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# Chronic Pulmonary Aspergillosis in Post Tuberculosis Patients – A prospective study

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**KEYWORDS**

Chronic pulmonary aspergillosis; Pulmonary tuberculosis; Aspergillus; Post-tuberculosis lung disease; Fungal infection; Aspergillus culture; Lateral flow assay; Indonesia.,

**Abstract**

**Background:**

Chronic pulmonary aspergillosis (CPA) is a progressive fungal infection that frequently develops in patients with residual lung damage following pulmonary tuberculosis (TB). The burden of CPA is increasing globally, particularly in TB-endemic regions such as Indonesia. Early diagnosis remains challenging due to overlapping clinical features with post-TB lung disease and limited access to diagnostic tools.

**Methods:**

This prospective study evaluated patients aged >18 years who presented with persistent respiratory symptoms after completion of TB therapy. Participants with negative GeneXpert and/or acid-fast bacilli smear results were enrolled. Patients with recent antifungal therapy or HIV infection were excluded. All participants underwent *Aspergillus* immunochromatographic technology (ICT) testing and fungal culture. CPA diagnosis was based on persistent respiratory symptoms, microbiological evidence of *Aspergillus* infection, and supportive clinical findings. Demographic, clinical, and laboratory variables were compared between CPA and non-CPA groups using appropriate statistical tests.

**Results:**

A total of 60 patients were included, with 30 patients in the CPA group and 30 in the non-CPA group. The majority were male (67%), with a mean age of 51 years. Cough (57% vs 27%, $p = 0.018$) and haemoptysis (53% vs 27%, $p = 0.030$) were significantly more common among CPA patients. CPA patients also had a longer duration of TB treatment (12.4 vs 8.1 months, $p < 0.001$) and a higher

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prevalence of smoking history (67% vs 33%, p = 0.008). *Aspergillus* culture positivity was significantly higher in CPA patients (100%) compared with non-CPA patients (30%) (p < 0.001). *Aspergillus fumigatus* was the most commonly isolated species, followed by *Aspergillus niger* and *Aspergillus flavus*. Mixed fungal infections, particularly *Aspergillus* with *Candida*, were more frequently observed in CPA patients.

**Conclusion:**

CPA is a significant complication among patients with prior tuberculosis. Persistent respiratory symptoms, prolonged TB treatment, smoking history, and positive *Aspergillus* cultures were strongly associated with CPA in this study population. Early screening for CPA in patients with persistent symptoms after TB treatment may improve diagnosis and clinical management, particularly in TB-endemic settings.

## INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a chronic and slowly progressive fungal infection of the lungs caused by *Aspergillus* species. Globally, CPA is an emerging health concern affecting more than 3 million individuals, particularly among survivors of pulmonary tuberculosis (TB). It is estimated that over 100,000 new cases of CPA develop each year as a complication following TB infection. The long-term prognosis of CPA is often poor, with reported survival rates as low as 47% at 10 years depending on the extent of lung damage and the presence of additional risk factors. Previous research from Nigeria reported that approximately 14.5% of smear-negative, HIV-negative patients developed CPA after completing TB treatment. [1,2,3]

Indonesia bears one of the highest tuberculosis burdens worldwide. In 2019, the estimated TB incidence in the country was 312 cases per 100,000 population, with mortality rates reaching 34 deaths per 100,000 among HIV-negative individuals. Furthermore, Indonesia has contributed significantly to the global rise in newly reported TB cases, with a 69% increase recorded between 2015 and 2019. National surveillance data estimate that approximately 83,000 individuals in Indonesia currently live with CPA, with about 17,561 new cases occurring annually following pulmonary tuberculosis. A recent study also reported that nearly 13% of patients developed CPA at the completion of TB therapy in Indonesia. [4-6]

