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Original Research

Occurrence of Chronic Pulmonary Aspergillosis in Pulmonary Tuberculosis: A Hospital-Based Cross-Sectional Study

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Abstract

Background: Chronic pulmonary aspergillosis (CPA) is a recognized complication in patients with pulmonary tuberculosis, particularly in high TB burden regions. Misdiagnosis and inappropriate treatment occur due to overlapping clinicoradiological features, leading to increased morbidity and mortality. Data on CPA occurrence and its association with PTB in tertiary care settings remain limited in resource-constrained countries.

Methods: This study enrolled 143 adults from outpatient and inpatient departments. Newly and previously diagnosed PTB patients were included. The CPA diagnosis was based on symptoms lasting over three months, radiological findings, and microbiological/immunological evidence using Aspergillus IgG and BAL galactomannan testing. Data were analyzed using STATA 14.0. Descriptive statistics summarized demographic and clinical data, and comparative analyses between CPA and non-CPA groups used chi-square or Fisher's exact tests for categorical variables and Student's t-test for continuous variables.

Results: CPA was diagnosed in 34.3% (49/143) of PTB patients. The CPA cohort showed male predominance (male-to-female ratio, 4:1), with associations with diabetes mellitus (70.8%, p=0.038) and post-tuberculosis lung disease (61.4%, p=0.040). Radiological features, including cavitation (47.4%, p=0.009), aspergilloma (55.9%, p=0.009), and infiltrates (72.3%, p=0.10) were more frequent in CPA patients. Aspergillus-specific IgG was positive in 69.4% (p<0.001) and BAL galactomannan in 43.9% (p<0.001) of CPA patients.

Conclusion: CPA is prevalent among PTB patients, especially those with TB history and comorbidities like diabetes. Integrated diagnostic approaches, including immunological and antigen testing, are recommended to improve differentiation and management in resource-limited settings.

Keywords: Chronic pulmonary aspergillosis, pulmonary tuberculosis, bronchoalveolar lavage, aspergillus-specific IgG, galactomannan

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Quick Response Code:

Introduction

Chronic pulmonary aspergillosis (CPA) occurs in patients with subtle immune defects and underlying lung diseases, especially previous tuberculosis [1]. It presents with chronic symptoms, progressive upper-lobe cavities (with or without fungal balls), pericavitary infiltrates, and pleural thickening [1]. Diagnosis relies on clinical, radiological, and microbiological findings [2]. Long-term antifungal therapy, mainly itraconazole, is required, and surgery is reserved for select cases [1]. India has an estimated 1.58 million CPA cases [3], mostly post-TB. Studies from Pakistan, Iran, and Indonesia report 8–13% CPA in TB patients [4-7]. This study investigated CPA occurrence in primary and relapse pulmonary tuberculosis (PTB) using clinical, radiological, and serological tools, including IgG and bronchoalveolar lavage (BAL) galactomannan.

Methods

This hospital-based cross-sectional study was conducted at the Department of Pulmonary Medicine, IGIMS, Patna. The study enrolled adult patients (≥18 years), between November 2022 and April 2023, who were either newly diagnosed with pulmonary tuberculosis (within seven days of starting anti-tubercular therapy) or had previously confirmed PTB. Both outpatient and inpatient cases were included to ensure a comprehensive representation. Patients who had symptoms for longer than three months and were either microbiologically or clinic-radiologically evident for PTB were included. The exclusion criteria were patients with extrapulmonary TB, MDR/XDR TB cases, HIV/HBsAg/HCV-positive patients, and those who declined informed consent.

