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ORIGINAL ARTICLE

Prevalence of chronic pulmonary aspergillosis regarding time of tuberculosis diagnosis in Brazil

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Abstract

Background: Data on the prevalence of chronic pulmonary aspergillosis (CPA) in patients with active or cured tuberculosis (TB) are scarce, mainly due to diagnostic difficulties. The diagnosis of CPA is based on pulmonary symptoms and chest computed tomography (CT) scans and is considered confirmed when there is microbiological or serological evidence of *Aspergillus* spp. infection.

Objectives: To estimate the prevalence of CPA in patients treated or undergoing treatment for PTB, seen in two referral hospitals in Mato Grosso do Sul, Brazil.

Patients and Methods: A total of 193 consecutive patients who were treated or previously treated for pulmonary tuberculosis underwent prospective evaluation: (a) clinical evaluation; (b) chest CT scan; (c) sputum examination—culture for fungi and smears for direct mycology; (d) detection of anti-*Aspergillus fumigatus* antibodies using an enzyme-linked immunosorbent assay Platelia® test; and (e) anti-*Aspergillus* spp. antibodies were assessed via a DID test.

Results: The global prevalence of CPA was 10.9% (95% confidence interval, 7.2%–16.1%), but it increased with the time of TB diagnosis. The variables independently associated with CPA were previous pulmonary tuberculosis over 4 years ago and haemoptysis. Cavities, pleural thickening and the presence of a fungal ball were the most frequent tomographic findings in patients with CPA.

Conclusions: The high prevalence observed and its increase over time suggest the need for continuous surveillance of CPA in patients with active or previous pulmonary tuberculosis and throughout life, with clinical, tomographic and serological evaluations (ELISA) for a timely diagnosis and a better prognosis.

KEYWORDS
Aspergillus, chronic cavitary pulmonary aspergillosis, chronic pulmonary aspergillosis, Brazil, fungal ball, pulmonary aspergilloma, pulmonary tuberculosis, enzyme-linked immunosorbent assay

1 | INTRODUCTION

Chronic pulmonary aspergillosis (CPA), a neglected disease with severe progression, is one of the clinical forms of aspergillosis.[1] It affects immunocompetent patients or those with mild immunosuppression,[1–3] mainly with preexisting cavities due to chronic lung disease, such as tuberculosis (TB).[3]

The residual cavity after treatment for pulmonary tuberculosis (PTB) is identified in 20%–30% of patients.[4] It is estimated that 112,000–160,000 people will develop CPA each year after PTB therapy worldwide, with a case fatality rate of 38%–85% in 5 years.[3,5–7]

Few studies have reported the prevalence of CPA in PTB and reported rates between 8.3% and 25.0%.[8–10] This variation occurs mainly due to the difficulty in establishing the diagnosis of CPA.[3]

The diagnosis of CPA is based on pulmonary symptoms and chest computed tomography (CT) scan findings and is confirmed when microbiological or serological evidence of *Aspergillus* spp. infection is associated with these findings.[11]

Serum antibody tests are helpful in the diagnosis of CPA because they are not aggressive to the patient, and their presence differentiates infection from colonisation.[12,13] Our group recently published a systematic review showing that the sensitivity of a commercial enzyme-linked immunosorbent assay (ELISA) was higher than that of precipitation tests.[14]

This study aimed to estimate the prevalence of CPA in patients treated or undergoing treatment for PTB, seen in two referral hospitals in Mato Grosso do Sul, Brazil. We found a prevalence of 10.9% and described the main associated findings in our study.

2 | PATIENTS AND METHODS

A cross-sectional analytical study was conducted in patients with PTB who have consecutively been treated at the Maria Aparecida Pedrossian University Hospital (MAPUH) outpatient clinic or admitted to the Regional Hospital of Mato Grosso do Sul (RHMS) in Campo Grande, Mato Grosso do Sul, between February 2016 and November 2019. The study was prospective, and the patients were assigned consecutively. This study was approved by the Ethics Committee of the Federal University of Mato Grosso do Sul. All enrolled patients signed an informed consent form.

Patients aged >18 years with prior or active PTB were evaluated. Patients with other infectious, inflammatory or neoplastic diseases and pregnant and lactating women were excluded.

