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Original research

A prospective longitudinal study of chronic pulmonary aspergillosis in pulmonary tuberculosis in Indonesia (APICAL)

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ABSTRACT

Objectives Chronic pulmonary aspergillosis (CPA) can complicate recovery from pulmonary TB. CPA may also be misdiagnosed as bacteriologically negative TB. This study aimed to determine the incidence of CPA in patients treated for TB in Indonesia, a country with a high incidence of TB.

Methods In this prospective, longitudinal cohort study in patients treated for pulmonary TB, clinical, radiological and laboratory findings were analysed. Sputum was collected for fungal culture and TB PCR. Patients were assessed at baseline (0–8 weeks) and at the end (5–6 months) of TB therapy. CPA diagnosis was based on symptoms (≥ 3 months), characteristic radiological features and positive *Aspergillus* serology, and categorised as proven, probable and possible.

Results Of the 216 patients recruited, 128 (59%) were followed up until end of TB therapy. At baseline, 91 (42%) had microbiological evidence for TB. *Aspergillus*-specific IgG was positive in 64 (30%) patients and went from negative to positive in 16 (13%) patients during TB therapy. The incidence rates of proven and probable CPA at baseline were 6% (n=12) and 2% (n=5) and end of TB therapy 8% (n=10) and 5% (n=7), respectively. Six patients (two with confirmed TB) developed an aspergilloma. Diabetes mellitus was a significant risk factor for CPA (p=0.040). Persistent cough (n=5, 50%; p=0.005) and fatigue (n=6, 60%; p=0.001) were the most common symptoms in CPA.

Conclusion CPA should be considered a relatively frequent differential diagnosis in patients with possible or proven TB in Indonesia. Lack of awareness and limited access to *Aspergillus*-specific IgG tests and CT imaging are obstacles in establishing a CPA diagnosis.

INTRODUCTION

The link between pulmonary TB and the subsequent development of chronic pulmonary aspergillosis (CPA) is well established for those who have recovered from TB.^{1,2} Studies to date have addressed the relative rate of development of CPA with slightly different incidence rates depending on the modes of testing, timing, diagnostic criteria used and the patient population.^{3–5} No prospective studies have yet addressed the occurrence of both CPA and TB

Key messages

What is the key question?

⇒ To what extent is chronic pulmonary aspergillosis (CPA) both (a) mistaken for TB and (b) coexists with TB during the course of 6-month therapy?

What is the bottom line?

⇒ Features consistent with CPA were present in 6% of patients when starting TB therapy and 8% at the end of therapy, with some resolving and some developing CPA de novo during TB therapy. At the end of TB therapy symptoms, cavitations with *Aspergillus*-specific IgG detectable were the key features of CPA.

Why read on?

⇒ Coexistence of TB and CPA is present in a substantial minority of patients starting and ending TB therapy, and needs addressing in terms of diagnosis, dual therapy and follow-up.

during anti-tuberculous therapy, although a few such cases are described.⁶ Misdiagnosis of CPA as pulmonary TB is relatively common in clinical practice, but hard to quantify as it is difficult to absolutely rule TB out as a diagnosis.⁵ No prospective studies of CPA have been done in Indonesia. In 2019, Indonesia reported 845 000 TB cases to the WHO, 87% pulmonary⁷ so the numerical impact of misdiagnosis could be large.

Once a diagnosis of pulmonary TB is considered based on clinical symptoms, disease duration and radiological appearance, the standard approach and general clinical recommendation is to commence anti-TB therapy. In a review of older studies before the HIV era and before effective therapy for pulmonary TB was available, Tiemersma *et al*⁸ found that even in those with smear-positive TB, the spontaneous recovery was 30% (14%–47%) and in those with smear negative TB was ~80%. So the drive to immediately treat patients with suspected TB is driven by concern for transmissibility, rather than immediate death of the patient. In the era of

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coinfection of HIV and TB, the 1-year mortality is still excessively high, but this is not the predominant problem in Indonesia.⁹

This longitudinal study was designed to address the timing of the development of CPA during the course of treated TB. A very common feature of TB is pulmonary cavitation, and we know that this is an important precursor to CPA,^{2 10} and given that (a) *Aspergillus* inhalation is inevitable and daily and (b) that some genetic variants of humans are strongly associated with CPA, it would seem likely that some patients might develop CPA early in the course of TB.^{11 12} This early *Aspergillus* infection could be progressive, or it could be self-limited in those with adequate immune defences, and in both cases be marked by a raised *Aspergillus* antibody. This is not currently known.^{13–15}

Furthermore, in those with a clinical presentation of TB, it may be that some patients do not have TB, but an alternative diagnosis. The differential diagnosis includes CPA, non-tuberculous mycobacterial infection, chronic cavitary pulmonary histoplasmosis, coccidioidomycosis or paracoccidioidomycosis, pulmonary cryptococcal infection, necrotising lung cancer, pulmonary hydatid disease, actinomycosis or a subacute bacterial infection on a background of bullous emphysema which appears radiologically similar to TB.^{16–19} Histoplasmosis is endemic in Indonesia, but coccidioidomycosis and paracoccidioidomycosis are not, so only international travel would allow these infections to manifest.²⁰ We hypothesised that some smear-negative and TB PCR-negative patients might have CPA and not TB, as described in Nigeria by Oladele *et al.*⁵ By excluding patients with those previously treated for TB (based on the medical records and verbal confirmation from patients), we have taken out of consideration other populations of patients who might have CPA or a broader differential diagnosis.

