

Lipoarabinomannan (LAM) Urine Antigen Test In Diagnosis Of Pulmonary Tuberculosis: *Literature Reviews*

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Abstract- Introduction: The global impact of 2020 due to the COVID-19 pandemic will be a large global decline in TB in terms of the number of people newly diagnosed with TB. The gap is due to being underdiagnosed with TB because the person does not have access to health care or is not diagnosed correctly. The diagnosis of TB cases in Indonesia is still on microscopic examination of sputum which has a low accuracy value, while the culture of sputum takes a long time. One alternative option is the lipoarabinomannan (LAM) urine antigen test. The literature review was compiled to determine the effectiveness of the lipoarabinomannan (LAM) urine antigen test in establishing the diagnosis of pulmonary TB. **Methods:** The writing method used is a narrative review. The search was carried out on 2 databases, namely *PubMed* and *Cochrane Library* in February 2022. The research article search strategy was carried out by selecting inclusion criteria and exclusion criteria and found 12 literature studies. **Results:** The lipoarabinomannan urine antigen (LAM) test has low sensitivity and high specificity so it is not recommended as a pulmonary TB screening tool, but has a higher sensitivity accuracy in hospitalized cases in HIV-positive patients with high-risk patients. TB and high accuracy were found in immunosuppressed HIV cases or CD4+ count levels 100 cells/ μ L and in seriously ill patients. **Conclusion:** The combination of lipoarabinomannan (LAM) urine antigen test with sputum microscopy showed increased sensitivity for active TB.

Index Terms- Urine LAM, antigen test, lipoarabinomannan, tuberculosis

I. INTRODUCTION

Tuberculosis (TB) is an infectious disease that is a major cause of poor health and one of the leading causes of death worldwide. Until the COVID-19 coronavirus pandemic, tuberculosis was the leading cause of death from single infectious agents, ranking above cases of HIV/AIDS.¹ The development of this disease (about 90%) occurs in adults, more cases in men than women.¹ Tuberculosis is an infectious disease of the lung parenchyma caused by the *Mycobacterium tuberculosis*.^{2,3} Transmission is through particles that can be carried through the air in the form of sputum droplets (droplet nuclei).⁴

By 2020, global the most obvious impact caused by the COVID-19 pandemic will be a large global decline in TB in terms of the number of people newly diagnosed with TB.¹ The decline in cases of new people diagnosed with TB in 2020 was 5.8 million compared to 2019 with 7.1 million, representing a decrease of 18%.¹ The countries that made the largest contributors to the global decline between 2019 and 2020 were India (41%), Indonesia (14%), the Philippines (12%), and China (8%).¹ A direct consequence of the large decline in the number of people newly diagnosed with TB in 2020 will be an increase in the number of people dying. The global number of deaths officially classified as caused by TB (1.3 million) in 2020 is almost double the number caused by HIV/AIDS (0.68 million), and TB deaths have been more severely affected by the COVID-19 pandemic in 2020 than HIV/AIDS.^{1,5} By 2020, 10 countries collectively accounted for 74% of the global gap between the estimated incidence of TB and the number of people newly diagnosed with TB. The top three countries are India (24%), Indonesia (11%), and the Philippines (8.3%).^{1,6} The gap is due to being underdiagnosed with TB because the person does not have access to health care or is not diagnosed correctly.⁶

The gold standard for the diagnosis of TB is the culture of pulmonary or extrapulmonary specimens.^{2,3} However, it can take several weeks to produce results. Another diagnostic test is the automated real-time PCR (Xpert MTB/RIF) known as GeneXpert as recommended by WHO. The GeneXpert test had high sensitivity (98.2% TB smear-positive and 72.5% smear-negative) and specificity (99.2%). However, the cost of machines, reagents, and cartridges is one of the main factors hindering the increase in early TB diagnosis with limited resources. Conventional diagnostic tests for microbiological confirmation rely on sputum samples, which may be difficult to obtain and have low diagnostic sensitivity in children, patients with extrapulmonary TB (EPTB), and people living with HIV (PLWHA).⁷

Therefore, an alternative specimen that can be obtained is urine. Detection of *Mycobacterium tuberculosis* (MTb) antigen in urine in recent years has become an option for TB diagnosis because it can indicate infection without being influenced by immune status. In addition, urine is a better sample than phlegm because urine is easier to obtain compared to phlegm which also has the potential to produce harmful bioaerosols.⁸ Urine samples

are safer to handle in the laboratory, and urine samples have relatively few contaminants making them a potential source of examination material. The MTb antigen can be detected in the urine of patients with pulmonary TB, the antigen in question is the cell wall of the MTb bacteria, namely lipopolysaccharide lipoarabinomannan (LAM).

