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Diagnostic Efficiency of the Blood-Based Cepheid 3-Gene Host Response Test and Urine-Based Lipoarabinomannan for Active Tuberculosis Case Detection at a General Hospital in China

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Objective: To assess the diagnostic performance of the blood-based Cepheid 3-gene Host Response test (MTB-HR), urine-based Lipoarabinomannan (LAM), and a combination of MTB-HR and LAM (MTB-HR & LAM) for detecting active tuberculosis (ATB).

Methods: All participants were recruited from the First Affiliated Hospital, Zhejiang University School of Medicine, between June 8, 2023 and September 13, 2023. Subsequently, the participants were classified into the ATB group or non-active tuberculosis (non-ATB) group based on microbiological evidence. MTB-HR and LAM tests were performed using fingerstick blood and urine samples from each participant, respectively. The diagnostic performance of the tests was evaluated based on the sensitivity, specificity, Youden index, and Kappa value. Pairwise comparisons of the areas under the receiver operating characteristic curves (AUROCs) between different tests were conducted using nonparametric methods.

Results: A total of 297 participants were included. The MTB-HR test demonstrated diagnostic efficacy with a sensitivity of 77.37% (95% CI: 70.37–84.38) and a specificity of 85.63% (95% CI: 80.19–91.06). The LAM test demonstrated a high specificity of 97.50% (95% CI: 95.08–99.92), albeit with a lower sensitivity of 54.74% (95% CI: 46.41–63.082). The sensitivity and specificity of the MTB-HR & LAM were 83.21% (95% CI: 76.95–89.47) and 83.13% (95% CI: 77.32–88.93), respectively. Only MTB-HR & LAM exhibited higher values of area under the receiver operating characteristic curve than the LAM test (MTB-HR & LAM vs LAM: 0.83 vs 0.76, P=0.0031).

Conclusion: In this study, although both non-sputum-based triage MTB-HR and LAM do not meet the WHO diagnostic target currently, they show possible values for triage and diagnosis in ATB. Compared to single MTB-HR or LAM test, the combined MTB-HR & LAM does not demonstrate advantages.

Keywords: active tuberculosis, diagnostic, three-gene host response, Lipoarabinomannan, AUROC

Introduction

Tuberculosis (TB), which is primarily caused by Mycobacterium tuberculosis (MTB), is prevalent worldwide in all age groups. With more than 10 million new cases reported annually, TB persists as one of the foremost causes of mortality among human populations (1.3 million people die of TB).[1] TB is curable; however, its diagnosis remains challenging. The symptoms of TB are non-specific, and patients with pulmonary TB who present with a full spectrum of symptoms

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and signs are unusual in developed countries.[2] MTB cultivation is the GOLD standard for the diagnosis of MTB.[3] Traditional diagnostic methods, such as culture or smear microscopy, are slow or have low sensitivity.[4] Chest radiography is widely used, but is limited by infrastructure and instrumentation requirements and its lack of specificity.[5] Traditional tuberculin skin testing and interferon γ release assays cannot distinguish between latent and active TB.[6]

The more developed Xpert MTB/RIF method has significantly improved TB detection.[7] Additionally, the new Xpert MTB/RIF Ultra assay has improved diagnostic power, especially in patients with paucibacillary disease, and provides more reliable detection of rifampin resistance.[8] Notably, Xpert MTB/RIF relies on induced sputum, which is difficult to obtain from adults after symptomatic improvement and from pediatric patients. Although molecular techniques have provided quick, sensitive, and specific tests for MTB, these methods can be costly, technically demanding, and often unavailable in primary care settings owing to infrastructure requirements.[2,4] Despite the endorsement of several new tests and diagnostic approaches by the World Health Organization (WHO) since 2007, an accurate and rapid point-of-care test suitable for field conditions remains elusive, as stated in the WHO's 'End TB Strategy'.[9] Widespread screening and rapid diagnosis are crucial for achieving the goal of reducing the global TB incidence by 80% between 2015 and 2030, as set by the WHO in 2014.[10]