Serological detection of *Aspergillus*-specific IgG antibodies remains a key component in the laboratory diagnosis of CPA. These antibodies can be detected using several diagnostic techniques, including enzyme-linked immunosorbent assay (ELISA), immunoprecipitation, complement fixation, haemagglutination, immunoblotting, and lateral flow assays (LFA). In recent years, LFA has gained attention as a rapid diagnostic tool because it provides results quickly and requires minimal laboratory infrastructure. The LDBio *Aspergillus* immunochromatographic technology (ICT) is currently the only commercially available LFA for detecting *Aspergillus* IgG antibodies. It has demonstrated high diagnostic performance, with reported sensitivity ranging from 88.9% to 91.6% and specificity between 96.3% and 98%, although further validation in TB-affected populations is still required. In low- and middle-income countries, the diagnosis and management of CPA remain difficult due to limited awareness and restricted access to appropriate diagnostic facilities. The availability of a reliable point-of-care diagnostic test would therefore greatly facilitate early detection and management of CPA in Indonesia. [7-10] Accordingly, we determined the prevalence of CPA among GeneXpert-negative patients following tuberculosis.

## METHODS

Patients who were aged over 18 years presented with respiratory symptoms after completing tuberculosis (TB) treatment were recruited in this prospective

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study from march 2020 to march 2021. Eligible participants were those with negative GeneXpert results and/or negative acid-fast bacilli (AFB) smear microscopy at the time of enrolment. Patients were excluded if they had received antifungal therapy within the previous month or had a confirmed HIV infection. All enrolled participants underwent testing using *Aspergillus* immunochromatographic technology (ICT) lateral flow assay. Written informed consent was obtained from all participants prior to their inclusion in the study.

The primary variables assessed included the presence and duration of respiratory symptoms. *Aspergillus* ICT test, fungal culture findings, and full blood count parameters.

A diagnosis of chronic pulmonary aspergillosis (CPA) was established when the following criteria were met: (1) the presence of at least one persistent respiratory symptom—such as haemoptysis, cough, fatigue, chest pain, or dyspnea—lasting longer than three months; (2) a positive sputum culture for *Aspergillus* species

Categorical variables were summarized using frequencies and percentages, while continuous variables were expressed as means with ranges. Associations between categorical variables were analysed using Fisher's exact test or chi-square test, and Student's *t*-test was used to compare continuous variables. Variables with a *p*-value less than 0.2 were selected for inclusion in the multivariate logistic regression model.

## RESULTS

### Patient Characteristics

Table 1 presents the demographic and clinical characteristics of the study population, comparing patients with chronic pulmonary aspergillosis (CPA) and those without CPA. A total of 60 patients were included in the study, with 30 patients in each group. The majority of participants were male (67%), and the gender distribution was identical in both groups (p = 1.000). The mean age of the overall cohort was 51 years, with no significant difference between CPA and non-CPA patients (p = 0.910).

Regarding clinical symptoms lasting more than three months, cough and haemoptysis were significantly more common among CPA patients compared with non-CPA patients. Cough was reported in 57% of CPA patients compared with 27% in the non-CPA group (p = 0.018), while haemoptysis was observed in 53% of CPA patients and 27% of non-CPA patients (p = 0.030). Other symptoms such as dyspnoea and chest pain were more frequent in the CPA group but did not show statistically significant differences between groups.

Among comorbid conditions, diabetes mellitus was more frequently observed in the CPA group (20%) compared with the non-CPA group (7%), although the difference was not statistically significant (p = 0.130). Other chronic conditions including hypertension, asthma, chronic obstructive pulmonary disease, and pneumothorax showed similar distributions between the two groups.

A significant difference was observed in the duration of tuberculosis (TB) treatment. CPA patients had a longer mean duration of TB treatment compared with non-CPA patients (12.4 vs 8.1 months, p < 0.001). Similarly, a higher proportion of CPA patients had received TB treatment for more than six months (57% vs 17%, p = 0.002). In addition, a history of smoking was significantly more common among CPA patients than in the non-CPA group (67% vs 33%, p = 0.008).

Overall, these findings suggest that prolonged TB treatment, smoking history, and symptoms such as cough and haemoptysis were more frequently associated with CPA in this study population.