Lipoarabinomannan (LAM) is a specific glycolipid component of the *Mycobacterium tuberculosis* cell wall sheath. During *Mycobacterium tuberculosis* infection, LAM is present in various body fluids; therefore, it could be an ideal candidate biomarker for the detection of *Mycobacterium tuberculosis*.⁹ In 2015, the World Health Organization (WHO) published recommendations for the Alere Determine TB-LAM Ag (AlereLAM; Abbott, Palatine, IL) urine lateral flow test for assists in the diagnosis of tuberculosis in PWH with a CD4 cell count of 100 cells/L or "severely ill".¹⁰ WHO policy was updated in 2019 to include recommendations for the use of AlereLAM in a wider group of people, both inpatient and outpatient.¹¹ AlereLAM is easy to use and gives results in 25 minutes. Nathaviharana *et al.* found that using the lateral flow lipoarabinomannan (LF-LAM) assay as part of a TB diagnostic testing strategy is likely to reduce mortality and possibly result in a slight increase in the initiation of anti-tuberculosis therapy in HIV patients.^v In recent years, a new detection technology, the Fujifilm test The SILVAMP TB LAM (FujiLAM; Fujifilm, Tokyo, Japan) has been developed.¹³ This method is similar to the urine-based point-of-care test, Alere Determine TB LAM Ag (AlereLAM; Abbott, Palatine, IL, USA), which is based on the detection of lipoarabinomannan antigen in urine.¹³

II. METHODS

The writing method used is narrative review. The search was carried out on 2 databases, namely *PubMed* and *Cochrane Library* in February 2022. The keywords were "*Pulmonary Tuberculosis*" AND "*Urine Lipoarabinomannan*" AND "*LAM*" AND "*Culture Smears*" AND "*Tuberculosis Diagnosis*". Research article search strategy is done by selecting those that meet the inclusion criteria and exclusion criteria. Inclusion criteria: adults >18 years old, LAM urine examination as a TB diagnostic tool, publications for the last 5 years (January 2017 to January 2022), the language used in English, and articles are available in full text. Exclusion criteria: the study was conducted on animals, pediatric TB cases, extrapulmonary TB cases, without culture results as the gold standard.

III. RESULTS AND DISCUSSION

The literature review will discuss the examination of the lipoarabinomannan urine antigen (LAM) test in establishing the diagnosis of pulmonary TB. In the 23 kinds of literature found, there were 12 kinds of literature used in the literature review. Of the 12 kinds of literature containing a discussion of the lipoarabinomannan (LAM) urine antigen test to establish a TB diagnosis compared to culture examination as the gold standard for pulmonary TB diagnosis, 12 kinds of literature will be described in Table 1.

Table 1. Literature related to the examination of urine antigen lipoarabinomannan (LAM) in the diagnosis of pulmonary tuberculosis