The sample size for the proportion[15] was calculated assuming a type α error equal to 5% (0.05), a type β error of 20% (0.20), the estimated prevalence of the fungal ball of 14%,[16] and the number of TB cases ($n = 813$) reported in Mato Grosso do Sul state in 2017. [17] The smallest number of patients included in this study was 151.

PTB was confirmed by the presence of compatible clinical manifestations and identification of acid-fast bacilli (AFB) in the sputum smear (AFS) or a positive culture for *Mycobacterium tuberculosis* (MTB) and/or positive molecular tests in the sputum, tracheal aspirate or bronchoalveolar lavage (BAL).

PTB was considered probable when suggestive clinical manifestations and chest X-rays were present, but without microbiological identification of AFB and had responded to therapy.

Based on the modified version of the Denning et al.[11] patients with CPA were characterised according to clinical (I), radiological (II), mycological (IIIA and IIIB) and serological criteria (IV):

1. Clinical manifestations: pulmonary or systemic symptomatology compatible with CPA, for a minimum of 3 months, including at least one of the following: weight loss, productive cough or haemoptysis; although common, fatigue, chest pain, dyspnoea and sputum production are not required.
2. Radiological findings: cavitary pulmonary lesion(s) with evidence of paracavitary infiltrates and/or pleural thickening and/or fungal ball and/or fibrotic lesions.
3. Mycological evidence of *Aspergillus* infection: identification in bronchoalveolar lavage (BAL) or biopsied pulmonary material on direct examination or culture (IIIA); identification of *Aspergillus* on direct examination or culture of sputum or tracheal aspirate, if associated with the fungal ball on thoracic imaging (IIIB).
4. Serological evidence: positive anti-*Aspergillus* IgG was determined by agar gel precipitation test or ELISA.

CPA case definition. The case definitions were characterised according to the combination of the four criteria presented above. CPA cases were defined according to the following criteria: proven: criteria I, II and IIIA; probable: criteria I, II plus IIIB and/or IV; possible: only criteria I and II, without mycological or serological evidence of aspergillosis, but when other differential diagnoses (histoplasmosis, paracoccidioidomycosis, cryptococcosis, neoplasm, abscess and Wegener's granulomatosis) were discarded.

Based on Denning et al.[18] patients with aspergillosis were classified as simple aspergilloma (SA), chronic cavitary pulmonary aspergillosis (CCPA), chronic fibrosing pulmonary aspergillosis (CPFA), *Aspergillus* nodule (AN) or subacute invasive aspergillosis (SAIA).

Clinical and sociodemographic information was obtained by interviewing the patient. Sputum, tracheal aspirate or BAL samples were collected for direct mycological examination and culture of *Aspergillus* spp.

The samples were cultured on Sabouraud Dextrose agar with chloramphenicol. The identification of the genus and sections of the isolates was performed by analysing the morphological characteristics of the microscopic structures in potato agar.[19,20]

Serum samples from 157 patients were drawn and thawed only once and subjected to a DID test and ELISA simultaneously. The ELISA Platellia® Bio-Rad was performed considering a positive test >10 IU/ml. The qualitative DID test was performed according to the Ouchterlony method, using antigens from *A. fumigatus*.[21,22] the formation of a precipitation line indicated a positive reaction.

High-resolution chest CT scans were performed using the Toshiba tomographer–Aquillion 64-slice model in the MAPUH and the

Siemens tomographer–Somaton Emotion model in the RHMS. The images were independently evaluated by two researchers, as in a study by Denning et al.[11] Discordant cases were resolved by consensus.

2.1 | Ethics statement

This study was approved by the Ethics Committee of the Federal University of Mato Grosso do Sul (N°. 1.840.731). All patients provided informed consent for this study.

2.2 | Statistical analysis

Categorical variables were compared using the chi-square test and Fisher's exact test for independent variables, and the binomial test and the Q Cochran test for dependent variables, while numerical ones were compared using the Mann–Whitney *U* test. After the univariate analysis, correction for confounding variables was performed using multivariate logistic regression analysis. Significance was set at $p < .05$. The analyses were performed using EPI Info 7 and SAS (Statistical Analysis System version 6.12, SAS Institute Inc.).

