid T-SPOT.TB assay for diagnosing tuberculous pleurisy in China: A two-center prospective cohort study. Frontiers in Cellular and Infection Microbiology. 2019; 9:10. https://doi.org/10.3389/fcimb.2019.00010 PMID: 30761274

69. Mechal Y, Benaissa E, El Mrimar N, Benlahlou Y, Bssaibis F, Zegmout A, et al. Evaluation of GeneXpert MTB/RIF system performances in the diagnosis of extrapulmonary tuberculosis. BMC Infect Dis. 2019; 19(1):1069. Epub 2019/12/21. https://doi.org/10.1186/s12879-019-4687-7 PMID: 31856744

70. Meldau R, Randall P, Pooran A, Limberis J, Makambwa E, Dhansay M, et al. Same-day tools, including Xpert Ultra and IRISA-TB, for rapid diagnosis of pleural tuberculosis: a prospective observational study. J Clin Microbiol. 2019; 57(9):e00614–19. Epub 2019/07/05. https://doi.org/10.1128/JCM.00614-19 PMID: 31270183

71. Tadesse M, Abebe G, Bekele A, Bezabih M, Yilma D, Apers L, et al. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a diagnostic evaluation study. Clin Microbiol Infect. 2019; 25(8):1000–5. Epub 2018/12/26. https://doi.org/10.1016/j.cmi.2018.12.018 PMID: 30583052

72. Tahseen S, Ambreen A, Masood F, Qadir M, Hussain A, Jamil M, et al. Primary drug resistance in extra-pulmonary tuberculosis: a hospital-based prospective study from Pakistan. Int J Tuberc Lung Dis. 2019; 23(8):900–6. Epub 2019/09/20. https://doi.org/10.5588/ijtld.18.0531 PMID: 31533879

73. Wang G, Wang S, Jiang G, Yang X, Huang M, Huo F, et al. Xpert MTB/RIF Ultra improved the diagnosis of paucibacillary tuberculosis: A prospective cohort study. J Infect. 2019; 78(4):311–6. Epub 2019/02/24. https://doi.org/10.1016/j.jinf.2019.02.010 PMID: 30796951

74. Wu X, Tan G, Gao R, Yao L, Bi D, Guo Y, et al. Assessment of the Xpert MTB/RIF Ultra assay on rapid diagnosis of extrapulmonary tuberculosis. Int J Infect Dis. 2019; 81:91–6. Epub 2019/02/11. https://doi.org/10.1016/j.ijid.2019.01.050 PMID: 30738907

75. Zhou X, Wu H, Ruan Q, Jiang N, Chen X, Shen Y, et al. Clinical evaluation of diagnosis efficacy of active Mycobacterium tuberculosis complex infection via metagenomic next-generation sequencing of direct clinical samples. Front Cell Infect Microbiol. 2019; 9:351. Epub 2019/11/05. https://doi.org/10.3389/fcimb.2019.00351 PMID: 31681628

76. Abdelfattah SR, Elhefny RA, Ahmed RI, AbdelHamid JR. Evaluation of GeneXpert MTB for detection of Mycobacterium tuberculosis in Fayoum Governorate. Egyptian Journal of Chest Diseases and Tuberculosis. 2020; 69(2):303–9. https://doi.org/10.4103/ejcdt.ejcdt_90_19

77. Chen P, Sun W, He Y. Comparison of metagenomic next-generation sequencing technology, culture and GeneXpert MTB/RIF assay in the diagnosis of tuberculosis. J Thorac Dis. 2020; 12(8):4014–24. Epub 2020/09/19. https://doi.org/10.21037/jtd-20-1232 PMID: 32944313

78. Dahiya B, Prasad T, Singh V, Khan A, Kamra E, Mor P, et al. Diagnosis of tuberculosis by nanoparticle-based immuno-PCR assay based on mycobacterial MPT64 and CFP-10 detection. Nanomedicine (Lond). 2020; 15(26):2609–24. Epub 2020/10/23. https://doi.org/10.2217/nnm-2020-0258 PMID: 33090059

