

# Epidemiological, clinical, and radiological characteristics of chronic pulmonary aspergillosis in Sri Lanka – A single centre experience

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## Abstract

**Introduction and objectives:** Chronic Pulmonary Aspergillosis (CPA) is a spectrum of chronic progressive lung disease with similar clinical and radiological features as pulmonary tuberculosis (PTB). The aim of this study was to evaluate the epidemiological, clinical, and radiological characteristics of CPA in Sri Lankan patients.

**Methods:** A cross-sectional descriptive study was carried out on 43 patients with the diagnosis of CPA in the National Hospital of Respiratory Diseases, Welisara, Sri Lanka. Epidemiological, clinical, and radiological data were gathered through an interviewer-administered questionnaire and patient records.

**Results:** The median age of the population was 61 years and 76.7% were men. Smoking and alcohol consumption were common among them, the odds ratios were not significant for the common types of CPA. The odds ratio was significant (11.73, 95% CI- 1.34- 102.2) for betel and arecanut chewing for the occurrence of the commonest type of CPA. Most of the patients (72.1%) had a personal history of PTB but majority of them (54.9%) did not have a microbiological diagnosis of TB. In the spectrum of CPA, the fibrosing type was the commonest (39.5%) followed by the cavitary type (27.9%). Both lungs were affected in 46.5% of cases, whereas the right lung was commonly involved in unilateral diseases. Itraconazole was the commonest antifungal agent used for treatment.

**Conclusions:** Fibrosing and cavitary types were the commonest types of CPA in the study population.

Predilection of right lung involvement in unilateral CPA is another finding of this study. Betel and arecanut consumption may be a potential risk factor that needs confirmation through large-scale studies.

**Key words:** aspergillosis, pulmonary tuberculosis, aspergilloma, fungal, betel arecanut


## Introduction

Chronic pulmonary aspergillosis (CPA) is a spectrum of chronic progressive fungal lung disease due to the *Aspergillus* species, commonly seen in patients with underlying structural lung diseases. Symptom duration of more than 3 months is required for pulmonary aspergillosis to be defined as CPA. Around 3 million of the population is affected by CPA worldwide and it may be commoner in resource-poor settings due to the higher prevalence of pulmonary tuberculosis (PTB). The diagnosis of CPA is multimodal and involves clinical, radiological, mycological, and immunological parameters. Unlike invasive aspergillosis, CPA occurs in immunocompetent patients.<sup>1</sup> The higher prevalence of PTB and the limitation of resources in diagnosis may lead to significant health impacts in developing countries like Sri Lanka. A further concern is the misdiagnosis of CPA as smear negative PTB and starting the patient on anti-tuberculous medication which can lead to a delay in the diagnosis of CPA.<sup>2</sup>

According to the World Health Organization, Sri Lanka is considered as a country with low burden of

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tuberculosis (TB).<sup>3</sup> However, tuberculosis is still commonly encountered in clinical practice and these patients are susceptible to develop CPA as a long-term sequela. There is also a possibility to under-diagnose CPA due to the tendency towards the diagnosis and management as smear negative PTB since both conditions have clinical and radiological similarities. According to the study by Jayasekara et al in 2015, the estimated CPA cases were 2886 in Sri Lanka, which included 1443 CPA cases in post-PTB patients. However, studies regarding the patterns and epidemiology of CPA are sparse in Sri Lanka.

The objective of this study was to identify the clinical, radiological, and demographical patterns of CPA in Sri Lanka. The identification of the prevalence of different types of CPA, clinical diversity, and potential high-risk demographic categories for CPA would be important for clinical practice and to plan further research on the subject.

## Methods

This cross-sectional descriptive study was carried out in the National Hospital for Respiratory Diseases, Welisara which is the largest hospital for adult respiratory diseases in the country. The hospital has the highest number of inward respiratory patients and is the only hospital with thoracic surgical facilities in the country. The ethical approval for the study was granted through the Ethics Review Committee of Colombo North Teaching Hospital, Ragama (Reference number: 001903/CNTH/ECC).

