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The Contribution Hypoalbumin Status on Diagnosing LF-LAM TB Ag Versus Xpert MTB/Rif in Patients Pulmonary Tuberculosis

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ABSTRACT

In 2023, the global prevalence of tuberculosis (TB) reached 8.2 million cases. This represents the highest recorded figure associated with delayed diagnostics and a rising incidence of tuberculosis cases. Tuberculosis prevalence is elevated among individuals with compromised immune systems, including those with HIV and hypoalbuminemia, who exhibit increased vulnerability to infection. The challenge of sputum ejection impedes diagnosis, highlighting the need for a rapid and economical early detection method. The LF-LAM TB-Ag assay provides an alternative method for determining the presence of Lipoarabinomannan in urine, which is a component of the Mycobacterium tuberculosis cell wall. This study evaluated the efficacy of the LF-LAM TB-Ag assay compared to the Xpert MTB/RIF method for diagnosing tuberculosis. A comparative cross-sectional study was conducted at Abdoel Moeloek Hospital in Lampung Province, Indonesia, between January 2023 and June 2024. A total of 52 suspected pulmonary tuberculosis patients, who were HIV-negative and had hypoalbumin status, were evaluated using both the LF-LAM TB-Ag and Xpert MTB/RIF assays. The Wilcoxon and Chi-square tests have been utilised to assess the efficacy of LF-LAM TB-Ag in comparison to Xpert MTB/RIF. A p-value below 0.002 was considered statistically significant. Xpert MTB/RIF demonstrated improved diagnostic accuracy for tuberculosis in individuals with hypoalbuminemia. This study emphasises the necessity for early detection of pulmonary tuberculosis in patients with hypoalbuminemia. The combining of LF-LAM TB-Ag with Xpert MTB/RIF improves detection, especially among high-risk populations, thereby enabling prompt treatment and enhanced disease management.

Keywords: tuberculosis, Xpert MTB/Rif, LF-LAM TB-Ag, hypoalbumin, diagnostic

ABSTRAK

Pada tahun 2023, kejadian tuberkulosis (TBC) di seluruh dunia mencapai 8,2 juta kasus. Angka ini merupakan angka tertinggi yang pernah tercatat, yang disebabkan oleh keterlambatan diagnosis dan meningkatnya insiden kasus tuberkulosis. Tuberkulosis lebih sering terjadi pada individu dengan sistem kekebalan tubuh yang lemah, seperti mereka yang mengidap HIV dan hipoalbumin, yang menunjukkan kerentanan yang lebih tinggi terhadap infeksi. Kesulitan mengeluarkan dahak menghambat diagnosis, sehingga diperlukan metode deteksi dini yang cepat dan ekonomis. Tes LF-LAM TB-Ag memiliki pendekatan alternatif untuk mendeteksi Lipoarabinomannan dalam urin, komponen dinding sel *Mycobacterium tuberculosis*. Penelitian ini bertujuan untuk mengevaluasi kemanjuran uji LF-LAM TB-Ag dibandingkan dengan metode Xpert MTB/RIF untuk diagnosis tuberkulosis. Sebuah studi potong lintang komparatif dilakukan di Rumah Sakit Abdoel Moeloek di Provinsi Lampung, Indonesia, dari Januari 2023 hingga Juni 2024. Sebanyak 52 pasien terduga tuberkulosis paru dengan status HIV-negatif dan hipoalbumin dinilai menggunakan tes LF-LAM TB-Ag dan

Xpert MTB/RIF. Uji Wilcoxon dan Chi-square digunakan untuk membandingkan efektivitas LF-LAM TB-Ag dengan Xpert MTB/RIF. Nilai p-value kurang dari 0,002 dianggap signifikan secara statistik. Xpert MTB/RIF menunjukkan peningkatan efektivitas diagnostik untuk tuberkulosis pada pasien dengan hipoalbuminemia. Studi ini menyoroti pentingnya identifikasi dini tuberkulosis paru pada individu dengan hipoalbumin

Kata kunci: tuberculosis, Xpert MTB/Rif, LF-LAM TB-Ag, hipoalbumin, diabostik

INTRODUCTION

Tuberculosis continues to pose a considerable global health concern and is a primary cause of morbidity. The WHO Global TB Report 2024 indicates that there were 8.2 million new tuberculosis cases in 2023, up from 7.5 million in 2022. This increase indicates diagnostic delays, partially attributable to the enduring effects of the COVID-19 pandemic, alongside a general rise in illness prevalence (WHO, 2024).