Diagnostic Workup

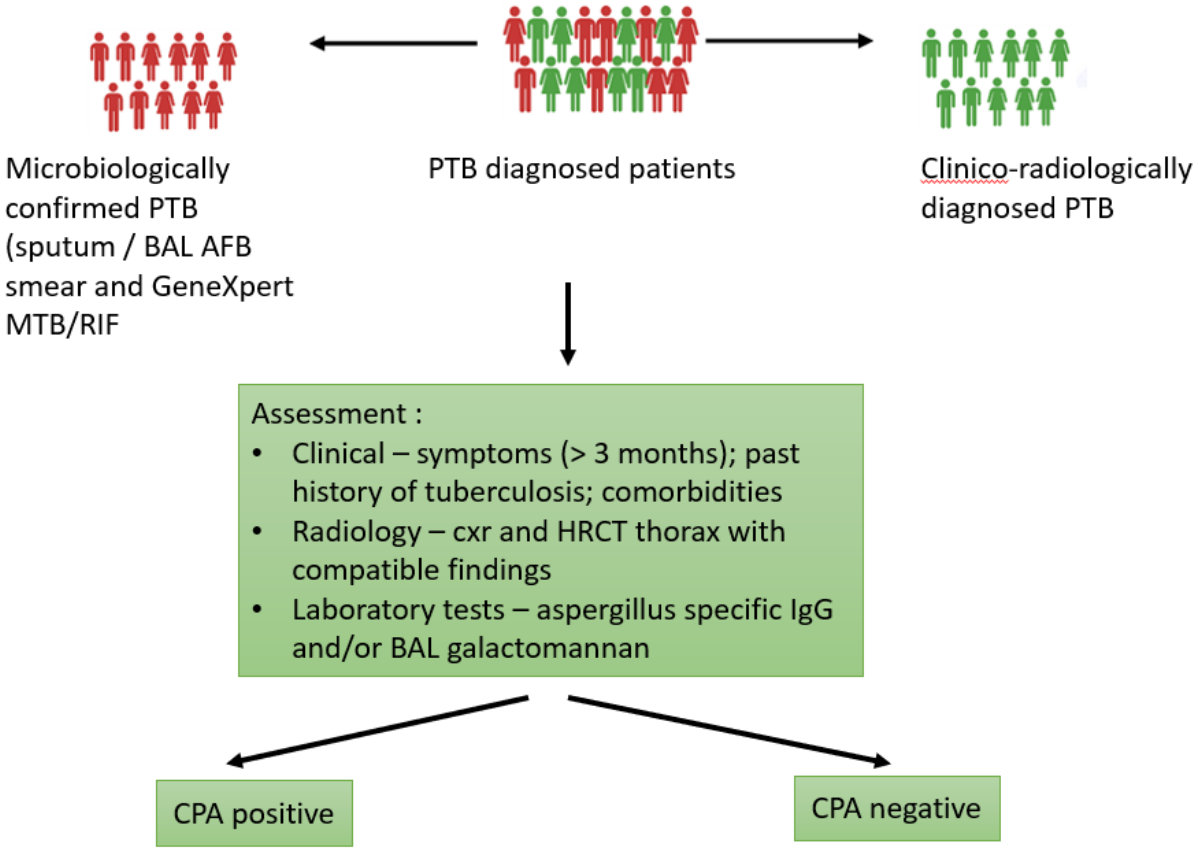
All participants underwent thorough clinical evaluation, radiological assessment (preferably chest computed tomography [CT]), and laboratory tests. The diagnosis of CPA was based on accepted global standards [8]:

- Clinical symptoms (cough, hemoptysis, chest pain, dyspnea, fatigue, and/or weight loss lasting ≥3 months).
- Radiological features: infiltration, cavitation, fungal balls, pleural thickening, or progressive radiological abnormalities.
- Microbiological/immunological confirmation: positive Aspergillus IgG (cutoff >27 mg/L) and/or BAL galactomannan (>2.5) testing [9,10].

Data collection

At presentation, a standardized proforma was used to record the patient's age, sex, comorbidities, history of TB therapy, and symptom profile, which included cough, fever, hemoptysis, dyspnea, weight loss, and fatigue. All participants underwent chest radiography and high-resolution computed tomography (HRCT). Two radiologists independently evaluated the imaging scans using the established diagnostic criteria for CPA. The sputum and, wherever required, bronchoalveolar lavage (BAL) for microscopy, TB PCR, and BAL for galactomannan antigen testing were collected, and serological analysis for Aspergillus-specific IgG levels was performed. **Figure.1.** shows the study flow plan diagram depicting the screening and assessment of patients with pulmonary tuberculosis for chronic pulmonary aspergillosis.

Figure 1. Study Flow Plan



Sample collection and processing

Sputum and/or bronchoalveolar lavage samples (wherever necessary) were obtained following decontamination with the provided buffer sent for the acid-fast bacilli smear using the ZN staining method and/or molecular test: nucleic acid amplification test GeneXpert MTB/RIF (Cepheid, California, USA) for microscopic examination.

