# Clinical features and risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis

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**Abstract.** – OBJECTIVE: This study was carried out to explore the clinical features and risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis.

**PATIENTS AND METHODS:** Through a retrospective analysis of 3,000 patients with pulmonary tuberculosis history or active pulmonary tuberculosis complicated with pulmonary aspergillosis in the inpatient department of pulmonary tuberculosis in Shandong Provincial Public Health Clinical Center from January 2017 to January 2021, 70 cases of pulmonary aspergillosis were selected and diagnosed. In addition, 70 patients with pulmonary tuberculosis without other fungal infections in the same period were randomly selected as the control group. The risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis were analyzed by multi-factor logistic analysis, and the clinical characteristics of pulmonary tuberculosis complicated with pulmonary aspergillosis were analyzed by collecting the basic information of patients, drug use of pulmonary tuberculosis, imaging characteristics, past medical history, and test indicators.

**RESULTS:** Univariate analysis showed that the single risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis were: the types of pulmonary tuberculosis (initial diagnosis or previous reexamination), hormone application time, antibiotic application time (rifampicin), hemoptysis/sputum blood, C-reactive protein, and pulmonary cavity were significantly correlated with pulmonary tuberculosis complicated with pulmonary aspergillosis (p-value <0.05). The proportion of patients with pulmonary tuberculosis complicated with pulmonary aspergillosis was higher than that of patients with simple pulmonary tuberculosis in the follow-up of pulmonary tuberculosis, the time of antibiotics application  $\geq$  1 month, the time of hormone application  $\geq$  1 week and C-reactive protein. The incidence of hemoptysis/blood in sputum in the clinical symptoms of pulmonary aspergillosis group (24/70) was higher than that of simple pulmonary tuberculosis group (20/70),

and the difference was statistically significant (*p*-value < 0.05). Multivariate logistic regression analysis showed that there were significant differences between the two groups in the two indexes of "hormone application time  $\ge$  1 week" and "antibiotic application time  $\ge$  1 month" (*p*-value < 0.05).

**CONCLUSIONS:** Hemoptysis/blood in sputum can be considered as the main clinical feature of pulmonary tuberculosis complicated with pulmonary aspergillosis. The main risk factors for pulmonary tuberculosis complicated with pulmonary aspergillosis were the application time of antibiotics  $\geq$  1 month and the application time of hormones  $\geq$  1 week.

Key Words:

Pulmonary tuberculosis, Pulmonary aspergillosis, Aspergillus infection, Clinical feature, Risk factor.

#### Introduction

Pulmonary tuberculosis is mainly transmitted by bacterial droplets transmitted to the air by contact with coughing or sneezing in patients with pulmonary tuberculosis, which are then inhaled by healthy individuals. China ranks third among the world's tuberculosis countries and second among the countries that die of infectious diseases<sup>1</sup>. Tuberculosis is one of the world's top ten fatal diseases, especially occupying the top of the single infectious disease death series<sup>2</sup>. Humans have been fighting tuberculosis for hundreds of years. In order to completely cure pulmonary tuberculosis and prevent the recurrence of pulmonary tuberculosis, different measures have also been taken in various countries around the world<sup>3</sup>. However, due to the high incidence of pulmonary tuberculosis, many drug resistance, and serious infectious complications, there are still millions of new cases and deaths each year. The probability of pulmonary tuberculosis in males is higher than that in females, and the probability of pulmonary tuberculosis in minors is increasing. It is estimated that in 2017 alone, more than 10 million people worldwide have tuberculosis, of which 58% are males and 32% are females, and 1 million are minors<sup>4</sup>. It was found that more than 1.3 million HIV-negative people die of tuberculosis and more than 300,000 HIV-positive people die of tuberculosis<sup>5</sup>. About 90% of tuberculosis patients are adults aged 15 years and older and about 9% are HIV-infected<sup>6-8</sup>.