Indonesia has the second-highest tuberculosis incidence in the world, behind India. Several

In 2023, the tuberculosis case detection rate (CDR) in Lampung Province, Indonesia, was only 57%, far below the government's target of 90%. This low detection rate indicates that many tuberculosis cases remain undiagnosed and untreated, increasing the risk of further transmission within the community. Several factors, such as limited access to healthcare facilities, low public awareness, and logistical challenges in remote areas, may contribute to this issue. As a result, tuberculosis continues to be a major public health concern in the region, emphasizing the urgent need for enhanced screening efforts, early diagnosis, and improved access to healthcare services. (Kemenkes RI, 2024)

Pulmonary tuberculosis is more prevalent among malnourished individuals, as inadequate nutrition weakens the body's immune defenses. Malnutrition plays a significant role in causing hypoalbuminemia through various immunopathogenic mechanisms that disrupt protein metabolism and immune function, making individuals more vulnerable to tuberculosis infection and its progression. (Maaz et al., 2024) (Chandrasekaran et al., 2017)·(Feleke et al., 2019).

Malnutrition with hypoalbuminemia weakens the immune system and affects the performance of diagnostic tests. Malnourished individuals often struggle to produce sputum, making it difficult to collect samples for the Xpert MTB/Rif test as the primary diagnostic tool for pulmonary TB in Indonesia. A weakened immune system also allows *Mycobacterium tuberculosis* to replicate more easily and escape from lung granulomas, spreading through the bloodstream and lymphatic system. If the bacteria reach the kidneys via the bloodstream, they may be detected in urine. The LF-LAM test for detecting MTB antigens in urine becomes more effective as degraded MTB increases in the urine. Meanwhile, the accuracy of the Xpert MTB/Rif test may be compromised due to insufficient sputum samples. Therefore, a tailored diagnostic approach is needed to ensure accurate detection based on the patient's condition.. (Maaz et al., 2024)·(Harjatmo et al., 2017)·

The Xpert MTB/Rif test is highly effective in detecting and diagnosing tuberculosis from sputum samples, offering greater accuracy than acid-fast bacilli (AFB) microscopy. It exhibits a sensitivity of 99% and a specificity of 98%, compared to 60% and 95% for AFB, respectively. With a swift turnaround time of 2-3 hours, it functions as a reliable tool for identifying pulmonary tuberculosis. The test requires high-quality sputum specimens (mucopurulent or purulent) with a minimum volume of 3-5 cc. The Xpert machine necessitates regular maintenance and is vulnerable to dust and physical disturbances (Cepheid, 2019) (Pramana et al., 2021) (Perhimpunan Dokter Paru Indonesia, 2021)·

The microbiological diagnosis of pulmonary tuberculosis is generally conducted by sputum-based assays, such as acid-fast bacilli microscopy and Xpert MTB/Rif molecular testing. Nonetheless, these techniques include limitations, as certain patients, particularly those who are malnutrition or have advanced HIV, encounter difficulties in producing sputum. Moreover, sputum-

based assays are incapable of identifying extrapulmonary tuberculosis unless there is pulmonary involvement. This has propelled investigations into alternate diagnostic methodologies, including urine-based tuberculosis detection (Ricks et al., 2020) (Kusumawardani et al., 2021).

Urine-based tuberculosis testing provides numerous advantages, such as a less intrusive collection method, simplified laboratory prerequisites, and reduced infection risk for healthcare personnel. Furthermore, it can diagnose extrapulmonary tuberculosis by identifying circulating *Mycobacterium tuberculosis* antigens. This technique selectively targets lipoarabinomannan (LAM) antigens, which are critical constituents of the mycobacterial cell wall (Ricks et al., 2020a),(Liu et al., 2022).