**Table 1. Patient Characteristics**

| Variables | ALL (n = 60) | CPA (n = 30) | Non-CPA (n = 30) | p-Value |
|---|---|---|---|---|
| **Gender** | | | | |
| Male | 40 (67%) | 20 (67%) | 20 (67%) | |
| Female | 20 (33%) | 10 (33%) | 10 (33%) | 1.000 |

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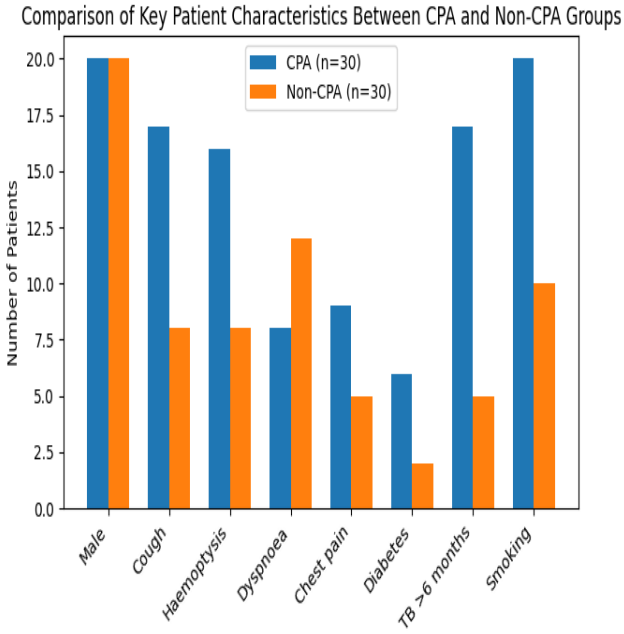
| | | | | |
|---|---|---|---|---|
| **Age, mean (range)** | 51 (18–80) | 50.8 (29–66) | 51.2 (18–80) | 0.910 |
| **Symptoms (≥3 months)** | | | | |
| Cough | 25 (42%) | 17 (57%) | 8 (27%) | 0.018 |
| Haemoptysis | 24 (40%) | 16 (53%) | 8 (27%) | 0.030 |
| Dyspnoea | 20 (33%) | 8 (27%) | 12 (40%) | 0.280 |
| Chest pain | 14 (23%) | 9 (30%) | 5 (17%) | 0.220 |
| **Chronic diseases** | | | | |
| Diabetes mellitus | 8 (13%) | 6 (20%) | 2 (7%) | 0.130 |
| Hypertension | 9 (15%) | 4 (13%) | 5 (17%) | 0.720 |
| Asthma | 4 (7%) | 1 (3%) | 3 (10%) | 0.300 |
| Chronic pulmonary obstructive disease | 7 (12%) | 3 (10%) | 4 (13%) | 0.690 |
| Pneumothorax | 3 (5%) | 1 (3%) | 2 (7%) | 0.550 |
| **Duration of TB treatment, mean (range), months** | 9 (6–26) | 12.4 (6–26) | 8.1 (6–20) | <0.001 |
| TB treatment >6 months | 22 (37%) | 17 (57%) | 5 (17%) | 0.002 |
| Smoking history | 30 (50%) | 20 (67%) | 10 (33%) | 0.008 |

Figure 1: **Patient Characteristics**




**Laboratory Results**

Table 2 summarizes the fungal culture findings and *Aspergillus* species distribution among the study participants, comparing patients with chronic pulmonary aspergillosis (CPA) and those without CPA. Overall, *Aspergillus* culture positivity was observed in 65% of the total study population. All CPA patients (100%) had positive *Aspergillus* cultures, whereas only 30% of patients in the non-CPA group showed culture positivity, demonstrating a statistically significant difference between the two groups ($p < 0.001$).