To diagnose chronic pulmonary aspergillosis in patients who exhibited concurrent symptoms (lasting longer than three months) and radiological findings, a blood sample (5-10 ml) was obtained for aspergillus-specific IgG, which was measured using the ImmunoCAP Asp IgG assay, and a cutoff of >27 mg/L was deemed positive [9]. BAL sample was obtained for galactomannan test, which was tested for antigen using the enzyme-linked immunosorbent assay (ELISA) from BioRad, with a cut-off of 2.5 considered positive based on the sensitivity and specificity provided by Sehgal et al [10].

Radiological interpretation

All HRCT scans were independently reviewed by two experienced radiologists blinded to the clinical and serological results. Radiological assessment focused on cavity morphology, wall thickness, intralesional fungal balls, pericavitary fibrosis, pleural thickening, infiltrates, bronchiectasis, and fibrotic sequelae. Inter-observer agreement for the identification of CPA-defining radiological features was assessed using Cohen's kappa statistics to evaluate diagnostic consistency. Discrepancies were resolved through consensus discussion. Kappa values were interpreted as follows: <0.20 (poor), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (good), and >0.80 (excellent)

Statistical Analysis

Trained professionals (AR and AD) evaluated the data using STATA 14.0. Qualitative data are presented as frequency and percentages, while quantitative data are presented as mean/standard deviation or median (with interquartile range) based on the normalcy of data distribution. To establish a link between qualitative factors, the chi square/Fisher exact test was used, whereas the Student's t-test / Wilcoxon signed-rank test was used for quantitative variables. P-values < 0.05 were considered statistically significant.

Ethical Consideration

This study was conducted after obtaining ethical clearance from the Institute Ethical Committee of IGIMS, Patna vide letter no. 619/IEC/IGIMS/2022 dated 18/07/2022. Written informed consent was obtained from all patients before enrolling them in the study.

Results

This study enrolled 143 patients who underwent sputum and/or BAL (if necessary) ZN staining and GeneXpert MTB/RIF testing; of these, 58% (n = 83) had microbiologically proven PTB and 42% (n = 60) had clinicoradiologically diagnosed cases. The overall prevalence of CPA among the studied PTB population was 34.26% (95% CI: 25.8–43.6%), with 49 patients fulfilling the diagnostic criteria. Within this subset, 44.9% had microbiologically confirmed PTB and 55.1% had clinic-radiological evidence.

Data were entered into an electronic database and cleaned by cross-checking against the source records. Continuous variables (e.g., age, duration of symptoms, and biomarker levels) and categorical variables (e.g., presence of chronic diseases, radiological features, and IgG/GM positivity) were compared between the CPA and non-CPA groups using appropriate statistical tests. The primary outcome was CPA prevalence in the PTB cohort. Secondary outcomes included the distribution of clinical and radiological features, proportion of patients positive for IgG and/or BAL-GM, and association of key risk factors with CPA.

Men outnumbered women in CPA cases, with a male predominance (79.59%; 95% CI: 65.7–89.8%), producing a male-to-female ratio of approximately 4:1. The mean age of the study cohort was 42.88 years **(Table 1)**, with the 31–40 year age group representing the largest proportion of CPA-positive patients. The most frequent symptoms in CPA patients were cough (57.7%; 95% CI 46.6%–68.0%), fatigue (79.0%; 95% CI 63.7%–88.9%), dyspnea (67.7%; 95% CI 55.4%–78.0%), and hemoptysis (59.0%; 95% CI 46.5%–70.5%). There was a significant difference in the proportions of fatigue (78.95% in CPA-positive vs. 21.05% in CPA-negative, p=0.002) and cough (57.69% in CPA-positive vs. 42.30% in CPA-negative, p=0.001). Other symptoms included chest pain (67.44%; 95% CI 52.5%–79.5% in CPA-positive vs. 32.56% in CPA-negative, p=0.056), fever (59.18%; 95% CI 45.2%–71.8% in CPA-positive vs. 40.82% in CPA-negative, p=0.120), and weight loss (64.29%; 95% CI 45.8%–79.3% in CPA-positive vs. 35.71% in CPA-negative, p=0.112) **(Table 1)**.

