Public Health of Indonesia
E-ISSN: 2477-1570 | P-ISSN: 2528-1542

Original Research

The Combination Diagnostic Test for Tuberculosis Screening in HIV Patients in Referral Hospitals in Indonesia

Rosamarlina[1], Asep Purnama[2], Nur Farhanah[3], Made Susila Utama[4], Heidy Agustin[5], Armaji Kamaludi Sarif[6], Aninda Dinar Widintari[7], Farida Murtiani[7], Armedy Ronny Hasugian[8*]

[1]Department of Pulmonology and Respiratory, Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
[2]TC Hiller Sikka District Hospital, Maumere, East Nusa Tenggara, Indonesia
[3]Kariadi Central Hospital, Semarang, Indonesia
[4]Ngoerah Hospital, Denpasar, Indonesia
[5]Persahabatan Hospital, Jakarta, Indonesia
[6]Health Policy and Development Agency, Ministry of Health Republic of Indonesia, Jakarta, Indonesia
[7]Clinical Research Unit, Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
[8]National Institutes of Research and Innovation, Jakarta, Indonesia

*Corresponding author
Armedy Ronny Hasugian
National Institutes of Research and Innovation, Indonesia
Raya Jakarta-Bogor St., KM 46, Pakansari, Cibinong Subdistrict, District of Bogor, West Java 16911, Phone: +62 81214068314.
Email: medyrh@gmail.com

DOI: https://doi.org/10.36685/phi.v11i3.1094

Copyright: © 2025 the Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium provided the original work is properly cited.

Abstract

Background: Screening tests are needed to help screen suspected Tuberculosis (TB) pulmonary with HIV positive. With the limitation of specificity of the screening test and the need for combination with laboratory tools to increase that, a combination with standard examination is still needed, especially for limited healthcare facilities.

Objective: This study aimed to determine Pulmonary TB screening tests with Human Immunodeficiency Syndrome (HIV) positive.

Method: This observational study with a cross-sectional design was conducted in four government hospitals. Study subjects were inpatients and outpatients who met study inclusion criteria (> 14 years of age, HIV positive based on HIV test results, had clinical symptoms of episodic history of fever, and volunteered to take part in the study). Total subjects were 193 people, with episodic history of fever from <24 hours to 120 hours.

Result: This study assessed a subject's clinical manifestation, physical examination and X-ray test. The "Night Sweat", Infiltrates in the Upper Lobe", "Enlargement of Lymph Nodes and "Left Rhonchi" and their combination have a sensitivity of>85%. Still, only the complete combination has a specificity of> 70%. The combination of "Night Sweat + Enlargement of Lymph Nodes + Left Rhonchi + Infiltrates in the Upper Lobe" and then "Enlargement of Lymph Nodes + Left Rhonchi + Infiltrates in the Upper Lobe" can be an alternative for screening Pulmonary TB-HIV positive with history of fever.

Conclusion: Pulmonary TB screening in HIV patients with a history of fever can be used by completely combining clinical manifestation, physical examination, and X-ray. the variables "Night Sweat, Enlarged Lymph Nodes, left rhonchi breath sounds and pulmonary upper lobe infiltrates" in a gradual manner.

Article History:
Received 10 January 2025
Revised 7 May 2025
Accepted 19 June 2025

Keywords: Diagnostic Combination Test; HIV-Tb Coinfection; Tuberculosis Screening; Clinical Manifestations in TB-HIV; Pulmonary TB in HIV Patients

Background

Tuberculosis pulmonary (pulmonary TB) cases have increased globally, especially HIV-positive. The World Health Organization reported 214,000 TB-related deaths among HIV-positive patients in 2020 (World Health Organization, 2020). Pulmonary tuberculosis cases in Indonesia are also high, ranking second globally, with 351,936 cases documented in 2020 by the Ministry of Health. Notably, the proportion of TB pulmonary cases co-infected with HIV has increased from 1.85% in 2016 to 2.4% in 2019 (Ministry of Health Republic of Indonesia, 2018, 2020, 2021). Although the percentage of TB-HIV co-infection may seem small compared to the overall TB burden, the upward trend is alarming because HIV weakens the immune system, accelerates TB progression, and worsens treatment outcomes-increasing patient morbidity and mortality. The surge in cases also indicates weaknesses in screening and prevention programs, especially in remote areas. Therefore, there is a need for effective screening strategies in PLHIV populations for early detection, rapid treatment, and transmission control to break the TB-HIV dual epidemic in Indonesia.

The problem is that diagnosing pulmonary TB in HIV-positive patients is challenging. Moreover, TB pulmonary diagnostic tests and cultures rarely detect the presence of Mycobacterium tuberculosis bacteria in the early phase. This diagnostic difficulty is further compounded by systemic challenges in healthcare delivery, particularly in remote areas of Indonesia. For instance, approximately 64.5% of healthcare facilities lack standardized guidelines for diagnosing and treating TB/HIV co-infection, which hampers effective management of these patients. Most of these facilities are located in remote regions where access to advanced diagnostic tools is limited (National Institutes of Health Reserach and Development Minsitry of Health of Republic of Indonesia, 2019). This has the potential to lead to delayed diagnosis, inappropriate treatment, and suboptimal patient management. As a result, patients face the risk of more severe complications, higher mortality rates, and increased disease transmission in the community.

