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RESEARCH ARTICLE

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Diagnostic value of Lipoarabinomannan antigen for detecting *Mycobacterium tuberculosis* in adults and children with or without HIV infection

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Abstract

Objectives: Even today, tuberculosis (TB) remains a leading public health problem; yet, the current diagnostic methods still have a few shortcomings. Lipoarabinomannan (LAM) provides an opportunity for TB diagnosis, and urine LAM detection seems to have a promising and widely applicable prospect.

Design or methods: Four databases were systematically searched for eligible studies, and the quality of the studies was evaluated using the quality assessment of diagnostic accuracy studies-2 (QUADAS-2). Graphs and tables were created to show sensitivity, specificity, likelihood ratios, diagnostic odds ratio (DOR), the area under the curve (AUC), and so on.

Results: Based on the included 67 studies, the pooled sensitivity of urine LAM was 48% and specificity was 89%. In the subgroup analyses, the FujiLAM test had higher sensitivity (69%) and specificity (92%). Furthermore, among patients infected with human immunodeficiency virus (HIV), 50% of TB patients were diagnosed using a urine LAM test. Besides, the CD4+ cell count was inversely proportional to the sensitivity.

Conclusions: Urine LAM is a promising diagnostic test for TB, particularly using the FujiLAM in HIV-infected adults whose CD4+ cell count is ≤100 per μl. Besides, the urine LAM test shows various sensitivities and specificities in different subgroups in terms of age, HIV infection status, CD4+ cell count, and testing method.

KEYWORDS
Lipoarabinomannan, sensitivity, specificity, tuberculosis, urine

1 | INTRODUCTION

According to the World Health Organization (WHO) report on global tuberculosis (TB), TB is one of the most onerous infectious diseases, with 7.1 million people newly diagnosed[1] and 1.5 million people dying from TB in 2019.[2] Furthermore, when this TB pandemic collides with threats such as the human immunodeficiency virus (HIV), it will worsen due to the limited access to healthcare.[3,4]

Bacterial culture is a common method for diagnosing TB.[5] The culture can be obtained successfully for a vast majority of patients. However, the process consumes a disproportionate amount of time.[6] Currently, Xpert MTB/RIF is widely used in molecular diagnostic testing due to its ability to rapidly identify *Mycobacterium tuberculosis* (MTB).[6] However, several limitations have been observed for this method. Although published data demonstrated Xpert's improved smear microscopy accuracy, patients must provide adequate quality and volume sputum samples.[7] Xpert's inflated cost is also seen as a major impediment to its implementation.[8] That is why we urgently require advanced tests that are accurate, rapid, inexpensive, and simple.

Lipoarabinomannan (LAM), a cell surface-associated glycolipid component, was found in the MTB cell wall, which has been the most common antigen for MTB detection.[9,10] At present, the commonly used LAM detection includes the enzyme-linked immunosorbent assay (ELISA), Determine LAM assay,[11] and Fujifilm SILVAMP TB LAM (FujiLAM). In addition, unlike sputum, urine is determined to be easy to obtain and store, noninvasive, and has a lower risk of nosocomial transmission.[12]

In this study, we perform a meta-analysis based on the pooled eligible studies. Subgroup analyses, particularly regarding HIV status and detection methods, were settled after a recent review revealed that they increased heterogeneity.[13] The purpose is to assess the diagnostic accuracy of urine LAM antigen testing for MTB in urine specimens, laying the foundation for clinical prevention and control decision-making.

2 | MATERIALS AND METHODS

2.1 | Search strategy and source

The electronic databases, including PubMed, Embase, Cochrane Library, and Web of Science, were searched using the key terms "Mycobacterium tuberculosis" "lipoarabinomannan" as detailed in Table S1. Embase EmTree and PubMed MeSH were utilized to broaden synonyms. All papers were published from September 1986 to September 2020 and scrutinized by two reviewers independently.

The study protocol was registered as CRD42021273056 in PROSPERO which is an international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/). The PRISMA Statement guidelines were followed in all of our review processes (http://www.prisma-statement.org/).