No	Writer	Topics	Results
1	Gompol Suwanpimol kul, et al. ¹⁴ (2017)	<i>Utility of Urine Lipoarabinomannan (LAM) in Diagnosing Tuberculosis and Predicting Mortality with and without HIV: prospective TB cohort from the Thailand Big City TB-research Network</i>	The sensitivity of urine LAM test for group 1 (TB/HIV positive patients) for CD4 T cell counts >100, .100 and ≤.50 cells/mm ³ was 38.5%, 40.6% and 45%, respectively. The specificity and PPV of urinary LAM were more than 80%. In group 2 (disseminated TB/HIV neg) and group 3 (HIV neg immunocompromised TB patients), the test sensitivity was 20% and 12.5%, respectively, and the specificity and PPV were 100% for both groups.
2	Daniël Jacobus Van Hoving, et al. ¹⁵ (2019)	<i>The real-world performance and inter-observer agreement of urine lipoarabinomannan in diagnosing HIV-associated tuberculosis in an emergency center</i>	388 samples (3 samples/participant) were sent for microbiological testing for TB in 411 participants; 170 had confirmed TB (41.4%). Treatment site and laboratory urine LAM had the same sensitivity (41.8% vs 42.0%, p=1.0) and specificity (90.5% vs 87.5%, p=0.23).
3	Munjit Na Songkhla, et al. ¹⁶ (2019)	<i>Lateral Flow Urine Lipoarabinomannan Assay for Diagnosis of Active Tuberculosis in Adults With Human Immunodeficiency Virus Infection: A Prospective Cohort Study</i>	Of the 280 included patients, 72 (25.7%) confirmed and 65 (23.2%) probable TB. Among patients with definite tuberculosis, the LF-LAM test yielded a sensitivity of 75.0% and a specificity of 76.0%. It has the highest sensitivity (90.5%) in HIV-infected patients with CD4 count <50μL

4	Stephanie Bjerrum Tobias Broger, et al. ¹⁷ (2019)	<i>Diagnostic Accuracy of a Novel and Rapid Lipoarabinomannan Test for Diagnosing Tuberculosis Among People With Human Immunodeficiency Virus</i>	Urine samples from 532 PWH (462 outpatients, 70 inpatients). Against microbiological reference standards, the sensitivity of FujiLAM was 74.2% (95% confidence interval [CI], 62.0–84.2) compared with 53.0% (95% CI, 40.3–65.4) for AlereLAM. , a difference of 21.2% (CI, 13.1–32.5). Specificity was 89.3% (95% CI, 85.8–92.2) versus 95.6% (95% CI, 93.0–97.4) for FujiLAM and AlereLAM, a difference of 6.3% (95% CI 9.6 to 3.3). The estimated specificity for FujiLAM increased sharply to 98.8% (95% CI, 96.6–99.8) in patients with CD4 >100 cells/μL and when using the composite reference standard.
5	Helena Huerga, Loide Cossa, et al. ¹⁸ (2020)	<i>Systematic, Point-of-Care Urine Lipoarabinomannan (Alere TB-LAM) Assay for Diagnosing Tuberculosis in Severely Immunocompromised HIV-Positive Ambulatory Patients</i>	Of the 360 patients, half had never used ART. Lipoarabinomannan positivity was 11.9% (43/360), higher among symptomatic patients compared with asymptomatic: 18.5% (30/162), and 6.6% (13/198), respectively, P =0.001. Tuberculosis was bacteriologically confirmed in 6/35 LAM-positive patients (2 of whom were asymptomatic).
6	Akshita Gupta, Ajay Kumar, Asem Ali Ashraf et al. ¹⁹ (2020)	<i>A pilot study to evaluate urine LAM assay for diagnosis of pulmonary tuberculosis among non-HIV patients</i>	A total of 56 patients (Xpert MTB/Rif were positive in 27 (48.21%) patients. Urine TB LAM test was positive in 18 (32.14%) cases. The sensitivity and specificity of the LAM test were 48.2% and 82.8%, respectively. In a comparison of microscopic smear and LAM test, 8 (14.28%) samples were positive with both tests 20 (17.86%) and the total number of positive and negative final interpretations was found to be 50% (28/56). The sensitivity and specificity for this combination were 85.2% and 82.8%, respectively. Increased sensitivity of 37% and negative predictive value of 20.7%.
7	Tobias Broger, Mark P. Nicol, et al. ²⁰ (2020)	<i>Diagnostic accuracy of 3 urine lipoarabinomannan tuberculosis assays in HIV-negative outpatient</i>	Of the 372 patients, HIV-negative and the prevalence of microbiologically confirmed TB was 30%. The sensitivities of AlereLAM, FujiLAM, and EclLAM were 10.8%, 53.2%, and 66.7%, respectively. The specificities of AlereLAM, FujiLAM, and EclLAM were 92.3%, 98.9%, and 98.1%, respectively.
8	Helena Huerga, et al. ²¹ (2020)	<i>Should Urine-LAM Tests Be Used in TB Symptomatic HIV-Positive Patients When No CD4 Count Is Available? A Prospective Observational Cohort Study From Malawi</i>	Of the 485 patients, 171 (35.3%) had CD4 <200 cells/mm ³ and 32 (7.2%) were “seriously ill”. LAM was positive in 24.9% of patients with CD4 <200 (50% LAM grade 2–4) and 12.5% with CD4 ≥200 (12.8% LAM grade 2–4). Xpert is positive by 14.1% (44/312). Among Xpert-positive patients, positive LAM was 56.7% (CD4<200) and 42.9% (CD4≥200), P = 0.393. Of the patients without an Xpert result, 13.4% (23/172) were LAM positive (potentially missed patients).
9	Chakrapani Chatla, et al. ²² (2020)	<i>A Systematic Review of Utility of Urine Lipoarabinomannan in Detecting Tuberculosis</i>	A systematic review of 37 studies and the mean study sample size was 464 (range = 81–2528; SD = 427). The mean crude sensitivity of urine LAM in culture-confirmed TB cases was 44.1% (range = 8.3–93) while SSM was 38.6% (range = 14–65).