The Lateral Flow Lipoarabinomannan TB Antigen (LF-LAM TB-Ag) test is a diagnostic tool for the prompt detection of *Mycobacterium tuberculosis* (MTB). This test kit is less invasive than sputum specimens, necessitates a more straightforward examination room configuration, presents a reduced risk of exposure and infection to examiners, and can detect extrapulmonary TB through *Mycobacterium tuberculosis* in human urine. The World Health Organisation first endorsed the LF-LAM TB-Ag as an early diagnostic instrument for tuberculosis in HIV-positive persons in 2015, followed by an updated recommendation in 2019. However, its utilisation is limited by insufficient sensitivity and specificity, as demonstrated by numerous studies. Research demonstrates that LF-LAM TB-Ag is not especially effective in detecting tuberculosis in individuals without HIV co-infection, severe clinical conditions, or other immunocompromised states (World Health Organization, 2019a)

Tessema et al. (2016) reported that LF-LAM TB-Ag testing may aid in identifying undernourished tuberculosis, exhibiting a sensitivity of 65.4% and a specificity of 82.9%. This economical test necessitates only 60 µl of urine and delivers results in 25 minutes. LF-LAM TB-Ag serves as a helpful screening instrument for severe tuberculosis cases, especially in individuals with HIV or malnutrition, owing to its simplicity and efficacy, thereby presenting a promising option for tuberculosis diagnosis (World Health Organization, 2019a),(Tessema et al., 2016). Our goal was to evaluate the LF-LAM TB-Ag diagnostic test in comparison to Xpert MTB/Rif for detecting pulmonary TB in hypoalbuminea status who are non-HIV TB suspects.

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METHOD

Ethics statement

The Institutional Review Board of the Research Ethics Committee of Abdoel Moeloek Hospital, Lampung Province, Indonesia, accepted this study under approval number 010/KEPK-RSUDAM/VIII/2022. All participants furnished written informed consent, which was appropriately witnessed. The study consistently upheld humanitarian values and principles of research ethics during its implementation.

Study design

This study utilised a cross-sectional design. Data were collected through the observation of patients in inpatient wards at Abdul Moeloek Hospital, Lampung Province, from January 2023 to June 2024. A total of 52 suspected pulmonary tuberculosis patients with hypoalbumin status were evaluated using both the LF-LAM TB antigen test in urine and the Xpert MTB/Rif assay in sputum, and their diagnostic efficacy was analysed. The research focused on newly suspected pulmonary tuberculosis cases in patients capable of expectorating sputum. Patients with chronic conditions, including diabetes mellitus, hepatitis, chronic renal failure, malignancy or HIV, were excluded to eliminate potential confounding factors.

LF-LAM TB-Ag assay

Obtain a midstream morning urine sample from the patient utilising a sterile urine collection tube. The test must be performed within 30 to 60 minutes post-collection. The LF-LAM TB-Ag test is valid for performance within 8 hours when stored at room temperature, and it remains valid for up to 3 days when refrigerated at 2-8°C. Commence the test by opening the Alere Determine LAM TB-Ag kit, which involves removing the front foil seal from the top. Affix the patient's identification code to the kit. Dispense 60 µl of urine onto the sample pad of the test kit using a micropipette. Allocate 25 minutes for the reaction to take place. Results must be interpreted under standard room lighting within 25 minutes, but not exceeding 35 minutes to maintain accuracy.

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Xpert MTB/RIF assay

The Xpert MTB/Rif assay is a rapid molecular diagnostic test designed to detect MTB and rifampicin resistance (RIF-R) from sputum samples. The procedure initiates with the combination of morning sputum and a sample reagent in a 2:1 ratio, followed by shaking for 10-15 minutes to achieve liquefaction and inactivation of the sample. The processed sample is subsequently transferred into the Xpert MTB/Rif cartridge, which is then positioned in the Xpert machine. The system conducts DNA extraction, amplification, and real-time PCR analysis autonomously, yielding results in roughly 2 hours.

Statistical analysis

The efficacy of the LF-LAM TB-Ag assay was assessed by juxtaposing its sensitivity and specificity with those of the Xpert MTB/Rif assay. The analysis employed IBM SPSS version 21.0. The Chi-square test was employed to ascertain significant differences between the two methodologies at a 95% confidence level. A p-value less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Performance LF-LAM TB-Ag as compared to Xpert MTB/Rif

A bivariate analysis was performed to evaluate the efficacy of the LF-LAM TB-Ag test vs to the Xpert MTB/Rif in suspected tuberculosis patients with hypoalbuminemia. The investigation employed a 2×2 contingency table (Table 2-3), demonstrating that the LF-LAM TB-Ag test displayed a sensitivity of 79.59% and a specificity of 100%.