Our primary objective was to determine the incidence of CPA during the course of and at the end of TB therapy, and to assess if the criteria for CPA diagnosis are suitable for this population of patients who are already ill with TB. A second objective was to assess how many patients who are thought to have TB, but lack microbiological evidence for this, actually have CPA and how many have dual infection. We also hoped to determine if any patients had ‘self-resolving CPA’, or ‘subclinical CPA’ which does not progress, entities not yet adequately described in the literature and which challenge the current general concept of CPA as a progressive disorder.²¹ Our hypotheses are that: CPA is common and underdiagnosed in patients with TB in Indonesia, there is dual infection between CPA and TB, CPA starts to develop during active infection of TB and the current diagnostic criteria for resource-constrained settings are applicable in Indonesia.

METHODS

Study population

This was a prospective, longitudinal study. Patients were enrolled at two tertiary care hospitals (National Referral Centre Persahabatan Hospital and National Referral Centre Cipto Mangunkusumo Hospital) and four district hospitals (Grha Permata Ibu Hospital, Universitas Kristen Indonesia Hospital, Cempaka Putih Jakarta Islamic Hospital and MH Thamrin Hospital), serving greater Jakarta (12 million). Patients were referred from primary care because of diagnostic uncertainty, patient request or comorbidity.

All consecutive consenting patients with newly diagnosed pulmonary TB were recruited into the study. The exclusion criteria were history of TB, multidrug-resistant TB, less than 16 years of age and non-consenting patients.

Pulmonary TB was diagnosed by the attending clinical team based on typical symptoms, positive TB PCR by GeneXpert MTB/RIF (Cepheid, California, USA) and/or acid fast bacilli (AFB) smear and/or radiology finding positive for TB, as per national guidelines.²² Culture for *Mycobacterium* spp was not done, except in exceptional circumstances. Many patients were treated empirically if the suspicion for pulmonary TB was high.

Data collection

Patients were assessed at the start of TB therapy (baseline, 0–8 weeks) and at the end of TB therapy (at 5–6 months). The main variables, collected at both time points, were serum *Aspergillus*-specific IgG levels, symptoms and quality of life scores.

A validated quality of life instrument used in respiratory disease—the St Georges Respiratory Questionnaire (SGRQ)—was used in addition to CPA-specific questions.^{23–25} This questionnaire consists of three domains (activity, impact and symptoms, each with range of 1–100) and high scores reflect worse quality of life.

Sample collection and processing

Blood samples (5–10 mL) and sputum (if produced) were collected from patients in the clinic at both time points. *Aspergillus*-specific IgG level was measured using the Immulite 2000 system (Siemens, Berlin, Germany) according to the manufacturer’s instructions using a cut-off of 11.5 mg/L.²⁶ Prior to testing, serum was stored in –80°C. Sputum from patients with productive cough was tested for TB using GeneXpert MTB/RIF PCR. AFB smear results were collected from patients’ medical records. Any remaining sputum was cultured for fungi.

Radiological interpretation

All patients had a chest radiograph at baseline and end of TB therapy. CT scans were also done for patients who could afford them. All images were digitised and reviewed by an experienced radiologist (FN) who coded the appearances systematically and provided a narrative report. All radiographs were also reviewed by one of the authors (DWD) who specialises in aspergillosis. All radiographs were interpreted in the absence of data on symptoms or any laboratory findings or the interpretation of the other reviewer. The presence of pleural thickening adjacent to a cavity was required to suspect CPA, as opposed to anywhere on the radiograph—the only finding where there was some difference between the two reviewers who were in agreement for all other criteria.

Definitions

Proven CPA was diagnosed based on three criteria: (1) at least one of the following symptoms—cough, haemoptysis, chest pain, dyspnoea, fatigue, and/or weight loss ≥ 3 months, AND (2) radiological features indicative of CPA (cavitation, fungal ball or pleural thickening) and/or progressive cavitation on serial chest radiographs, AND (3) positive *Aspergillus* IgG and/or *Aspergillus* spp detected by culture. The diagnosis of probable CPA was made when criteria 1 and 2 but not 3 were met AND (4) the PCR for *M. tuberculosis* was negative. Possible CPA was diagnosed in those who met criteria 1 and 2 but not 3 or 4. Criteria for proven, probable and possible CPA were modified versions from Denning *et al.*¹⁵ ‘CPA’ in the tables and text refers to proven CPA, unless otherwise stated.

Data analysis

Statistical analysis was performed with the use of IBM SPSS V.25 statistic software. A p value of <0.05 was considered statistically

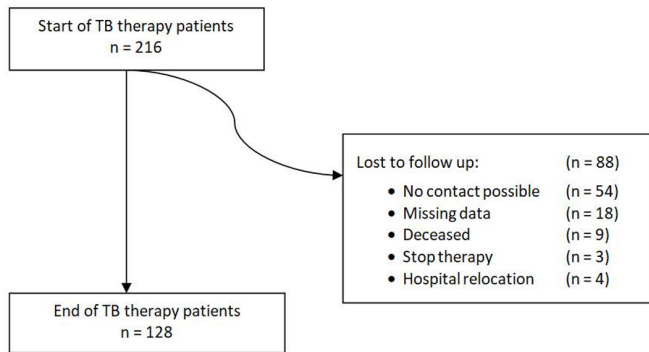


Figure 1 Overview of the study population.

significant. Data were presented using frequencies and percentages for binary and categorical variables, medians and range for non-normally distributed, continuous variables. The difference between non-parametric continuous variables was analysed using Mann-Whitney U test for CPA and non-CPA groups. Fisher's exact tests or χ^2 tests were used for categorical variables for CPA and non-CPA groups. Comparisons of median results across different time points were assessed by Wilcoxon signed-rank test. In addition, post hoc analyses were carried out with McNemar's test with adjusted Bonferroni corrections between two time point comparisons.