Pulmonary aspergillosis is a fungal infectious disease resulting from Aspergillus invasion of deep lung tissues9. The common symptoms of pulmonary aspergillosis patients are mainly cough, sputum, hemoptysis, chest pain, shortness of breath, and fever, which cause great pain to patients<sup>10,11</sup>. Allergic bronchopulmonary aspergillosis is a disease caused by hypersensitivity reactions caused by Aspergillus allergens, which occurs mostly in patients with chronic respiratory diseases, such as asthma and cystic fibrosis for a long time. The main causes of invasive aspergillosis are immunodeficiency, including congenital or acquired immunodeficiency, and long-term use of glucocorticoids or other immunosuppressive drugs, mainly manifested as secondary infections<sup>12,13</sup>. Patients with AIDS, chronic obstructive pulmonary disease, and asthma have a higher probability of occurrence.

In recent years, there are more and more reports on pulmonary basic diseases, such as chronic obstructive pulmonary disease, pulmonary tuberculosis, bronchiectasis and pulmonary aspergillosis. Pulmonary tuberculosis can cause pulmonary aspergillosis, which can lead to more severe acute pulmonary tuberculosis and even lung cancer<sup>14</sup>. The main clinical manifestations of pulmonary tuberculosis are as follows: patients will always cough, hemoptysis or expectoration, or even wheezing. Chest CT examination shows that pulmonary cheese-like necrosis, pulmonary cavity with fibrous hyperplasia in both lungs, pulmonary nodules, calcification or unclear edges, most of which are spherical and other substantive pathological features. The main clinical symptoms of pulmonary aspergillosis are persistent cough and asthma, expectoration, bloody sputum, fever, chest pain, sweating, dyspnea, fatigue, etc., which are often found in the upper or lower lobe of the lung<sup>15</sup>. However, since the clinical symptoms of

pulmonary tuberculosis and pulmonary aspergillosis are basically the same, and the imaging is also similar, there are few studies on pulmonary tuberculosis complicated with pulmonary aspergillosis. Therefore, it is possible to explore the risk factors and clinical characteristics of pulmonary tuberculosis complicated with pulmonary aspergillosis, and understand the specific clinical indications of complications, so as to reduce the incidence and mortality of the disease by early warning, early diagnosis and early treatment. The clinical characteristics of pulmonary tuberculosis patients and pulmonary aspergillosis patients in the same period and the risk factors of the two groups of patients were retrospectively analyzed, providing a reference for the clinical prevention and treatment of pulmonary tuberculosis and pulmonary aspergillosis.

# **Patients and Methods**

# Research Objects

From January 2017 to January 2021, a total of 3,000 active pulmonary tuberculosis cases were selected from the inpatient department of pulmonary tuberculosis in Shandong Provincial Public Health Clinical Center. 70 cases diagnosed as pulmonary aspergillosis were selected as the observation group, and 70 cases of pulmonary tuberculosis (without pulmonary fungal infection) were randomly selected as the control group, including 106 males and 34 females. Age ranged from 14 to 80, with an average age of 47.

- **Inclusion criteria:** (1) the patients according to WS288-2017: Diagnostic for pulmonary tuberculosis clear diagnosis of tuberculosis, the patients according to 2016 Infectious Diseases Society of American (IDSA) Practice Guidelines for the Diagnosis and Management of Aspergillus clear diagnosis of pulmonary aspergillosis; (2) the patients aged from 14 to 80 years; (3) the patients without other pulmonary diseases.
- **Exclusion criteria:** (1) the patients do not meet the diagnostic criteria for tuberculosis or pulmonary aspergillosis; (2) persons under 14 or over 80 years of age; (3) the patients underwent organ transplantation or HIV infection; (4) the patients with mental or conscious obstacles; (5) the patients with viral pneumonia or chronic

interstitial lung disease; (6) patients who develop resistance to rifampicin and other tuberculosis drugs; (7) patients who come from areas with a high incidence of endemic mycosis.

Patients themselves or their authorized persons signed informed consent, and the study was approved by the Medical Ethics Committee of Shandong Provincial Public Health Clinical Center.