Table 1. Effectiveness LF-LAM TB-Ag as compared to Xpert MTB/Rif among TB hypoalbumin status in patients

Sensitivity :
a/(a+c) x 100% = 39/49 x 100% = 79,59%
Specificity :
d/(b+d) x 100% = 3/3 x 100% = 100%

A comparative analysis of test data between LF-LAM TB-Ag and Xpert MTB/Rif was performed using Chi Square (Pearson), yielding a significance value of p 0.002, as presented in Table 3. This result indicates the performance of LF-LAM TB-Ag in relation to Xpert MTB/Rif for diagnosing TB patients.

Table 2. Performance LF-LAM TB-Ag as compared to Xpert MTB/Rif among TB malnourished patients

		Xpert MTB/Rif		Total	P Value
		Positive	Negative		
LF-Lam TB-Ag	Positive	39 (a)	0 (b)	39	0.002
	Negative	10 (c)	3 (d)	13	
Total		**49**	**3**	**52**	

Impact of hypoalbumin status on the Diagnostic Performance of Both Assays

We assessed hypoalbumin status as a potential risk factor for heightened susceptibility to pulmonary tuberculosis infection. Subgroup analysis indicated that the LF-LAM TB-Ag test utilising urine specimens demonstrated greater efficacy in identifying pulmonary tuberculosis among severely hypoalbumin individuals (91.6%) relative to those with mild hypoalbumin (60.7%), as presented in Table 4.

Table 3. Performance LF-LAM TB-Ag in detecting TB among hypoalbumin status

		Hypoalbumin status		Total
		Severe	**Mild**	
LF-Lam TB-Ag	Positive	22	17	39
	Negative	2	11	13
Total		**24**	**28**	**52**

The performance of Xpert MTB/RIF was assessed using sputum specimens across the same subgroups, revealing comparable detection rates for pulmonary TB in individuals with severe hypoalbumin (100%) and mild hypoalbumin (89.3%).

Table 4. Performance Xpert MTB/Rif in detecting TB among hypoalbumin status

		Hypoalbumin status		Total
		Severe	**Mild**	
Xpert MTB/Rif	Positive	24	25	49
	Negative	0	3	3
Total		**24**	**28**	**52**

DISCUSSION

The study revealed that most respondents were males aged 19 to 44 years. This aligns with the findings of Marcoa et al. (2018), which indicated that the peak prevalence of pulmonary TB was observed after the second decade of life, particularly within the 20–59 age group, where males accounted for 65.8% of cases. Males exhibit a higher prevalence of comorbidities and risk factors for pulmonary tuberculosis, including elevated rates of smoking, alcohol use, and extramarital sexual activity across all age demographics, along with an increased likelihood of co-infection with HIV (Marcoa et al., 2018)

Victoria Peer et al. (2023) demonstrated that the incidence of pulmonary tuberculosis was significantly greater in men compared to women, with an incidence rate ratio (IRR) between 1.25 and 1.81. This suggests that men have a 1.25 to 1.81 times higher likelihood of developing pulmonary tuberculosis in comparison to women. This disparity can be attributed to biological, behavioural, and social factors, such as variations in immune response, occupational exposure, and differences in healthcare-seeking behaviour between genders (Peer et al., 2023)

In this study, most respondents suspected of having pulmonary TB with hypoalbuminemia were classified as having severe hypoalbuminemia (<2.5 mg/dL) and mild hypoalbuminemia (2.5 -

<3.5 mg/dL), with 24 individuals (46.2%) and 28 individuals (53.8%), respectively. A cross-sectional study by Xin Guo et al. in Shandong, China (2022) found that individuals with hypoalbuminemia had a 2.61 times higher risk of developing TB. Additionally, hypoalbuminemia was associated with a 1.75 times higher rate of positive sputum tests, more severe clinical symptoms, and increased mortality among hospitalized pulmonary TB patients compared to those with normal albumin levels.(Guo et al., 2022).