		<i>among HIV-Positive Tuberculosis Suspects</i>	However, the sensitivity of urine LAM+SSM was 60.4% (range = 38.3-92.7), indicating the utility of the combination SSM + urine LAM for detecting TB. The specificity was similar between urine LAM and SSM with 92.7% (range = 76-100) and 97.9% (range = 93.9-100).
10	Kim de Vasconcellos, et al. ²³ (2021)	<i>The utility of point-of-care urinary lipoarabinomannan testing for the diagnosis of tuberculosis in critically ill patients: a prospective observational study</i>	Of the 50 patients, 12 were confirmed to have tuberculosis. All patients received mechanical ventilation, and mortality in the ICU was 60%. Urinary LAM had a sensitivity of 50.0% (95% CI, 21.1 to 78.9%) and specificity of 84.2% (95% CI, 68.8 to 94.0%) for confirmed tuberculosis.
11	Zhenzhen Li, et al. ²⁴ (2021)	<i>The Value of FujiLAM in the Diagnosis of Tuberculosis: A Systematic Review and Meta-Analysis</i>	In 9 articles in a meta-analysis and using the microbiological reference standard (MRS), FujiLAM had a sensitivity of 0.70 and a specificity of 0.93 in adults with TB, whereas the sensitivity and specificity of FujiLAM in children with TB were 0.51 and 0, respectively. 87. When using the comprehensive reference standard (CRS), FujiLAM has a sensitivity of 0.59 and a specificity of 0.96 in adults with TB while in children with TB the sensitivity and specificity of FujiLAM are 0.27 and 0.86, respectively. Subgroup analysis showed FujiLAM had a higher diagnostic sensitivity in patients with HIV infection or CD4 count < 200 cells/ μ L
12	XinYin, et al. ²⁵ (2021)	<i>Diagnostic value of Lipoarabinomannan antigen for detecting Mycobacterium tuberculosis in adults and children with or without HIV infection</i>	Based on the 67 included studies, the pooled sensitivity of urinary LAM was 48% and specificity was 89%. In the subgroup analysis, the FujiLAM test had higher sensitivity and specificity (69%) (92%). Furthermore, among patients infected with human immunodeficiency virus (HIV), 50% of TB patients were diagnosed using the urine LAM test. In addition, the CD4+ count is inversely related to the sensitivity

Studies of LAM as a molecule with the ability to regulate immune responses, and given that even during localized TB infection (e.g., pulmonary TB) LAMs are found at the site of infection (e.g., in circulating blood and urine), there is a movement to include LAM as a molecule targets in the development of new point of care assays to improve TB diagnosis. Correct and timely diagnosis is essential for implementing effective and successful TB treatment. Some characteristics must be guaranteed by a TB diagnostic test, such as sensitivity, specificity, and speed, as well as the ability to differentiate the pathophysiological spectrum of TB. In addition, clinical specimens must be easily collected. Gold standard diagnostic tests should be low-cost (as much as possible) and easy to interpret.²⁶