2.2 | Study selection and screening criteria

Before data extraction, the study's inclusion and exclusion criteria were prespecified. The criteria for inclusion in the reviewed studies were as follows: (i) participants were patients with suspected or diagnosed TB; (ii) the diagnostic method was based on lipoarabinomannan; (iii) the urine sample was used; (iv) the diagnostic accuracy was achieved using a gold standard method; (v) the data provided by the study could identify true positive (TP), false positive (FP), true negative (TN), false negative (FN), sensitivity, and specificity; and (vi) English literature was included.

The exclusion criteria were as follows: (i) duplicate or overlapping publications; (ii) review articles, editorials, conference abstracts, letters, case reports, etc.; (iii) studies that were preprinted only; (iv) sensitivity or specificity is unclear. The researchers used EndNote version X9 (Thomson Corporation, Stamford, CT, USA) to sort out eligible studies with the predetermined screening.

2.3 | Data extraction

Six reviewers working in pairs screened and extracted data independently. When two reviewers' opinions differed, a third reviewer was consulted to reach a final decision. Two reviewers independently extracted all of the following information from all incorporated publications using a standardized form: first author, publication year, country, study group, sample size, detection method, reference standard, HIV status, CD4+ cell count, TP, FP, TN, and FN.

2.4 | Quality assessment standard

Quality Assessment of Diagnostic Accuracy Study 2 (QUADAS-2) guideline[14] was conducted by two investigators to assess the quality of the included studies. Then, we analyzed the risk of bias and applicability concerns using Review Manager 5.4 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012), which includes four domains: patient selection, reference standard, index test, flow, and timing. Each domain was assessed in terms of the risk of bias (low, high, or unclear), and the first three domains were taken into consideration in the clinical applicability evaluation. If the assessment results conflicted, a third investigator referred to the original study to reach a consensus.

2.5 | Meta-regression and subgroup analyses

Meta-regression and subgroup analyses were carried out based on various independent variables: age (children or adults), HIV status (positive or negative), detection test (ELISA, Determine TB assay, or FujiLAM), reference test (culture or composite reference standard), pulmonary tuberculosis (PTB) (yes or no), and CD4+ cell count, etc.

2.6 | Statistical analysis

Using Meta-DiSc version 1.4 (Clinical Biostatistics Unit, Madrid, Spain) software,[15] we independently analyzed the data, including sensitivity, specificity, positive likelihood ratio (PLR), negative

likelihood ratio (NLR), diagnostic odds ratio (DOR), the area under the curve (AUC), and their 95% confidence intervals (CIs). Moreover, heterogeneity was assessed by the inconsistency index I^2, for which both threshold effect and nonthreshold effect are responsible. The Spearman correlation was used to determine whether there was a threshold effect, as a strong correlation showed a threshold effect. The P-value of the DOR plot was computed to ascertain the nonthreshold effect.

Effect models were determined based on the degree of heterogeneity among studies. If the heterogeneity was not significant ($I^2 <$ 75%), a fixed-effect model could be chosen to analyze the results. If significant heterogeneity ($I^2 \geq$ 75%) existed, a random-effect model (DerSimonian-Laird method) was applied.

All analyses were conducted using the Midas package in Stata version 13.0 (Stata Corp, College Station, Texas, USA). A bivariate boxplot was used to assess the heterogeneity in the included studies. The Deeks' funnel plot was verified to confirm publication bias.

3 | RESULTS

3.1 | Included studies

After searching databases, the literature search yielded 1622 articles, of which 615 were reduplicative. Following a review of all abstracts and titles, 845 studies were found to be unrelated. Then we went over the text, and 95 studies were eliminated for various reasons. Finally, 67 articles with a total of 164 reports and 23727 samples were included[6,16–81] (Figure S1).

3.2 | Characteristics of included studies

Studies that met our selection criteria are described in Table S2. The majority of patients came from African sites, particularly South Africa (33/67, 52.2%). In total, 17 of 67 articles studied PTB, and others looked at PTB and extrapulmonary TB like tuberculous meningitis and lymph node TB.

3.3 | Methodological quality evaluation

We evaluated the quality of the included studies, and the summaries according to the QUADAS-2 criteria are shown in Figure 1 and S2. In the field of the index test, reference standard, flow, and timing, more than 90% of studies had a low risk of bias and applicability concerns. It is worth noting that more than 10% of the studies had high applicability concerns in patient selection because they did not include continuous or random participants.