RESULTS

A total of 216 patients with pulmonary TB were recruited at the start of their TB therapy and 128 (59%) patients reattended the end of TB therapy follow-up appointment (figure 1). The recruitment phase for the baseline appointments is from February 2017 until April 2018. At baseline, 91 (42%) of 216 patients had microbiological evidence for TB (positive TB PCR and/or AFB smear), 91 (42%) patients were clinically diagnosed as TB but had no microbiological evidence of it (negative TB PCR and/or AFB), and 34 (16%) patients were clinically diagnosed as TB but microbiological diagnostics had not been performed. Additionally two patients had a positive TB PCR result at the end of TB therapy. Twelve (6%) patients met the criteria of proven CPA, 5 (2%) patients as probable CPA and 15 (7%) patients as possible CPA, an incidence of 7.9% (95% CI: 4.7% to 12.3%) or 14.4% if possible cases are included. Six patients grew *Aspergillus* in sputum culture, two of whom met the criteria of possible CPA. None of the patients with proven CPA grew *Aspergillus* in their sputum.

Men outnumbered women in CPA cases with a 3:1 ratio (table 1). Diabetes mellitus appeared to be a significant risk factor for CPA at baseline assessment ($p=0.040$, relative risk=3.346, 42% in patients with CPA vs 16% in patients without CPA). There was a significant difference in the proportion of cough (93% in patients with CPA vs 13% in patients without CPA), fatigue (42% in patients with CPA vs 8% in patients without CPA), and weight loss (17% in patients with CPA vs 1% in patients without CPA) between CPA and non-CPA cases ($p<0.05$). Baseline quality of life SGRQ scores are shown in table 2. There was a significant difference between patients with CPA and patients without CPA in SGRQ in the symptoms domain ($p=0.029$, median 58 (CPA) vs 39 (non-CPA)). Cavitation (92% in patients with CPA vs 52% in patients without CPA), air fluid level in cavities (50% in patients with CPA vs 22% in patients without CPA) and pleural thickening (84% in

Table 1 Patients' characteristics at baseline assessment

Variables	All (n=216)	CPA (n=12)	non-CPA (n=204)	P value
Gender				
Male	102 (47%)	9 (75%)	93 (46%)	
Female	114 (53)	3 (25%)	111 (54%)	0.047
Age (mean with range)	39.8 (17–78)	44.4 (23–77)	39.5 (17–78)	0.300
Symptoms (≥ 3 months)				
Cough	38 (18%)	11 (93%)	27 (13%)	<0.001
Fatigue	22 (10%)	5 (42%)	17 (8%)	0.003
Dyspnoea	18 (8%)	2 (17%)	16 (8%)	0.263
Chest pain	18 (8%)	3 (25%)	15 (7%)	0.067
Weight loss	4 (2%)	2 (17%)	2 (1%)	0.016
Haemoptysis	2 (1%)	1 (8%)	1 (1%)	0.108
Intermittent haemoptysis (<3 months)	47 (22%)	5 (42%)	42 (21%)	0.140
Radiology				
Infiltrates	184 (85%)	7 (58%)	177 (87%)	0.019
Cavitation	117 (54%)	11 (92%)	106 (52%)	0.007
Air fluid level in cavities	50 (23%)	6 (50%)	44 (22%)	0.034
Paracavitary fibrosis	65 (30%)	6 (50%)	59 (29%)	0.191
Pleural thickening	65 (30%)	10 (84%)	55 (27%)	<0.001
Nodules	32 (15%)	0	32 (16%)	0.221
Bronchiectasis	31 (14%)	3 (25%)	28 (14%)	0.386
Aspergilloma*	6 (3%)	0	6 (3%)	1
Chronic diseases				
Diabetes mellitus	38 (18%)	5 (42%)	33 (16%)	0.040
Hypertension	20 (9%)	1 (8%)	19 (9%)	1.000
Asthma	13 (6%)	1 (8%)	12 (6%)	0.535
COPD	5 (2%)	0	5 (3%)	1.000
Chronic kidney disease	4 (2%)	0	4 (2%)	1.000

Bold values indicate statistical significance.

*One aspergilloma in non-CPA group (*Aspergillus*-specific IgG negative) was confirmed on CT scan, the other five were unconfirmed aspergilloma diagnosed on chest X-ray. CPA, chronic pulmonary aspergillosis.

patients with CPA vs 27% in patients without CPA), were all more common in CPA cases ($p<0.05$) (table 1).

The overall prevalence of *Aspergillus*-specific IgG positivity was 30% (64 of 216) at baseline. All (n=12) patients from the CPA group had positive levels of *Aspergillus*-specific IgG. In the non-CPA group, 52 (26%) patients showed positive *Aspergillus*-specific IgG. There was a statistical significance between positive *Aspergillus*-specific IgG across CPA and non-CPA groups ($p<0.001$, median 15.4 (CPA) vs 8.3 (non-CPA)) (table 2).