#### Data Collection

The data of 3,000 patients were retrieved from the HIS system of the medical record management department of the hospital. If the same patient in the observation group and the control group was admitted to hospital several times, the diagnosis result of the first admission treatment was pulmonary aspergillosis. Through the patient's medical records, the patient's data were obtained, the main contents include: (1) basic information (age, gender, smoking history, whether there is a basic disease); (2) medication [whether to use glucocorticoids, whether to use antibiotics (mainly refers to rifampicin)]; (3) clinical manifestations: cough, expectoration, fever, chest tightness, hemoptysis/sputum with blood; (4) past medical history [combined type of pulmonary] tuberculosis (initial diagnosis or reexamination)], pulmonary aspergillosis diagnosis period (from pulmonary tuberculosis diagnosis); (5) test indicators [CT images of the lung, such as nodular type, cavity type, T cell subsets (CD4/CD8, CD4)], and alveolar lavage fluid GM. If the same index is tested many times, the first test results are recorded in the final statistical data.

#### Statistical Analysis

SPSS 20.0 statistical software version 20.0 (SPSS Corp., Armonk, NY, USA) was used to process and analyze all experimental results and data. Normal distribution of measurement data results is represented in the form of mean  $\pm$  standard deviation, compared between the two groups using single factor analysis. General data are tested by independent sample *t*-test. Further multivariate logistic regression analysis is used to analyze the risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis. When *p*-value<0.05, the difference is statistically significant.

#### Results

#### *Comparison of General Data Between the Two Groups*

Table I shows the comparison of general data between the two groups, mainly including gender, age, smoking, underlying diseases, diagnosis history, duration of glucocorticoid use, and duration of rifampicin antibiotic use. Univariate analysis was used to analyze the general data of patients in the observation group and the control group, and it was found that there was no significant difference in gender, age, smoking history, and underlying diseases between the two groups (p-value>0.05). There were significant differences in the diagnostic history, glucocorticoid use time, and rifampicin antibiotic use time between the two groups. The proportion of initial diagnosis in the control group was significantly higher than that in the observation group. The proportion

Table I. Univariate analysis of the general data of patients in the two groups.

Risk factor	Types	Observation group (n = 70)	Control group (n = 70)	P
Gender	Male	51	55	0.455
	Female	19	15	
Age	< 50	26	21	0.240
	$\geq$ 50	44	49	
Smoking or not	Yes	36	35	0.273
	No	34	35	
Combined underlying diseases	Have	39	43	0.672
	No	31	27	
Diagnostic history	Initial diagnosis	41	60	0.001
0	reexamination	29	10	
Hormone application time	< 1 week	13	40	0.006
(Glucocorticoid)	$\geq 1$ week	57	30	
Application time of antibiotics (rifampicin)	< 1 month	22	46	0.004



**Figure 1.** Comparison of the number of patients with clinical symptoms between the two groups.

of patients with glucocorticoid use time  $\geq 1$  week and the proportion of patients with rifampicin antibiotic use time  $\geq 1$  month in the observation group were significantly higher than those in the control group, and the differences had statistical significance (*p*-value< 0.05).

# Univariate Comparison of Clinical Characteristics Between the two Groups

Figure 1 shows the comparison of the number of patients with clinical symptoms between the two groups while Figure 2 shows the comparison of the incidence rate of various clinical symptoms between the two groups. The number of patients with cough, expectoration, fever, chest tightness, and hemoptysis/sputum blood in the observation group was significantly higher than that in the control group (*p*-value<0.05), and the incidence rate of cough, expectoration, fever, chest tightness, and hemoptysis/sputum blood in the observation group was higher than that in the control group, and the differences had statistical significance (p-value<0.05). The probability of cough and expectoration was higher, and the probability of chest tightness was lower in the clinical symptoms of patients in both groups.

# *Comparison of Relevant Indicators Between the two Groups*

Figure 3 indicates the comparison of relevant indicators between the two groups. The white blood cell count and C-reactive protein content in the observation group were higher than those in the control group, and the difference had statistical significance (*p*-value<0.05). The CD4 and CD4/CD8 in the observation group were lower than those in the control group. The bronchoalveolar lavage fluid GM and serum GM levels in the observation group were significantly higher than those in the control group, and the difference had statistical significance (*p*-value< 0.05).