The screening to detect the possibility of pulmonary TB in HIV-positive patients remains a challenge in health services. Even though the WHO TB-HIV algorithm using clinical assessment and chest X-ray has a sensitivity of >90%, its specificity is still below 20%. To increase specificity, systematic reviews recommend using molecular tests, which are rapid diagnostic methods that detect the genetic material of Mycobacterium tuberculosis and can also identify drug resistance. Examples of molecular tests include the Xpert MTB/RIF assay. To increase the specificity, the systematic review recommended using the molecular test (Dhana et al., 2022a). However, the use of molecular tests is limited, especially in remote areas due to cost and infrastructure requirements. This means that screening is not useless without molecular or golden standard TB tests. The golden standard TB test typically refers to sputum culture, which involves growing Mycobacterium tuberculosis bacteria from patient samples in a laboratory. Although highly accurate, culture tests take several weeks to yield results and require specialized laboratory facilities, making them less feasible for rapid diagnosis in many settings. A cohort study in Yogyakarta, Indonesia, showed that the screening method using a combination of sputum examination and thoracic photographs has a sensitivity and specificity above 80% (Saktiawati et al., 2019a).

Given the increasing burden of pulmonary TB among HIV-positive patients, the diagnostic challenges posed by overlapping symptoms and limited sensitivity of existing tests, as well as systemic issues such as the lack of standardized guidelines in a majority of healthcare facilities, especially in remote areas there remains a critical gap in effective early screening methods. Therefore, this study aims to develop and evaluate a combination screening test model for pulmonary TB in HIV-positive patients that can improve diagnostic accuracy while being practical for use in referral hospitals across Indonesia.

Methods

Study design

This cross-sectional observational study included both inpatient and outpatient HIV-positive patients recruited at the time of their visit or admission to the referral hospitals: Persahabatan Hospital (DKI Jakarta), Sanglah Hospital (Bali), TC Hiller Hospital (Sikka, East Nusa Tenggara), and Kariadi Hospital (Central Java). Inpatients were defined as patients who had been formally admitted to the hospital wards for treatment or observation at the time of recruitment. Recruitment of inpatients occurred during their hospital stay, after confirming eligibility based on inclusion and exclusion criteria. Outpatients were patients attending hospital clinics or outpatient departments for routine visits, follow-ups, or initial consultations without being admitted. Recruitment of outpatients took place during their outpatient visits.

Sample

The subjects were HIV positive with suspected pulmonary TB infection. Sampling was based on the inclusion and exclusion criteria of the study with purposive sampling. The sample size taken based on the estimated proportion for one sample with an alpha value of 0.05 with an estimated proportion of the patient Pulmonary TB-HIV positive was 1,85 %, precision of 2% and an anticipated population proportion of 10%. The 10% threshold was chosen based on the likelihood

that cases will rise in the future since, although some Indonesian regions, including Papua, have seen cases above 10%, cases and their detection remain difficult in Indonesia. Hence, 190 HIV study subjects were needed.

Criteria sample

The inclusion criteria included HIV-positive subjects based on HIV test results who exhibited clinical symptoms suggestive of pulmonary tuberculosis. Specifically, subjects had an episodic history of fever, defined as recurrent episodes of elevated body temperature (≥38°C) lasting at least several days, with intermittent periods of normal temperature, not attributable to other known infections or causes. In addition to fever, other clinical symptoms considered for suspected pulmonary TB infection included persistent cough lasting more than two weeks, unexplained weight loss, night sweats, fatigue, and hemoptysis (coughing up blood). Subjects were adults aged 18 years and older, with no upper age limit specified, and who voluntarily agreed to participate by signing the informed consent form after receiving detailed information about the study. The exclusion criteria included HIV-positive subjects with other severe opportunistic infections unrelated to tuberculosis. Examples of such infections are cryptococcal meningitis, cytomegalovirus (CMV) disease, toxoplasmosis, progressive multifocal leukoencephalopathy (PML). Subjects who had been on anti-tuberculosis treatment for more than one month and pregnant women were also excluded from the study.

Data collection

The data collection instrument was the Case Report Form (CRF), which contained clinical questions, medical. The microbiological examination for pulmonary tuberculosis included three consecutive sputum samples tested for acid-fast bacilli (AFB) using sputum smear microscopy. This standard approach involves collecting sputum specimens on three separate occasions—typically spot-morning-spot samples to increase the sensitivity of detecting Mycobacterium tuberculosis. Chest X-rays were performed on all study subjects to evaluate radiological manifestations suggestive of pulmonary tuberculosis. The X-ray images were independently interpreted by experienced radiologists at each study site who were blinded to the patients' clinical and microbiological results to minimize bias. Radiological assessment followed standardized criteria for pulmonary TB, including the presence of infiltrates, cavitations, nodules, fibrotic changes, or pleural effusions consistent with active or past tuberculosis infection. These criteria were based on established guidelines such as those from the World Health Organization (WHO) and the American Thoracic Society (ATS).