The Cepheid MTB Host Response prototype cartridge (MTB-HR) is a GeneXpert-based RT-PCR test that assesses the relative mRNA levels in fingerstick blood samples.[11] A previous study revealed that a combinatory score based on three differentially expressed genes (GBP5, DUSP3, and KLF2) can be valuable for active tuberculosis (ATB) diagnosing, and is not confounded by HIV infection status, bacterial drug resistance, or BCG vaccination.[12]

Lipoarabinomannan (LAM), a unique structural component of the lipid-rich mycobacterial cell wall, provides a highly specific "antigen" that is excreted by the kidney, and its detection in urine could be a useful diagnostic test.[13] A previous study showed that the sensitivity and specificity of the Fujifilm SILVAMP Tuberculosis LAM (FujiLAM; Fujifilm, Tokyo, Japan) among adults with HIV were 71% and 91%, respectively.[14] The high specificity of FujiLAM (92%) represents a major advancement in pediatric TB diagnostics, including among children with HIV or malnutrition.[15]

The aim of this study was to assess the diagnostic efficacy of rapid and convenient tests, including MTB-HR, LAM, and the combined MTB-HR and LAM (MTB-HR & LAM), among individuals with ATB, other pulmonary diseases, and healthy participants in a general hospital setting in China.

Materials and Methods

Study Design and Participants

Participants in this study were recruited from June 8, 2023, to September 13, 2023, at the First Affiliated Hospital, Zhejiang University School of Medicine, encompassing inpatients, outpatients, and individuals undergoing health examinations. Basic information of the participants, including age, sex, typical clinical symptoms of TB (such as cough, fever, hemoptysis, fatigue, loss of appetite, weight loss, and night sweats), and comorbidities (such as hypertension, diabetes, tumors, and HIV infection), was collected. Written informed consent was obtained from all participants prior to recruitment. This study complied with the Declaration of Helsinki.

Participants were classified into two groups: ATB and non-active tuberculosis (non-ATB). The ATB group comprised individuals with microbiological evidence of TB in their sputum or lavage fluid, as confirmed by microbiological tests (culture or Xpert MTB/RIF [Cepheid, Sunnyvale, CA, USA]). The non-ATB group included individuals who had negative results for microbiological evidence of TB, including individuals with other respiratory diseases (such as those caused by NTM and viruses) and healthy participants. At the time of enrolment, all participants were asked to provide fingerstick blood (≥100 μL) collected with a minivette containing an anticoagulant (Becton Dickinson, New Jersey, USA) and the midstream urine specimen (≥15 mL) collected in a sterile container. Laboratory testing, including culture, Xpert MTB/RIF, MTB-HR, and LAM, was performed by professional staff in accordance with the standard operating procedures at the clinical laboratory specialized in MTB detection.

The blood sample was transferred to an EDTA-microtainer (Becton Dickinson, New Jersey, USA) and inverted for mixing. Subsequently, 50 μL of the sample was added to a MTB-HR cartridge (Cepheid, Sunnyvale, CA, USA) and loaded into a GeneXpert machine. Ct values for individual genes (DUSP, GBP5, and TBP) were obtained, and a score

was calculated using the formula: (Ct GBP5 + Ct DUSP3)/2 − Ct TBP.[16] A score of ≤ −0.8 indicates a positive result for ATB in the MTB-HR test, while a score of > −0.8 indicates a negative result according to the instruction. In cases where invalid results were obtained, a parallel sample from each participant was retested.