Morris et al. found that as many as 72% of pulmonary TB patients who had low serum albumin levels (<3.5mg/dl) had more severe cases. Ganesan et al. (2019) in India also found that 60% of pulmonary TB patients had serum albumin levels below 3.5 mg/dL. Additionally, hypoalbuminemia was significantly associated with a low body mass index (p=0.007), highlighting the link between poor nutritional status and tuberculosis severity.(Ganesan & Gopinath, 2019)

This study found that the sensitivity of the LFLAM TB-Ag test compared to Xpert MTB/RIF was 79.59%, with a specificity of 100% (p=0.002) for diagnosing pulmonary tuberculosis in HIV-negative malnourished (hypoalbumin) patients. LF-LAM TB-Ag was more effective in detecting pulmonary tuberculosis in severely hypoalbumin individuals (91.6%) compared to those who were mildly hypoalbumin (60.7%). The evaluation of Xpert MTB/RIF performance in the same group showed that its ability to detect pulmonary TB was sensitive in severely hypoalbumin compared to mildly hypoalbumin individuals, at 100% and 89.3%, respectively. This indicates that although the performance of LF-LAM TB-Ag to detect pulmonary TB in individuals with a hypoalbumin is still lower than the Xpert MTB/RIF test, its sensitivity shows an increase when used in suspected TB cases with severe hypoalbumin rather than mild hypoalbumin (91.6% vs. 60.7%).

This study aligns with the findings of Elhalawany et al. (2021) in Egypt, which indicated that the urinary LF-LAM TB-Ag test exhibited a sensitivity of 95.7% and a specificity of 98.1%. The study exhibited a positive predictive value (PPV) of 95.7% and a negative predictive value (NPV) of 98.1%, resulting in an overall accuracy of 97.4% in identifying tuberculosis in individuals co-infected with HIV. Moreover, LF-LAM TB-Ag concentrations exhibited a robust correlation with diminished CD4 counts, deteriorating nutritional condition, and notable anomalies in radiological assessments (Elhalawany et al., 2021). In contrast to the research conducted by Ogundeji et al. (2018) in Nigeria, which indicated that the LF-LAM test exhibited a low sensitivity of 57.5% while maintaining a specificity of 100% in patients with co-infection of TB and HIV (Ogundeji et al., 2018)

Multiple factors may enhance the sensitivity of the LF-LAM TB Ag test in patients with hypoalbuminemia, who may be experiencing a decline in immune function. A potential explanation is that an increased bacterial load results in enhanced replication of Mycobacterium tuberculosis in immunocompromised individuals. The lack of cavity formation in malnourished patients facilitates bacterial proliferation within tissues, thereby enhancing the diffusion of LAM into the bloodstream. One theory posits that in non-immunosuppressed tuberculosis patients, elevated levels of antigen-antibody complexes may hinder the excretion of LAM in urine, thereby diminishing test sensitivity in this population (Ricks et al., 2020)

Pulmonary tuberculosis initiates upon the inhalation of MTB bacilli, which subsequently reach the alveoli and are phagocytised by alveolar macrophages. In individuals with severe malnutrition, a weakened immune response fails to effectively contain the bacteria, allowing MTB to multiply and spread through the bloodstream to other parts of the body. During active infection, Mycobacterium tuberculosis (MTB) releases lipoarabinomannan (LAM), a glycolipid component of its cell wall, into the bloodstream (Ricks et al., 2020)

Hypoalbumin exacerbates this process by compromising the structural integrity of the glomerular basement membrane, thereby increasing its permeability. Consequently, elevated levels of LAM are excreted in the urine. The elevation of urinary LAM improves the sensitivity of the LF-LAM TB Ag assay, thereby enhancing its efficacy as a diagnostic tool for identifying TB in patients experiencing severe malnutrition or notable hypoalbuminemia (Tessema et al., 2016)

Malnutrition induces hypoalbuminemia via many immunopathogenic pathways that impair protein metabolism and immunological function. Deficiencies in protein and energy hinder the liver's

capacity to synthesise albumin owing to an insufficiency of necessary amino acids. Moreover, damage to the intestinal lining in malnourished persons diminishes food absorption, consequently decreasing albumin levels and impeding adequate nutrient distribution throughout the body. Inadequate nutritious consumption, particularly in economically disadvantaged persons, elevates the risk of hypoalbuminemia. This syndrome compromises the immune system by diminishing the production of T cells and macrophages, hence increasing susceptibility to tuberculosis infection and its advancement (Maaz et al., 2024) (Chandrasekaran et al., 2017) (Feleke et al., 2019).