Analysis data

The selection of statistical methods in this study was done systematically to support the study objectives. Univariate analysis was used as an initial step to identify variables significantly associated with pulmonary tuberculosis in HIV patients, so that these variables could be considered in further analysis. Diagnostic analysis was performed to assess the performance of diagnostic tests by measuring sensitivity, specificity, predictive value and area under the curve (AUC), to ensure accuracy and reliability of diagnosis. The diagnostic test analysis in this study involved evaluating the performance of both each diagnostic method separately and the combination of methods used to detect pulmonary tuberculosis in HIV patients. Metrics such as sensitivity, specificity, positive and negative predictive values, area under the curve (AUC), and likelihood ratios were calculated for each of the main diagnostic methods like sputum smear microscopy, GeneXpert MTB/RIF, and radiologic examination as well as for their combination when used together as a diagnostic strategy. This approach aims to provide a comprehensive picture of the accuracy and reliability of each method individually and in synergy to improve TB detection.

Furthermore, multivariate logistic regression was chosen because the primary outcome is binary (presence or absence of pulmonary tuberculosis), allows the determination of independent relationships between multiple predictor variables and the incidence of pulmonary tuberculosis while controlling for confounding variables, and provides easy-to-interpret results in the form of odds ratios. This method is also standard in epidemiological studies for the analysis of risk factors with categorical outcomes, and allows the selection of simple but informative models to avoid overfitting and improve the generalizability of the results. Moreover, Youden Index is a measure used to determine the optimal cut-off point on a diagnostic test by combining sensitivity and specificity, thus helping to accurately differentiate positive and negative results. Brier Score measures the accuracy of probability prediction by assessing how close the prediction is to the actual outcome, where a lower value indicates a more precise prediction. Spiegelhalter's z-statistic is used to test the calibration of the prediction model, i.e. how well the predicted probability matches the actual event, with a non-significant result indicating a well-calibrated and trustworthy model.

Ethical consideration

This study was conducted with the Declaration of Helsinki and approved by the National Institutes of Health Research and Development, Ministry of Health Republic of Indonesia Number LB.02.01/5.2/KE.177/2015.

Results

The total number of subjects analysed was 193, with the characteristics described in Table 1. There were 170 (88.1%) HIV positive without pulmonary TB and 23 HIV positive with pulmonary TB (11.9%). Based on an episodic history of fever that occurred from less than 24 hours to 120 hours, an assessment of the clinical manifestations, physical examination and X-rays of the respondents were made. The results of the study found that the most common assessments of the clinical manifestations were "cough with phlegm", "night sweat", "fatigue", and "weight loss" (Table 2). The diagnostic test results showed that the sensitivity value was more than 80%. However, assessing the positive predictive value and positive ratio showed that the false positive value is still high (Table 3).

Table 1. Subject characteristics

Characteristic	n	HIV No TB (%)	TB (%)
Sex			
Male	127	87.4	12.6
Female	66	89.4	10.6
Marriage status			
Married	115	88.7	11.3
Unmarried	58	84.5	15.5
Widow	12	91.7	8.3
Widower	8	100.0	0.0
Direct contact with TB Patients			
Yes	24	83.3	16.7
No	169	88.8	11.2
Age			
(Average ±SD) (Min-Max)		34.98±9 (19-62)	36.96±9.8 (25-60)

Table 1 presents the characteristics of the study subjects based on their HIV and TB status. A total of 193 participants were included in the analysis. By sex, there were 127 males and 66 females. Among males, 87.4% had HIV without TB, while 12.6% were co-infected with TB. Among females, 89.4% had HIV without TB, and 10.6% were co-infected with TB. Regarding marital status, most participants were married (n=115), with 88.7% having HIV without TB and 11.3% with TB. Among unmarried participants (n=58), 84.5% had HIV without TB and 15.5% had TB. For widows (n=12), 91.7% had HIV without TB and 8.3% had TB. Notably, all widowers (n=8) had HIV without TB (100%) with no reported TB co-infection (0%). When looking at direct contact with TB patients, 24 participants reported such contact, with 83.3% having HIV without TB and 16.7% having TB. In contrast, among the 169 participants with no direct TB contact, 88.8% had HIV without TB, and 11.2% had TB. For age, the average age of participants with HIV without TB was 34.98 ± 9 years (ranging from 19 to 62 years), while those with TB co-infection had a slightly higher average age of 36.96 ± 9.8 years (ranging from 25 to 60 years).