Nine (4%) patients died before the end of their TB therapy appointment. Eight of them (90%) had extensive infiltrates and/or cavitation in both lungs. Immature *Aspergillus*-specific IgG level was positive in four (44%) of these patients. Chronic kidney diseases (n=3, 33%) and diabetes mellitus (n=1, 11%) were linked to mortality. One patient with possible CPA with multicavitary TB disease died with no other underlying disease. There were no deaths in patients with proven and probable CPA.

At the end of TB therapy, those assessed (n=128) had a similar spectrum and frequency of symptoms with the exception of fatigue (60% vs 13%, $p=0.001$) and cough (50% vs 11%, $p=0.005$) which were more common in CPA (table 3). The overall prevalence of *Aspergillus*-specific IgG positivity was 52% (66 of 128). Ten of 128 patients had CPA, an incidence

Table 2 IgG tests and SGRQ results at baseline

Variables	All (n=216)	CPA (n=12)	non-CPA (n=204)	P value
Serology tests				
<i>Aspergillus</i> IgG (mg/L)	8.7 (6.2–12.3)	15.4 (12.4–25.3)	8.3 (6.1–11.5)	<0.001
SGRQ scores				
Symptoms	40.3 (24.6–57)	58 (38.3–69.6)	39 (24.4–56.3)	0.029
Impact	40.6 (21.7–53.7)	45.8 (32.3–52.2)	39.6 (21.2–53.9)	0.549
Activity	34.1 (0–67.7)	40 (5–64)	34.1 (0–67.7)	0.944
Total	39.5 (20.6–55)	45.7 (29.3–54.3)	39 (20.4–55)	0.492

Data are given as median (IQR).
 Bold values indicate statistical significance.
 CPA, chronic pulmonary aspergillosis; SGRQ, St Georges Respiratory Questionnaire.

of 7.8% (95% CI: 7.9% to 20.4%). All (n=10) patients from the CPA group had positive levels of *Aspergillus*-specific IgG. In the non-CPA group, 45 (42%) patients showed positive *Aspergillus*-specific IgG. Immulite *Aspergillus*-specific IgG level increased in patients with CPA compared with patients without CPA (p<0.001, median 24.2 (CPA) vs 9 (non-CPA)). Quality of life scores dropped dramatically during TB therapy, reflecting improved well-being, from a median of 35.9 to 4.8 for overall score (p<0.001) (table 4). However, this drop was smaller in

those with proven CPA (62% decrease in SGRQ total score) than in those without CPA (91% decrease in SGRQ total score). Radiological findings improved during TB therapy with the exception of pleural thickening, and the interval development of one aspergilloma (table 3). There was also a slight increase in bronchiectasis (on plain radiography).

Of the 12 patients with features of CPA at baseline, 7 (58%) were categorised as non-CPA cases at the end of TB therapy without any antifungal therapy or surgery. This was mainly due

Table 3 Results for end of TB therapy assessment compared with baseline for all those assessed at both time points, using the CPA categorisation at the second time point

Symptoms	Early TB therapy (n=128)	End of therapy (n=128)	P value	CPA* (n=10)	non-CPA (n=118)	P value
Gender						
Male	52 (41%)	52 (41%)		5 (50%)	47 (40%)	
Female	76 (59%)	76 (59%)	–	5 (50%)	71 (60%)	0.526
Age (mean; range)	38.3 (17–77)	38.3 (17–77)	–	52 (22–77)	37.1 (17–72)	0.004
Symptoms (≥3 months)						
Cough	22 (17%)	18 (14%)	0.556	5 (50%)	13 (11%)	0.005
Fatigue	9 (7%)	21 (17%)	0.031	6 (60%)	15 (13%)	0.001
Dyspnoea	7 (6%)	16 (13%)	0.064	3 (30%)	13 (11%)	0.111
Chest pain	6 (5%)	7 (6%)	1	2 (20%)	5 (4%)	0.094
Weight loss	5 (4%)	3 (2%)	0.727	0	3 (3%)	1.000
Haemoptysis	3 (2%)	3 (2%)	0.727	1 (10%)	2 (2%)	0.218
Intermittent haemoptysis (<3 months)	24 (19%)	3 (2%)	<0.001	1 (14%)	2 (3%)	0.286
Radiology						
Infiltrates	123 (96%)	102 (80%)	<0.001	8 (80%)	94 (80%)	1.000
Cavitation	67 (52%)	45 (35%)	<0.001	7 (70%)	38 (32%)	0.033
Paracavitary fibrosis	43 (34%)	28 (22%)	0.001	4 (40%)	24 (20%)	0.224
Pleural thickening	32 (25%)	31 (24%)	1	5 (50%)	26 (22%)	0.061
Nodules	23 (18%)	15 (12%)	0.039	0	15 (13%)	0.605
Air fluid level in cavities	21 (16%)	4 (3%)	<0.001	1 (10%)	3 (3%)	0.281
Aspergilloma†	3 (2%)	4 (3%)	1	1 (10%)	3 (3%)	0.281
Bronchiectasis	8 (6%)	13 (10%)	0.125	1 (10%)	12 (10%)	1.000

Bold values indicate statistical significance.
 *Proven CPA.
 †One aspergilloma at baseline (non-CPA) was confirmed on CT scan, the rest were unconfirmed aspergilloma diagnosed on chest X-ray.
 CPA, chronic pulmonary aspergillosis.

