ORIGINAL RESEARCH

Risk Factors of Chronic Pulmonary Aspergillosis in Patients with Etiology Positive Pulmonary Tuberculosis

Fei Wang, BM; Lihui Zhao, MM; Lifeng Chen, MM; Jun Chen, PhD; Shufang Chen, MM; Yi Ren, BM

ABSTRACT

Objective • Pulmonary tuberculosis (PTB) and chronic pulmonary aspergillosis (CPA) have many similarities in clinical symptoms. In patients with etiology-positive pulmonary tuberculosis (EPTB), Aspergillus infection is easily overlooked, and missed diagnosis occurs. We attempted to analyze the clinical characteristics and risk factors of EPTB combined with CPA (EPTB-CPA), and to suggest to clinicians the possibility of CPA in EPTB patients.

Methods • 58 patients with EPTB-CPA diagnosed and treated in Wuhan Pulmonary Hospital from April 2021 to March 2022 were retrospectively collected as the case group. According to the age group of the case group, 174 patients with EPTB were randomly selected as the control group at a ratio of 1:3. Multivariate logistic regression analysis was utilized to analyze the risk factors.

Results • Multivariate Logistic regression analysis was performed on the pulmonary cavity, chronic obstructive pulmonary disease (COPD), bronchiectasis, emphysema, lung damage, anemia, and hypoproteinemia. Among them, pulmonary cavity ($P = .001$), COPD ($P = .006$), and bronchiectasis ($P = .020$) were statistically significant.

Conclusion • Our findings suggest that when EPTB patients present with pulmonary cavities and comorbidities such as COPD or bronchiectasis, clinicians should consider the possibility of CPA. Identifying these risk factors can help improve the accuracy of diagnosis and facilitate early detection and management of EPTB-CPA. (*Altern Ther Health Med.* 2024;30(1):83-87).

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INTRODUCTION

CPA is a common complication of post-TB lung disease (PTBLD).[1] The lung parenchyma and airway lesions left after tuberculosis treatment provide conditions for Aspergillus' colonization and growth.[2] China bears a high burden of tuberculosis, making it a relevant context for this study. Understanding the clinical characteristics and risk factors of EPTB combined with CPA in this population can contribute to improving the diagnosis and management of these conditions in a country heavily affected by TB. The ESCMID-ECMM-ERS guidelines point out that alternative diagnosis, especially mycobacterial infection, should be excluded from diagnosing CPA. Since the clinical symptoms and processes of mycobacterial infection are similar to those of CPA,[3] it is sometimes difficult to identify. The IDSA guideline for diagnosing CPA indicated that '3 months of chronic pulmonary symptoms or chronic illness', 'usually with one or more underlying pulmonary disorders',[4] among which 'chronic illness' and 'underlying pulmonary disorders' include ongoing PTB or PTBLD. It is difficult for EPTB patients to diagnose CPA before obtaining microbiological or immunological evidence of pulmonary aspergillosis. In the absence of aspergilloma in radiology, it is bound to lead to missing diagnosis of CPA, especially in areas where aspergillosis-related laboratory tests are unavailable. CPA patients with underlying lung diseases often have a poor prognosis,[5,6,] and timely detection and treatment are very important. In this study, we refer to guidelines provided by organizations such as ESCMID-ECMM-ERS (European Society of Clinical Microbiology and Infectious Diseases, European Confederation of Medical Mycology, and European Respiratory Society) and IDSA (Infectious Diseases Society of America). These guidelines provide valuable recommendations for the diagnosis and management of