A more severe degree of hypoalbuminemia increases the detection of TB LAM in urine due to significant pathophysiological changes caused by malnutrition. Severe hypoalbuminemia weakens cellular immunity, particularly by reducing the number of CD4+ and CD8+ lymphocytes, which are essential for controlling MTB. The decline in CD4+ and CD8+ cells impairs the function of immune cells such as macrophages, dendritic cells, neutrophils, and fibroblasts, which collectively form granulomas to contain and restrict bacterial spread. However, when immune function further deteriorates due to severe malnutrition, granulomas may undergo caseous necrosis, allowing MTB to escape, proliferate within lung tissue, and potentially disseminate to other organs. This leads to a higher bacterial load in the body, resulting in increased LAM release into the bloodstream. Furthermore, malnutrition-related hypoalbuminemia can increase the permeability of renal blood vessels, facilitating LAM leakage into the urine, thereby enhancing its detectability in diagnostic tests (Zhang et al., 2023), (Suwanpimolkul et al., 2017).

Patients with hypoalbuminemia are more vulnerable to severe or disseminated tuberculosis, which can further elevate LAM levels in the blood and increase its excretion through the kidneys. However, research on the effectiveness of the LF-LAM TB-Ag test for diagnosing pulmonary TB in non-HIV patients remains limited. As of 2019, the WHO recommends using the LF-LAM TB-Ag assay only for TB-HIV co-infected patients with a CD4 count below 100 cells/μL or those with severe clinical symptoms, even without prior CD4 testing. This guideline is based on previous studies indicating that the sensitivity and specificity of LF-LAM TB-Ag remain suboptimal for broader clinical use (WHO, 2019)

This study examines the specific diagnostic advantages and drawbacks of the LF-LAM TB-Ag and Xpert MTB/Rif assays in identifying pulmonary tuberculosis in patients with hypoalbuminemia. The LF-LAM TB-Ag assay exhibited moderate sensitivity at 79.59%, especially among patients with advanced disease or severe hypoalbuminemia. Nonetheless, its diminished sensitivity in early-stage tuberculosis and lower predictive values constrain its utility as an independent diagnostic instrument. The Xpert MTB/Rif assay demonstrated consistently high sensitivity and predictive values across all hypoalbumin levels, highlighting its superior diagnostic accuracy and reliability in this population. These findings indicate that severe hypoalbuminemia increases the sensitivity of the LF-LAM TB-Ag assay, but simultaneously diminishes its predictive values, highlighting the necessity for a combined diagnostic strategy.

LIMITATION OF THE STUDY

This study is limited by the exclusion of a large and diverse sample size within a multi-center framework. A larger sample size would facilitate more comprehensive subgroup analyses, enhancing comparisons across different patient groups. The LF-LAM TB-Ag urinary test lacks specificity for Mycobacterium tuberculosis and may yield positive results for other Mycobacterium species, such as M. bovis, M. leprae, and M. avium. Future research is required to compare sputum culture, considered the gold standard for diagnosing pulmonary tuberculosis, to enhance test accuracy and improve research outcomes.

CONCLUSIONS AND SUGGESTIONS

This study emphasizes the need for a patient-centered diagnostic approach that considers the clinical profile and nutritional status of pulmonary tuberculosis patients with hypoalbuminemia. The LF-LAM TB-Ag test aligns with the physiological changes seen in malnourished individuals, while the Xpert MTB/RIF assay provides molecular precision for reliable detection across various disease stages. These findings highlight the importance of an integrated diagnostic strategy that combines both methods to improve the accuracy of pulmonary tuberculosis diagnosis.

World Health Organization has previously advised that LF-LAM TB-Ag should not serve as a substitute for Xpert MTB/RIF or sputum culture, which provide superior sensitivity and specificity. LF-LAM TB-Ag can enhance these tests, thereby facilitating early tuberculosis diagnosis. This tool is particularly effective for screening individuals at high risk, including those with immunocompromised conditions, malnutrition, hypoalbumin, or HIV co-infection. In endemic regions where delayed or missed diagnoses frequently occur, the use of LF-LAM TB-Ag in conjunction with established diagnostic methods can enhance TB detection, facilitate timely treatment initiation, and contribute to efforts aimed at disease eradication.

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