Table 4 IgG tests and SGRQ comparisons for all patients assessed at baseline and at end of TB therapy, using the CPA categorisation at the second time point

Variables	Early TB therapy (n=128)	End of therapy (n=128)	P value	CPA (n=10)	non-CPA (n=118)	P value
Serology tests						
<i>Aspergillus</i> -specific IgG (mg/L)	9.2 (6.5–12.7)	9.7 (6.9–14.2)	0.078	24.2 (13.8–76.1)	9 (6.6–13.1)	<0.001
SGRQ scores						
Symptoms	37.2 (18.4–56.7)	3 (0–22.5)	<0.001	23.3 (9.6–37.3)	3 (0–21.1)	0.002
Impact	39 (21.5–51.9)	4 (0–13.6)	<0.001	9.2 (5–37.7)	3.7 (0–13.1)	0.007
Activity	21.9 (0–59.4)	0 (0–8.4)	<0.001	23.6 (0–53.9)	0 (0–0)	0.002
Total	35.9 (16.3–51.4)	4.8 (4–12.8)	<0.001	17.4 (8–36.8)	3.4 (0–12.2)	0.003

Data are given as median (IQR).

Bold values indicate statistical significance.

CPA, chronic pulmonary aspergillosis; SGRQ, St Georges Respiratory Questionnaire.

to decrease in symptoms and in infiltrates seen in chest X-rays (figure 2). Two (17%) were lost to follow-up and not assessed. The remaining three patients continued to have CPA features at the end of TB therapy. An additional seven patients developed CPA during their TB therapy, resulting in a total of 10 (8%) CPA cases at the end of TB therapy. The risk of developing CPA during TB therapy appears to increase with age ($p=0.004$, mean 52 years (CPA) vs 37.1 years (non-CPA)) (table 3).

Of five probable CPA cases at baseline, two improved clinically (resolution of symptoms) and one patient became a possible CPA with decreased persistent symptoms but stable pleural thickening by the end of TB therapy. Two patients were lost to follow-up. Of 15 possible CPA at the baseline, 1 patient improved clinically, another met the criteria for probable CPA and 3 patients did not have features of CPA cases at the end of TB therapy assessment; 10 patients were lost to follow-up. At the end of TB therapy, probable CPA and possible CPA were detected in seven (5%) patients and four (3%) patients, respectively. The clinical and radiology profiles of patients at both time points are compared in tables 3 and 4.

DISCUSSION

The incidence of proven and probable CPA was 7.9% (95% CI: 4.7% to 12.3%) at baseline and increased to 13.3% (95% CI: 7.9% to 20.4%) at the end of TB therapy, although the latter

figure is marred by substantial loss of follow-up, including some deaths, probably of CPA, between these two time points. There are three confounding factors that need to be considered when interpreting this finding. First, different patients met the criteria for CPA diagnoses at baseline and end of TB therapy. Second, a notable number of patients were lost to follow-up. Third, the accuracy of the CPA diagnosis is a challenge with 5 patients with probable CPA and 15 patients with possible CPA at baseline and 7 probable and 4 possible at the end of TB therapy. Furthermore, some patients had aspergillomas visible on their chest radiograph without clinical or serological features of CPA; five at baseline and one at the end of TB therapy. If all these patients are assumed to have CPA (which is unlikely for the possible group), the incidence of CPA was 17% both at baseline and at the end of TB therapy. Nevertheless, it is likely that the true prevalence of CPA during the course of treatment of TB is somewhere between 6% and 17% at baseline and 8% and 17% at the end of therapy, in Indonesia. These are the first estimates of CPA incidence during anti-TB therapy made globally.

One of the study objectives was to determine how many patients have dual infection. Coinfection of active pulmonary TB and CPA is reported in previous studies.^{6,27–29} Our data indicate more frequent dual infection than previously thought. However, many of these patients appear to resolve their *Aspergillus* infection and had ‘self-resolving CPA’. Several other patients failed to

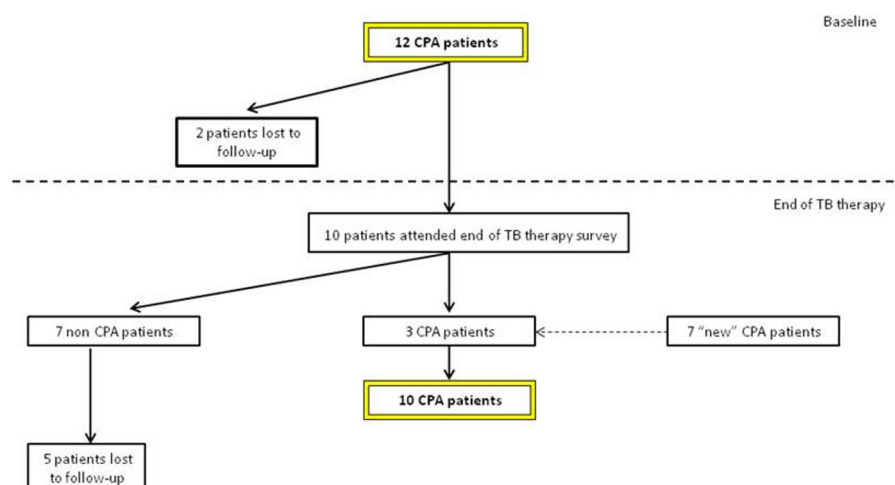


Figure 2 Patients with CPA during two time point assessments. CPA, chronic pulmonary aspergillosis.

attend the second assessment, so their fate is uncertain. The cause of death in those lost to follow-up in our study was uncertain, including determining whether any patients with dual infection died before assessment. In Japan, the term chronic progressive pulmonary aspergillosis was coined to separate those who deteriorated from those who remained clinically and radiologically stable.²¹ We have clear-cut evidence of this divergence of disease behaviour in this study.