# *Comparison of Imaging Findings Between the two Groups*

The imaging examination results of patients in the two groups are shown in Figure 4 and Figure 5. It can be suggested that the probability of nodules, cavities, and pleural effusion in the observation group was higher than that in the control group, especially the probability of cavities, which was much higher than that in the control group. The probability of plaques in the observation group was lower than that in the control group, and the difference had statistical significance (*p*-value <0.05). Figure 6 indicates pulmonary tuberculosis complicated with pulmo-



Figure 2. Incidence of various clinical symptoms in the two groups. A, is the observation group and B, is the control group.



**Figure 3.** Comparison of relevant indicators between the two groups of patients. **A**, White blood cells. **B**, C-reactive protein. **C**, CD4 and CD4/CD8. **D**, Bronchoalveolar lavage fluid GM and serum GM.

nary aspergillosis in the pulmonary cavity. VIA shows right lower lobe cavity with pulmonary aspergillosis, and a small amount of exudation is observed in the periphery. VIB shows left upper lobe cavity with pulmonary aspergillosis, nodules are observed in the chest, and there is a half moonlight transmission area between the cavity and the inner wall.



**Figure 4.** Imaging findings of patients in the observation group.

# Multivariate Analysis of Risk Factors for Pulmonary Tuberculosis Complicated With Pulmonary Aspergillosis

Diagnostic history, hemoptysis/sputum with blood, C-reactive protein, corticosteroids, and duration of antibiotic use were included in the multivariate analysis. Table II displayed the multivariate Logistic analysis of patients in the two



Figure 5. Imaging findings of patients in the control group.

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**Figure 6.** Pulmonary tuberculosis complicated with pulmonary aspergillosis in pulmonary cavity. **A**, Right lower lobe cavity with pulmonary aspergillosis. **B**, Left upper lobe cavity with pulmonary aspergillosis).

groups. It was found that the numerical value and odds ratio (OR) of glucocorticoid's application time and rifampicin antibiotic application time were significantly higher (*p*-value<0.05). This indicated that long-term use of glucocorticoids and antibiotic rifampicin was an independent risk factor for pulmonary tuberculosis with pulmonary aspergillosis infection.

## Clinical Prognostic Score of Patients with Pulmonary Tuberculosis Complicated with Pulmonary Aspergillosis

According to the assignment of the regression coefficient (b) in the multivariate Logistic regression analysis, the minimum b value was 0.422, which was defined as 1 point. All b values were divided by 0.422, and then, rounded to an integer to obtain the score of each item. The score range was between 0 and 7, which was shown in Figure 7. A regression equation was worked out for each item with its corresponding assignment. The prognostic scoring system for patients with pulmonary tuberculosis and pulmonary aspergillosis =  $5 \times (revisited patients) + 6 \times (hormone application time \ge 1 week) + 7 \times (antibiotic application)$ 

time  $\geq 1$  month) + 1  $\times$  (hemoptysis/sputum with blood) + 4 × (C-reactive protein  $\ge$  30 mg/L). The clinical prognostic scoring system for patients with pulmonary tuberculosis and pulmonary aspergillosis was shown as Table III. The goodness of fit of the model was tested by Hosmer-Lemeshow; as *p*-value > 0.05, the goodness of fit of the model was considered to be good. It could be concluded that the clinical prognostic scores of the hormone application time  $\geq 1$  week and antibiotic application time  $\geq 1$  month were higher. The patients in two groups were divided into 3 groups on the ground of the score. Those who had a score of 0-7 were divided into the low-risk group, those of 8-14 were divided into the medium-risk group, and those of more than 14 were divided into the high-risk group.

# Kaplan-Meier Survival Curve of Patients in the Two Groups

Figure 8 represented the Kaplan-Meier survival curves of patients in the two groups, where A was of the control group and B was of the observation group. It could be observed that the cumulative survival rates of the high-risk, medium-risk, and low-risk groups in the observation

 Table II. Logistic regression analysis of risk factors in patients with pulmonary tuberculosis complicated with pulmonary aspergillosis.