3 | RESULTS

This study included 193 patients, as shown in the flowchart in Figure 1. The patients were between 18 and 87 years old (median, 51 years), and 78.8% of them were male, and 64 (33.2%) reported PTB before inclusion in the study. The vast majority (155 patients [80.3%]) had active PTB at the time of inclusion and 26 of them in the second episode. The global prevalence rate of CPA was 10.9% (95% confidence interval [CI], 7.2%–16.1%). Of the 21 CPA cases, 1 (4.8%) presented with proven CPA, fifteen (71.4%) presented probable CPA and five (23.8%) presented with possible CPA (Table S1). The prevalence ratio of CPA varied according to the time between the first diagnosis of TB and enrolment in the study (Table 1), increasing primarily after 4 years (Figure 2).

The univariate analysis of demographic, epidemiological and clinical variables showed a higher prevalence of prior PTB, chronic obstructive pulmonary disease (COPD) and haemoptysis in patients with CPA and a higher frequency of active PTB and night sweating in patients without CPA (Table 2). However, the multivariate analysis showed differences only in the variables 'prior PTB for over 4 years' and 'hemoptysis' (Table 3). Patients who had TB for more than 4 years had 17.55 times more chance of having CPA than those who had TB for up to 4 years. Furthermore, the chance of having CPA is 9.61 times greater in patients with haemoptysis than in those without it (Table 3).

Hyaline hyphae suggestive of *Aspergillus* spp were identified in 23.2% (6/21) of patients with CPA and 1.2% (2/172) without CPA ($p = .001$), while its isolation in culture was 19.0% (4/21) and 8.1% (14/172), respectively, ($p = .66$). Suggestive hyphae were identified in the sputum (83.3%) and in lung biopsy (16.7%). *Aspergillus* section *Fumigati* was identified in 75% (3/ 4) of CPA patients.

The most prevalent findings on the chest CT scans of patients with CPA were cavity (100.0%), pleural thickening (95.2%) and fungal ball (90.5%) (Figure 3). Among the 94 patients with a past history of PTB or active PTB but with cavities on chest CT scan, only 21 (22.3%) showed CPA.

We have present chest images of three patients with aspergillosis (Figure 4).

According to the clinical presentation of CPA, 20 (95.2%) patients were classified as CCPA and one (4.7%) as CFPA. The evaluation of

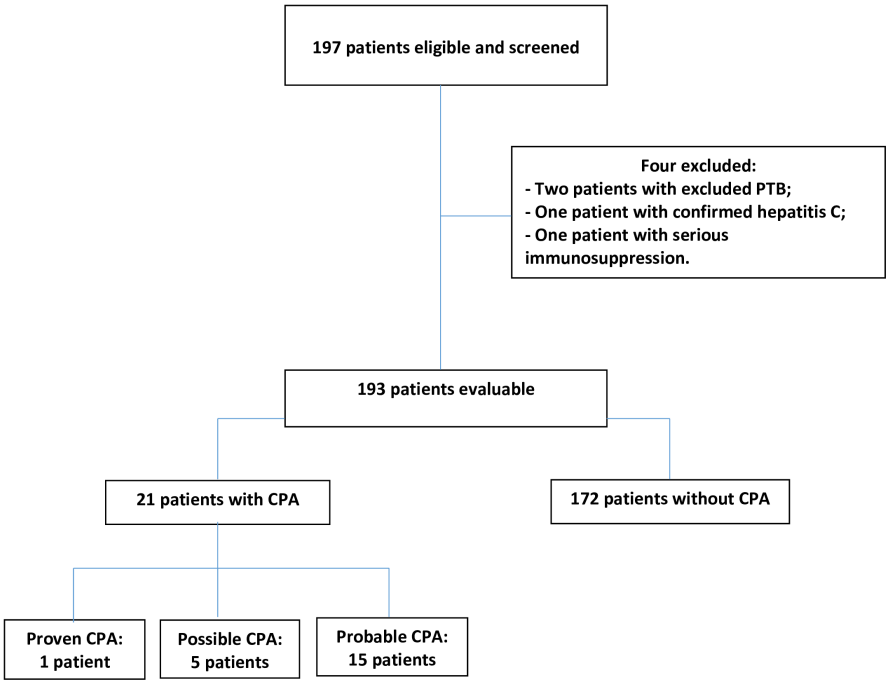

FIGURE 1 Screening and enrolment of study participants on the prevalence of chronic pulmonary aspergillosis