When examining the pattern of fungal growth, isolated *Aspergillus* species were detected in 15% of all patients, with a higher proportion in the CPA group (20%) compared with the non-CPA group (10%), although this difference was not statistically significant ($p = 0.300$). Mixed fungal cultures were also identified. Co-isolation of *Aspergillus* with *Candida* was significantly more common in CPA patients than in non-CPA patients (30% vs 10%, $p = 0.048$). Mixed cultures involving *Aspergillus* and *Penicillium* were infrequent and showed no significant difference between groups. Similarly, the presence of triple fungal growth (*Aspergillus*, *Penicillium*, and *Candida*) was observed only

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among CPA patients, but this finding did not reach statistical significance.

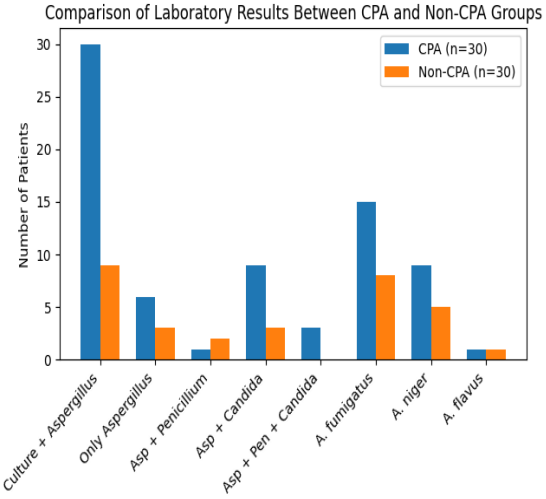
Regarding species distribution, *Aspergillus fumigatus* was the most commonly isolated species, identified in 38% of all patients and more frequently in the CPA group (50%) compared with the non-CPA group (27%). *Aspergillus niger* was the second most common species, detected in 23% of patients, followed by *Aspergillus flavus*, which was rarely isolated. However, the differences in species distribution between CPA and non-CPA groups were not statistically significant.

Overall, the results indicate that *Aspergillus* culture positivity and mixed fungal infections—particularly with *Candida*—were more commonly associated with CPA patients in this study population.

**Table 2. Laboratory Results**

| Variables | ALL (n = 60) | CPA (n = 30) | Non-CPA (n = 30) | p-Value |
|---|---|---|---|---|
| **Culture positive Aspergillus** | **39 (65%)** | **30 (100%)** | **9 (30%)** | **<0.001** |
| **Only Aspergillus** | **9 (15%)** | **6 (20%)** | **3 (10%)** | **0.300** |
| **Aspergillus & Penicillium** | **3 (5%)** | **1 (3%)** | **2 (7%)** | **0.550** |
| **Aspergillus & Candida** | **12 (20%)** | **9 (30%)** | **3 (10%)** | **0.048** |
| **Aspergillus, Penicillium & Candida** | **3 (5%)** | **3 (10%)** | **0** | **0.080** |
| **Aspergillus species distribution** | | | | |
| ***Aspergillus fumigatus*** | **23 (38%)** | **15 (50%)** | **8 (27%)** | **0.070** |
| ***Aspergillus niger*** | **14 (23%)** | **9 (30%)** | **5 (17%)** | **0.240** |
| ***Aspergillus flavus*** | **2 (3%)** | **1 (3%)** | **1 (3%)** | **1.000** |

**Figure 2. Laboratory Results**




## DISCUSSION

### Discussion (with numbered in-text citations)

In the present study, 60 patients with persistent respiratory symptoms following tuberculosis (TB) treatment were evaluated, with equal numbers in the chronic pulmonary aspergillosis (CPA) and non-CPA groups. The majority of participants were male (67%), and the mean age of the cohort was 51 years. These findings are consistent with previous studies reporting that CPA predominantly affects middle-aged or older adults and occurs more frequently in males, particularly in populations with a high burden of pulmonary tuberculosis and smoking. Earlier epidemiological investigations have similarly demonstrated a male predominance and mean age between 45 and 60 years among patients diagnosed with CPA.[11-13]