3.4 | Accuracy estimates

The overall sensitivity was 48% (95% CI 48%–49%) and specificity was 89% (95% CI 89%–89%), with 94.8% and 95.2% heterogeneity in Figures S3 and S4, respectively.

3.5 | Threshold effect of heterogeneity analysis

In the threshold effect analysis, Spearman correlation coefficient was 0.392 ($p < 0.001$), indicating a strong positive correlation (Table 1). Moreover, the distribution of the shoulder-arm points on the summary receiver operating characteristic (SROC) curve indicated the existence of the threshold effect (Figure 2). The threshold effect suggested the difference in judging criteria between diagnostic tests as a result of different thresholds.

3.6 | Nonthreshold effect and meta-regression

In the case of DOR, the Cochran-Q was 946.50 ($p < 0.05$), indicating that a nonthreshold effect was a potential source of heterogeneity (Figure S5). The nonthreshold effect can be caused by various factors, age, reference standards, testing techniques, and so on. Meta-regression was performed and suggested that the nonthreshold effect was most likely due to age, as the diagnostic accuracy of the adult was 4.13 times that of the nonadult.

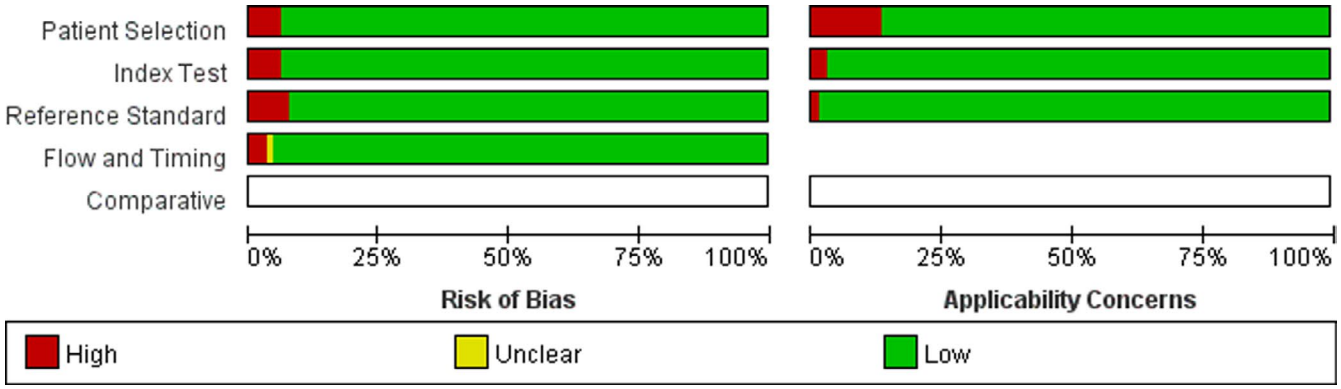

FIGURE 1 Pooled bias risks and applicability concerns using the QUADAS-2 criteria

TABLE 1 Analysis of diagnostic threshold

Variate	Coefficient	Standard error	*T*	*p*-value
a	2.335	0.160	14.584	0.0000
b	0.051	0.048	1.058	0.2919

Note: Spearman correlation coefficient = 0.392 ($p < 0.001$).

3.7 | DerSimonian-Laird method

DerSimonian-Laird was used to fit the SROC curve, while the *p*-value of *b* was >0.05, which indicated the SROC curve was symmetrical (Table 1). The AUC was 0.83 (Figure 2), and the combined DOR was 8.96 (95% CI 7.45 to 10.79), indicating good diagnostic performance (Figure S5). However, since the significant heterogeneity