CPA	Time (months) after the first tuberculosis diagnosis							
	<6	6–12	13–24	25–36	37–48	49–60	>60	Total
CPA present	02	1	2	2	0	3	11	21
CPA absent	127	12	8	4	4	1	16	172
Total	129	13	10	6	4	4	27	193
Ratio (%)	1.6	7.7	20.0	33.3	–	75.0	40.7	10.9

TABLE 1 Prevalence rate of chronic pulmonary aspergillosis (CPA) cases as to time after the first tuberculosis diagnosis

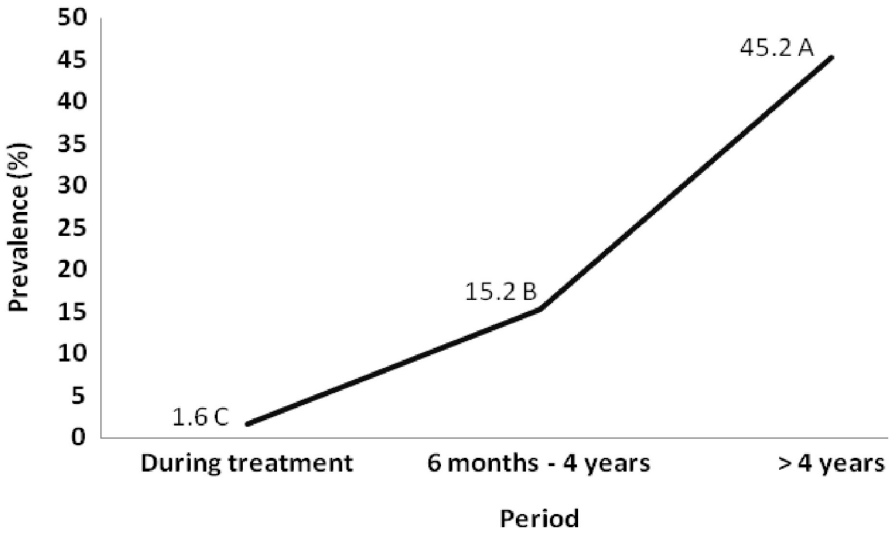

FIGURE 2 Prevalence of chronic pulmonary aspergillosis in tuberculosis patients regarding time after the introduction of specific treatment in the first episode. Capital letters compare prevalence; different letters indicate values with statistically significant differences ($p < .05$) (Fisher's exact test and chi-square test)

the outcome showed that seven (33.3%) patients died. The distribution of these patients concerning TB activity demonstrated a higher incidence of death among patients with active PTB (71.4%) than among those with nonactive disease (15.4%) ($p = .04$) (Table S1).

ELISA and DID were performed in 17 CPA patients, with the following results: (1) concordance: a) both positive, five patients; b) both negative, four patients; (2) Discordance: ELISA positive and DID negative: eight patients. Therefore, ELISA showed higher positivity than DID (76.5% vs. 29.4%; binomial test: $p = .004$).

4 | DISCUSSION

The present investigation was based on a cross-sectional population-based study using a probabilistic sample of adequate size and with no losses. The main findings of this study were that the prevalence of CPA was 10.9% in patients with active PTB or its sequelae, low frequency of mycological diagnosis, higher positivity of the ELISA Platelia® serological test than that in DID, high prevalence of fungal balls, cavity and pleural thickening on chest CT, and, finally, the high rate of case fatality due to haemoptysis in patients with and without CPA.

Few studies have assessed clinical presentation, tomographic images, and microbiological and serological findings to estimate the prevalence of CPA in individuals with PTB worldwide. [3,23–27] The prevalence rate observed in these studies ranged from 2.3% to 13,7%.

Several other studies have also been reported, but the prevalence of CPA was based only on serological tests or imaging findings and in populations other than PTB.[8–10,16,28–37] Recent studies[38–41] with methodologies that included only patients with treatment for previous TB and persistence of symptoms compatible with CPA found a higher prevalence (between 22 and 57%).