Permission to access patients and collect the data were obtained from the Director of the Hospital and the relevant consultants in the respiratory units. Written informed consent was obtained from the participants and the study was performed in accordance with the ethical principles of the Declaration of Helsinki.

Patients attending respiratory wards and clinics from November 2020 to April 2021, with a diagnosis of any type of active CPA above the age of 18 years were recruited. The patients, whose diagnosis and classification had been made according to the European Respiratory Society (ERS) consensus on the diagnosis of CPA were included.<sup>5</sup> Chest x-ray, computed tomography (CT) scanning, broncho-alveolar lavage for fungal studies, and sputum fungal studies were used along with the aspergillus specific immunoglobulin G (IgG) levels and serum galactomannan antigen test to make the diagnosis as per ERS consensus.

Data was gathered using an interviewer-administered questionnaire along with the patient records. The data elements which were included in the questionnaire were demographic data, clinical presentation, medical and respiratory comorbidities, PTB status, clinical, radiological, serological, and mycological patterns of CPA, and the treatment status. Data analysis was done with the 26<sup>th</sup> version of Statistical Package for Social Sciences (SPSS) software. Demographics, clinical status, comorbidities, disease status, PTB status, radiological/serological/mycological variables were summarized using descriptive statistics. Means and medians were calculated for continuous variables, while counts and percentages were calculated for categorical variables.

## Results

### Participant characteristics

A total of 43 patients with any type of active CPA participated in the study. Their ages ranged from 24 to 81 years with a median of 61 (53-68) years (mean=60.02, SD=11.73). Most of the participants were males (76.7%) and their body mass indices (BMI) were in the normal range according to the Asian classification (mean=21.06 kg/m<sup>2</sup>, median=21 kg/m<sup>2</sup>, and SD=2.97 kg/m<sup>2</sup>). The residence types of the participants were categorized into urban (32.6%), sub-urban (41.9%), rural (20.9%), and estate (4.7%). The median monthly income of the study population was 30,000 LKR (SD=15,424 LKR), keeping the majority in the low-income category. Both smoking (44.2%) and alcohol consumption (46.5%) were prevalent among the participants. However, the odds of smoking in patients with chronic fibrosing pulmonary aspergillosis (CFPA) (OR=1.8, 95%CI 0.52- 6.20) and chronic cavitory pulmonary aspergillosis (CCPA) (OR=2.76, 95% CI 0.72-10.57) in comparison to other patients with CPA were not statistically significant. Similarly, consumption of alcohol also failed to show a significant odds ratio to the occurrence of CFPA (OR=1.53, 95% CI 0.45 -5.28) or CCPA (OR=1.53, 95% CI 0.41-5.64). However, we noted that active betel and arecanut chewing was significantly prevalent in the group, 72.1% (n=31). Out of them, 77.4% (n=24) were regular chewers and the rest were occasional chewers. Interestingly, increased odds were observed in betel and arecanut chewing in the occurrence of CFPA (OR=11.73, 95% CI 1.34-102.2) against other types of CPA.

### The clinical details and the comorbid conditions

The symptoms of the participants were analysed according to their frequency. Most had more than one

symptom and considering the frequency of individual symptoms, the cough was the commonest (93%, n=40), followed by haemoptysis (67.4%, n=29), constitutional symptoms (62.8%, n=26), and dyspnoea (58.1%, n=25). One fourth (25.6%, n=11) of the study group had undergone at least one blood transfusion due to haemoptysis and bronchial artery embolization had been done, at least once, among 20.9% (n=09) of them. Diabetes mellitus was the most frequent medical comorbidity (39.5%, n=17), followed by hypertension (30.2%, n=13).

**Table 1.**

Medical comorbidity	Frequency
Diabetes mellitus	39.5% (n=17)
Hypertension	30.2% (n=13)
Chronic kidney disease	4.7% (n=2)
Cirrhosis	7% (n=3)
Ischaemic heart disease	7% (n=3)
Neurological disease	4.7% (n=2)
Rheumatoid arthritis	4.7% (n=2)
On steroids	4.7% (n=2)
On other immunosuppressives	7% (n=3)

Considering the respiratory comorbidities, 72.1% (n=31) of participants had been treated for PTB at some point in their life. After PTB, chronic obstructive pulmonary disease (COPD) was the commonest (27.9%, n=12) pulmonary comorbidity. The other respiratory comorbidities were interstitial lung diseases (ILD) (7%, n=3), bronchiectasis (4.7%, n=2), and asthma (2.3%, n=1). Two patients have had pneumothorax either as a complication or an association.