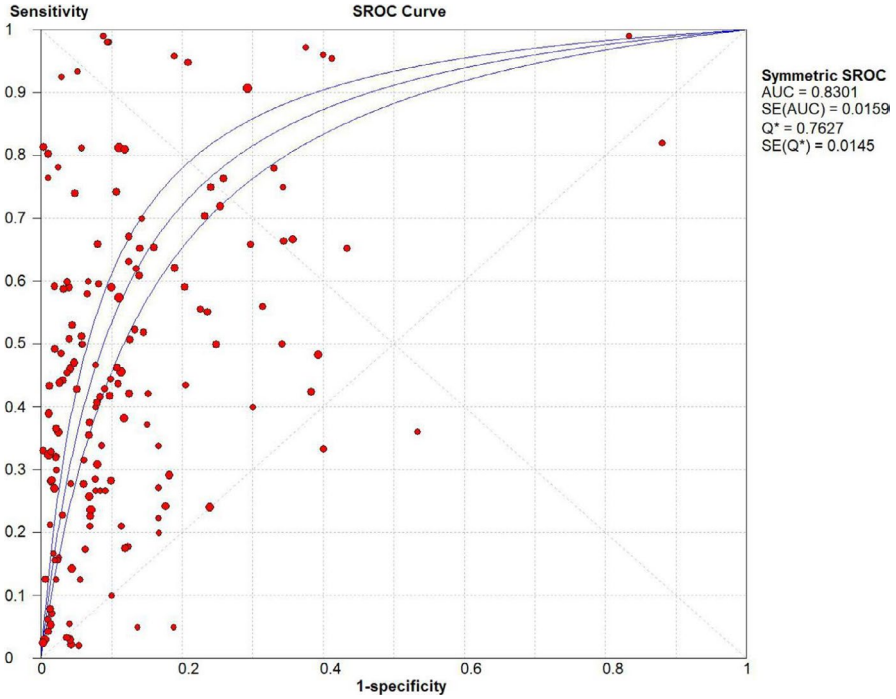

FIGURE 2 Overall SROC plot of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis. *SROC, summary receiver operating characteristic; AUC, the area under the curve; SE, standard error

	Patients	Sensitivity	Specificity
All	23,727	0.48[0.48, 0.49]	0.89[0.89, 0.89]
Age			
Adults	22,709	0.49[0.48, 0.50]	0.90[0.90, 0.91]
Children	1018	0.37[0.34, 0.40]	0.80[0.79, 0.82]
HIV statues			
HIV+	17,779	0.50[0.49, 0.51]	0.90[0.89, 0.90]
HIV−	2758	0.31[0.28, 0.34]	0.90[0.88, 0.91]
CD4+ Cell Count(/mm3)			
<100/≤100	5360	0.63[0.62–0.65]	0.88[0.87–0.89]
>100/≥100	9648	0.29[0.27–0.31]	0.97[0.96–0.97]
<200/≤200	11,040	0.58[0.56–0.60]	0.87[0.86–0.89]
>200/≥200	3968	0.30[0.27–0.33]	0.97[0.96–0.98]
Detection method			
ELISA	7683	0.42[0.41, 0.44]	0.94[0.93, 0.94]
Determine TB-LAM assay	17,213	0.44[0.43, 0.45]	0.87[0.87, 0.88]
FujiLAM	1622	0.69[0.67, 0.71]	0.92[0.90, 0.93]
Reference method			
Culture included	19,958	0.49[0.48, 0.49]	0.89[0.88, 0.89]
Composite reference	5507	0.51[0.50, 0.53]	0.91[0.90, 0.92]

TABLE 2 Subgroup analyses on the sensitivity and specificity of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis

of sensitivity (I^2 = 94.8%) and specificity (I^2 = 95.2%) still limited TB diagnosis with LAM, we performed subgroup analyses to further clarify the potential sources of heterogeneity.

3.8 | Subgroup analyses

The results of subgroup analyses are detailed in Tables 2–5. The diagnostic sensitivity, specificity, and DOR of children were lower than that of adults. HIV-negative patients had significantly lower sensitivity and DOR than HIV-positive patients, but no difference in specificity. In the acquired immune deficiency syndrome (AIDS) patients, CD4+ cell count less than 100 per cubic millimeter was more sensitive than CD4+ cell count more than 100 (63% vs 29%) but less specific (88% vs 97%). The overall sensitivity for FujiLAM TB detection was 69%, specificity was 92%, and DOR was 19.73. For the clinical reference standard comparison, the pooled sensitivity and specificity were 51% and 91%, respectively (Tables 2 and 3).

Children had a PLR of 1.89 and a NLR of 0.80. The NLR of HIV- was 0.86. For the CD4+ cell count, the PLR in those with counts more than 100 per cubic millimeter was 9.22. For CD4+ cell counts less than 100, the NLR was 0.47, and for counts greater than 100, it was 0.77. The PLR and NLR of the FujiLAM method were 7.40 and 0.40, respectively.

