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Review Article

Chronic pulmonary aspergillosis in Taiwan: Disease burden, diagnosis, treatment, and outcomes

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Abstract *Aspergillus* is a common filamentous fungus found in various natural environments, with spores frequently inhaled by humans. While healthy individuals typically resist infection, immunocompromised individuals and those with pre-existing lung diseases are at higher risk for aspergillosis. Chronic pulmonary aspergillosis (CPA) often develops in individuals with conditions like tuberculosis and chronic obstructive pulmonary disease. Recent studies in Taiwan reveal a significant incidence of CPA among elderly patients with these underlying conditions. The most common clinical manifestations include cavitation, nodules, and consolidation in the lungs. *Aspergillus*-specific IgG antibodies have emerged as key diagnostic markers, with varying optimal cut-off values across different regions. Studies indicate a strong correlation between high IgG levels and severe CPA, alongside associations with specific radiographic features. Additionally, elevated inflammatory markers such as IL-1β and TNF-α are linked to poor outcomes, emphasizing the need for early detection and intervention. The preferred treatment regimen consists of itraconazole, voriconazole, posaconazole, and isavuconazole, with itraconazole and voriconazole being the most extensively documented in the context of CPA. Overall, this review underscores the importance of localized diagnostic validation and comprehensive studies to improve the understanding and treatment of CPA in Taiwan.

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Introduction

Aspergillus is a ubiquitous filamentous fungus commonly found in natural environments, including soil, water, food, and air. Its spores are pervasive and can be easily inhaled by humans and animals. While inhalation of *Aspergillus* spores occurs frequently, it does not typically lead to infection in healthy individuals due to the immune system's ability to effectively combat these spores. However, infections predominantly occur in individuals with compromised immune systems, such as those undergoing chemotherapy, organ transplant recipients, individuals with HIV/AIDS or critically ill patients with influenza or COVID-19.[1–6] Additionally, people with pre-existing structural lung diseases, such as chronic obstructive pulmonary disease (COPD) or cystic fibrosis, are at a higher risk of developing Aspergillosis.

The lungs are the most commonly affected organ by *Aspergillus*, but the pulmonary manifestations can vary widely, depending on the host's immune status and underlying health conditions (Fig. 1).[7] In healthy individuals, *Aspergillus* can cause allergic reactions and tracheobronchitis, specifically allergic bronchopulmonary aspergillosis (ABPA).[8] ABPA is characterized by a hypersensitivity reaction to *Aspergillus* antigens, leading to symptoms such as wheezing, coughing, and bronchial obstruction. This condition is particularly common in patients with asthma or cystic fibrosis, where the chronic inflammatory response can exacerbate lung function impairment.[8] In immunocompromised patients, *Aspergillus* can cause invasive pulmonary infections, known as invasive pulmonary aspergillosis (IPA).[7] This form of aspergillosis frequently developed in patients with immunocompromised conditions such as leukemia, organ transplants, those undergoing prolonged corticosteroid therapy, and critically ill patients with influenza or COVID-19.[2,5–7,9] IPA could be associated with high mortality rates and poses a significant health risk, particularly among vulnerable populations. Annually, it is estimated that over 2,113,000 people develop invasive aspergillosis, and the crude annual mortality rate for IPA is approximately 1,801,000 deaths, representing a mortality rate of 85.2%.[10]

In addition to ABPA and IPA, chronic pulmonary aspergillosis (CPA) represents another spectrum of persistent and progressive *Aspergillus* infections.[11,12] CPA is almost exclusively seen in patients without obvious immune compromise but with preexisting structural lung diseases such as tuberculosis (TB), nontuberculous mycobacterial (NTM) infections, sarcoidosis, chronic obstructive pulmonary disease (COPD), pneumothorax, or previously treated lung cancer.[7,13,14] CPA is characterized by its chronic nature, often leading to a gradual decline in lung function over time. The typical presentation includes symptoms such as chronic cough, hemoptysis, fatigue, and weight loss, which can be mistaken for the underlying lung condition, thereby delaying diagnosis and treatment.[11,12] CPA could be further classified as several types, defined as classified into several types. CPA is defined by fibrobronchiectasis in the lung parenchyma with pleural thickening, which may include fungal balls in a cavity (CCPA). CPA can be interchangeable with subacute invasive aspergillosis (SIA) or chronic necrotizing pneumonia (CNPA) and may progress to chronic fibrosing pulmonary aspergillosis (CFPA) without recovery, often resulting in poor survival outcomes.[12] This condition is significant because it affects a large number of individuals worldwide and contributes to considerable morbidity and mortality.