Table 1. Patient's characteristics

Variables	**All**	**CPA**	**Non - CPA**	**p-value**
Gender				
Female	47	10 (21.27%)	37 (78.72%)	0.287
Male	96	39 (40.62%)	57 (59.37%)	

Age (mean with range)		42.88 (19-79)	40.48 (19-67)	0.198
Symptoms				
Cough	78	45 (57.69%)	33 (42.30%)	**<0.001**
Fatigue	38	30 (78.95%)	8 (21.05%)	**0.002**
Dyspnea	62	42 (67.74%)	20 (32.26%)	0.260
Chest pain	43	29 (67.44%)	14 (32.56%)	0.056
Hemoptysis	61	36 (59.01%)	24 (39.34%)	0.110
Fever	49	29 (59.18%)	20 (40.82%)	0.120
weight loss	28	18 (64.29%)	10 (35.71%)	0.112
Radiology				
Infiltrate	47	34 (72.34%)	13 (27.66%)	0.10
Cavitation	57	27 (47.37%)	30 (52.63%)	**0.009**
Air Fluid in Cavity	22	9 (40.91%)	13 (59.09%)	0.023
Aspergilloma	34	19 (55.88%)	15 (44.12%)	**0.009**
Bronchiectasis	43	18 (41.86%)	25 (58.14%)	0.275
Fibrosis	27	14 (51.85%)	13 (48.15%)	0.110
Chronic diseases				
T2DM	24	17 (70.83%)	7 (29.17%)	**0.038**
COPD	23	10 (43.48%)	13 (56.52%)	0.900
Bronchial Asthma	16	12 (75%)	4 (25%)	0.424
Silicosis	7	6 (85.71%)	1 (14.29%)	0.117
Post Tuberculosis Lung Disease	57	35 (61.40%)	22 (38.60%)	**0.040**
Hypertension	16	11 (68.75%)	5 (31.25%)	0.275

The most frequent imaging findings were infiltrates (72.34%; 95% CI 58.2%–83.1% in CPA-positive vs. 27.66% in CPA-negative, p=0.10), cavitation (47.37%; 95% CI 35.0%–60.1% in CPA-positive vs. 52.63% in CPA-negative, p=0.009), and aspergilloma (55.88%; 95% CI 39.5%–71.1%) in CPA-positive vs. 44.12% in CPA-negative, p=0.009). Other findings included bronchiectasis (41.86%; 95% CI 28.4%–56.7% in CPA-positive vs. 58.14% in CPA-negative, p=0.275), fibrosis (51.85%; 95% CI 34.0%–69.3% in CPA-positive vs. 48.15% in CPA-negative, p=0.110), and air-fluid in the cavity (40.91%; 95% CI 23.3%–61.3% in CPA-positive vs. 59.09% in CPA-negative, p=0.023) **(Table 1)**.

Significant associations were found between CPA and diabetes mellitus (70.83%; 95% CI, 51.8%–84.3% in CPA-positive vs. 29.17% in CPA-negative patients, p=0.038), post-tuberculosis lung disease (61.40%; 95% CI, 47.6%–73.7% in CPA-positive vs. 38.60% in CPA-negative patients, p=0.040), and silicosis (85.71%; 95% CI, 48.7%–97.4% in CPA-positive vs. 14.29% in CPA-negative patients, p=0.117). Other comorbidities included COPD (43.48%; 95% CI 25.5%–63.2% in CPA-positive vs. 56.52% in CPA-negative, p=0.900), bronchial asthma (75%; 95% CI 47.6%–91.7% in CPA-positive vs. 25% in CPA-negative, p=0.424), and hypertension (68.75%; 95% CI 41.3%–87.9% in CPA-positive vs. 31.25% in CPA-negative, p=0.275) **(Table 1)**.

A comparison of the immunological results for Aspergillus-specific IgG and Galactomannan (GM) is shown in **Table 2**. For CPA-positive participants, the range of Aspergillus-specific IgG levels was 28–236 mg/L. According to the study, 69.38% (95% CI: 54.6–81.8%) of chronic pulmonary patients had positive aspergillus-specific IgG. The p-value was less than 0.001 (x2 = 85.57), and the degree of freedom was 1, indicating a statistically significant difference. On the other hand, the BAL GM test was positive in 43.85% (95% CI: 29.8–58.8%) of CPA cases, with a range of 2.63 to 7.32. The p-value was less than 0.001 with x^2 = 25.65, and the degree of freedom was 1, indicating a statistically significant difference. The findings indicated a substantial correlation between CPA and aspergillus-specific IgG (≥ 27 mg/L) and BAL GM (≥ 2.5).