Except for subgroup CD4+ cell count ≥200 with poor diagnostic performance (AUC < 0.7), the diagnostic accuracy was high (Table 4).

TABLE 3 Subgroup analyses on the positive likelihood ratio (PLR) and negative likelihood ratio (NLR) of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis

	PLR	NLR
All patients	4.56[3.93, 5.28]	0.61[0.57, 0.65]
Age		
Adults	5.34[4.54, 6.28]	0.58[0.54, 0.63]
Children	1.89[1.49, 2.39]	0.80[0.72, 0.90]
HIV statues		
HIV+	5.10[4.40, 5.90]	0.58[0.54, 0.62]
HIV−	2.99[2.03, 4.40]	0.86[0.78, 0.95]
CD4+ Cell Count(/mm^3)		
<100/≤100	5.03[4.03–6.29]	0.47[0.39–0.55]
>100/≥100	9.22[5.32–15.98]	0.77[0.70–0.85]
<200/≤200	4.72[3.27–6.80]	0.45[0.39–0.52]
>200/≥200	7.28[3.61–14.67]	0.73[0.66–0.82]
Detection method		
ELISA	4.71[3.76, 5.91]	0.66[0.58, 0.74]
Determine TB-LAM assay	4.04[3.43, 4.74]	0.65[0.62, 0.70]
FujiLAM	7.40[5.73, 9.54]	0.40[0.31, 0.53]
Reference method		
Culture included	4.51[3.87, 5.26]	0.61[0.57, 0.65]
Composite reference	7.24[5.04, 10.42]	0.55[0.48, 0.64]

Postpositive and postnegative probability in children was 70% and 41%, respectively. Besides, a positive value revealed an 89% post-test probability of a correct diagnosis based on FujiLAM detection, whereas a 29% probability of TB patients was ignored but tested negative (Table 5).

3.9 | Bivariate boxplot

According to the bivariate boxplot, we found the source of considerable heterogeneity. The heterogeneity may be resulted from the points outside the circle, thus we reviewed papers these points represent in Figure 3[20,64,79].

3.10 | Publication bias

The Deeks' funnel plot (Figure 4) was symmetric, which showed that $p = 0.69$ (>0.1), and therefore, suggests no potential published offset for the included studies.

4 | DISCUSSION

Throughout the past decade, TB remains a major public health challenge around the world.[82] Therefore, there is a critical need for a clear and rapid diagnosis of TB, guiding drug use, and controlling the development of diseases.[83] With low infection control risks, non-invasive, and convenient sample collection, the urine-based LAM assay was identified as a focus.[84] The urine-based LAM assay, a simple point-of-care test, has been used in the commercial development of rapid detection of MTB.[85] In addition, LAM assay reduces costs over culture and diagnoses patients with extrapulmonary TB with slightly higher accuracy than smear.[86]

The detecting efficacy of LAM antigen in serum, sputum, cerebrospinal fluid samples was also evaluated. However, a low number of eligible studies and a great heterogeneity showed insufficient evidence to compare with the urine samples.

In our study, the overall sensitivity was 48% and specificity was 89%. A meta-analysis of 15 studies with 6814 participants and 1761 TB patients reported the pooled sensitivity and specificity to be 42% and 91%, respectively.[11] The results are relatively consistent. We do, however, have the following advantages: (1) huge sample size; (2) not limited to HIV-positive TB patients; (3) not limited to adults. Slow-growing nontuberculous mycobacteria cause reduced specificity,[87] while moderate sensitivity can be interpreted as MTB deficiency in primary and extrapulmonary TB.

To explore the reasons for high heterogeneity indicated by I^2, the threshold effect and the nonthreshold effect analyses should be performed.[15] We found that heterogeneity occurs due to age, HIV status, CD4+ cell count, detection method, and reference standard method.