It is estimated that the annual incidence of CPA is 1,837,272 cases globally and the mortality rate for CPA is also substantial, with approximately 340,000 deaths annually, accounting for 18.5% of those affected.[10] These figures highlight the need for increased awareness and better management strategies for CPA. However, the

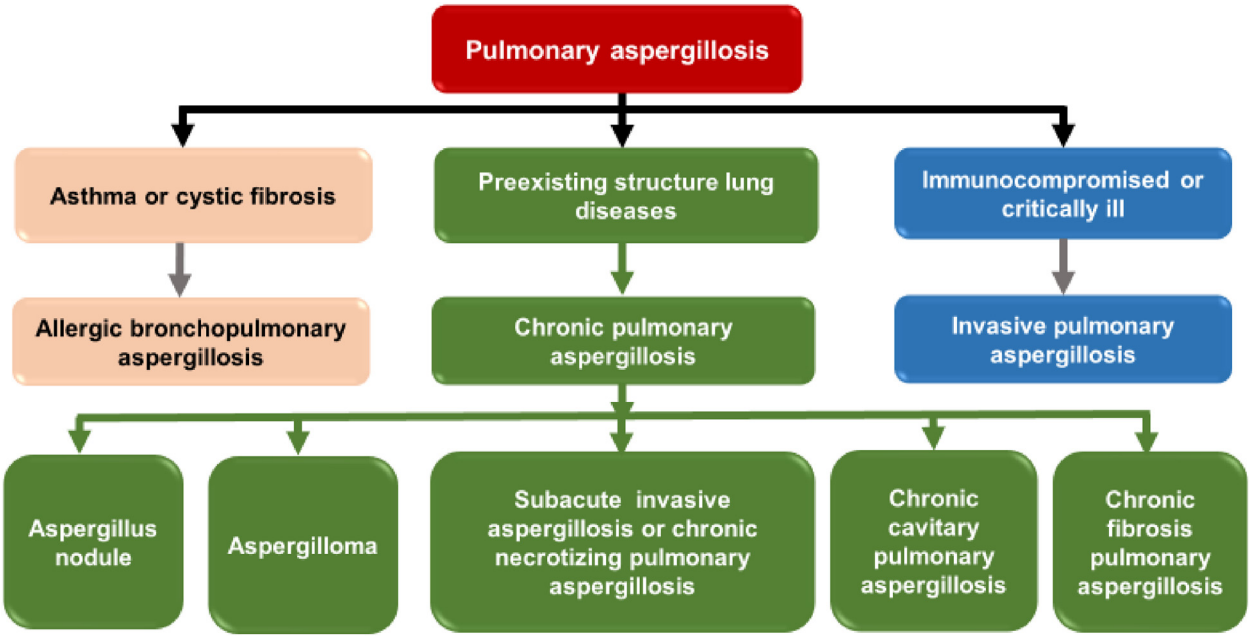

Fig. 1. Disease spectrum of pulmonary aspergillosis.

epidemiology of CPA could differ geographically, influenced by differences in healthcare infrastructure, availability of diagnostic tools, and regional prevalence of underlying lung diseases such as TB and COPD. Therefore, national health systems should implement robust surveillance programs to monitor the incidence, prevalence, and outcomes of CPA. Understanding the local epidemiology will be essential for identifying high-risk populations, and developing targeted public health interventions. To contribute to this understanding, this review was conducted to provide an updated overview of the disease burden and diagnosis of CPA in Taiwan.