In Brazil, studies on the prevalence of CPA in patients with PTB are scarce. In a cohort of 350 patients enrolled due to radiographic findings of chronic pulmonary disease, aspergillosis was confirmed by DID test in 29 (8.3%) patients, 27 of whom reported a past history of PTB.[8] Furthermore, the incidence of CPA in Brazil was estimated to be 6.2 cases per 100,000 inhabitants by the Leading International Fungal Education.[42] Therefore, our study is the only Brazilian report on the prevalence of CPA in patients with PTB regarding the time from the first treatment of TB, using ELISA as the method for serological diagnosis.

Our study showed that CPA is rarely observed during the treatment of PTB, increasing its prevalence after discontinuation of therapy and for over 4 years. The long period between PTB treatment and CPA diagnosis has been previously reported.[3,16] However, the follow-up of patients with PTB is usually maintained during the specific treatment when the prevalence of CPA is very low. Therefore, new respiratory complaints due to CPA, years after complete recovery from PTB, can be confounded (mistaken) with TB relapse, mainly in the presence of haemoptysis.

However, AFB was not identified in sputum smears, and culture in appropriate media was negative, except in cases of the

TABLE 2 Epidemiological and clinical variables of 193 patients with previous or current pulmonary tuberculosis, regarding the presence of chronic pulmonary aspergillosis (Chi-square test)

Variable	With CPA (21 patients) *n* (%)	Without CPA (172 patients) *n* (%)	*p*-value
Male	18 (85.7)	134 (88.2)	.587
Age ≥ 50 years	13 (61.9)	87 (50.6)	.453
Colour			
White	9 (45.0)	41 (25.5)	.115
No White	11 (55.0)	120 (74.5)	
Years of study			.786
≤9	12 (75.0)	90 (68.2)	
>9	4 (25.0)	42 (31.8)	
Smoking	14 (66.7)	89 (53.0)	.339
Alcoholism	7 (33.3)	84 (50.0)	.226
Drug addicted	3 (14.3)	55 (32.7)	.139
Residents in Campo Grande – MS	17 (81.0)	146 (84.9)	.880
Prior PTB	19 (90.5)	45 (26.2)	**<.001**
Prior PTB (>4 years)	14 (66.7)	21 (12.2)	**<.001**
Active PTB	8 (38.1)	147 (85.5)	**<.001**
Proven active PTB	6 (28.6)	104 (60.5)	**<.001**
Signals and symptoms			
Fever	14 (66.7)	117 (68.8)	1.000
Evening fever	7 (35.0)	82 (48.5)	.363
Cough	17 (85.0)	134 (79.3)	.758
Productive cough	12 (60.0)	89 (52.7)	.700
Haemoptysis	12 (60.0)	41 (24.3)	**.001**
Night sweating	3 (15.0)	82 (49.1)	**.007**
Weakness	14 (66.7)	117 (68.8)	1.000
>10% weight loss	12 (57.1)	101 (60.5)	.953
Comorbidities	11 (52.4)	57 (33.1)	.133
DM	5 (23.8)	23 (13.4)	.340
SAH	5 (23.8)	29 (16.9)	.627
COPD	6 (28.6)	7 (4.1)	**<.001**
Bronchial asthma	1 (4.8)	6 (3.5)	1.000
Hospitalised patients	12 (57.1)	87 (50.6)	.736
Hospitalisation (days)	12 [6–22]	15 [6–22]	.976
Death	6 (28.6)	28 (16.3)	.220
From respiratory failure	3 (14.3)	25 (14.5)	1.000
From haemoptysis	2 (9.5)	1 (0.6)	**.032**
From septic shock	2 (9.5)	23 (13.4)	1.000

Note: p values in bold indicate statistical significance.

Abbreviations: COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; DM, diabetes mellitus; MS, Mato Grosso do Sul; *n* (%), number and percentage of cases; PTB, pulmonary tuberculosis; SAH, systemic arterial hypertension.

second episode of active PTB, as was reported in some of our cases. Therefore, CPA has to be investigated, but mycological identification is difficult and can only indicate colonisation. In this condition, radiographic and tomographic findings play an important role, and the demonstration of specific serum antibodies is crucial because they are present only when the tissue is invaded by fungal cells (fungus balls is not invasive). Our findings also demonstrated the higher positivity of ELISA, which should be the serological test of choice.