TABLE 4 Subgroup analyses on the diagnostic odds ratio (DOR) and the area under the curve (AUC) of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis

	DOR	AUC
All patients	8.96[8.45, 10.79]	0.8301
Age		
Adults	10.96[9.12,13.81]	0.8474
Children	2.65[1.83, 3.83]	0.7039
HIV statues		
HIV+	10.07[8.38, 12.09]	0.7917
HIV−	5.24[2.88, 9.52]	0.8474
CD4+ Cell Count(/mm3)		
<100/≤100	12.22[8.83, 16.93]	0.8645
>100/≥100	12.73[6.75, 24.01]	0.7013
<200/≤200	11.76[7.94, 17.42]	0.7940
>200/≥200	10.40[5.05, 21.44]	0.5450
Detection method		
ELISA	8.64[6.22, 12.00]	0.8558
Determine TB-LAM assay	7.05[5.65, 8.79]	0.7215
FujiLAM	19.73[12.60, 30.88]	0.9291
Reference method		
Culture included	8.87[7.32, 10.75]	0.8257
Composite reference	15.00[9.36, 24.03]	0.8700

TABLE 5 Subgroup analyses on the post-test probability of positive or negative of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis

	Positive (%)	Negative (%)
All patients	86	37
Age		
Adults	88	37
Children	70	41
HIV statues		
HIV+	87	36
HIV−	82	44
CD4+ Cell Count(/mm^3)		
<100/≤100	85	32
>100/≥100	92	44
<200/≤200	84	30
>200/≥200	92	41
Detection method		
ELISA	87	42
Determine TB-LAM assay	84	39
FujiLAM	89	29
Reference method		
Culture included	85	38
Composite reference	90	36

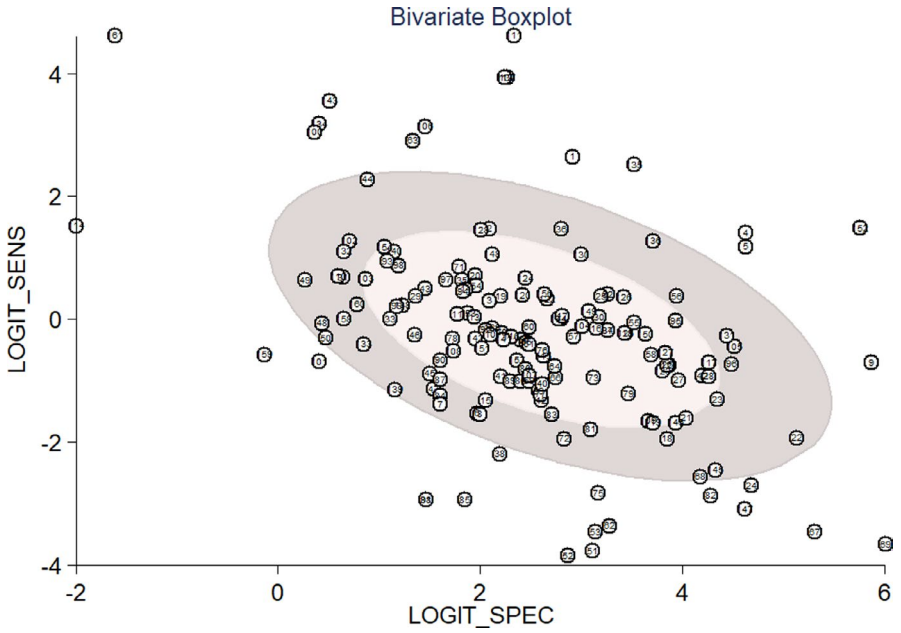

FIGURE 3 Bivariate boxplot of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis. *LOGIT_SENS, logit sensitivity; LOGIT_SPEC, logit specificity

The sensitivity and specificity of diagnosing TB suspected adult were higher than that of children (49% vs 37% & 90% vs 80%). As the primary vaccine for TB prevention, the possibility of Bacillus Calmette Guerin (BCG) vaccination cross-reaction in children is greater than in adults, which may result in FP results.[88,89] Furthermore, children's poor susceptibility to MTB culture may result in falsely low estimates of specificity.[38] In conclusion, the urine LAM test has limited diagnostic efficacy in TB children.