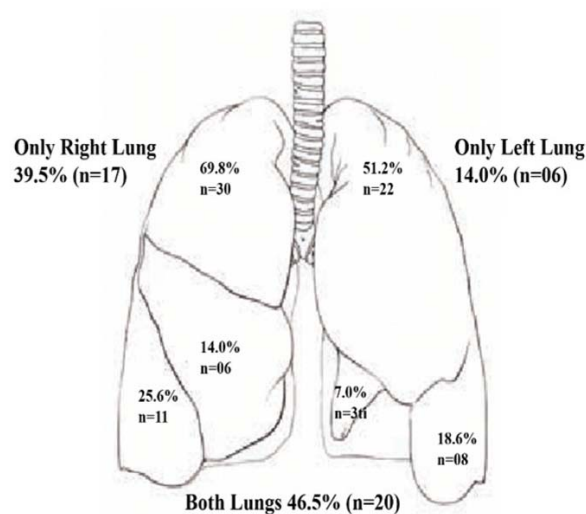
**The clinical spectrum of CPA**

Regarding the types of CPA in the group, the commonest type was chronic fibrosing pulmonary aspergillosis (CFPA) counting for 39.5% (n=17). Other types of CPA and the frequencies are given in Table 2. Cavities were present in 81.4% (n=35) cases while at least one aspergilloma was present in 65.1% (n=28) patients.

**Table 2. Types of the CPA**

Type of CPA	Frequency
Chronic Fibrosing Pulmonary Aspergillosis (CFPA)	39.5% (n=17)
Chronic Cavitory Pulmonary Aspergillosis (CCPA)	27.9% (n=12)
Simple Aspergilloma (SA)	14% (n=6)
Subacute Invasive Aspergillosis (SAIA)	18.6% (n=8)
Aspergillus Nodules (AN)	0%

We assessed the affected lobes in this group of CPA patients. In 46.5% (n=20) of cases both lungs were involved and in unilateral cases, the right lung and the left lung were affected in 39.5% (n=17) and 14% (n=6) respectively. Figure 1 illustrates the affected frequency of each lobe. The most affected lobe with CPA was the right upper lobe (69.8%, n=30) followed by the left upper lobe (51.2%, n=22).



**Figure 1. Schematic illustration of affected lobes in CPA.**

An elevated immunoglobulin G (IgG) for Aspergillus was seen in 83.7% (n=36) while only 16.3% (n=7) had a culture positivity for Aspergillus species on bronchoalveolar lavage specimens. Most of the patients (76.7%, n=33) were on anti-fungal agents at the time of study and itraconazole was the commonest agent (n=20) followed by voriconazole (n=13). Five patients

(11.6%) had either undergone or were awaiting surgical management for CPA. Nine patients who were on anti-fungal agents (27.3%) had developed adverse events due to the medication. The commonest adverse events were gastrointestinal disturbances and mild elevation of liver enzymes. Each occurred in 21.2% (n=7) of patients. Two patients had to discontinue treatment due to deranged liver function tests while on itraconazole. A skin rash occurred in one patient who was on itraconazole and he was switched to voriconazole.

Out of the patients who had PTB, only 45.1% (n=14) had a microbiologically confirmed disease, while the rest (54.9%, n=17) had been managed as clinically diagnosed PTB. All patients who had been managed as PTB mentioned that they had some clinical response with anti-TB medications irrespective of whether it is microbiologically confirmed or clinically diagnosed. However, the extent of the clinical response and the radiological response they showed were not assessed in our study. We have also not assessed the extent of investigations that had been performed to exclude CPA among those patients who were managed as clinically diagnosed PTB.