Figure 1. Flow chart of Study patients screening

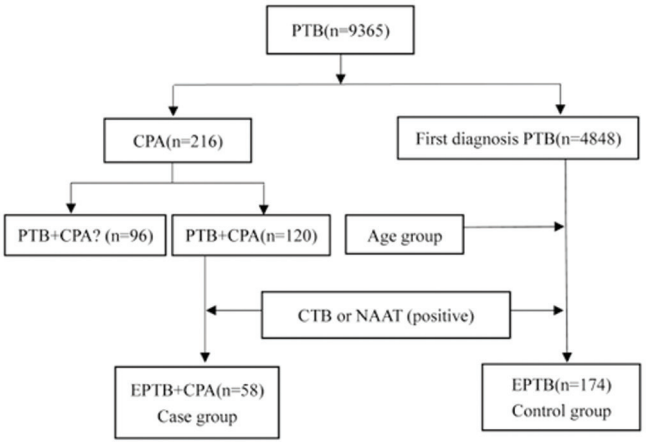

Figure 2. Age group comparison between the PTB group and Chinese TB cases notified by WHO

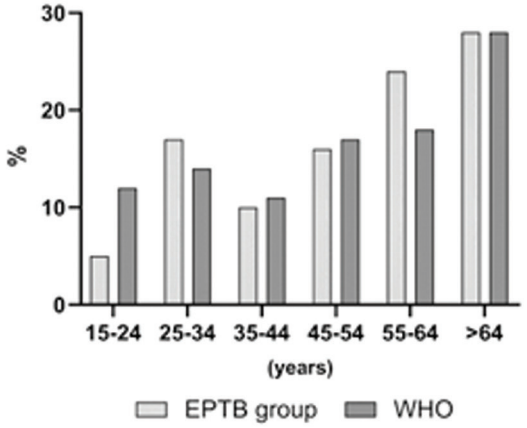

Table 1. Age group of EPTB-CPA group and EPTB group

Age group (years)	EPTB-CPA group (n = 58)	EPTB group (n = 174)	Precent (%)
15-24	3	9	5.2
25-34	10	30	17.2
35-44	6	18	10.3
45-54	9	27	15.5
55-64	14	42	24.1
>64	16	48	27.6

CPA. It is important to follow these guidelines to ensure standardized and evidence-based approaches to the diagnosis and treatment of CPA in EPTB patients. Through a retrospective case-control study, we tried to discover the risk factors of EPTB-CPA, find significantly related clinical symptoms and associated lung diseases, and give clinicians tips as soon as possible. At the same time, China is one of the countries with a high burden of tuberculosis,[7] and the burden of CPA after tuberculosis is huge.[8] It is necessary in order to conduct research on CPA in the Chinese tuberculosis population. This retrospective case-control study focuses on analyzing the clinical characteristics and risk factors associated with EPTB-CPA. Our objective is to identify significant clinical symptoms and underlying lung diseases related to EPTB-CPA, providing clinicians with early identification tips. By identifying these risk factors, we hope to improve the accuracy of diagnosis and facilitate timely detection and appropriate management of EPTB-CPA.

PATIENTS AND METHOD

Patients

Design and conduct a retrospective case-control study. The data of 9365 patients diagnosed with PTB (not diagnosed as tuberculous pleurisy alone) in Wuhan Pulmonary Hospital from April 1, 2021, to March 31, 2022, were retrospectively retrieved by electronic medical record system. Among them, 216 patients were diagnosed as pulmonary tuberculosis and CPA simultaneously, including 120 patients with clinical diagnoses of CPA and 96 suspected patients. Through screening the laboratory test results of the 120 patients, 62 cases of suspected pulmonary tuberculosis and clinical diagnosis were excluded. Through screening the laboratory test results of the 120 patients, a total of 62 suspected cases and clinical diagnosis cases of pulmonary tuberculosis were excluded, and 58 patients with etiological diagnosis of pulmonary tuberculosis were enrolled in the case group. A total of 4848 patients with the principal diagnosis (first diagnosis) of pulmonary tuberculosis (excluding patients diagnosed with aspergillosis and suspected aspergillosis) were selected. According to the age group and the case group 1:3 matching, 174 confirmed cases of EPTB were randomly selected as the control group. Age group matching data is shown in Table 1. The screening process of the case and control groups' shown in Figure 1. The control group was compared with the age group of the Chinese tuberculosis population reported by WHO in 2021,7, as shown in Figure 2.