Table 2 presents the results of clinical variable diagnostic tests, physical examinations, and chest X-ray findings for patients, along with diagnostic performance indicators including sensitivity (Sens), specificity (Spec), area under the curve (AUC), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR). For clinical variables, common symptoms include fever (sensitivity 48.7%, specificity 91.1%, AUC 0.58) and productive cough (sensitivity 48.9%, specificity 91.1%, AUC 0.57). Symptoms such as weight loss (sensitivity 48.9%, specificity 91.2%) and shortness of breath (sensitivity 48.9%, specificity 92.2%) also showed moderate diagnostic accuracy, with AUC values around 0.55–0.60. Night sweats and sleeping disturbances presented lower diagnostic performance, with specificity below 60% and AUC values around 0.52–0.54. For physical diagnostic findings, right dullness (sensitivity 5.35%, specificity 95.9%) and left dullness (sensitivity 8.8%, specificity 95.7%) demonstrated low sensitivity but high specificity. Enlargement of lymph nodes had a moderate AUC of 0.63, reflecting its potential as a supportive indicator, while candidiasis and Kaposi's sarcoma showed limited diagnostic relevance with lower AUC scores. Regarding chest X-ray results, several findings demonstrated strong diagnostic performance. Lymphadenopathy in the intrathoracic area showed the highest AUC (0.73), with sensitivity of 48.8% and specificity of 93.1%. Consolidation also yielded a relatively high AUC (0.72) with high specificity (87.0%) and a PPV of 88.3%, indicating good reliability for TB diagnosis. Other findings, such as infiltrates in the upper lobe and fibrosis, showed moderate accuracy but lower

sensitivity. These results highlight that chest X-ray findings, particularly lymphadenopathy and consolidation, provide higher diagnostic accuracy compared to clinical symptoms and basic physical findings.

Table 2. Results of Clinical Variable Diagnostic Test, Physical Examination, Chest X-ray

			sens (%)	spec (%)	AUC	PPV (%)	NPV (%)	PLR	NLR
Clinical									
Fever	93	4.7	9.1	77.6	0.58	19.1	90.4	1.75	0.78
Productive Cough	93	0.8	5.7	1.2	.58	4.1	7.3	.21	.21
Coughing Blood	93	.6	.7	7.1	.53	8.6	8.7	.96	.94
Night Sweat	193	60.1	87.0	43.5	0.65	17.2	96.1	1.54	0.30
Easily Fatigue	193	84.5	87.0	15.9	0.51	12.3	90.0	1.03	0.821
Sleeping Disturbance	193	43	60.9	59.4	0.60	16.9	91.8	1.5	0.66
Shortness of Breath	193	34.7	52.2	67.6	0.60	17.9	91.3	1.61	0.71
Diarrhoea	193	39.4	52.2	62.4	0.57	15.8	90.6	1.39	0.77
Weight Loss	193	82.9	91.3	18.2	0.55	13.1	93.9	1.12	0.48
Physical Diagnostic									
Candidiasis	193	48.7	60.9	52.9	0.57	14.9	90.9	1.29	0.74
Right dullness	187	5.35	4.55	94.5	0.50	10.0	88.1	0.83	1.01
Left dullness	187	5.88	4.55	93.9	0.49	9.09	88.1	0.75	1.02
Right Rhonchi	190	18.1	39.1	84.7	0.62	25.7	91.1	2.56	0.72
Left Rhonchi	190	14.5	39.1	88.9	0.64	32.1	91.5	3.50	0.69
Enlargement of Lymph Nodes	193	11.4	34.8	91.8	0.63	36.4	91.2	4.22	0.71
Kaposi's Sarcoma	193	3.60	4.35	96.5	0.50	14.3	88.2	1.23	0.99
Chest X-Ray									
Lymphadenopathy intrathoracic	193	8.8	13	91.8	0.52	17.6	88.6	1.58	0.95
Infiltrate interstitial	193	20.2	39.1	82.4	0.61	23.1	90.9	2.22	0.74
Upper lobe infiltrate	193	18.1	52.2	86.5	0.69	34.3	93.0	3.86	0.55
Double infiltrate	193	25.9	39.1	75.9	0.58	18.0	90.2	1.62	0.80
Lung Fibrosis	193	5.2	8.7	95.3	0.52	20.0	88.5	1.85	0.96
Miliar	193	2.1	8.7	98.8	0.54	50.0	88.9	7.39	0.92
Fibroinfiltrat	193	5.7	8.70	94.7	0.52	18.2	88.5	1.64	0.96
Consolidation	193	6.7	8.70	93.5	0.51	15.4	88.3	1.34	0.98

Sens=" Sensitivity", Spes=" Spesificity", AUC=" Area Under Curve", PPV=" Positive Predictive Value", NPV=Negative Predictive Value", PLR=" Positive Likelihood Ratio", NLR=" Negative Likelihood Ratio".

Table 3. Analysis of diagnostic test combination of clinical manifestation, physical examination and Rontgen