The chance of presenting with haemoptysis was approximately 10 times higher in our patients with CPA than in those with PTB and can be fatal. This finding supports the first hypothesis for haemoptysis from relapse of PTB to CPA, mainly when observed a long

TABLE 3 Results of univariate and multivariate logistic regression analysis based on the presence of chronic pulmonary aspergillosis. Only the epidemiological and clinical variables with $p \leq .20$ in the univariate analysis were included in the multivariate analysis

Variables	With CPA (21 patients) *n* (%)	Without CPA (172 patients) *n* (%)	Crude OR (CI 95%)	Adjusted OR (CI 95%)
White colour	9 (45.0)	41 (25.5)	2.39 (0.93–6.12)	1.47 (0.39–5.55)
Drug addiction	3 (14.3)	55 (32.7)	0.34 (0.10–1.21)	2.11 (0.34–13.28)
Prior PTB	19 (90.5)	45 (26.2)	26.81 (6.01–119.70)	2.88 (0.57–14.49)
Prior PTB (>4 years)	14 (66.7)	21 (12.2)	14.38 (5.21–39.71)	17.54 (1.85–166.67)
Active PTB	8 (38.1)	147 (85.5)	0.11 (0.04–0.28)	1.29 (0.26–6.33)
Haemoptysis	12 (60.0)	41 (24.3)	4.68 (1.79–12.25)	9.61 (2.21–41.67)
Night sweating	3 (15.0)	82 (49.1)	0.18 (0.05–0.65)	0.21 (0.04–1.12)
Comorbidities	11 (52.4)	57 (33.1)	2.22 (0.89–5.53)	1.81 (0.45–7.19)
COPD	6 (28.6)	7 (4.1)	9.43 (2.81–31.68)	3.89 (0.54–27.78)
Death from haemoptysis	2 (9.5)	1 (0.6)	18.00 (1.56–7.93)	1.64 (0.07–38.46)

Abbreviations: COPD, chronic obstructive pulmonary disease; CPA, chronic pulmonary aspergillosis; *n* (%), number and percentage of cases; OR, odds ratio; PTB, pulmonary tuberculosis.