Diagnostic criteria

PTB diagnostic criteria. The diagnostic criteria for PTB followed the "Health Industry Standard of the People's Republic of China" WS288-2017. In this study, the diagnosis of extrapulmonary tuberculosis (EPTB) was based on positive results from sputum or bronchoalveolar lavage fluid (BALF) mycobacterial culture or nucleic acid amplification test (NAAT), which is a type of nucleic acid amplification test used to detect specific DNA or RNA sequences. The diagnostic criteria for CPA were based on the IDSA 2016 guidelines, which include the presence of chronic pulmonary symptoms or illness lasting at least 3 months, progressive radiographic abnormalities (such as cavitation, pleural thickening, and pericavitary infiltrates), and sometimes the formation of a fungal ball. These criteria are important because they help in identifying patients who have a higher likelihood of having chronic pulmonary aspergillosis.

CPA diagnostic criteria. The case group included patients with EPTB-CPA who were diagnosed with CPA after their first admission and had no previous diagnosis of CPA. Patients younger than 15 years old, those with pleural tuberculosis alone, non-tuberculous mycobacterial disease, HIV infection, autoimmune diseases, hematological diseases, extrapulmonary tumors, and organ transplantation were excluded from both the case and control groups. The exclusion of patients with a previous diagnosis of CPA was

done to ensure that only newly diagnosed patients were included in the case group, allowing for a more accurate assessment of the relationship between PTB and CPA.[4]

Inclusion criteria

Patients in the case group must have a diagnosis of pulmonary tuberculosis (PTB) and chronic pulmonary aspergillosis (CPA) together (EPTB-CPA).

Patients with a previous diagnosis of CPA were excluded from the case group to ensure that only newly diagnosed cases of EPTB-CPA were considered in this study.

All CPA patients were diagnosed after the first admission to ensure that the diagnosis of CPA occurred during the course of treatment for PTB, rather than being a pre-existing condition.

Patients younger than 15 years old, those with pleural tuberculosis alone, non-tuberculous mycobacterial disease, HIV, autoimmune diseases, hematological diseases, extrapulmonary tumors, and organ transplantation were excluded from both the case and control groups to maintain homogeneity and focus on the specific population of interest.

For the control group selection, patients with similar characteristics and disease progression as the case group werechosen. The control group was selected from other patients admitted to the same hospital during the same time period, ensuring that they represented a comparable patient population.

Statistical analysis

Data analysis was performed using SPSS 25 statistical software (Statistical Product and Service Solutions). Chi-square test or Fisher's exact test was used for single-factor analysis of count data and classification data. A significance level of $P < .05$ was considered statistically significant, indicating that the observed results were unlikely due to chance. Based on the results of univariate analysis, multivariate logistic regression analysis was carried out for variables that showed statistical significance in the univariate analysis. This analysis aims to determine the independent predictors or risk factors for the occurrence of EPTB-CPA, taking into account the potential confounding effects of multiple variables simultaneously. By identifying significant predictors, this analysis contributes to a better understanding of the factors associated with the development of EPTB-CPA, providing valuable insights for clinical management and preventive strategies.

RESULTS

Comparison of characteristics between EPTB-CPA group and EPTB group

The basic features, clinical symptoms, main radiological features, underlying disease and complications of EPTB-CPA and EPTB (etiology-positive pulmonary tuberculosis). groups were compared, as shown in Table 2.Cough symptoms were reported by 75.9% of patients in the EPTB-CPA group, compared to 70.10% of patients in the EPTB group. This suggests that patients with EPTB-CPA are more likely to develop cough. Sputum discharge was reported by 46.6% of patients in the EPTB-CPA group, compared to 35.6% of patients in the EPTB group. This suggests that patients with EPTB-CPA are more likely to produce sputum. In the EPTB-CPA group, 41.4% of patients had hemoptysis symptoms, compared with 12.1% of patients in the EPTB group. This suggests that EPTB-CPA patients are more likely to cough up blood. Chest pain was reported by 3.4% of patients in the EPTB-CPA group, compared to 9.8% of patients in the EPTB group. This suggests that patients with EPTB are more likely to experience chest pain. Respiratory failure was reported in 13.8% of patients in the EPTB-CPA group, compared with 2.3% in the EPTB group. This suggests that EPTB-CPA patients are more likely to develop respiratory failure. Pleural thickening was observed in 44.8% of patients in the EPTB-CPA group, compared to 20.1% of patients in the EPTB group. This suggests that EPTB-CPA patients are more prone to pleural thickening. In the EPTB-CPA group, 41.4% of patients were diagnosed with bronchiectasis, compared with 21.8% of patients in the EPTB group. This suggests that EPTB-CPA patients are more likely to have a history of bronchiectasis. In addition, univariate analysis showed differences in several other characteristics, such as chronic obstructive pulmonary disease, damaged lung, respiratory failure, and lung cancer. These results showed significant differences in characteristics between the EPTB-CPA and EPTB groups.