Co-infection provides reciprocal advantages to both MTB and HIV and is the leading cause of death in AIDS patients.[90] For TB patients with HIV infection, the sensitivity was significantly higher than patients without HIV infection (50% vs 31%). The reason could be that antigenemia in HIV-infected TB patients has a higher bacterial burden.[10] In symptomatic participants with CD4+ count >100 cells/μl, the combined sensitivity was only 29%. Patients with CD4+ count <100 cells/μl may be affected by advanced

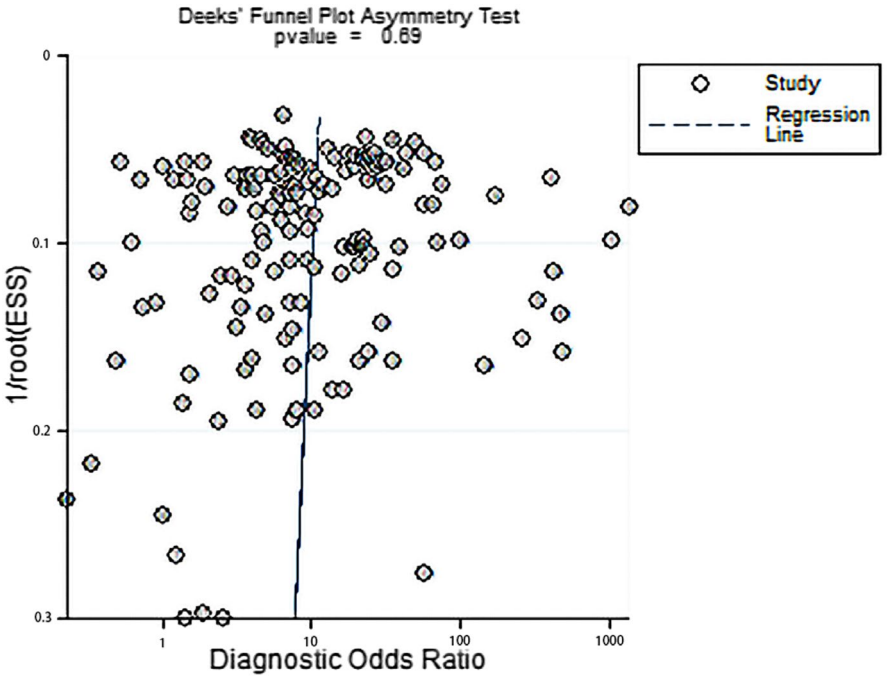

FIGURE 4 The Deeks' funnel plot of urine lipoarabinomannan (LAM) antigen in the diagnosis of tuberculosis

diseases, which have a combined sensitivity of 63%. Urine LAM test has great application potential in the diagnosis of advanced HIV-infected TB patients, especially in economically backward developing countries.[13]

We found that differences in detection techniques can result in significant heterogeneity. In 2003, Inverness commercialized Clearview® TB ELISA, which changed the name into the Determine TB LAM antigen lateral flow assay (Determine TB-LAM assay, Alere, Waltham, MA, USA) in 2010. The sensitivity (42% vs 44%) and specificity (94% vs 87%) of ELISA and Determine LAM assay are similar due to the same polyclonal antibody. A novel urine-based assay, Fujifilm SILVAMP TB LAM (FujiLAM; Fujifilm, Tokyo, Japan), showed potential for further clinical application with 69% sensitivity, which is more than 65% as WHO recommended.[83]

An imperfect golden standard has a disproportional effect on a more sensitive test, resulting in increased FP results.[68] Furthermore, both the Determine TB-LAM assay and the FujiLAM are inspected by eye when interpreting the measured stripe, which may lead to a subjective result. It should be noted that grade 1 of 4 strips since 2014 is consistent with that of grade 2 of 5 strips before 2014; thus, different interpretations may result in heterogeneity of results.[11]

The subgroup analyses were set to reduce the heterogeneity, and the bivariate boxplot was used to obtain further in-depth information. Amin's study only included 100 TB patients, so his findings should be interpreted cautiously.[64] Huerga reported the highest sensitivity (81%) and specificity (100%), but only patients with HIV-positive and CD4+ <100 cells/μl were enrolled.[79]

Nonetheless, the current study has a few limitations. In terms of research design and quality assessment, not all selected studies are included in a random or continuous manner, which may result in a lack of reasonable sampling methods. The lack of inpatients and outpatients may obscure some meaningful results by ignoring differences in their population characteristics.[11] Furthermore, studies published in all languages were not included (only English included). In conclusion, the evidence from this study suggests that urine LAM antigen may be a promising biomarker for TB, particularly using FujiLAM. The effect on HIV-positive TB patients is encouraging, with advanced HIV diseases benefiting more. This is consistent with the findings in previous research works.[84] However, considering the clinical effect of the urine LAM test, more research is recommended.

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CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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