A simple diagnostic test that can be performed at the point of care (POC) is AlereLAM (Alere Determine TB LAM Ag). Determinant TB LAM Ag is a lateral flow assay (LF LAM) that detects LAM from urine samples within 30 minutes. The test is

non-invasive and does not require laboratory or technical equipment. The health worker places a 60 L urine sample into one end of the test strip and a positive result appears on the other end as a tape within 30 minutes.²⁷ One of the most important advantages of AlereLAM is its price, which is 3 or 4 times lower than nucleic acid amplification tests.²⁸ However, AlereLAM has suboptimal sensitivity, which is not recommended for the detection of LAM in patients with CD4⁺ T cell count >200 cells/mm³. AlereLAM has resulted in a large number of misinterpretations depending on clinical characteristics such as CD4⁺ lymphocyte count, bacillary load, or clinical symptoms that have been exposed in 2019 WHO guidelines.^{11,16,29} Unfortunately, AlereLAM has limited its use in clinical practice.

In recent years, a new detection technology, the Fujifilm SILVAMP TB LAM test (FujiLAM; Fujifilm, Tokyo, Japan) has been developed.¹³ This method is similar to the urine-based point-of-care test, Alere Determine TB LAM Ag (AlereLAM; Abbott, Palatine, IL) the USA, which is based on the detection of

lipoarabinomannan antigen in urine.¹³ However, FujiLAM used silver-strengthened immuno-chromatography in lateral flow lanes, and the analytical sensitivity was 30 times higher than AlereLAM.³⁰ More importantly, FujiLAM requires only a simple 5-step process to obtain results, and the time required to obtain test results is < 1 hour.³¹

Of the 12 kinds of literature used in this literature review, 9 kinds of literature are stating that urine LAM examination results in higher diagnostic sensitivity and specificity in TB patients infected with HIV and having a CD4+ count < 200 cells/ μ L, while four kinds of literature describe the Fujifilm SILVAMP TB LAM examination (FujiLAM) has a significantly increased diagnostic sensitivity compared to AlereLAM. to correctly diagnose tuberculosis patients in individuals with low CD4+ counts.

IV. LIPOARABINOMANNAN (LAM) URINE ANTIGEN TEST IN THE DIAGNOSIS OF HIV-POSITIVE PULMONARY TB

Lipoarabinomannan (LAM) is a glycolipid found in the cell walls of all mycobacterial species. The TB-LAM AG lateral flow assay (LF-LAM) examination detects LAM in the urine of HIV patients. This test is recommended by WHO to diagnose TB in hospitalized HIV patients with CD4 levels 100 cells/ μ L and in “seriously ill” patients.³² Several studies have shown evidence that the Urine Lipoarabinomannan (LAM) test is recommended for diagnosing TB in HIV patients. Positive.^{14,16,17,22,24,25} A study Systematic Review by Chakrapani Chatla *et al.* The 37 literature studies reflect the added value of urine LAM assay in the diagnostic algorithm for the detection of Mtb among HIV-infected patients presenting with TB symptoms, particularly those with immunocompromised conditions, non-self-expectorants sputum, children, seriously ill patients, and poor resource conditions where Xpert MTB/Rif or Mtb cultures are not readily available. This became more significant among patients who had a CD4 cell count of 100 cells/L.²² Recent study in 2021 by Xin Yin *et al.* in 67 studies that urinary LAM sensitivity was 48% and specificity was 89%. In the subgroup analysis, the FujiLAM test had higher sensitivity and specificity of 69% and 92%, respectively. Furthermore, among patients infected with human immunodeficiency virus (HIV), 50% of TB patients were diagnosed using the urine LAM test. And concluded that urinary LAM is a potential diagnostic test for establishing TB, particularly the use of FujiLAM in HIV-infected adults with CD4+ counts 100 per L.⁹