Sens (%)	Spec (%)	AUC	PPV (%)	NPV (%)	PLR	NLR	Brier Score	Spiegelhalter's z-statistic	
Combination									
Night Sweat									p
87.0	43.5	0.65*	17.2	96.1	1.54	0.3	0.10	-0.24	0.59
66.4-97.2	36-51.3	0.58-0.72	14.5-20.4	89.4-98.6	1.3-1.9	0.1-0.9			
Night Sweat + Enlargement of Lymph Nodes + Left Rhonchi									
52.17	86.47	0.76#	34.3	93	3.86	0.55	0.08	-0.08	0.53
30.6-73.2	80.4-91.2	0.69-0.82	23.2-47.4	89.7-95.4	2.2-6.7	0.4-0.9			
Night Sweat + Infiltrates in the Upper Lobe									
100	40.59	0.79#	18.5	0 (-)	1.68	0 (-)	0.09	0.25	0.40
85.2-100	33.1-48.4	0.73-0.84	16.7-20.5		1.5 – 1.9				
Night Sweat + Enlargement of Lymph Nodes + Left Rhonchi + Infiltrates in the Upper Lobe									
86.96	75.3	0.86#	32.3	97.7	3.52	0.17	0.08	0.25	0.40
66.4-97.2	68.1-81.6	0.80-0.91	26-39.3	93.7-99.2	2.6-4.8	0.06-0.5			
Enlargement of Lymph Nodes + Left Rhonchi									
56.5	81.2	70.4*	28.9	93.2	3	0.54	0.09	0.03	0.49
34.5-76.8	74.5-86.8	0.63-0.77	20.2-39.5	89.6-95.7	1.9-4.8	0.3-0.9			
Enlargement of Lymph Nodes + Left Rhonchi + Infiltrates in the Upper Lobe									
86.9	70.6	0.84#	28.6	97.6	2.96	0.18	0.08	0.19	0.42
66.4-97.2	63.1-77.3	0.78-0.89	23.2-34.6	93.3-99.1	2.2-3.9	0.06-0.5			
Infiltrates in the Upper Lobe									
52.2	86.5	0.69*	34.3	93	3.86	0.55	0.09	-0.32	0.63
30.6-73.2	80.4-91.2	0.62-0.76	23.2-47.4	89.7-95.4	2.2-6.7	0.4-0.9			
Acid Fast Bacilli									
78.3	99.4	0.89#	94.7	97.1	133.04	0.22	0.03		
56.3-92.5	96.8-100	0.84-0.93	71.6-99.2	94-98.7	18.6-950.3	0.1-0.5			

* p=0.0004 # p<0.0001, n=193; Sens="Sensitivity", Spes="Spesificity", AUC="Area Under Curve", PPV="Positive Predictive Value", NPV=Negative Predictive Value", PLR="Positive Likelihood Ratio", NLR="Negative Likelihood Ratio". P Spiegelhalter's z-statistic >0.05 = good accuracy

In the final evaluation of the multivariate test, the included variables examined by culture test that were considered to have an association with HIV positive with pulmonary TB were "Nights Sweat" (clinical sign), "lymph nodes enlargement" plus "left rhonchi" (clinical examination), and "Upper Lobe Infiltrates" (radiological examination) (table 3). Based on the Brier value, it was found that the one with the lowest value was the calibration with better accuracy than that of the above value or the one with better accuracy, namely Acid-Fast Bacilli examination and so on. To confirm the results of the Brier score assessment, Spiegelhalter's z-statistic test was continued, and it was found that all combinations had good accuracy ($p > 0.05$).

Discussion

The combination of the episodic history of fever with Night Sweat (clinical manifestation) and Enlargement of Lymph Nodes (physical examination) and Left Rhonchi and Infiltrates in the Upper Lobe (Chest-X Ray) can be used as an alternative screening test for TB in HIV patients. The results of this study indicate that a more comprehensive combination of symptoms and clinical signs increases the sensitivity and specificity of TB screening, and this is consistent with that the combination of them will increase the possibility of screening even the diagnosis (Saktiawati et al., 2019b). Other studies have demonstrated that combining clinical manifestations with chest X-ray findings can significantly enhance the accuracy of diagnostic tests—improving results by approximately 38% (Nalunjogi et al., 2021). In comparison, a meta-analysis study showed that using the WHO symptom-based algorithm—which includes cough, fever, night sweats, or weight loss—combined with C-reactive protein (CRP) concentration ≥5 mg/L yields high sensitivity (≥96%) but suffers from low specificity (≤12%). Alternatively, combining symptoms such as cough ≥2 weeks with haemoglobin <8 g/dL, a body mass index <18.5 kg/m^2, and lymphadenopathy improves specificity (<90%) but still results in suboptimal sensitivity (<57%). Another approach that combines the WHO algorithm with GeneXpert testing demonstrated a balanced performance, with a sensitivity of 76% and a specificity of 93% (range 88–96; n=637), while GeneXpert alone showed similar accuracy (sensitivity 78%, specificity 93%).

Through this study, the combination of "Night Sweat + Enlargement of Lymph Nodes + Left Rhonchi + Infiltrates in the Upper Lobe" emerged as the most comprehensive indicator to identifying pulmonary TB-positive cases in HIV-positive individuals in pulmonary conditions. This combination reflects both systemic and localized manifestations of disease and reflects the typical presentation of pulmonary TB in individuals with HIV, where systemic symptoms such as night sweats and generalized lymphadenopathy are frequently observed due to the underlying immunosuppression. The presence of localized pulmonary signs, including left-sided rhonchi and radiographic infiltratesparticularly in the upper lobe further supports active pulmonary involvement. In patients with HIV, TB may be presented atypically; however, this combination offers a valuable screening clue by integrating systemic immune response with pulmonary pathology.