Male sex was an independent risk factor for CPA in this study. Earlier studies also showed male predominance in CPA compared with *Aspergillus* colonisation in Japan,³⁰ and in a large CPA cohort in Manchester.²⁵ It can be speculated that this is due to a higher prevalence of other risk factors such as smoking, but supportive data are lacking.

Prior studies have demonstrated that the rate of CPA in post-TB therapy populations varies between 4.9% and 14.3%.^{2,10} In Nigeria, the CPA rate was reported to be 8.7% at the end of TB therapy⁵ and in Uganda, 9% of HIV-infected patients had *Aspergillus*-specific IgG detectable at the end of TB therapy.³¹ A cross-sectional study from Iran reported 13.7% of 124 HIV-negative TB patients developed CPA (76% patients were on active TB treatment).⁴ All of these CPA rates are within the ranges of our study. However, these studies provide no or minimal information about the status of the patients at baseline and reflect pooled patient populations assessed at varied time points after TB therapy.^{2,10}

One element of the diagnosis of CPA is symptoms for ≥ 3 months (weight loss and/or cough and/or haemoptysis).¹⁵ But as can be seen, this definition component is challenged by our data. TB gives rise to weight loss and cough and many patients have some degree of haemoptysis. We found the relative frequency for CPA and TB to be: cough 93% vs 13%, fatigue 42% vs 8% and weight loss 17% vs 1%, respectively (table 1). Three months of cough is more discriminatory than any cough. Fatigue has been studied and a score devised for patients with COPD applied to patients with CPA appears to be useful, but has yet to be translated into routine clinical practice.³² Chest pain appeared to be a useful discriminator in Nigeria but was only present in 25% of patients with CPA.⁵ Three months of haemoptysis was found in only 8% of patients with CPA, compared with 1% with TB, but shorter periods of haemoptysis were common and not very discriminatory (table 1).

In addition to specific symptoms, the SGRQ quality of life score was recorded at baseline. Unremarkably for patients with TB, scores were moderately high (table 2), but not at all discriminatory between those with only TB and those with CPA and TB, at baseline. However at 4–6 months after starting anti-tuberculous therapy, those with CPA had persistently raised SGRQ scores in all domains, and there was almost complete resolution of all symptoms in those without (table 4). Therefore, this score might be very useful in Indonesia for identifying CPA at the end of anti-TB therapy. It is worth noting that the SGRQ scores in this study are remarkably low compared with other patients who have recovered from TB in the USA,³³ but not Papua, Indonesia.³⁴

The radiological appearances of CPA and TB partially overlap, with upper lobe predominance and cavitation. While TB does not usually cause pleural thickening in the apices, consolidation can occur which can appear like pleural thickening. Likewise pericavitary infiltrates are very typical of CPA, but local consolidation can mimic these findings too. The first description of an aspergilloma by Deve in 1938 described a huge cavity with a fungal ball, which is unmistakable, but more subtle findings are now understood to be typical of CPA.³⁵ The typical appearance

of a fungal ball or aspergilloma includes the air crescent or air meniscus sign, first described in the context of pulmonary hydatid disease.^{36,37} Our study lacks confirmation from CT of the findings seen on chest radiographs in 97.7% of patients. This is a clear-cut study weakness and arises primarily from a lack of funds to afford CT scanning for most patients and an inability to identify in real time those whose disease required better anatomical definition with CT, as serology was done in batches months after the patients were seen.

There is intrinsic uncertainty in the interpretation of chest radiographs. Concordance between readers is far from 100%, both in ascertaining cavitation in TB (50%–70%) and in aspergillosis.^{38,39} Our radiographs were read by an experienced radiologist in Indonesia (where the only aspergillosis radiological diagnosis made currently is an aspergilloma) with confirmation by a highly experienced clinician focused on pulmonary aspergillosis. Separating CPA from TB with a chest radiograph alone with any certainty is not possible.

Partly using this dataset (end of TB therapy only), and a separate cross-sectional study population (n=71) and both normal and disease controls (n=190), we derived the optimum cut-off for *Aspergillus*-specific IgG (11.5 mg/L) in Indonesia for the Immulite assay.²⁶ The antibody titres varied substantially between both time points, indicative of a complex interaction between *Aspergillus* and the immune system during the months of anti-TB therapy.

The presence of an aspergilloma is highly indicative of CPA, with echinococcus and necrotising lung tumours really the only differential diagnoses. An aspergilloma may represent a single aspergilloma, without symptoms or be a feature of chronic cavitary pulmonary aspergillosis. In this study, aspergillomas were detected in 11 patients, with 8 (72.7%) patients having positive PCR TB and/or AFB smears at baseline, indicating coinfection of *Aspergillus* in patients with active TB. Five (45.5%) patients had positive *Aspergillus*-specific IgG by Immulite, four (36.4%) patients in the end and/or post TB therapy and one (9.1%) patient showed persistent positive *Aspergillus*-specific IgG by Immulite but with no accompanying symptoms. Two patients had CT scan-confirmed aspergilloma, both with bacteriologically confirmed TB.