LAM detection was performed within 72 h of sample collection using AIMLAM kits (Leide Biosciences Co., Ltd., Guangdong, China), in accordance with the manufacturer's instructions. Initially, 4.0 mL of the urinary sample was transferred into a 15 mL centrifuge tube. Subsequently, 50 μL of the magnetic bead reagent containing LAM-capturing antibodies was added to the centrifuge tube and thoroughly mixed. The mixture was incubated at room temperature with a rotation speed of 30 rpm for 2 h. Following the incubation, the centrifuge tube was positioned on a magnetic rack for adsorption. After the complete separation of the components, the supernatant was discarded. Subsequently, 200 μL of diluted sample solution was added to each tube. The mixture was thoroughly homogenized using a vortex mixer, and within 5 min, the sample was processed according to the operational guidelines outlined in the manual of the LAM detection chemiluminescence analyzer SMART 500S (Keysmile Biological Technology Co. Ltd., Chongqing, China). If the allotted time was exceeded, it was necessary to thoroughly remix the samples before proceeding. The LAM concentration of ≤ 0.45 pg/mL indicates a positive result for ATB, while a concentration of > 0.45 pg/mL indicates a negative result according to the instruction. In cases where one replicate could not be read by the instrument because of poor image quality, the parallel sample was retested.

MTB-HR or LAM tests were conducted simultaneously by a laboratory technologist who was blinded to the patient's history, and the results were reported independently. A positive result for ATB in MTB-HR & LAM was defined as either MTB-HR being positive or LAM being positive. Ethical approval was obtained from the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2024–0338).

Statistical Analysis

Basic information of the participants was described and compared between the ATB and non-ATB groups. Continuous variables are presented as median (P25, P75) and compared using the Kruskal–Wallis test, while categorical variables are presented as number (percentage) and compared using the Chi-square test or Fisher's exact test. The diagnostic efficiency of the test was evaluated using the sensitivity, specificity, accuracy rate, Youden index, positive predictive value, and negative predictive value. Additionally, the consistency levels between the tests and microbiological references were assessed using the calculated values of Kappa. Kappa values between 0.41 and 0.60 indicate moderate consistency, values between 0.61 and 0.80 indicate substantial consistency, and values between 0.81 and 1.00 indicate almost perfect consistency. The area under the ROC curve (AUROC) and 95% confidence interval (CIs) were evaluated for each test. Additionally, pairwise comparisons of the AUROCs were conducted using nonparametric comparisons based on Mann–Whitney U-statistics.[17] All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Origin 2021 (Microcal Software Inc., Northampton, MA, USA) was used to draw figures. The significance level for the statistical tests was set at 0.05 (two-sided).

Results

A total of 297 participants were enrolled with a median age of 51 years (P25, P75:36, 62). Among them, 164 (55.22%) were male and 133 (44.78%) were female (Table 1). Of the participants, 137 (46.13%) were diagnosed with ATB, while the remaining 160 (53.87%) were diagnosed with non-ATB. The median age of the participants was 57 years (P25, P75:40–68) in the ATB group, which was higher than that in the non-ATB group (P=0.0005). Additionally, participants in the ATB group exhibited a higher rate of typical clinical symptoms of TB than did those in the non-ATB group (62.04% vs 14.38%, P<0.0001). Most of the participants in the ATB group received anti-TB drug treatment. Additionally, the prevalence of hypertension, diabetes, and tumors was higher in the ATB group than in the non-ATB group (all P<0.05). In the ATB group, 115 (83.94%) patients had pulmonary TB, and 22 (16.06%) had extrapulmonary TB. In contrast, the non-ATB group consisted mostly of healthy participants, with 15 (5.05%) cases of pulmonary infections, two (0.47%) cases of non-tuberculosis mycobacteria, four (1.35%) cases of Influenza A, and eight (2.69%) cases of other diseases.

Table 2 shows the sensitivity and specificity of MTB-HR, LAM, and MTB-HR & LAM in terms of sensitivity and specificity compared with the microbiological diagnosis of ATB. The sensitivity of the MTB-HR test was 77.37% (95% CI:

Table 1 Demographic characteristics of the participants

	Clinical diagnosis [median (P25, P75) or n (%)]			P
	Active tuberculosis (n=137)	Non-active tuberculosis (n=160)	Total	
Age	57(40-68)	47(36-57.5)	51(36-62)	0.0005
Sex				
Male	77(56.20)	87(54.38)	164(55.22)	0.7520
Female	60(43.80)	73(45.63)	133(44.78)	
Typical clinical symptoms of tuberculosis[a]				
Yes	85(62.04)	23(14.38)	108(36.36)	<0.0001
No	52(37.96)	137(85.63)	189(63.63)	
Anti-tuberculosis drugs use				
Yes	130(94.89)	2(1.25)	132(44.44)	<0.0001
No	7(5.11)	158(98.97)	165(55.56)	
Hypertension				
Yes	15(10.95)	1(0.63)	16(5.39)	<0.0001
No	122(89.05)	159(99.38)	281(94.61)	
Diabetes				
Yes	12(8.76)	0(0.00)	12(4.04)	0.0001
No	125(91.24)	160(100.00)	285(95.96)	
Tumors				
Yes	11(8.03)	0(0.00)	11(3.70)	0.0003
No	126(91.97)	160(100.00)	286(96.30)	
HIV infection				
Yes	5(3.65)	0(0.00)	5(1.68)	0.0201[b]
No	132(96.35)	160(100.00)	292(98.32)	
Other comorbidities				
Yes	26(18.98)	4(2.50)	30(10.10)	<0.0001
No	111(81.02)	156(97.50)	267(89.90)	
Type of diseases				
Pulmonary tuberculosis	115(83.94)	-	115(38.72)	-
Extrapulmonary tuberculosis	22(16.06)	-	22(7.41)	-
Pulmonary infections	-	15(9.36)	15(5.05)	-
Non-tuberculosis mycobacteria	-	2(1.25)	2(0.67)	-
Influenza A	-	4(2.50)	4(1.35)	-
Other diseases	-	8(5.00)	8(2.69)	-
Healthy participants	-	131(81.88)	131(44.11)	-

Notes: [a]: Typical clinical symptoms of tuberculosis include cough, fever, fatigue, loss of appetite, weight loss, and night sweats; [b]: Fisher's exact test.

Table 2 Diagnostic efficiencies of the MTB-HR, LAM and the combination of MTB-HR and LAM for active tuberculosis

Test	Result	Active tuberculosis (n=137)	Non-active tuberculosis (n=160)	Sensitivity (95% CI)	Specificity (95% CI)	Youden index	Accuracy rate (%)	Positive predictive value (95% CI)[a]	Negative predictive value (95% CI)	Kappa (95% CI)
MTB-HR	Positive	106	23	77.37	85.63	0.63	81.82	82.17	81.55	0.63
	Negative	31	137	(70.37, 84.38)	(80.19, 91.06)			(75.57, 88.78)	(75.68, 87.41)	(0.54, 0.72)
LAM	Positive	75	4	54.74	97.50	0.52	77.78	94.94	71.56	0.53
	Negative	62	156	(46.41, 63.08)	(95.08, 99.92)			(90.10, 99.77)	(65.57, 77.55)	(0.45, 0.63)
MTB-HR&LAM	Positive	114	27	83.21	83.13	0.66	83.17	80.85	85.26	0.66
	Negative	23	133	(76.95, 89.47)	(77.32, 88.93)			(74.36, 87.35)	(79.69, 90.82)	(0.58, 0.75)

Notes: MTB-HR: blood-based Cepheid 3-gene Host Response test; LAM: urine-based Lipoarabinomannan test; MTB-HR&LAM: combination of MTB-HR and LAM; [a]: Positive predictive values were estimated at the 46% prevalence of active tuberculosis.

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Table 3 AUROCs and comparisons of the MTB-HR, LAM and the combination of MTB-HR and LAM for active tuberculosis

Test	AUROCs (95% CI)	Contrasts (Chi-Square/P value)	Contrasts between tests (Chi-Square/P value)		
			MTB-HR	LAM	MTB-HR&LAM
MTB-HR	0.82(0.77, 0.86)	12.02/0.0025	-	-	-
LAM	0.76(0.72, 0.80)		3.71/0.0542	-	-
MTB-HR&LAM	0.83(0.79, 0.87)		2.00/0.1573	8.74/0.0031	-

Notes: MTB-HR: blood-based Cepheid 3-gene Host Response test; LAM: urine-based Lipoarabinomannan test; MTB-HR&LAM: combination of MTB-HR and LAM; AUROC: the area under the receiver operating characteristic curve.