Persistent respiratory symptoms were an important clinical feature in this cohort. Cough and haemoptysis were significantly more common

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among CPA patients compared with non-CPA patients. These findings are consistent with earlier studies reporting that chronic cough and haemoptysis are among the most common clinical manifestations of CPA.[14, 15] Haemoptysis is believed to occur due to fungal colonization within pre-existing pulmonary cavities, which may lead to erosion of adjacent blood vessels.[14] Studies conducted in tuberculosis-endemic regions have also reported cough and haemoptysis as the most frequent symptoms among patients with post-tuberculosis CPA.[15, 16] In contrast, symptoms such as dyspnoea and chest pain were observed in both groups but were not significantly associated with CPA, a finding that has also been described in previous observational studies.[14]

Although diabetes mellitus was more frequently observed among CPA patients in this study, the difference did not reach statistical significance. Diabetes is recognized as a potential risk factor for fungal infections due to impaired immune responses and altered host defenses.[13, 14] Previous studies have reported a higher prevalence of diabetes among CPA patients, particularly in regions where both TB and metabolic disorders are common. However, the absence of statistical significance in this study may be attributed to the relatively small sample size.

A notable finding in this study was the significantly longer duration of TB treatment among CPA patients compared with non-CPA patients. Patients with CPA had a longer mean duration of TB treatment, and a higher proportion had received TB treatment for more than six months. Similar observations have been reported in previous studies where CPA was frequently misdiagnosed as recurrent or treatment-resistant TB, leading to prolonged anti-tuberculosis therapy before the correct diagnosis was established.[11,15] Structural lung damage caused by tuberculosis, particularly cavitary lesions, provides a favorable environment for colonization and growth of *Aspergillus* species.[12] Consequently, prolonged TB treatment may sometimes reflect undiagnosed CPA rather than persistent tuberculosis infection.

Smoking history was also significantly more common among CPA patients in the present study. Smoking has been recognized as a contributing factor to chronic lung damage and impaired mucociliary clearance, which may facilitate colonization by opportunistic fungal pathogens such as *Aspergillus*.[13, 14] Previous studies have also reported higher rates of smoking among patients with CPA, supporting its role as a potential risk factor for disease development.

Laboratory findings in this study further supported the diagnosis of CPA. Overall, *Aspergillus* culture positivity was observed in 65% of patients and was significantly more frequent among CPA patients compared with the non-CPA group. Previous studies have demonstrated that *Aspergillus* species are commonly isolated from respiratory samples of patients with CPA, although culture results alone cannot distinguish colonization from active infection. Therefore, microbiological findings should always be interpreted in conjunction with clinical and radiological features. [14-16]

Mixed fungal cultures were also identified in this study, with co-isolation of *Aspergillus* and *Candida* being significantly more common in CPA patients. Similar observations have been reported in previous studies, suggesting that structural lung damage following TB may create a favorable environment for colonization by multiple fungal species. Mixed fungal infections may complicate diagnosis and management, highlighting the need for comprehensive microbiological evaluation in patients with suspected CPA. [14-16]

Regarding species distribution, *Aspergillus fumigatus* was the most frequently isolated species, followed by *Aspergillus niger* and *Aspergillus flavus*. This distribution is consistent with global epidemiological data identifying *A. fumigatus* as the predominant species responsible for CPA. The predominance of *A. fumigatus* is attributed to its thermotolerance, ability to colonize damaged lung tissue, and capacity to evade host immune defenses. [14-16]

Overall, the findings of this study are consistent with existing literature demonstrating that CPA commonly develops in patients with prior tuberculosis and structural lung damage. Persistent respiratory symptoms—particularly cough and

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haemoptysis—prolonged TB treatment, smoking history, and positive *Aspergillus* cultures were more frequently associated with CPA in this population. These results highlight the importance of early recognition and appropriate diagnostic evaluation for CPA among patients with persistent respiratory symptoms after TB treatment, particularly in regions with a high burden of tuberculosis [14-16]

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