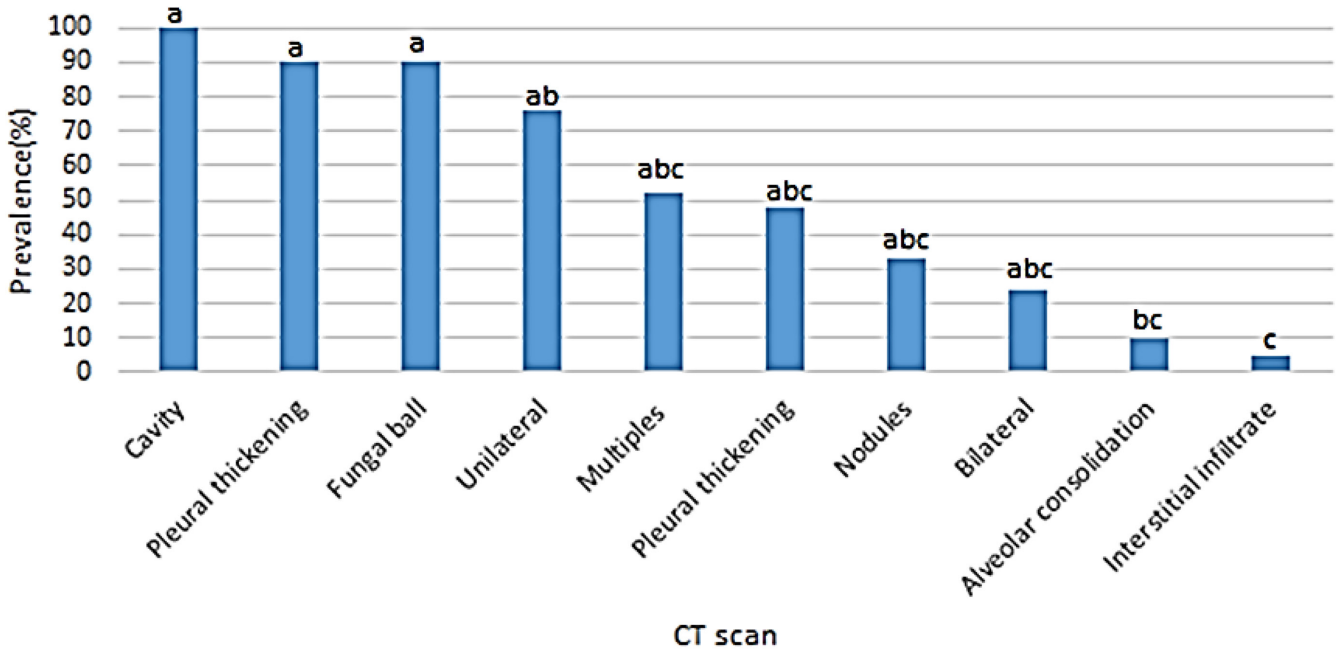

FIGURE 3 High-resolution chest computed tomography scan in 21 patients with chronic pulmonary aspergillosis. Prevalence of tomographic findings compared using the Cochran Q test

time after recovery from TB. The pathogenesis of this haemoptysis is multifactorial: neovascularisation of the bronchial artery and transpleural hypervascularisation, friction and erosion of the vascularised epithelium by fungal balls, endotoxins and/or fibrinolytic enzymes produced by *Aspergillus*, and hypersensitivity reactions mediated by immune complexes in the cavity wall.[43–46]

In approximately 25% of our patients, the direct mycological examination of the sputum or another respiratory sample showed septate hyaline hyphae suggestive of *Aspergillus* sp. Microscopy is a consistent tool in diagnosing CPA, as it is less susceptible to environmental contamination than culture.[11] However, the possibility of colonisation instead of infection cannot be disregarded. *A. fumigatus* was the most prevalent species in our study, in agreement with a previous study.[23]

Microscopy results revealing hyphae consistent with *Aspergillus* on respiratory samples have been considered microbiological evidence of *Aspergillus* infection.[11,18] In our study, only one case was considered confirmed through our criteria. We identified typical hyphae suggestive of *Aspergillus* in the lung biopsy histopathology. Other hyalohyphomycoses are rare, especially as fungal ball etiologic agents, and do not usually respond to treatment with itraconazole.[18,47] Our patient had a satisfactory therapeutic response (data not shown).

The positivity of ELISA Platelia was higher than that of DID, confirming the sensitivity of these two tests.[14] However, the specificity