In most patients with aspergillomas, *Aspergillus* IgG was negative when first seen and most were therefore classified as non-CPA. Seroconversion of Immulite from negative to positive *Aspergillus*-specific IgG occurred in all five patients with persistent aspergilloma. Aspergillomas with negative *A. fumigatus* IgG antibody have been observed in Africa and may relate to non-*fumigatus* infections or a muted antibody response.^{2,5}

The other study objective was to determine how many patients are misdiagnosed as TB when in fact they have CPA. Ruling out TB can be difficult, so complete confidence in this assertion for individual patients is usually difficult. Community-acquired *Aspergillus* community-acquired pneumonia (CAP) without any evidence of immunocompromise can occur,^{40,41} often following significant environmental exposures such as bark chippings, compost and gardening.^{42,43} Some of these patients fail to completely resolve their *Aspergillus* infection, and if they do not die develop CPA. It is highly likely that some of the clinically diagnosed cases of TB in this study with positive *Aspergillus* IgG had community-acquired *Aspergillus* CAP and some went on to develop CPA.

We therefore propose that CPA should be included as an alternative diagnosis of pulmonary TB, especially if there is no clinical and radiological improvement after starting TB therapy. Pulmonary TB and CPA may coexist and both diseases require their own

management plan. In the context of non-tuberculous mycobacterial infection and CPA, the outcomes of those with dual infection were much worse (11.5-fold increased mortality);¹⁹ this has yet to be ascertained for those with TB. The availability of *Aspergillus* antibody testing and CT scanning is an important component of optimal CPA diagnosis. This study is important for the future study of CPA in Indonesia. As an alternative or coexisting disease in patients with TB in Indonesia, CPA is important for clinicians and also to galvanise social and political will of multiple stakeholders to support improvement of diagnostic capacity of fungal disease in Indonesia.

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REFERENCES

- 1 Denning DW, Pleuvry A, Cole DC. Global burden of chronic pulmonary aspergillosis as a sequel to pulmonary tuberculosis. *Bull World Health Organ* 2011;89:864–72.
- 2 Page ID, Byanyima R, Hosmane S, *et al*. Chronic pulmonary aspergillosis commonly complicates treated pulmonary tuberculosis with residual cavitation. *Eur Respir J* 2019;53:1801184–13.
- 3 Rodríguez NB, Juan-Galán JLS, Andreu CMF. Chronic pulmonary aspergillosis in patients with underlying respiratory disorders in Cuba—A pilot study. *J Fungi* 2019;5:4–11.
- 4 Hedayati MT, Azimi Y, Drouinia A, *et al*. Prevalence of chronic pulmonary aspergillosis in patients with tuberculosis from Iran. *Eur J Clin Microbiol Infect Dis* 2015;34:1759–65.
- 5 Oladele RO, Irohe NK, Foden P, *et al*. Chronic pulmonary aspergillosis as a cause of smear-negative TB and/or TB treatment failure in Nigerians. *Int J Tuberc Lung Dis* 2017;21:1056–61.
- 6 Bekele A, Ali A, Biluts H. Surgically treated pulmonary tuberculosis: report on cases from Tikur Anbessa Hospital, Addis Ababa, Ethiopia. *Ethiop Med J* 2008;46:261–6.
- 7 WHO. *Tuberculosis profile (Indonesia) in estimates of TB and MDR-TB burden*, 2019.
- 8 Tiemersma EW, van der Werf MJ, Borgdorff MW, *et al*. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. *PLoS One* 2011;6:e17601.
- 9 Trinh QM, Nguyen HL, Nguyen VN, *et al*. Tuberculosis and HIV co-infection-focus on the Asia-Pacific region. *Int J Infect Dis* 2015;32:170–8.
- 10 The Research Committee of The British Tuberculosis Association. *Aspergillus* in persistent lung cavities after tuberculosis. *Tubercle* 1968;49:1–11.
- 11 Smith NLD, Hankinson J, Simpson A, *et al*. Reduced expression of TLR3, TLR10 and TREM1 by human macrophages in chronic cavitary pulmonary aspergillosis, and novel associations of VEGFA, DENND1B and PLAT. *Clin Microbiol Infect* 2014;20:0960–8.
- 12 Kwon-Chung KJ, Sugui JA. *Aspergillus fumigatus*—what makes the species a ubiquitous human fungal pathogen? *PLoS Pathog* 2013;9:e1003743–4.
- 13 Chakaya J, Kirenga B, Getahun H. Long term complications after completion of pulmonary tuberculosis treatment: a quest for a public health approach. *J Clin Tuberc Other Mycobact Dis* 2016;3:10–12.
- 14 Godet C, Alastruey-Izquierdo A, Flick H. A CPAnet consensus statement on research priorities for chronic pulmonary aspergillosis: a neglected fungal infection that requires attention. *J Antimicrob Chemother* 2017;73:1–7.
- 15 Denning DW, Page I, Chakaya J. Case definition of chronic pulmonary aspergillosis in resource-limited settings: catalysing research and clinical care. *Emerg Infect Dis* 2018;24:e1–13.
- 16 Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including simple aspergilloma. *Eur Respir J* 2011;37:865–72.
- 17 Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax* 2015;70:270–7.
- 18 Denning DW, Riniotis K, Dobrashian R, *et al*. Chronic cavitary and fibrosing pulmonary and pleural aspergillosis: case series, proposed nomenclature change, and review. *Clin Infect Dis* 2003;37 Suppl 3:S265–80.
- 19 Jhun BW, Jung WJ, Hwang NY, *et al*. Risk factors for the development of chronic pulmonary aspergillosis in patients with nontuberculous mycobacterial lung disease. *PLoS One* 2017;12:e0188716–11.
- 20 Baker N, Setianingrum F, Wahyuningsih R, *et al*. Mapping histoplasmosis in South East Asia - implications for diagnosis in AIDS. *Emerg Microbes Infect* 2019;8:1139–45.
- 21 Tashiro T, Izumikawa K, Tashiro M, *et al*. A case series of chronic necrotizing pulmonary aspergillosis and a new proposal. *Jpn J Infect Dis* 2013;66:312–6.
- 22 Information and data center Ministry of health Republic of Indonesia. *Tuberkulosis*; Jakarta 2015.
- 23 Al-Shair K, Atherton GTW, Kennedy D, *et al*. Validity and reliability of the St. George's respiratory questionnaire in assessing health status in patients with chronic pulmonary aspergillosis. *Chest* 2013;144:623–31.
- 24 Al-Shair K, Atherton GT, Harris C, *et al*. Long-Term antifungal treatment improves health status in patients with chronic pulmonary aspergillosis: a longitudinal analysis. *Clin Infect Dis* 2013;57:828–35.
- 25 Bongomin F, Harris C, Hayes G, *et al*. Twelve-month clinical outcomes of 206 patients with chronic pulmonary aspergillosis. *PLoS One* 2018;13:e0193732–17.
- 26 Setianingrum F, Rozaliyani A, Syam R, *et al*. Evaluation and comparison of automated and manual ELISA for diagnosis of chronic pulmonary aspergillosis (CPA) in Indonesia. *Diagn Microbiol Infect Dis* 2020;98:115124–6.
- 27 Iqbal N, Irfan M, Zubairi ABS, Bin A, *et al*. Clinical manifestations and outcomes of pulmonary aspergillosis: experience from Pakistan. *BMJ Open Respir Res* 2016;3:1–7.
- 28 Singh UP, Aneja P, Patel A. Co-existence of HIV, active tuberculosis and aspergilloma in a single individual—a case report. *Indian J Tuberc* 2013;60:55–8.
- 29 Boghani A, Patel M, Leuva A. Aspergilloma with active pulmonary tuberculosis. *Ind J Tub* 1987;34:206–7.
- 30 Ohara S, Tazawa Y, Tanai C, *et al*. Clinical characteristics of patients with *Aspergillus* species isolation from respiratory samples: comparison of chronic pulmonary aspergillosis and colonization. *Respir Investig* 2016;54:92–7.