Table 2. Comparison of characteristics between EPTB-CPA group and EPTB group

Characteristic	EPTB-CPA group (n=58) [n (%)]	EPTB group (n=174) [n (%)]	χ^2	*P* value
Basic feature				
Gender			2.14	.143
Male	47(81.0)	124(71.3)		
Female	11(19.0)	50(28.7)		
Age[a]	52.5(21-83)	51.9(19-83)	0.05	.827
Smoking	20(34.5)	50(28.7)	0.68	.409
Clinical feature				
Cough	44(75.9)	122(70.1)	0.71	.401
Expectoration	27(46.6)	62(35.6)	2.19	.139
Hemoptysis	24(41.4)	21(12.1)	23.9	.000
Fever	6(10.3)	24(13.8)	0.46	.498
Chest pain	2(3.4)	17(9.8)	1.55	.170
Dyspnea	1(1.7)	0(0.0)	0.33	.250
Radiographic feature				
Pulmonary cavity	41(70.7)	76(43.7)	12.7	.000
Pleural thickening	26(44.8)	35(20.1)	13.7	.000
Underlying pulmonary disease or complications				
Bronchiectasis	24(41.4)	38(21.8)	8.5	.004
Emphysema	17(29.3)	22(12.6)	8.6	.003
Chronic obstructive pulmonary disease	13(22.4)	12(6.9)	10.9	.001
Damaged lung	10(17.2)	8(4.6)	9.7	.002
Respiratory failure	8(13.8)	4(2.3)	11.7	.001
Lung cancer	3(5.2)	1(0.6)	3.05	.049
Underlying extrapulmonary disease				
Diabetes	14(24.1)	46(26.4)	0.12	.729
Hypertensive disease	9(15.5)	29(16.7)	0.04	.838
Hepatitis B	8(13.8)	23(13.2)	0.01	.911
Anemia	21(36.2)	39(22.4)	4.3	.038
Hypoproteinemia	19(32.8)	40(23.0)	2.2	.139

[a]Average age (Age range)

Table 3. Multivariate Logistic regression analysis of PTB patients with CPA

Variable	β	S	Wald	Sig	Exp(B)	95%CI
Pulmonary cavity	1.129	0.339	11.095	0.001	3.092	1.591-6.008
Chronic obstructive pulmonary disease	1.271	0.459	7.656	0.006	3.564	1.449-8.769
Bronchiectasis	0.795	0.342	5.409	0.020	2.215	1.133-4.328

Risk factors of EPTB-CPA

Multivariate Logistic regression analysis was performed on pulmonary cavity, COPD, bronchiectasis, emphysema, lung damage, lung cancer, anemia and hypoproteinemia. Among them, pulmonary cavity, COPD and bronchiectasis were statistically significant. The risk factors were identified through multivariate logistic regression analysis as presented in Table 3.