70.37–84.38), and the specificity was 85.63% (95% CI: 80.19–91.06), resulting in a Youden index of 0.63. In contrast, the sensitivity of the LAM test was 54.74% (95% CI: 46.41–63.082), whereas the specificity was 97.50% (95% CI: 95.08–99.92), yielding a Youden index of 0.52. The MTB-HR & LAM exhibited a sensitivity of 83.21% (95% CI: 76.95–89.47), a specificity of 83.13% (95% CI: 77.32–88.93), and a Youden index of 0.66. The accuracy rates for MTB-HR, LAM, and MTB-HR & LAM were 81.82%, 77.78%, and 83.17%, respectively. Furthermore, MTB-HR (Kappa: 0.63, 95% CI: 0.54–0.72) and MTB-HR & LAM (Kappa: 0.66, 95% CI: 0.58–0.75) demonstrated substantial consistency, whereas LAM exhibited moderate consistency (Kappa: 0.53, 95% CI: 0.45–0.63).

Comparisons of the AUROCs for MTB-HR, LAM, MTB-HR & LAM are presented in Table 3 and Figure 1. The overall difference among the three groups was statistically significant (P=0.0025). Compared with LAM, MTB-HR & LAM had higher AUROC values (MTB-HR & LAM vs LAM: 0.83 vs 0.76, P=0.0031). However, there were no significant differences in the AUROCs between MTB-HR and MTB-HR & LAM (P=0.1569), and between MTB-HR and LAM (P= 0.0542).

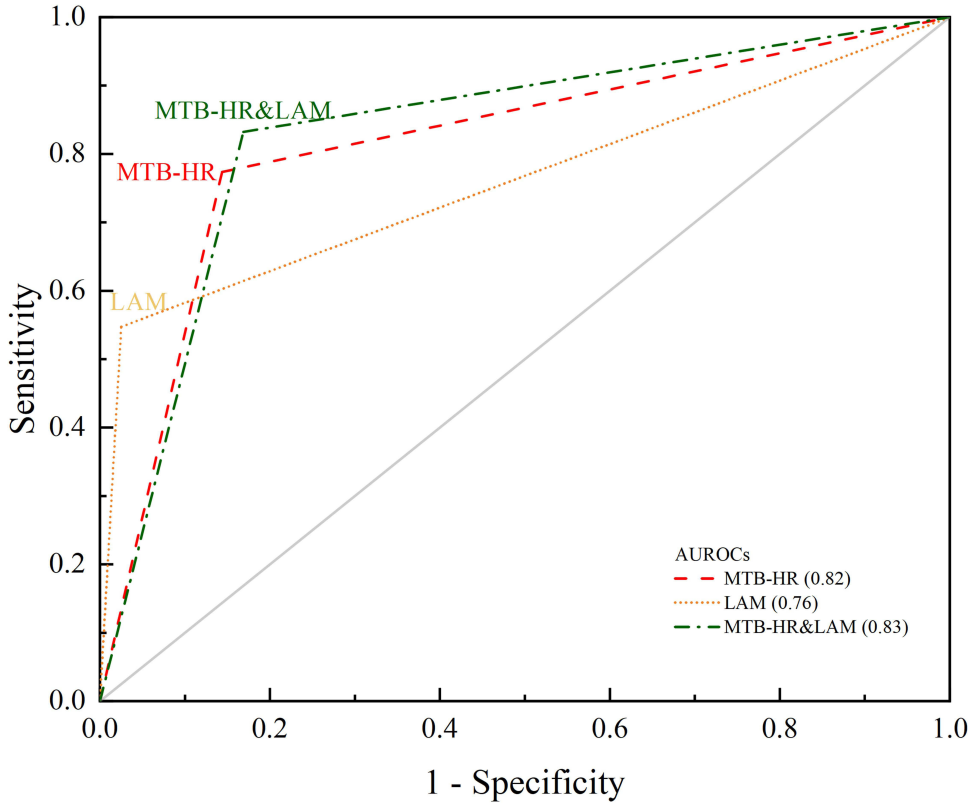

Figure 1 Area under the receiver operating characteristic curves (AUROCs) of the MTB-HR, LAM and combination of MTB-HR and LAM for active tuberculosis.