Some have suggested that LAM as a diagnostic test for TB in HIV-infected patients with measured CD4+ counts, in a prospective observational cohort study by Helena Huerga, *et al.* conducted a study on 485 HIV-positive patients with TB symptoms regardless of the CD4+ count, performed a fresh urine examination with LF-LAM [determine the TB-LAM Ag test; Abbott, Waltham, MA) concluded that the urine LAM test can be used to diagnose TB in HIV-positive individuals with TB symptoms without a CD4+ cell count.²¹ Clinical studies using Mtb ELISA are known as “Clearview ELISA” and TB-LAM Ag (TB-LAM; Alere Inc.), found a sensitivity of 14% for patients with active TB and no HIV infection and 51% for HIV coinfecting patients.³²

Although it is easier to perform, the sensitivity of the urine test for LAM is still low, if it is performed as a single test for the diagnosis of TB. A study report by Akshita Gupta, *et al.* As many as 56 patients suspected of having TB were examined for sputum and urine samples, the sensitivity and specificity of the LAM4 urine test were 8.2% and 82.8%, and there was an increase in sensitivity of 37% if the combination of microscopic smear and LAM urine test had a sensitivity and specificity of 85.2% and 82.8%.¹⁹ This is also supported by the Systematic Review study by Chakrapani Chatla *et al.* that the combination of SSM (sputum smear microscopy) + urine LAM for detecting TB has a sensitivity of 60.4% (range = 38.3-92.7), compared to urine examination with LAM sensitivity of 44.1% (range = 8, 3-93) while the sensitivity of the SSM examination alone is 38.6%. Combination of LAM urine examination with sputum microscopy showed increased sensitivity for active TB when compared to either test alone.²²

V. PROGRESS OF THE DEVELOPMENT OF URINE LAM TESTING IN THE DIAGNOSIS OF PULMONARY TB

In 2003, Inverness commercialized the Clearview® TB ELISA, and in 2010 it was renamed the Determinant TB LAM antigen lateral flow assay (Determine TB-LAM assay, Alere, Waltham, MA, USA). The sensitivity (42% vs 44%) and specificity (94% vs 87%) of the ELISA and Determinant LAMP assays were similar due to having the same polyclonal antibody. A new urine-based assay, Fujifilm SILVAMP TB LAM (FujiLAM; Fujifilm, Tokyo, Japan), demonstrated potential for further clinical application with a sensitivity of 69%, which is more than the 65% recommended by WHO.¹¹ Objectives of developing the Fujifilm SILVAMP TB LAM assay (FujiLAM) is to increase the sensitivity of AlereLAM.²⁰ Studies show that FujiLAM is a viable technology for urinary LAM detection with the potential to improve the rapid diagnosis of TB in the care setting. FujiLAM has been recommended for use in children, including hospitalized children with HIV infection or malnutrition.^{13,33} It has recently been shown that the combined use of the Xpert and FujiLAM tests for diagnostic testing of TB in HIV-infected persons hospitalized is a cost-effective test compared to *sequential testing* and *CD4+-stratified testing*. In addition, the adoption of the use of Xpert plus FujiLAM is associated with an increase in life expectancy, possibly because it is very helpful in obtaining a fast and accurate TB diagnosis.³⁴

Another emerging technology as a point-of-care (POC) platform for real-time evaluation of urinary LAM is the so-called “*photonic biosensor*”. The principle of this method is based on a change in the refractive index, which occurs when a specific antibody (anti-LAM) is bound to the analyte. Then, the signal can be measured as a resonant wavelength shift through the interferometer and spectral chip.³⁵ Evidence on the use of the POC platform is limited, but the authors report that this test gives results in a short time (15 minutes) and the urinary LAM detection limit is 475 pg/ml.³⁶

VI. CONCLUSION

Based on the results of the collected literature review, it shows that the lipoarabinomannan (LAM) urine antigen test has low sensitivity and high specificity so it is not recommended as a pulmonary TB screening tool, but has a higher sensitivity accuracy in diagnosing TB cases in hospitalized patient populations. HIV positive in patients at high risk of TB and high accuracy was found in immunosuppressed HIV cases or CD4+ count 100 cells/ μ L and seriously ill patients. The combination of LAM urine examination with sputum microscopy showed increased sensitivity for active TB.

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