## Discussion

Chronic pulmonary aspergillosis is a relatively uncommon pulmonary disease complicating most of the underlying lung diseases.<sup>5</sup> The data regarding CPA from the South Asian region as well as from Sri Lanka are lacking. Estimations have been studied in India and assumed that the annual incidence of CPA varied from 27,000 to 0.17 million cases.<sup>6</sup> Jayasekara et al in 2015 concluded that the estimated prevalence of CPA in Sri Lanka was 2886 cases.<sup>4</sup> However, the demographic pattern, clinical associations, radiological and clinical patterns of CPA had not been published in Sri Lanka before this study. The disease burden of CPA in the region should be more than that of the developed regions of the world due to the higher prevalence of PTB.

The close relationship of CPA with PTB in our study can be interpreted from two different perspectives. CPA is a known sequela of PTB, and the evidence suggests that a high prevalence of PTB leads to a higher prevalence of CPA.<sup>1</sup> Secondly, regarding clinically diagnosed PTB cases which were later diagnosed as CPA, it is possible that CPA had been erroneously diagnosed and managed in the first instance as PTB. In our study, all the clinically diagnosed PTB patients have had some clinical improvement with anti-TB treatment. However, we have

not assessed the level of clinical response and the radiological response they had with initial anti TB. Further, we did not have data on the extent of investigations carried out to exclude CPA prior to management of PTB in clinically diagnosed PTB patients.

Most of the study population were in the low-income group category. However, we were unable to demonstrate any association between the occurrence of CPA and the income because the study sample was not equally distributed among different income categories. Smoking was more prevalent in the study group compared to the general population. According to Katulanda et al, the overall smoking rate in Sri Lankan population has been 18.3% in 2014 which is lower than that of this study population.<sup>7</sup> However, we could not demonstrate a significant odds ratio with smoking for the occurrence of two common types of CPA. Although the prevalence of alcohol consumption was comparable to that seen in the general population<sup>8</sup>, we were unable to demonstrate a significant odds ratio for alcohol consumption and the occurrence of CPA.

It was noted that 72.1% of the study population were consuming betel and arecanuts. The reported prevalence of betel and arecanut chewing in the general population in Sri Lanka is 17.6% in rural areas and 1.7% in urban areas according to the data from 2009.<sup>9</sup> Therefore, the consumption of betel and arecanut appears to be more prevalent among the study group than that of the general population. Moreover, the analysis showed a significant odds ratio with betel and arecanut consumption for the occurrence of the commonest type of CPA which is CFPA. Although we did not find any reported literature on the association of CPA with the consumption of betel and arecanuts, the growth of the *Aspergillus* species on betel nuts and their toxins-related carcinogenicity has been reported.<sup>10,11</sup> Therefore, it is possible to assume that betel and arecanut chewing is a potential risk factor for CPA which need to be further investigated with large scale studies.

The symptoms of CPA reported from our study group were similar to those from published studies.<sup>1,5</sup> Cough, constitutional symptoms, dyspnoea and haemoptysis were common symptoms making the clinical resemblance to PTB. The data also emphasized that CPA is an important cause for haemoptysis and it had been severe to require blood transfusion in 11 patients (25.6%) and bronchial artery embolization in 9 patients (20.9%).

The prevalence of diabetes mellitus in the Sri Lankan urban population is estimated at 26.7% in 2019.<sup>12</sup> The national prevalence of COPD was estimated at 10.5% in 2017.<sup>13</sup> Therefore, the prevalence of diabetes and COPD in the study population was higher than that of the general population. COPD is a known predisposing factor of CPA,<sup>5</sup> and there is evidence of invasive aspergillosis and poor outcome of CPA among patients with diabetes mellitus.<sup>14</sup>

The types of the CPA in our study were comparable to available data with CFPA and CCPA are being the commonest types.<sup>5</sup> The involvement of the right lung was commoner than in the left in our study. Preference for the right lung has not been published in previous studies and would be an interesting finding of our study.

The rarity of the disease and the limited time frame resulted recruitment of only 43 participants to the study. Therefore, the sample size, the absence of control group/non-diseased participants might have contributed in assessment of odds and a future extensive study of a longer duration or a case control study would aid in confirming associations of above discussed risk factors.