Discussion

Currently, the global targets set at the first UN high-level meeting on TB for the 5-year period of 2018–2022 have not been achieved.[1] TB diagnosis is a pivotal first step and a crucial component of disease control. However, the commonly used test system is insufficient. For years, the TB community has prioritized the development of a simple diagnostic test that can be conveniently performed at the point-of-care in primary care settings. One of the highest priority target product profiles is a community-based non-sputum triage or referral test with a minimum sensitivity of 90% and specificity of 70% (ideally 95% sensitivity and 80% specificity), intended for use by first-contact providers to identify patients who require further confirmatory testing.[18]

The evidence presented in this validation study on the evaluation of MTB-HR exhibits a relatively high diagnostic efficiency with an AUC of 0.82 among participants in a general hospital, which closely aligns with previously reported AUCs in adults (0.88 and 0.89)[11,19] and in children younger than 15 years (AUC of 0.85).[20] Notably, the results of this study were based on the new MTB-HR test, which differed from the formula used in a previous study[12] and included TBP instead of KLF2 in the three-gene signature. This change was recommended by the manufacturer due to improved stability and performance across blood collection methods. A prospective study reported the diagnostic accuracy of the new MTB-HR test, with a sensitivity of 90.3% (95% CI: 86.5–93.3) and a specificity of 62.6% (95% CI: 59.7–65.3). In particular, to achieve a sensitivity of $\geq$ 90% while maximizing specificity, the cut-off value for the MTB-HR test was set as ≤ -1.25 for positive result.[16] The consistency level between MTB-HR and the microbiological reference is substantial, with a Kappa value of 0.63 (95% CI: 0.54–0.72). A multicenter prospective study demonstrated that MTB-HR showed promising diagnostic accuracy for culture-confirmed TB in children younger than 15 years, highlighting its operational characteristics.[20]

Previous perspectives suggest that the LAM detection test comes close to meeting the desired criteria owing to its simplicity, low cost, and suitability for use in decentralized settings. This is particularly important given that no existing TB test meets all point-of-care target product profile requirements.[21] In this study, the sensitivity of LAM was only 54.74% and the specificity was 97.50%, which is close to the results of a previous study (sensitivity of 44% and specificity of 92%).[22] Another study conducted among children reported the sensitivity (41.7%) and specificity (97.4%) of the Fujifilm SILVAMP Tuberculosis Lipoarabinomannan test and the sensitivity (50.0%) and specificity (74.4%) of the Alere Determine Tuberculosis Lipoarabinomannan test compared to the microbiological reference standard. The sensitivity values of the aforementioned LAM tests were similar, and lower than that of the Xpert MTB/RIF of sputum (74%).[15]

Despite the limitations of low sensitivity, the high specificity of LAM with a "clean catch" urine specimen represents a major advancement in TB diagnostics. This is particularly crucial for children, who may find it challenging to provide samples, such as induced sputum, gastric or nasopharyngeal aspirates, and stool, thus highlighting the importance of alternative respiratory specimens.[13] Although limited by the test sample size, promising results have been shown with a sensitivity of 96% and specificity of 81% by the high-sensitivity LAM test under the condition of specialized training of the test operator, specialized equipment and additional reagents required, and data on the correlation between LAM positivity and mycobacterial burden.[23] Tests with high specificity can help to reduce the rate of misdiagnosis and control the level of false positives. This evidence underscores the significant opportunity for improvement in the LAM test, particularly in terms of sensitivity. Enhancing the sensitivity of LAM or developing an enhanced version of the test would greatly increase its utility and effectiveness in TB diagnosis.[13] The relatively large difference between the values of sensitivity and specificity of the LAM test indicates that the joint detection scheme may have a role in improving diagnostic efficiency.