- 31 Kwizera R, Parkes-Ratanshi R, Page ID, *et al.* Elevated Aspergillus-specific antibody levels among HIV infected Ugandans with pulmonary tuberculosis. *BMC Pulm Med* 2017;17:149.
- 32 Al-Shair K, Muldoon EG, Morris J, *et al.* Characterisation of fatigue and its substantial impact on health status in a large cohort of patients with chronic pulmonary aspergillosis (Cpa). *Respir Med* 2016;114:117–22.
- 33 Pasipanodya JG, McNabb SJ, Hilsenrath P, *et al.* Pulmonary impairment after tuberculosis and its contribution to TB burden. *BMC Public Health* 2010;10:259.
- 34 Ralph AP, Kenangalem E, Waramori G, *et al.* High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena. *PLoS One* 2013;8:e80302–11.
- 35 Deve F. Une Nouvelle forme Anatomique-Radiologique de Mycose Pulmonaire primitive. *Arch Med Chir Appl Resp* 1938;13:337–61.
- 36 Weens HS, Thompson EA. The pulmonary air meniscus. *Radiology* 1950;54:700–5.
- 37 Roberts CM, Citron KM, Strickland B. Intrathoracic aspergilloma: role of CT in diagnosis and treatment. *Radiology* 1987;165:123–8.
- 38 Hamilton CD, Stout JE, Goodman PC, *et al.* The value of end-of-treatment chest radiograph in predicting pulmonary tuberculosis relapse. *Int J Tuberc Lung Dis* 2008;12:1059–64.
- 39 Zaspel U, Denning DW, Lemke AJ, *et al.* Diagnosis of ipa in HIV: the role of the chest X-ray and radiologist. *Eur Radiol* 2004;14:2030–7.
- 40 Clancy CJ, Nguyen MH. Acute community-acquired pneumonia due to Aspergillus in presumably immunocompetent hosts: clues for recognition of a rare but fatal disease. *Chest* 1998;114:629–34.
- 41 Kennedy WP, Malone DN, Blyth W. Necrotizing pulmonary aspergillosis. *Thorax* 1970;25:691–701.
- 42 Batard E, Renaudin K, Morin O, *et al.* Fatal acute granulomatous pulmonary aspergillosis in a healthy subject after inhalation of vegetal dust. *Eur J Clin Microbiol Infect Dis* 2003;22:357–9.
- 43 Arendrup MC, O'driscoll BR, Petersen E, *et al.* Acute pulmonary aspergillosis in immunocompetent subjects after exposure to bark chippings. *Scand J Infect Dis* 2006;38:945–9.