Epidemiology

Lee et al. reported the finding of one prospective multicenter study between June 2019 and August 2020, in which 36 patients was diagnosed as CPA.[15] Among them, 20 (55.6%) aged >65 years, and 13 (36.1%) had body mass index <18. Old TB (n = 22, 61.1%) was the most common underlying condition.[15] The most common presentation on chest image was cavitation (n = 32, 88.9%), followed by nodule/mass (n = 23, 63.9%) and consolidation (n = 22, 61.1%), and bronchiectasis (n = 19, 52.8%).[15]

One prospective study conducted from May 2018 to December 2019 in a medical center in northern Taiwan reported the clinical manifestations of 35 patients with CPA, including 9 confirmed, 14 possible and 11 probable cases.[16] The most common type was SIA or CNPA (n = 20, 58.8%), followed by CCPA (n = 11, 32.4%), Aspergillus granuloma or nodules (n = 11, 32.4%) and CFPA (n = 9, 26.5%). Among them, 21 (61.8%) were male, and more than two-thirds aged ≥70 years. COPD was the most common underlying disease (n = 24, 70.6%) and eight (22.9%) had history of anti-TB treatment. Thirty (85.7%) patients with CPA had respiratory symptoms or signs longer than 3 months, and eight (23.5%) had respiratory failure.[16] Overall, 31.4% of patients with CPA had positive cultures for *Aspergillus* species and 37.1% of patients had filamentous fungi other than *Aspergillus* species. *Aspergillus flavus* (14.3%) and *Aspergillus fumigatus* (14.3%) were the first two frequently isolated *Aspergillus* species.[16] Another prospective study conducted in a medical center in from 2018 to 2021 reported the clinical manifestation of 49 individuals with CPA.[17] Their mean age was 79.1 ± 12.1 years and 33 (68.3%) were male. CCPA (n = 22, 44.9%) was the most common presentation, followed by SIA or CNPA (n = 19, 38.8%), CFPA (n = 14, 28.6%), simple nodule (n = 14, 28.6%), aspergilloma (n = 4, 8.2%). Compared with mild CPA, severe CPA had more presentations of CFPA, and CCPA, but less simple nodule. COPD, and previous TB were the most common comorbidities.[17] Lastly, a small study involving 18 patients with CPA from June 2018 to September 2021[18] had the similar findings, in which the median age was 65.5 years, and 13 (72.2%) were male, and COPD was the most common underlying condition (n = 11, 61.1%), followed by TB (n = 8, 44.4%) and malignancy (n = 6, 33.3%).[18]

In summary, CPA presents a multifaceted clinical picture across various studies in Taiwan (Table 1). Common comorbidities such as COPD and previous TB are consistently identified. However, these studies from different centers underscored the diversity in CPA manifestations, including significant proportions of patients with CCPA, CNPA or SIA. The variability in CPA types, associated respiratory symptoms, and high isolation rates of *Aspergillus* species like *A. flavus* and *A. fumigatus* highlight the diagnostic challenges and clinical complexities in managing this condition. Nevertheless, the number of cases in these studies was limited, indicating a need for larger studies to comprehensively address the diverse clinical presentations and underlying conditions associated with CPA in Taiwan.

Serology

Diagnosing CPA can be challenging due to the low sensitivity of fungal cultures for *Aspergillus* species. Invasive diagnostic procedures are often intolerable and risky for vulnerable patients because of the severity of their underlying structural lung diseases. The detection of *Aspergillus* IgG antibodies, as part of blood serology tests, has become a key diagnostic tool.[12] It offers the advantage of being less invasive while providing excellent diagnostic performance. The sensitivity and specificity of Aspergillus IgG was estimated to be up to 96% and 99%,[19—21] respectively, offering better diagnostic performance compared to serum or bronchoalveolar lavage (BAL) tests and the galactomannan (GM) antigen test.[12,22,23] However, the optimal cut-off level for *Aspergillus* IgG antibodies varies by geographic region and remains undetermined. Therefore, each site should establish and validate its own optimal cut-off level of *Aspergillus* IgG antibodies for diagnosing CPA. In the following section, we discuss the diagnostic performance and clinical application of the *Aspergillus* IgG antibody test based on studies conducted in Taiwan — a country of intermediate burden of TB.