To the best of our knowledge, this study is the first attempt to evaluate the combination of two convenient tests, MTB-HR and LAM, for ATB. Compared to the single MTB-HR or LAM test, the combined MTB-HR & LAM did not demonstrate a superior position, as there was no difference between the AUROC values of these two comparisons. Overall, this study does not recommend the combination of MTB-HR & LAM as a screening method for ATB in the general population. This combination increases the frequency of sampling and types and increases the testing time and cost.

Owing to the accessibility of specimens and improved diagnostic efficiency, tests such as MTB-HR and LAM are gradually being developed and recognized as valuable alternatives to microbiological reference standard tests. Newly developed diagnostic and screening techniques have the potential to accelerate the identification of individuals with TB, allowing for the initiation of treatment before symptoms worsen, and even before they become capable of transmitting the disease to others.[10] Such enhanced and cost-effective tests are urgently required considering the substantial disease burden of TB worldwide, especially in highly endemic, low-resource countries or districts. Before scaling up the application, it is essential to ensure that new approaches are thoroughly evaluated through well-designed and controlled clinical trials conducted in highly endemic low-resource settings.[3]

Limitation

This study was conducted in a single-center setting and included participants with diverse diseases. These findings require validation through large prospective studies designed across multiple centers. Furthermore, it is crucial to acknowledge that the specific classification of participants, including age groups, latent infections, other pulmonary diseases, HIV status, and healthy individuals, was not addressed individually in this study. Finally, the optimal cut-off values of the MTB-HR and LAM were not reassessed, and the recommended values in instrumentation were used as references.

Conclusions

Currently, both MTB-HR and LAM do not meet the WHO target (a minimum sensitivity of 90%) for non-sputum-based triage tests for ATB. However, in general, these tests show the potential to enhance TB diagnosis through a more convenient approach using finger blood or urine samples from the population in clinical settings. These relatively convenient non-sputum triage tests could contribute to the control of TB worldwide, especially in districts with high disease burden and limited resources. The high specificity of the LAM test could serve as a screening tool for excluding ATB cases and reducing the rate of misdiagnoses among healthy participants in large-scale community settings. Compared with the single MTB-HR or LAM, applying the combined MTB-HR & LAM test does not demonstrate any advantages.

Role of the Funding Source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or manuscript writing. The corresponding author had full access to all data in the study and had the final responsibility for the decision to submit for publication.

Ethics Approval and Informed Consent

Ethical approval was obtained from the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (2024-0338).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