Variables	β	OR	95% CI	Ρ	Assignment
Reexamination	2.248	1.42	1.14-1.49	0.352	5
Hormone application time $\geq 1$ week	2.345	5.83	2.55-3.24	0.012	6
Antibiotic application time $\geq 1$ month	3.083	13.45	1.35-4.24	0.002	7
Hemoptysis/blood in sputum	0.422	1.18	0.22-1.24	0.642	1
C-reactive protein $> 30 \text{ mg/L}$	1.812	1.35	0.82-1.49	0.238	4



**Figure 7.** Assignment of risk factors in patients with pulmonary tuberculosis complicated with pulmonary aspergillosis.

**Table III.** Clinical prognostic scoring system for patients

 with pulmonary tuberculosis complicated with pulmonary

 aspergillosis.

Types	Score
Reexamination	5
nitial 1 week	0
1 week	0
1 month	7
Iave	1
$\sqrt{10}$	0
30 mg/L	4 0
	Types eexamination nitial 1 week 1 week 1 month 1 month lave 10 30 mg/L 30 mg/L

group were all higher than those in the control group. The cumulative survival rate of the highrisk group was lower than that of both the medium-risk group and the low-risk group.

#### Discussion

Tuberculosis is one of the top ten causes of death in the world. Pulmonary tuberculosis is a common chronic wasting disease in clinical practice, which will cause dysfunction of vital organs and decreased immune function, lead to poor body resistance to diseases, and patients will have malnutrition and other symptoms. Pulmonary tuberculosis is infected by Mycobacterium tuberculosis and transmitted through the respiratory tract<sup>16</sup>. Tuberculosis is difficult to cure clinically, and the resulting infectious complications and mortality make it a major public health and social event of tuberculosis in the world. Pulmonary tuberculosis has a long course of disease and high cost of medication, which is a high burden disease. Reports show that more than one-third of the world's population suffers from tuberculosis, while nearly 8 million people are diagnosed with a mortality rate of more than 20% each year<sup>17</sup>. Pulmonary tuberculosis ranks among the highest in the number of cases and deaths from Class A and B infectious diseases in China. The annual number of new patients accounts for about 11% of the world incidence, ranking second<sup>18</sup>. Pulmonary tuberculosis can cause damage to various normal tissues and organs of the human body, and the most important complication in patients is infection. When the human body is infected with Mycobacterium tuberculosis, clinical manifestations, such as cough, expectoration, and chest tightness occur if the immune system cannot effectively resist the infection<sup>19,20</sup>. Tuberculosis infection can be completely cured if detected



**Figure 8.** Kaplan-Meier survival curves of patients in the two groups. **A**, Showed that of the control group, while **B**, showed that of the observation group.

and treated early. In recent years, cytotoxic drugs and immunosuppressive agents have been widely used and the number of HIV-infected patients has been increasing, resulting in an increasing number of pulmonary fungal infections. The number of patients with pulmonary aspergillosis among patients with non-hematologic malignancies ranks first among pulmonary fungal infections<sup>21</sup>.