Table 2: IgG tests and BAL Galactomannan

Variables (positive)	All (n = 143)	CPA (n = 49)	Non-CPA (n = 94)	p-value
Aspergillus-specific IgG	34	34 (69.38%)	0	**<0.001**
BAL Galactomannan	28	21 (43.85%)	7	**<0.001**

Discussion

This study confirmed a significant prevalence of CPA among PTB patients, particularly among those with previous tuberculosis and diabetes. Combination diagnostic approaches are required because of clinical and radiological overlap with PTB. Regular screening and the inclusion of Aspergillus-specific IgG and BAL galactomannan tests in TB-centered clinical protocols are essential, particularly in high-incidence areas and among patients who have persistent symptoms or poor response to treatment, as evidenced by the finding that 34.26% of PTB patients exhibited evidence of CPA.

The prevalence of CPA among PTB patients in the current study significantly surpasses previous national and international estimates, highlighting the variation in CPA burden according to population characteristics, diagnostic techniques, and evaluation timing [11,12]. The higher rate in our cohort may be attributed to the tertiary referral nature of our center, where patients with persistent or complicated symptoms are more likely to be referred, as well as to the inclusion of both newly diagnosed and relapsed PTB cases. According to a comprehensive systematic study (Madden et al., 2025), the pooled CPA prevalence rates between active TB treatment and after treatment were 9% and 13%, respectively, and increased to 48% among patients who maintained respiratory symptoms [11]. Likewise, a North Indian community study conducted by Soundappan et al. (2024) revealed a 10.3% frequency of CPA in individuals with post-TB lung abnormalities [12]. Owing to the tertiary referral status and inclusion of clinically difficult or symptomatic relapse TB cases, the current hospital-based study had a significantly higher rate.

Denning et al. (2022) predicted approximately 360,000 new cases annually in India, while Page et al. (2019) in Uganda estimated an annual CPA incidence of 4–10% among TB survivors in [3,13]. Therefore, the high CPA % in this study is consistent with epidemiological projections for nations with a high TB burden, where delayed referral and post-tubercular lung disease are common.

There was an overlap in the symptoms of CPA and PTB, including cough, hemoptysis, and fatigue, which is in line with earlier reports. This study confirmed what Baluku et al. (2021) and others had already found: aspergilloma, cavitation, and pleural thickening were more specific to CPA than to active TB [14]. Although radiological overlap can lead to diagnostic confusion, some patterns, especially paracavitary fibrosis and fungal balls, should prompt CPA testing according to clinical implications. The predominance of diabetes mellitus (71%) and prior tuberculosis (61%) among CPA patients mirrors findings from other Indian and global cohorts [15,16]. Residual cavities from prior tuberculosis provide ideal conditions for Aspergillus development, whereas diabetes weakens host defenses and promotes fungal colonization. According to Denning's 2022 research, up to 20% of patients with post-TB lung disease may develop CPA within five years [3]. This finding is consistent with the demographic trends observed in this study. The male predominance observed in our CPA cohort (male-to-female ratio, 4:1) is in line with previous studies that have also reported a higher incidence of CPA among males. This may reflect higher rates of TB and associated risk factors, such as smoking and occupational exposure, in males in our region. The mean age of CPA patients was 42.88 years, with the highest proportion in the 31–40 year age group, which is similar to findings from other Indian and global cohorts [17,18]. These demographic consistencies reinforce the representativeness of this study in a broader epidemiological context.

Immunological analysis demonstrated that the levels of Aspergillus-specific IgG showed considerable variation and a strong association with CPA, consistent with earlier research emphasizing the reliable diagnostic significance of IgG [17]. The elevated average IgG levels and statistically significant p-values highlight the reliability of its use in CPA diagnosis. On the other hand, the study revealed that BAL Galactomannan (GM) levels are also associated with CPA diagnosis, as evidenced by the significant p-value ($p<0.05$), thereby indicating that BAL-GM is a reliable diagnostic marker. The significant levels of GM in CPA-positive cases support its clinical significance, while its diagnostic accuracy is consistently reliable, confirming its additional function in CPA diagnosis, as depicted by Akram et al. and Sehgal et al. [10,19]. Studies confirm that BAL GM $\geq$ 1.3–1.5 offers the best epidemiologic balance for CPA–TB cohorts, whereas $\geq$ 2.5 is ideal for confirmatory hospital-based research and ensures accuracy [20]. The use of **Aspergillus-specific IgG** and **BAL galactomannan** in this study enhanced diagnostic specificity. Similar to previous reviews, these biomarkers have been repeatedly validated as key differentiators of CPA from recurrent and persistent TB.