79. Han M, Xiao H, Yan L. Diagnostic performance of nucleic acid tests in tuberculous pleurisy. BMC Infect Dis. 2020; 20(1):242. Epub 2020/03/27. https://doi.org/10.1186/s12879-020-04974-z PMID: 32209054

80. Hoel IM, Syre H, Skarstein I, Mustafa T. Xpert MTB/RIF ultra for rapid diagnosis of extrapulmonary tuberculosis in a high-income low-tuberculosis prevalence setting. Sci Rep. 2020; 10(1):13959. Epub 2020/08/20. https://doi.org/10.1038/s41598-020-70613-x PMID: 32811871

81. Li S, Lin L, Zhang F, Zhao C, Meng H, Wang H. A retrospective study on Xpert MTB/RIF for detection of tuberculosis in a teaching hospital in China. BMC Infect Dis. 2020; 20(1):362. Epub 2020/05/26. https://doi.org/10.1186/s12879-020-05004-8 PMID: 32448123

82. Sasikumar C, Utpat K, Desai U, Joshi J. Role of GeneXpert in the diagnosis of mycobacterium tuberculosis. Adv Respir Med. 2020; 88(3):183–8. Epub 2020/07/25. https://doi.org/10.5603/ARM.2020.0102 PMID: 32706101

83. Sumalani KK, Akhter N, Ahmed M, Chawla D, Rizvi NA. Diagnostic implications of bronchial lavage in patients with pleural tuberculosis. Adv Respir Med. 2020; 88(5):389–93. Epub 2020/11/11. https://doi.org/10.5603/ARM.a2020.0149 PMID: 33169809

84. Wang G, Wang S, Yang X, Sun Q, Jiang G, Huang M, et al. Accuracy of Xpert MTB/RIF Ultra for the diagnosis of pleural TB in a multicenter cohort study. Chest. 2020; 157(2):268–75. Epub 2019/08/23. https://doi.org/10.1016/j.chest.2019.07.027 PMID: 31437432

85. Yang X, Che N, Duan H, Liu Z, Li K, Li H, et al. Cell-free Mycobacterium tuberculosis DNA test in pleural effusion for tuberculous pleurisy: a diagnostic accuracy study. Clin Microbiol Infect. 2020; 26(8):1089.e1-.e6. Epub 2019/12/06. https://doi.org/10.1016/j.cmi.2019.11.026 PMID: 31805377

86. Yu G, Shen Y, Ye B, Chen D, Xu K. Comparison of CapitalBio™ Mycobacterium nucleic acid detection test and Xpert MTB/RIF assay for rapid diagnosis of extrapulmonary tuberculosis. J Microbiol Methods. 2020; 168:105780. Epub 2019/11/22. https://doi.org/10.1016/j.mimet.2019.105780 PMID: 31751598

87. Elbrolosy AM, El Helbawy RH, Mansour OM, Latif RA. Diagnostic utility of GeneXpert MTB/RIF assay versus conventional methods for diagnosis of pulmonary and extra-pulmonary tuberculosis. BMC Microbiol. 2021; 21(1):144. Epub 2021/05/14. https://doi.org/10.1186/s12866-021-02210-5 PMID: 33980173

88. Gao S, Wang C, Yu X, Teng T, Shang Y, Jia J, et al. Xpert MTB/RIF Ultra enhanced tuberculous pleurisy diagnosis for patients with unexplained exudative pleural effusion who underwent a pleural biopsy via thoracoscopy: A prospective cohort study. Int J Infect Dis. 2021; 106:370–5. Epub 2021/04/13. https://doi.org/10.1016/j.ijid.2021.04.011 PMID: 33845198