Night sweats are one of the classic symptoms of Tuberculosis, often reflect a chronic infectious or inflammatory process and are commonly reported in tuberculosis cases and this is one of the clinical manifestations of WHO screening for HIV- TB, consistent with other studies in Indonesia where have high sensitivity (Dhana et al., 2022b; Saktiawati et al., 2019b; Sander et al., 2019; World Health Organization, 2015). Although the exact explanation of fever's propensity to arise at night is unknown, the immunological response intended to reduce fever is impacted by the hormone cortisol, which rises in tuberculosis patients. This phenomenon is caused by lowering hormones at night (Laneke & Ilse, 2020). It is also claimed that this hormone, which is linked to CD4, plays a bigger role in HIV-positive patients (Zhang et al., 2021).

As a result, night sweats are supported as one of the study's screening markers. The "Upper Lobe Infiltrates" are a variable for pulmonary TB with HIV positive screening and could be related to the possibility that TB cases which occurred were still within the high CD4 limit, referring to the results of previous studies at the Sulianti Saroso Infection Hospital found that the lung image tends to be outside the apex meaning outside the upper part of the lung if CD4 <200 cells / Ul (Darraj, 2020; Hanifa et al., 2019; Naidoo et al., 2018; Rusli et al., 2019). Infiltrates in the upper lobe, as seen on chest imaging, are characteristic of reactivation pulmonary TB, which tends to be localized in oxygen-rich upper lung fields. In HIV-positive individuals, although TB can present atypically, the preservation of this classical radiologic pattern—especially in those with relatively higher CD4 counts—may still occur. The "Enlarged lymph" nodes were often found in patients with extrapulmonary TB and most often found in people with HIV due to generalized immune activation and can be caused by the incidence of immunosuppression, which facilitates the spread of TB bacteria to the outside of the lungs at the same time can also show TB progressivity. combination with pulmonary symptoms. In this study, the most number of lymph node enlargement was found in the superficial cervical and consistent with clinical manifestation of TB (A.Farhadi et al., 2020; Kumar et al., 2017; Thakkar et al., 2016; Trinh et al., 2015). Another variable for screening is "left rhonchi"; sounds are often found at the apex of the lung and can caused by the absence of specific cases (Adkinson NF et al, 2019), immunocompromise and immunosuppression factors(Hunter, 2016) or it could be due to involvement of the left bronchus lung (Bhalla et al., 2015). The presence of left-sided rhonchi on auscultation suggests localized airway involvement, possibly due to partial obstruction or endobronchial lesions caused by TB infection.

When combined, these four components represent the clinical and radiological range of immunocompromised active tuberculosis in individuals with HIV. As is common in cases of HIV-TB co-infection, this combination not only suggests the existence of a chronic infectious process but also the severity and scope of the illness. For HIV-TB screening, this combination pattern can be a powerful early clinical signal, particularly in primary care settings or places with restricted laboratory access. This method helps to speed up early detection and treatment of patients with HIV-TB co-infection by enabling a practical yet pathophysiologically meaningful physical and symptom-based screening. As a result, the study's findings may provide an alternative that indicates this combination may enhance the WHO algorithm's sensitivity, which when combined with GeneXpert exhibits a sensitivity of 78% and a specificity of 93%. (Dhana et al., 2022).

The fact that health facilities in Indonesia only have the capacity to test for HIV 83.4% and 56% for TB confirmation, and reporting of HIV-TB diagnosis is more than 50%, so that various strategies are needed to reduce the impact of health problems (National Institutes of Health Reserach and Development Minsitry of Health of Republic of Indonesia, 2019). The results of this study provide alternatives with various combinations that can be used as a substitute for screening in medical institutions that cannot provide molecular TB detection services, underserved geographic areas, while also being able to provide optimal management for HIV-TB. However, these implications are also very dependent on the policy direction of the HIV-TB Health program.

Limitations

This combination is only focused on the adult group because it does not recruit a group of children, so further research is needed in the use of the combination on the children, especially to find its safety, efficacy, and appropriate dosing in the pediatric population. Focusing on the adult group does not mean abandoning the more vulnerable group of children, but the approach to treating children requires a more specific strategy because they have different physiological characteristics than adults. A cross-sectional design only focuses the analysis to assess TB progression from the initial phase until it is detectable; however, these results are sufficient to explain that screening can be carried out in combination with existing combinations. To generalize the use of screening combinations, further testing is needed to compare it with other combinations from other studies and WHO standards; however, the results of this study can be used at least as a pilot study to screen for TB in HIV patients. Furthermore, referring to the decrease of value of Brier and Spiegelhalter's z-statistics was not significant mean with the limitation of the result, the accuracy of all combinations can be declared important to in practice condition because can give important probability, so that it can be used as an alternative for screening.

Conclusion

Pulmonary TB screening in HIV patients with a history of fever can be used by combining clinical manifestation, physical examination, and X-ray. the variables "Night Sweat, Enlarged Lymph Nodes, left rhonchi breath sounds and pulmonary upper lobe infiltrates" in a gradual manner. The result of this study could be used to conduct a pilot study to screen TB in HIV patients. Broadening the study by including children's participation thus recommendations could be used in the general population.