A prospective study conducted by Lee et al. across six hospitals in northern and southern Taiwan between 2012 and 2019 examined the seropositive rate of *A. fumigatus*-specific IgG among different groups according to the status of TB.[24] In this study, *A. fumigatus*-specific IgG positivity was defined as *A. fumigatus* IgG above 27 mgA/L (milligrams of antigen-specific antibodies per liter) and it was found that the seropositive rate was 33.0% (66/200) among healthy volunteers, 37.7% (123/326) among TB close contacts, 26.5% (139/524) among active TB patients, and 43.2% (83/192) among old TB cases. Notably, during the follow-up period, only one (0.2%) of the 528 active TB patients and four (2.1%) of the 192 old TB cases developed CPA.[24] In 2020, Huang et al. conducted the first pilot study[17] and reported that the levels of *A. fumigatus* IgG (44 ± 31 and 10.4 ± 6.3 mgA/L) and *A. flavus* IgG (43.4 ± 31.1 and 11.4 ± 5.9 mgA/L) were higher in CPA (n = 35) than in control groups (n = 50), respectively. The optimal cut-off value for *A. fumigatus* IgG was 21.7 mgA/L, achieving an area under the curve (AUC) of 0.934 in receiver operating characteristic (ROC) analysis, with 85.7% sensitivity and 92.0% specificity.[17] For *A. flavus* IgG, the optimal cut-off value was 22.1 mgA/L, yielding an AUC of 0.928, with 88.2% sensitivity and 94.1% specificity.[17]

Thereafter, Lee and colleagues conducted a prospective study in three centers across Taiwan from June 2019 to

Table 1 Summary of clinical manifestations of patients with chronic pulmonary aspergillosis in Taiwan.

Study (authors, year of report)	Site	Period	No. of patients	No of male (%)	Age, years	Comorbidities/ condition, n (%)	Category, n (%)	Level of anti-*Aspergillus* IgG, mgA/L
Huang et al. 2020[16]	Single center in northern Taiwan	From May 2018 to December 2019	35	21 (61.8)	51-70: 10 (29) 71-90: 14 (41) >90: 9 (27)	COPD: 24 (71) Malignancy: 9 (27) Old TB: 8 (23) DM: 7 (21) Autoimmune disorder: 7 (21) Dialysis: 3 (9)	Aspergilloma or nodule: 11 (32) SIA or CNPA: 20 (59) CCPA: 11 (32) CFPA: 9 (27)	*A. fumigatus* IgG: 44 ± 31 *A. flavus* IgG: 43 ± 31
Lee et al. 2021[15]	Two centers in northern and central Taiwan (derivation cohort)	Between June 2019 and August 2020	21	12 (57)	62.4 ± 11.6	Old TB: 12 (57) Smoking: 5 (24) DM: 2 (10) Malignancy: 2 (10) Immunosuppressant: 2 (10)	Cavitation: 18 (86) Nodule/mass: 11 (52) Consolidation: 14 (67) Bronchiectasis: 7 (33) Fibrosis: 3 (14)	*A. fumigatus* IgG: 73 ± 24
	Single center in Southern Taiwan (validation cohort)	Between June 2019 and August 2020	15	4 (27)	66.3 ± 11.1	Old TB: 10 (67) Smoking: 5 (33) DM: 4 (27) Malignancy: 2 (13) Immunosuppressant: 2 (13)	Cavitation: 14 (93) Nodule/mass: 12 (80) Consolidation: 8 (53) Bronchiectasis: 12 (80) Fibrosis: 5 (33)	*A. fumigatus* IgG: 98 ± 59
Huang et al. 2021[17]	Single center in northern Taiwan	from May 2018 to May 2021	49	33 (68)	79.1 ± 12.1	COPD: 21 (43) Malignancy: 17 (35) Old TB: 17 (35) Autoimmune disorder: 11 (22) DM: 9 (18) Asthma: 3 (6) Dialysis: 2 (4)	Aspergilloma: 4 (8) Nodule: 14 (29) SIA or CNPA: 19 (39) CCPA: 22 (45) CFPA: 14 (29)	*A. fumigatus* IgG: 48 ± 35 *A. terreus* IgG: 44 ± 33
Hsiao et al. 2022[18]	Single center in central Taiwan	From June 2018 to September 2021	18	13 (72)	65.5 (58—72)	COPD: 11 (61) TB: 8 (44) Malignancy: 6 (33) Asthma: 5 (28) CKD: 3 (17) Autoimmune disorder: 2 (11)	NA	*A. fumigatus* IgG: 90 (60—144) *A. niger* IgG: 57 (43—82)

COPD, chronic obstructive pulmonary disease; SIA, subacute invasive aspergillosis; CNPA, chronic necrotizing pulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis; CFPA, chronic fibrosing pulmonary aspergillosis: TB, tuberculosis; DM, diabetes mellitus; CKD, chronic kidney disease; NA, not applicable.