DISCUSSION

In this study, cough, expectoration and hemoptysis were the major clinical symptoms of EPTB-CPA patients, while fever, chest pain and dyspnea were relatively rare. Tuberculous pulmonary cavity or bronchiectasis is a common cause of hemoptysis.[9] Among 24 PTB-CPA patients with hemoptysis in the case group, 20 (83.3%) had pulmonary cavity, and 19 (79.2%) had bronchiectasis and / or bronchial tuberculosis. Patients with pulmonary cavity or bronchial disease accounted for 91.7% of all hemoptysis patients in the case group. Similarly, in the control group of 17 patients with hemoptysis, 15 patients (88.2%) had pulmonary cavity or bronchial disease. Therefore, pulmonary cavity, bronchiectasis or tuberculous bronchial lesions are the main causes of hemoptysis in EPTB and EPTB-CPA patients. Univariate analysis showed that hemoptysis was more common in EPTB-CPA patients (41.4%) than in EPTB patients (12.1%). Although hemoptysis, pleural thickening and respiratory failure were statistically different in univariate analysis, these factors resulted from pulmonary tuberculosis, CPA or other lung diseases. Therefore, these factors were excluded from multivariate logistic regression analysis. Although hemoptysis, pleural thickening, and respiratory failure were statistically different in univariate analysis, these factors were excluded from multivariate logistic regression analysis because they were the results of joint action of tuberculosis, CPA or other lung diseases. It was worth noting that hemoptysis and pleural thickening have a very important reference value for the diagnosis of EPTB-CPA.[2,4]

CPA is a chronic disease caused by a fungal infection, and one of the common symptoms is cough. Aspergillus infections can cause airway inflammation and excess mucus, which can cause persistent coughing and sputum production. In addition, CPA may also cause damage to lung tissue, leading to blood vessel rupture and resulting in hemoptysis. Traditionally, TB is usually accompanied by fever. However, one possible reason for the low reported rate of fever in EPTB-CPA patients is that CPA patients generally have a poor immune status, and the body's immune response to TB infection is relatively weak, so there may be no obvious fever symptoms. CPA patients may develop lung tissue damage and fibrosis, resulting in reduced lung function. This fibrosis may reduce the elasticity of the affected area, causing difficulty breathing and chest pain. In addition to the above CPA related factors, TB sequelae may also have an impact on the appearance of symptoms. Tuberculosis, when treated infrequently or incompletely, may lead to fibrosis and cavity formation in lung tissue. These TB sequelae may explain why pulmonary lumen formation, pleural thickening, and bronchiectasis are more common in EPTB-CPA patients. Pulmonary Aspergillus infection was opportunistic and conditional, and the risk of infection was very low in people with the complete structure and function of the respiratory tract and normal immune function.[10] Patients with immunodeficiency such as HIV or immune dysfunction such as stem cell and organ transplantation were prone to bacterial infection and invasive pulmonary aspergillosis (IPA).[11,12] The occurrence of CPA was closely related to the respiratory tract's structural damage and functional incompleteness. The local infiltration and growth of tuberculosis in the bronchus lead to bronchial deformation or stenosis and the invasion and growth of lung parenchyma form necrosis and cavities. These changes in lung structure and function were more frequent in PTBLD patients.[13, 14] The bronchi involved in bronchiectasis also have bacterial infection and infiltration of inflammatory cells, resulting in the destruction of cilia and the loss of local self-purification function.[15] These provide conditions for the colonization and growth of Aspergillus. Once the immune cells cannot effectively eliminate them, it is easy to cause aspergillosis. Especially in the lung cavity, the cavity wall may act as a barrier for the entry of immune phagocytes,[16] providing an opportunity for Aspergillus spores to grow. In this study, through multivariate analysis, pulmonary cavity and bronchiectasis are risk factors for EPTB-CPA, which just verifies the above assertion that changes in lung structure and function are the conditions for CPA in EPTB patients.

COPD is a common underlying lung disease associated with CPA,[5] The changes of pathological and physiological functions of small airway and lung parenchyma in COPD patients are related to CPA. The use of cortical hormones can interfere with the ability of macrophages to engulf conidia,[11] and long-term use may be one reason for CPA.[17,18] In this study, COPD is a risk factor for EPTB-CPA. In addition to the structural and functional changes in the lungs caused by COPD, the inhibition of immune function caused by the use of corticosteroids is also associated with CPA. Although corticosteroids were recorded in the medical records of COPD patients in the case group and the control group, the records of previous corticosteroid treatment were incomplete. Therefore, the use of corticosteroids was not included in the variables analyzed separately in this study.