## Conclusions

The occurrence of CPA can be a sequelae of PTB. It and can also be associated with COPD and diabetes mellitus. There is a high possibility of underdiagnosis of CPA in the first instance with a tendency to treat patients as clinically diagnosed PTB due to similar clinical and radiological features of the two diseases. Therefore, a high clinical suspicion is necessary to diagnose CPA in the early stages. The potential association of CPA with betel and arecanut chewing, the right lung predilection, and the involvement different lobes of the lungs in CPA are interesting findings of the study which need further evaluation.

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## Conflicts of interests

All the authors declare that they have no competing interests.

## Criteria for authorship

All the authors contributed equally to the conception and design of the work, drafting, revising, and have approved the final manuscript.

## References

- Bongomin F, Asio LG, Baluku JB, Kwizera R, Denning DW. Chronic pulmonary aspergillosis: Notes for a clinician in a resource-limited setting where there is no mycologist. *Journal of Fungi*. 2020; **6**(2): 75.
- Setianingrum F, Rozaliyani A, Adawiyah R, et al. A prospective longitudinal study of chronic pulmonary aspergillosis in pulmonary tuberculosis in Indonesia (apical). *Thorax* 2021; **77**(8): 821-8.
- Bhatia V, Srivastava R, Reddy KS, et al. Ending TB in Southeast Asia: Current Resources Are Not Enough. *BMJ Global Health* 2020; **5**(3): e002073.
- Jayasekera PI, Denning D, Perera P, Fernando A, Kudavidanage S. Is fungal disease in Sri Lanka underestimated? A comparison of reported fungal infections with estimated disease burden using global data. *Sri Lankan Journal of Infectious Diseases* 2015; **5**(2): 73.
- Denning DW, Cadranel J, Beigelman-Aubry C, et al. Chronic pulmonary aspergillosis: Rationale and clinical guidelines for diagnosis and management. *European Respiratory Journal* 2015; **47**(1): 45-68.
- Agarwal R, Denning DW, Chakrabarti A. Estimation of the burden of chronic and allergic pulmonary aspergillosis in India. *PLoS ONE* 2014; **9**(12): e114745.
- Katulanda P, Wickramasinghe K, Mahesh JG, et al. Prevalence and correlates of tobacco smoking in Sri Lanka. *Asia Pacific Journal of Public Health* 2010; **23**(6): 861-9.
- Sørensen JB, Konradsen F, Agampodi T, et al. A qualitative exploration of rural and semi-urban Sri Lankan men's alcohol consumption. *Global Public Health* 2019; **15**(5): 678-90.
- De Silva VA, Hanwella DRC, Gunawardena N. Prevalence of betel chewing among males in Colombo and Polonnaruwa districts. *Journal of the College of Community Physicians of Sri Lanka* 2011; **14**(1): 20.
- Mahdihassan S. Betel-nuts as contaminated with a cancer producing fungus. *Ancient Science of Life*. 1987; **6**(4): 244-6.
- Asghar MA, Ahmed A, Asghar MA. Comparison of aflatoxins contamination levels in betel nuts (*areca catechu* L.)

## Research article

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- imported from Asian countries. *Agriculture and Food Security* 2020; **9**(1).
12. Kaluarachchi VT, Bulugahapitiya DU, Arambewela MH, et al. Assessment of prevalence, associations, knowledge, and practices about diabetic foot disease in a tertiary care hospital in Colombo, *Sri Lanka. Int. J. Chronic Dis.* 2020; **2020**: 1-7.
  13. Amarasiri L, Gunasinghe W, Sadikeen A, et al. The prevalence of chronic obstructive pulmonary disease (COPD) in Sri Lanka: outcome of the bold study. *European Respiratory Journal* 2017; DOI: 10.1183/1393003.CONGRESS-2017.PA1212
  14. Akram W, Ejaz MB, Mallhi TH, Syed Sulaiman SA, Khan AH. Clinical manifestations, associated risk factors and treatment outcomes of chronic pulmonary aspergillosis (CPA): Experiences from a tertiary care hospital in Lahore, Pakistan. *PLOS ONE* 2021; **16**(11).