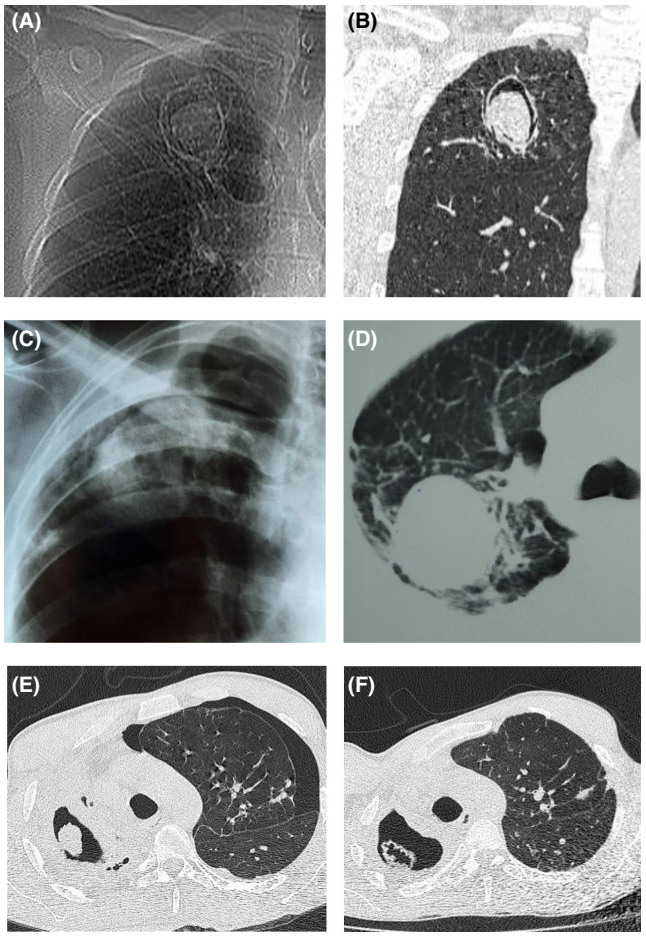

FIGURE 4 Chest images of three patients with aspergillosis. Patient no. 79: posteroanterior (PA) radiograph of the thorax (A) and high-resolution chest CT scan (B) showing a cavity with a fungus ball surrounded by an air crescent in the right upper lobe. Patient no.152: The PA chest radiograph (C) and high-resolution chest CT scan (D) show a mass without the typical air crescent signal. Patient no. 157: High-resolution chest CT scan (E) showing a cavity with fungal balls in the right apex at admission and 12 months after itraconazole therapy (F) showing that the disappearance of the fungal ball increased the size of the cavity and decreased pleural thickness

of DID is greater than that of ELISA Platelia,[14] and DID is also an important tool in the control of treatment, as it shows a reduction in titres with clinical improvement.[48] Thus, ELISA is the method of choice for diagnosing CPA and DID should be performed due to its specificity and usefulness in the follow-up of patients.

The prevalence of fungal balls was much higher in our patients than has been reported,[3,37] probably because the study participants were enrolled in referral hospitals and not in outpatient services. In our study, the prevalence of CPA in patients with cavities was 22.3%, an essential finding in the definition of the main risk factor for the development of CPA, as also reported by Page et al.[3] who found a prevalence of 26.1%. Individuals with residual cavities due to PTB on chest radiography have an annual rate of new CPA cases of 6.5%.[3] Considering that a residual cavity can be identified on chest radiography in 20%–30% of 7.7 million patients treated for PTB each year, it is possible to measure the magnitude of CPA load worldwide.[49]

Although pleural thickening adjacent to the cavity also occurs in patients with TB only, its finding requires an investigation of CPA, as was observed in almost all cases, consistent with the findings of Page et al.[3] The incidence of death among patients with CPA in the short period evaluated demonstrates the need for better follow-up, despite operational difficulties. Mortality rates in patients with CPA at 5 years have varied from 17.5% to 85%.[3,50] Moreover, progressive pulmonary injury results in significant loss of functional capacity and a decline in quality of life,[30] reinforcing the importance of timely diagnosis and treatment, oral antifungal compounds or surgical procedures in selected cases.[33]

This study had some limitations as follows: (1) the cohort was selected by convenience in two reference hospitals; (2) the majority of patients who agreed to participate in the study were symptomatic; therefore, cases of SA were not identified.

Our results show that CPA should be investigated in all patients with PTB, during active disease, and mainly after treatment, including those considered efficacious. The Brazilian follow-up schedule of patients with PTB should be reviewed, focusing on chest CT scan and serological investigation with ELISA, to provide an earlier diagnosis and treatment.

AUTHOR CONTRIBUTIONS

Cláudia Elizabeth Volpe-Chaves: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **James Venturini:** Methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Suse Barbosa Castilho:** Investigation (supporting); writing – original draft (supporting). **Simone Sousa Oliveira Fonseca:** Investigation (supporting); writing – original draft (supporting). **Thiago Franchi Nunes:** Methodology (supporting). **Eunice Atsuko Totumi Cunha:** Methodology (supporting). **Gláucia Moreira Espíndola Lima:** Methodology (supporting). **Maína de Oliveira Nunes:** Methodology (supporting). **Adriana P. Vicentini:** Methodology (supporting). **Sandra Maria do Valle Leone de Oliveira:** Investigation (supporting); writing – original draft (supporting). **Lídia R. Carvalho:** Formal analysis (supporting). **Luis Thompson:** Writing – review and editing (supporting). **Rinaldo Poncio Mendes:** Conceptualization (lead); formal analysis (lead); supervision (lead); validation (lead); writing – review and editing (lead). **Anamaria Mello Miranda Paniago:** Conceptualization (lead); formal analysis (lead); funding acquisition (lead); project administration (lead); resources (lead); supervision (lead); validation (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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