The study design was hospital-based and cross-sectional, allowing for the systematic assessment of CPA occurrence in a defined cohort of PTB suspects and confirmed cases, which is suitable for generating prevalence data in real-world settings. The inclusion of detailed demographic, clinical, radiological, and serological data provides a comprehensive profile of CPA in PTB patients, supporting the robust characterization of the disease burden and its clinical features. **Figure 1** (Study Flow Plan) illustrates the patient selection and diagnostic workup process, emphasizing the importance of a systematic approach to CPA diagnosis. The use of composite diagnostic criteria, including clinical, radiological, and immunological testing, aligns with international guidelines and enhances diagnostic accuracy, thereby reducing misclassification bias.

One of the disadvantages of this study is that its cross-sectional design limits its ability to establish temporal relationships or causal inferences, as it does not allow longitudinal follow-up to assess progression or outcomes. The sample size, although reasonable, may not be large enough to detect rare associations or subgroup differences, especially for less common comorbidities or CPA subtypes. The study was conducted in a single tertiary care center, which may limit the generalizability to primary or secondary care settings or to regions with different TB epidemiology or healthcare infrastructure. There is a potential for selection bias, as patients with severe or atypical presentations may be over-represented in a referral center.

From a practical perspective, diagnostic strategies must be adapted to resource availability. In peripheral or resource-limited centers, screening should prioritize persistent symptoms and chest radiography, with serum Aspergillus-IgG serving as the preferred first-line immunological test owing to its accessibility and cost-effectiveness. Secondary-level centers should incorporate HRCT when radiography is inconclusive and utilize BAL-GM testing when bronchoscopy is feasible. Tertiary-care facilities should employ comprehensive multimodal diagnostic workflows integrating radiology consensus reporting and dual-biomarker assessments. Routine screening for CPA in PTB patients is clinically relevant because a substantial proportion of individuals develop CPA during or after TB treatment, and symptoms frequently mimic recurrent or non-resolving TB, leading to misdiagnosis and inappropriate prolongation or repetition of antitubercular therapy. Early identification through systematic screening significantly improves diagnostic accuracy, enables timely antifungal therapy, and reduces morbidity, hemoptysis-related complications, progressive lung destruction, and mortality. Routine screening is particularly important in high TB burden settings, diabetic patients, individuals with structural lung disease, and those with persistent or progressive symptoms despite adequate TB treatment, as it supports differentiation from post-TB sequelae and prevents missed or delayed CPA diagnosis.

Study Limitations and Recommendations

Although this study offers valuable insights, it has certain limitations. A single-center design and moderate sample size may restrict the generalizability of the findings. Future studies should prioritize multicenter studies with larger cohorts to validate these results.

Conclusion:

This study underscores the high prevalence and clinical significance of CPA among patients with current or relapsed pulmonary tuberculosis in a high-burden setting. By employing a systematic approach that integrates clinical features, radiological evidence, and serological testing (Aspergillus-specific IgG and BAL galactomannan), this study revealed that CPA is frequently underdiagnosed and misdiagnosed as PTB, particularly among those with persistent respiratory symptoms or structural lung abnormalities after TB treatment. In this cohort, diabetes mellitus and a history of post-tubercular lung disease were the most significant risk factors for CPA. The results showed that the use of serological assays significantly increased the sensitivity and specificity of CPA diagnosis compared to radiography or microbiology alone, allowing for a more distinct differentiation from post-treatment sequelae or TB return. These results highlight the urgent need for routine CPA screening protocols in TB-endemic regions, especially for patients with persistent symptoms, those developing new symptoms during treatment for PTB, or ongoing symptoms after the completion of anti-TB therapy. To maximize CPA detection and care in resource-constrained TB-prevalent settings, more multicenter research and standardized diagnostic techniques are required.

CONFLICTS OF INTEREST: none

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