Tuberculosis is the most common risk factor for pulmonary aspergillosis. The clinical manifestations of pulmonary aspergillosis are atypical and easily confused with other diseases. The gold standard for diagnosis is pathological examination. It is difficult to obtain this examination, so it is difficult to find it in the early stage of the disease. Pulmonary aspergillosis, as a pulmonary mycosis involving multiple clinical departments, has an insidious onset, high morbidity, and high mortality and should be focused by researchers and clinicians<sup>22,23</sup>. The main clinical feature of pulmonary tuberculosis complicated with pulmonary aspergillosis infection is hemoptysis or sputum blood, which is mainly caused by Aspergillus that can release endotoxin and soluble protease substances, causing tissue vascular necrosis and bleeding. Inflammatory factor infection caused by pulmonary aspergillosis will also stimulate the occurrence of pulmonary cavity lesions, resulting in bleeding. Bleeding complications also occur in bronchial disease secondary to pulmonary aspergillosis. Mechanical movement of Aspergillus can also cause blood vessel rupture and bleeding. It was found that chronic pulmonary aspergillosis can complicate the treatment of pulmonary tuberculosis, with a high mortality rate within 5 years<sup>24</sup>. The clinical characteristics and risk factors of pulmonary tuberculosis patients and pulmonary aspergillosis patients were investigated to provide clinical guidance for the prevention and treatment of the two diseases. The results showed that there was no significant difference in gender, age, smoking history, and underlying diseases between the two groups (*p*-value > 0.05). The proportion of newly diagnosed patients in the control group was significantly higher than that in the observation group. The proportion of patients with glucocorticoid use time  $\geq 1$  week and the proportion of patients with rifampicin antibiotic use time  $\geq 1$  month in the observation group were significantly higher than those in the control group (*p*-value < 0.05). The number of patients with cough, expectoration, fever, chest tightness, and hemoptysis/sputum blood in observation group was significantly higher than that in control group (*p*-value < 0.05). The probability of cough and expectoration was higher, and the probability of chest tightness was lower in patients with pulmonary tuberculosis and pulmonary aspergillosis.

C-reactive protein is able to respond to non-specific indicators of peripheral inflammation<sup>25</sup>. Studies found that long-term use of antibiotics will not only break the balance of airway microecology, reduce airway resistance to fungi, and increase the risk of pulmonary aspergillosis. By detecting C-reactive protein levels and monitoring the duration of antibiotic use, the diagnostic accuracy of pulmonary tuberculosis complicated with pulmonary aspergillosis can be improved, and the rational use of antibiotics in patients with pulmonary tuberculosis can be guided. It can prevent the possibility of multidrug resistance and double infection to some extent<sup>26,27</sup>. CD4 is the main receptor of HIV, and its detection results play an important role in the judgment of immune function in patients<sup>28</sup>. In addition, CD4/CD8 is also an important indicator of the immune status of the body. Bronchoscopy can clinically diagnose patients with pulmonary tuberculosis, and bronchoalveolar lavage fluid can be obtained by bronchoscopy, which is important for the diagnostic yield of patients with pulmonary tuberculosis<sup>29,30</sup>. The results showed that the contents of white blood cell and C-reactive protein in the observation group were higher than those in the control group (*p*-value < 0.05), CD4 and CD4/CD8 in the observation group were lower than those in the control group, and the GM levels in bronchoalveolar lavage fluid and serum were significantly higher than those in the control group, and the differences had statistical significance (p-value < 0.05). The probability of nodules, cavities, and pleural effusion in the observation group was higher than that in the control group. The probability of cavities in the observation group was extremely high, the probability of plaque in the observation group was lower than that in the control group, and the differences were statistically significant (p-value < 0.05). Multivariate regression analysis revealed that the  $\beta$ -values and OR values of glucocorticoid use time and rifampicin antibiotic use time were significantly higher, and long-term use of glucocorticoids and rifampicin antibiotics was an independent risk factor for pulmonary tuberculosis with pulmonary aspergillosis infection (*p*-value < 0.05). It indicates that the use of hormones and antibiotics will exacerbate the condition of pulmonary tuberculosis patients with pulmonary aspergillosis. The clinical prognostic scores of hormone application time  $\geq 1$  week and antibiotic application time  $\geq 1$  month were higher, and the two factors were important high-risk factors. In the observation group, the cumulative survival rates of all the high-risk, medium-risk, and low-risk groups were higher than those in the control group. The cumulative survival rate of the high-risk group in both groups was lower than that of the medium-risk and the low-risk groups. However, the sample size is small, which needs to be complemented with justification in the future.

### Conclusions

The clinical characteristics and risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis were explored. The independent factor analysis showed that "hemoptysis and blood in sputum" could be considered as the main clinical features of pulmonary tuberculosis complicated with pulmonary aspergillosis. The main risk factors of pulmonary tuberculosis complicated with pulmonary aspergillosis were "antibiotic application time (rifampin)  $\geq 1$  month" and "hormone application time  $\geq 1$  week".

#### **Conflict of Interest**

The Authors declare that they have no conflict of interests.

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