Declaration of conflicting interest

The authors confirm that they do not have any affiliations or connections with any entity or organization that holds any financial interest in the subject matter or materials covered in this manuscript.

Funding

This study was supported financially by Ministry of Health Republic of Indonesia.

Acknowledgement

We would like to extend our sincere gratitude to the entire research team of the National Institute of Health Research and Development (former), Ministry of Health, the research team at RSPI Sulianti Saroso, Persahabatan Hospital, Sanglah/Ngoerah Hospital, Dr Kariadi Hospital and to all research subjects. We would thanks to our head office and suppoted team in who support all this study from beginning.

Author contributions

Conceptualization: ARH, R; Methodology including design, Interpretation: ARH, AP, NF, R, MSU, HA; Writing - original Manuscript: ARH, AKS, FM, ADW; Writing – review and editing: AP, NF, R, MSU, HA, FM, ADW. All authors approve the manuscript before submission.

Author's Biographies

Rosamarlina, pulmonologist at Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
Asep Purnama, internist at TC Hiller Sikka District Hospital, East Nusa Tenggara, Indonesia
Nur Farhanah, internist at Kariadi Central Hospital, Semarang, Indonesia
Made Susila Utama, internist at Sanglah Hospital, Denpasar, Indonesia
Heidy Agustin, pulmonologist at Persahabatan Hospital, Jakarta, Indonesia
Armaji Kamaludi Sarif, researcher at Health Policy and Development Agency, Ministry of Health, Jakarta, Indonesia
Aninda Dinar Widiantari, staff at Research Department, Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia
Farida Murtiani, staff at Research Department, Sulianti Saroso Infectious Disease Hospital, Jakarta, Indonesia.
Armedy Ronny Hasugian, researcher at the Research Center for Preclinical and Clinical Medicine, National Research and Innovation Agency, Jakarta, Indonesia.

References

Adkinson NF et al. (2019). Current Medical Diagnosis & Treatment 2019. In M. A. Papadakis, S. J. McPhee, & M. W. Rabow (Eds.), *a LANGE Medical Book* (Fifty-Eigh). McGraw-Hill Education. https://doi.org/10.1097/00004836-198103000-00028

A.Farhadi, Parhizagar, Rahman, S., & Haghshenas, M. (2020). Tuberculosi: The Most Common Cause of Fever of Undertermined Origin in Shiraz. *Archives of Iranian Medicine*, *23*(7), 1–5.

Bhalla, A. S., Goyal, A., Guleria, R., & Gupta, A. K. (2015). Chest tuberculosis: Radiological review and imaging recommendations. *Indian Journal of Radiology and Imaging*, *25*(3), 213–225. https://doi.org/10.4103/0971-3026.161431

Darraj, M. (2020). Pulmonary Tuberculosis among HIV/AIDS Patients: Chest X-ray Characteristics. *Suez Canal University Medical Journal*, *23*(1), 0–0. https://doi.org/10.21608/scumj.2020.36013.1014

Dhana, A., Hamada, Y., Kengne, A. P., Kerkhoff, A. D., Rangaka, M. X., Kredo, T., Baddeley, A., Miller, C., Gupta-Wright, A., Fielding, K., Wood, R., Huerga, H., Rücker, S. C. M., Heidebrecht, C., Wilson, D., Bjerrum, S., Johansen, I. S., Thit, S. S., Kyi, M. M., Maartens, G. (2022a). Tuberculosis screening among HIV-positive inpatients: a systematic review and individual participant data meta-analysis. *The Lancet HIV*, *9*(4), e233–e241. https://doi.org/10.1016/S2352-3018(22)00002-9

Dhana, A., Hamada, Y., Kengne, A. P., Kerkhoff, A. D., Rangaka, M. X., Kredo, T., Baddeley, A., Miller, C., Gupta-Wright, A., Fielding, K., Wood, R., Huerga, H., Rücker, S. C. M., Heidebrecht, C., Wilson, D., Bjerrum, S., Johansen, I. S., Thit, S. S., Kyi, M. M., Maartens, G. (2022b). Tuberculosis screening among HIV-positive inpatients: a systematic review and individual participant data meta-analysis. *The Lancet HIV*, *9*(4), e233–e241. https://doi.org/10.1016/S2352-3018(22)00002-9

Hanifa, Y., Toro Silva, S., Karstaedt, A., Sahid, F., Charalambous, S., Chihota, V. N., Churchyard, G. J., Von Gottberg, A., McCarthy, K., Nicol, M. P., Ndlovu, N. T., Stevens, W., Fielding, K. L., & Grant, A. D. (2019). What causes symptoms suggestive of tuberculosis in HIV-positive people with negative initial investigations? *International Journal of Tuberculosis and Lung Disease*, *23*(2), 157–165.