89. Guo S, Han C, He Y, Wang MS. Diagnostic incremental value of sputum in patients with pleural tuberculosis. Infect Dis (Lond). 2021; 53(3):184–8. Epub 2020/12/10. https://doi.org/10.1080/23744235.2020.1857431 PMID: 33295822

90. Kim SK, Chang J, Choi SH, Sung H, Kim MN. Performance of Xpert MTB/RIF for the diagnosis of extra-pulmonary tuberculosis. Clin Lab. 2021; 67(2):229–34. Epub 2021/02/23. https://doi.org/10.7754/Clin.Lab.2020.200423 PMID: 33616324

91. Kobra AT, Shahriar A, Shams R, Hossain MS, Mostofa Kamal SM, Alqahtani A, et al. Comparative and co-relative analysis of different tests for rapid diagnosis of tuberculosis (Tb) from pleural effusion. Latin American Journal of Pharmacy. 2021; 40(2):310–6.

92. Koumeka PP, Ouldittou I, Fikri O, Saidi I, Ait Batahar S, Amro L. Predictive factors and biomarkers of exudative lymphocytic tuberculous pleurisy. Rev Mal Respir. 2021; 38(3):231–9. Epub 2021/02/04. https://doi.org/10.1016/j.rmr.2020.11.001 PMID: 33531187

93. Lopez-Roa P, Martin-Higuera C, Ruiz-Serrano MJ, Toro C, Tato M, Simon M, et al. Performance of Xpert MTB/RIF Ultra assay on respiratory and extra-respiratory samples in a high-resource setting with a low tuberculosis prevalence. Diagn Microbiol Infect Dis. 2021; 99(2):115235. Epub 2020/11/02. https://doi.org/10.1016/j.diagmicrobio.2020.115235 PMID: 33130504

94. Mekkaoui L, Hallin M, Mouchet F, Payen MC, Maillart E, Clevenbergh P, et al. Performance of Xpert MTB/RIF Ultra for diagnosis of pulmonary and extra-pulmonary tuberculosis, one year of use in a multi-centric hospital laboratory in Brussels, Belgium. PLoS One. 2021; 16(4):e0249734. Epub 2021/04/09. https://doi.org/10.1371/journal.pone.0249734 PMID: 33831077

95. Penata-Bedoya A, Zuluaga-Avendano S, Castano-Sepulveda T, Bustamante-Mira J, Ospina-Ospina S. Performance of real-time semi-quantitative polymerase chain reaction assay for optimum diagnosis of extrapulmonary tuberculosis and sensitivity to rifampin in a tertiary care center. Rev Invest Clin. 2021. Epub 2021/05/18. https://doi.org/10.24875/RIC.21000040 PMID: 33999915

96. Sun W, Zhou Y, Li W, Wang Y, Xiong K, Zhang Z, et al. Diagnostic yield of Xpert MTB/RIF on contrast-enhanced ultrasound-guided pleural biopsy specimens for pleural tuberculosis. Int J Infect Dis. 2021; 108:89–95. Epub 2021/05/17. https://doi.org/10.1016/j.ijid.2021.05.023 PMID: 33992762

97. Takwoingi Y, Partlett C, Riley RD, Hyde C, Deeks JJ. Methods and reporting of systematic reviews of comparative accuracy were deficient: a methodological survey and proposed guidance. J Clin Epide-miol. 2020; 121:1–14. Epub 2019/12/18. https://doi.org/10.1016/j.jclinepi.2019.12.007 PMID: 31843693

98. Jiang J, Yang J, Shi Y, Jin Y, Tang S, Zhang N, et al. Head-to-head comparison of the diagnostic accuracy of Xpert MTB/RIF and Xpert MTB/RIF Ultra for tuberculosis: a meta-analysis. Infect Dis (Lond). 2020; 52(11):763–75. Epub 2020/07/04. https://doi.org/10.1080/23744235.2020.1788222 PMID: 32619114