August 2020, recruiting participants with clinical suspicion of CPA.[15] They evaluated the diagnostic performance of serum *A. fumigatus* IgG (Phadia, Uppsala, Sweden). In the derivation cohort (n = 262), it showed the AUC was 0.832 (95% CI, 0.781–0.875), with a sensitivity of 81.0% (95% CI, 58.1–98.3%) and specificity of 82.6% (95% CI, 77.2–87.1%) using an optimal cut-off level of 40.5 mgA/L. In the validation cohort (n = 111), it showed an AUC of 0.885 (95% CI, 0.808–0.936), with a sensitivity of 86.7% (95% CI, 59.5%–98.3% and specificity of 80.2% (95% CI, 70.8–87.6%) using the same cut-off value of 40.5 mgA/L. When applying this cut-off level to the entire cohort, lowering it to 27 mgA/L resulted in steady sensitivity (83.3%–86.1%), but specificity decreased from 81.9% to 63.5%.[15] Similarly, in the study by Hsiao et al., the AUC was 0.887 (95% CI, 0.819–0.936) and 0.811 (95% CI, 0.732–0.874) for *A. fumigatus* and *Aspergillus niger* IgG, respectively.[18] For *A. fumigatus* IgG, the optimal cut-off value was 41.6 mgA/L, yielding a sensitivity and specificity of 94.4% and 74.5%. For *A. niger* IgG, the optimal cut-off value was 40.8 mgA/L, resulting in a sensitivity and specificity of 83.3% and 81.8%.[18] Their finding suggested that using a higher cut-off point than traditionally considered may reduce false-positive results while maintaining satisfactory sensitivity.

Aspergillus IgG level was found to be highest among patients with CFPA (n = 7, 143 ± 48.1 mgA/L), followed by aspergilloma (n = 2, 88.8 ± 12.7 mgA/L) and CCPA (n = 21, 73.3 ± 39.6mgA/L).[15] Lastly, *Aspergillus* IgG levels were 37.3 ± 21.8 mgA/L and 57.8 ± 77.3 mgA/L for patients with aspergillus nodule (n = 3) and SIA (n = 3).[15] Similarly, Huang et al.[16] showed that the level of *A. fumigatus* or *A. flavus* IgG was correlated to the types of CPA, such as aspergilloma or CFPA ($P < .05$). The IgG levels also correlated with radiographic characteristics.[16] Both *A. fumigatus*- and *A. flavus*-specific IgG were higher in patients with fibro-bronchiectasis or volume reduction than with other radiological characteristics on chest CT ($p < .05$).[16] Lastly, the association between IgG level and disease severity was shown by Huang et al.[17] The levels of *Aspergillus* IgG were positively correlated with the "visual severity" of CPA ($p < 0.001$), with increasing concentrations in the peripheral blood associated with the increasing severity of CPA.[17] However, the IgG levels were not associated with the presence of different types of fungi such as non-*Aspergillus* molds or yeast-form fungi ($p > .05$). In CPA patients, the levels of *A. fumigatus* and *A. flavus* IgG were not correlated to the presence of corresponding *Aspergillus* species.[16]

In summary, studies in Taiwan have highlighted the variability in optimal cut-off values for *Aspergillus* IgG antibodies across different geographic regions and specific groups (Table 2), underscoring the need for local validation to enhance diagnostic accuracy. These studies have also elucidated associations between IgG levels and CPA severity, correlating higher antibody levels with more severe clinical and radiographic manifestations of the disease. Moreover, insights into IgG levels across various CPA types, such as chronic cavitary and fibrosing forms, provide valuable clinical implications for disease management and monitoring. Future large-scale studies are warranted to further refine diagnostic protocols and explore additional fungal species correlations, aiming to optimize diagnostic strategies for patients with CPA in Taiwan.

Table 2 Diagnostic performance of *Aspergillus* IgG based on the studies in Taiwan.