Hunter, R. L. (2016). Tuberculosis as a three-act play: A new paradigm for the pathogenesis of pulmonary tuberculosis. *Tuberculosis*, *97*, 8–17. https://doi.org/10.1016/j.tube.2015.11.010

Kumar, N., Agarwal, Y., Ish, P., & Gupta, A. (2017). Tuberculosis of the Lymph Nodes: Many Facets, Many Hues. *Astrocyte*, 34–44. https://doi.org/10.4103/astrocyte.astrocyte

Laneke, L., & Ilse, du P. (2020). The Echo of Pulmonary Tuberculosis: Mechanisms of Clinical Symptoms and Other Disease-Induced Systemic Complications. *Clinical Microbiology Reviews*, *33*(4), 10.1128/cmr.00036-20. https://doi.org/10.1128/cmr.00036-20

Ministry of Health Republic of Indonesia. (2018). InfoDatin Tuberculosis. In *Kementerian Kesehatan RI*.

Ministry of Health Republic of Indonesia. (2020). *The Republic of Indonesia Joint External Monitoring Mission for Tuberculosis*.

Ministry of Health Republic of Indonesia. (2021). *Indonesia Health Profile 2020*.

Naidoo, K., Dookie, N., Naidoo, K., Yende-Zuma, N., Chimukangara, B., Bhushan, A., Govender, D., Gengiah, S., & Padayatchi, N. (2018). Infection and Drug Resistance Dovepress Recurrent tuberculosis among hIV-coinfected patients: a case series from KwaZulu-natal. *Infection and Drug Resistance*, 11–1413.

Nalunjogi, J., Mugabe, F., Najjingo, I., Lusiba, P., Olweny, F., Mubiru, J., Kayongo, E., Sekibira, R., Katamba, A., & Kirenga, B. (2021). Accuracy and Incremental Yield of the Chest X-Ray in Screening for Tuberculosis in Uganda: A Cross-Sectional Study. *Tuberculosis Research and Treatment*, *2021*, 1–6. https://doi.org/10.1155/2021/6622809

National Institutes of Health Reserach and Development Minsitry of Health of Republic of Indonesia. (2019a). *Laporan Riset Fasilitas Kesehatan 2019 Puskesmas (Report of Health Facility)*.

National Institutes of Health Reserach and Development Minsitry of Health of Republic of Indonesia. (2019b). *Laporan Riset Fasilitas Kesehatan. Puskesmas (Report of Health Facility).*

Rusli, A., Lisdawati, V., Banggai, C. E., Putrantoro, R. Dw. S., Agoestien, O., Pakki, T. R., & Lestari, P. I. (2019). Profil Kadar CD4 dan Lokasi Infiltrat Paru Pada Pasien The Description of CD4 Levels and Location of Pulmonary Infiltrates in Tuberculosis Patients with HIV at RSPI Prof Profil Kadar CD4 dan Lokasi Infiltrat Paru Pada Pasien Tuberkulosis dengan HIV di RSP. *The Indonesian Journal of Infectious Disease*, *Vol 4 No 2*(January 2004).

Saktiawati, A. M. I., Subronto, Y. W., Stienstra, Y., Sumardi, Supit, F., & Van Der Werf, T. S. (2019a). Sensitivity and specificity of routine diagnostic work-up for tuberculosis in lung clinics in Yogyakarta, Indonesia: A cohort study. *BMC Public Health*, *19*(1), 1–11. https://doi.org/10.1186/s12889-019-6658-8

Saktiawati, A. M. I., Subronto, Y. W., Stienstra, Y., Sumardi, Supit, F., & Van Der Werf, T. S. (2019b). Sensitivity and specificity of routine diagnostic work-up for tuberculosis in lung clinics in Yogyakarta, Indonesia: A cohort study. *BMC Public Health*, *19*(1), 1–11. https://doi.org/10.1186/s12889-019-6658-8

Sander, M. S., Laah, S. N., Titahong, C. N., Lele, C., Kinge, T., de Jong, B. C., Abena, J. L. F., Codlin, A. J., & Creswell, J. (2019). Systematic screening for tuberculosis among hospital outpatients in Cameroon: The role of screening and testing algorithms to improve case detection. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, *15*, 100095. https://doi.org/10.1016/j.jctube.2019.100095

Thakkar, K., Ghaisas, S. M., & Singh, M. (2016). Lymphadenopathy: Differentiation between Tuberculosis and Other Non-Tuberculosis Causes like Follicular Lymphoma. *Frontiers in Public Health*, *4*(February), 10–13. https://doi.org/10.3389/fpubh.2016.00031

Trinh, Q. M., Nguyen, H. L., Nguyen, V. N., Nguyen, T. V. A., Sintchenko, V., & Marais, B. J. (2015). Tuberculosis and HIV co-infection-focus on the Asia-Pacific region. *International Journal of Infectious Diseases*, *32*, 170–178. https://doi.org/10.1016/j.ijid.2014.11.023

World Health Organization. (2015). *Systematic screening for active tuberculosis: an operational guide*. https://doi.org/ISBN 978 92 4 154860 1

World Health Organization. (2020). Global Tuberculosis Reports 2020. In *WHO*. https://doi.org/10.1016/S0140-6736(00)58733-9

Zhang, Q., Li, X., Qiao, S., Liu, S., Zhou, Y., & Shen, Z. (2021). *The relationship of hair glucocorticoid levels to immunological and virological outcomes in a large cohort of combination antiretroviral therapy treated people living with HIV*. https://doi.org/10.1186/s12879-022-07257-x