Although previous PTB was associated with CPA, common risk factors associated with PTB such as smoking, diabetes, anemia,[19-21] did not become a risk factor for EPTB-CPA in this study. Common underlying diseases such as hypertension and hepatitis B also had no significant relationship with CPA. EPTB-CPA is a pulmonary aspergillosis in addition to pulmonary tuberculosis, usually caused by immunosuppression. Factors such as smoking, diabetes, and anemia may play a role in the incidence of pulmonary aspergillosis, but may be less prominent in patients with EPTB-CPA. Therefore, in this particular patient population,

the influence of some other risk factors may be dominated by local immune status, and less so for factors such as smoking, diabetes, and anemia. The characteristics of the population in the study can influence the results. If the EPTB-CPA patients in the study had a relatively low prevalence of smoking, diabetes, and anemia overall, then these factors may not show significant risk in the statistical analysis because of differences in the distribution of risk factors in different populations. Studies may have limitations in data collection, such as a lack of detailed records of factors such as smoking, diabetes, and anemia. This may make it impossible to fully assess the relationship between these factors and EPTB-CPA. In addition, some risk factors may be self-reported and there is a possibility of memory bias or misinformation.

Because the control group was grouped according to the age of the case group as a reference, this study did not make a statistical analysis of age. WHO reported that among the new and recurrent tuberculosis patients in China in 2021, PTB patients accounted for 95%, of which 68% were male (>15 years old). In this study, male patients in the control group accounted for 71.3%, accounting for a similar proportion.[7] However, in the proportion of 55-64 years old, the control group in this study was higher than that reported by WHO, and advanced age would increase the susceptibility to lung diseases.[22] At the same time, Wuhan Pulmonary Hospital has received more patients with severe tuberculosis in the whole Wuhan area. These factors make this study have a systematic bias in the random screening of tuberculosis patients in the control group so some risk factors may be covered. This is also the limitation of single-center retrospective study. Therefore, it is necessary to carry out multi-center related research.

CONCLUSION

Early detection and intervention of EPTB-CPA has many potential benefits that can positively impact patient outcomes, treatment strategies, and overall disease management. Early detection and diagnosis can help start treatment early, thereby reducing the risk of disease progression and complications. Early treatment can improve survival and quality of life by reducing symptoms, controlling infection, and preventing the disease from spreading to other sites. Early detection provides doctors with more accurate diagnostic information, allowing them to develop individualized treatment strategies based on a patient's specific condition. By determining the sensitivity and resistance of pathogens, physicians can select the most appropriate antifungal and antituberculosis drugs, improving treatment effectiveness and reducing adverse reactions. Early detection also provides an opportunity for patients to participate in integrated disease management. This includes regular follow-up, monitoring of disease progression and treatment response, and taking necessary steps to manage complications and potential drug interactions. Early intervention contributes to better disease control, reduced hospitalizations and medical costs, and improved quality of life for patients. This study used current diagnostic criteria to determine the presence of EPTB-CPA. However, these criteria may still have limitations and may not capture all patients. Further research could explore and develop more accurate and sensitive diagnostic criteria for early detection and treatment of EPTB-CPA. By better understanding the relationship between TB and CPA, we can provide healthcare providers and policymakers with more accurate information to improve the prevention and control of pulmonary infectious disease and patient management. Such work has important practical implications for promoting public health and reducing the burden of lung infections.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

AUTHOR CONTRIBUTIONS

FW, LZ and YR designed the study and performed the experiments, LC and JC collected the data, LC, JC and SC analyzed the data, FW, LZ and YR prepared the manuscript. All authors read and approved the final manuscript. FW and LZ contributed equally to this work.

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ETHICAL COMPLIANCE

This study was approved by the ethics committee of Wuhan Pulmonary Hospital.

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