References

1. World Health Organization. Global tuberculosis report 2023, Availabe from: https://www.who.int/publications/i/item/9789240083851. Accessed March 1, 2024.
2. Campbell IA, Bah-Sow O. Pulmonary tuberculosis: diagnosis and treatment[J]. *BMJ*. 2006;332(7551):1194–1197. doi:10.1136/bmj.332.7551.1194
3. Palomino JC. Nonconventional and new methods in the diagnosis of tuberculosis: feasibility and applicability in the field[J]. *Eur Respir J*. 2005;26 (2):339–350. doi:10.1183/09031936.05.00050305
4. Maclean E, Broger T, Yerlikaya S, et al. A systematic review of biomarkers to detect active tuberculosis[J]. *Nat Microbiol*. 2019;4(5):748–758. doi:10.1038/s41564-019-0380-2
5. World Health Organization. Chest radiography in tuberculosis detection: summary of current WHO recommendations and guidance on programmatic approaches. Availabe from: https://iris.who.int/bitstream/handle/10665/252424/9789241511506-eng.pdf. 2016. Accessed May 3, 2024.
6. Wallis RS, Pai M, Menzies D, et al. Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice[J]. *Lancet*. 2010;375 (9729):1920–1937. doi:10.1016/s0140-6736(10)60359-5
7. Friedrich SO, Rachow A, Saathoff E, et al. Assessment of the sensitivity and specificity of Xpert MTB/RIF assay as an early sputum biomarker of response to tuberculosis treatment[J]. *Lancet Respir Med*. 2013;1(6):462–470. doi:10.1016/s2213-2600(13)70119-x
8. Chakravorty S, Simmons AM, Rowneki M, 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[J]. *mBio*. 2017;8(4). doi:10.1128/mBio.00812-17
9. WHO Press. Implementing the end TB strategy: the essentials, 2022 update 2022. Availabe from: https://www.who.int/publications/i/item/9789240065093. Accessed March 21, 2024.
10. Savage N. Tracking down tuberculosis - Improvements in screening and diagnosis could help to eradicate this curable disease. Nature. 2024. https://www.nature.com/articles/d41586-024-00087-8.
11. Sutherland JS, van der Spuy G, Gindeh A, et al. Diagnostic Accuracy of the Cepheid 3-gene Host Response Fingerstick Blood Test in a Prospective, Multi-site Study: interim Results[J]. *Clin Infect Dis*. 2022;74(12):2136–2141. doi:10.1093/cid/ciab839
12. Sweeney TE, Braviak L, Tato CM, et al. Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis[J]. *Lancet Respir Med*. 2016;4(3):213–224. doi:10.1016/S2213-2600(16)00048-5
13. Marais BJ. Improved Urine Lipoarabinomannan (LAM) Tests: the Answer for Child Tuberculosis Diagnosis?[J]. *Clin Infect Dis*. 2021;72(9):e289–e290. doi:10.1093/cid/ciaa1058
14. Broger T, Nicol MP, Székely R, et al. Diagnostic accuracy of a novel tuberculosis point-of-care urine lipoarabinomannan assay for people living with HIV: a meta-analysis of individual in- and outpatient data[J]. *PLoS Med*. 2020;17(5):e1003113. doi:10.1371/journal.pmed.1003113
15. Nicol MP, Schumacher SG, Workman L, et al. Accuracy of a Novel Urine Test, Fujifilm SILVAMP Tuberculosis Lipoarabinomannan, for the Diagnosis of Pulmonary Tuberculosis in Children[J]. *Clin Infect Dis*. 2021;72(9):e280–e288. doi:10.1093/cid/ciaa1052
16. Gupta-Wright A, Ha H, Abdulgadar S, et al. Evaluation of the Xpert MTB Host Response assay for the triage of patients with presumed pulmonary tuberculosis: a prospective diagnostic accuracy study in Viet Nam, India, the Philippines, Uganda, and South Africa[J]. *Lancet Glob Health*. 2024;12(2):e226–e234. doi:10.1016/s2214-109x(23)00541-7
17. Delong ER, Delong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837–845.
18. World Health Organization. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting 2014. Availabe from: https://iris.who.int/bitstream/handle/10665/135617/WHO_HTM_TB_2014.18_eng.pdf?sequence=1. Accessed March 28, 2024.
19. Södersten E, Ongarello S, Mantsoki A, et al. Diagnostic Accuracy Study of a Novel Blood-Based Assay for Identification of Tuberculosis in People Living with HIV[J]. *J Clin Microbiol*. 2021;59(3). doi:10.1128/jcm.01643-20
20. Olbrich L, Verghese VP, Franckling-Smith Z, et al. Diagnostic accuracy of a three-gene Mycobacterium tuberculosis host response cartridge using fingerstick blood for childhood tuberculosis: a multicentre prospective study in low-income and middle-income countries[J]. *Lancet Infect Dis*. 2024;24(2):140–149. doi:10.1016/s1473-3099(23)00491-7
21. Maclean E, Pai M. Urine Lipoarabinomannan for Tuberculosis Diagnosis: evolution and Prospects[J]. *Clin Chem*. 2018;64(8):1133–1135. doi:10.1373/clinchem.2018.286625
22. Gupta-Wright A, Peters JA, Flach C, et al. Detection of lipoarabinomannan (LAM) in urine is an independent predictor of mortality risk in patients receiving treatment for HIV-associated tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis[J]. *BMC Med*. 2016;14:53. doi:10.1186/s12916-016-0603-9
23. Paris L, Magni R, Zaidi F, et al. Urine lipoarabinomannan glycan in HIV-negative patients with pulmonary tuberculosis correlates with disease severity. *Sci Transl Med*. 2017;9(420). doi:10.1126/scitranslmed.aal2807