Study (authors, year of report)	Optimal cut-off value, mgA/L	Sensitivity, %	Specificity, %
Lee et al., 2021[15]			
A. fumigatus IgG			
derivation cohort	40.5	81.0	82.6
validation cohort		86.7	80.2
entire cohort		83.3	81.9
Old tuberculosis		90.9	81.8
Bronchiectasis		84.2	81.1
Pulmonary cavitation		87.5	75.4
Huang et al., 2021[17]			
A. fumigatus IgG	21.7	85.7	92.0
A. flavus IgG	22.1	88.2	94.1
Hsiao et al., 2022[18]			
A. fumigatus IgG	41.6	94.4	74.5
A. niger IgG	40.8	83.8	81.8

Treatment

Clinical decision-making for treating CPA should be based on the severity of pulmonary and general symptoms, along with any pulmonary function impairment or radiographic progression.[25] The preferred treatment regimen consists of oral triazole antifungals that are effective against *Aspergillus* species. These include itraconazole, voriconazole, posaconazole, and isavuconazole, with itraconazole and voriconazole being the most extensively documented in the context of CPA.[25,26] A network meta-analysis assessing the efficacy of various antifungal agents for CPA also confirmed that oral itraconazole might be preferred over other azoles as the initial treatment.[26] The recommended duration of antifungal therapy is at least six months, with follow-up evaluations every three to six months. These follow-ups should include clinical assessments, *Aspergillus* serology and/or microbiology tests, chest radiographs, and periodic computed tomography (CT) scans.

However, adverse events (AEs) associated with itraconazole and voriconazole are relatively common and can lead to treatment discontinuation in a significant proportion of patients.[27] A pooled analysis revealed that 36% of patients on voriconazole and 25% of those on itraconazole experienced AEs.[27] The most frequently reported AE with itraconazole was cardiotoxicity (29%), while skin-related AEs (28%) were the most common reported with voriconazole. Lastly, the discontinuation rates due to AEs were similar for both drugs, with 35% (47/366) for voriconazole and 35% (15/168) for itraconazole.[27]

Surgery should be considered for all CPA patients experiencing severe hemoptysis.[28] Surgical resection of aspergilloma can be a crucial therapeutic approach for CPA patients who have adequate pulmonary function. However, many patients may be physically frail, heightening the risk of mortality and perioperative complications. Therefore, meticulous patient selection is essential before opting for surgical intervention.[28]

Outcomes

CPA is associated with high morbidity and mortality. Several inflammation markers and disease severity indicators can predict poor outcomes in CPA patients.[17] Compared with survivors, patients who died had higher levels of IL-1β (2.4 ± 1.03 vs. 1.0 ± 0.8 pg/mL, $p = 0.001$), TNF-α (10.9 ± 4.8 vs. 5.0 ± 3.9 pg/mL, $p = 0.001$), and visual severity ($r^2 = 0.19$, $p = 0.026$). Moreover, patients with CPA had a poor prognosis if their blood IL-1β level was higher than 2 pg/mL or if their TNF-α level was higher than 7.5 pg/mL ($p < 0.05$). A long-term follow-up study on the 3-year survival of 49 CPA patients found an overall mortality rate of 18.3% ($n = 9$).[17]

Conclusions

In conclusion, the burden of CPA is significant, particularly among individuals with pre-existing lung conditions such as tuberculosis and COPD. CPA manifests in various forms, including chronic cavitary, fibrosing, and invasive types, each presenting unique diagnostic and management challenges. Studies in Taiwan have highlighted the importance of advanced serological testing, particularly the measurement of *Aspergillus*-specific IgG antibodies, for accurate diagnosis and monitoring of CPA. Optimal cut-off values for these antibodies vary geographically, emphasizing the need for localized validation to enhance diagnostic accuracy. Clinical data from Taiwan also reveal the associations between elevated levels of inflammatory markers, such as IL-1β and TNF-α, and poor prognosis in CPA patients. These findings underscore the critical role of early detection and intervention in improving patient outcomes. Enhanced clinical awareness and training of healthcare professionals, combined with robust surveillance programs, are essential for identifying high-risk populations.

Overall, the high morbidity and mortality rates associated with CPA call for coordinated efforts to improve diagnostic capabilities, treatment strategies, and patient monitoring. Larger, comprehensive studies are needed to further elucidate the epidemiology and clinical spectrum of CPA, ultimately leading to better management and reduced disease burden in affected populations.

CRediT authorship contribution statement

Chih-Cheng Lai: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — original draft. **Po-Ren Hsueh:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing — review & editing.

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