

Determinants of prognosis in *Talaromyces marneffe* infections with respiratory system lesions

Ye Qiu, Jian-Quan Zhang, Mian-Luan Pan, Wen Zeng, Shu-Dan Tang, Cai-Mei Tan

Department of Respiratory Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, China.

Abstract

Background: Little study has investigated the differences between *Talaromyces marneffe* (*T. marneffe*) respiratory infection and tuberculosis and the prognostic factors of such infection. This study investigated the characteristics and prognostic factors of *T. marneffe* infections with respiratory lesions and the causes of misdiagnosis.

Methods: Clinical characteristics and prognoses of patients with *T. marneffe* infections with respiratory system lesion were investigated. *T. marneffe* diagnosis followed isolation from clinical specimens using standard culture, cytology, and histopathology. Survival curves were estimated by using Kaplan-Meier analysis, with log-rank test to compare differences in survival rates between groups. Univariate and multivariate Cox regression analyses were also performed to assess significant differences in clinical characteristics of overall survival.

Results: Of 126 patients diagnosed with *T. marneffe* infections, 63 (50.0%) had *T. marneffe* respiratory system infections; 38.1% (24/63) were misdiagnosed as having tuberculosis. Human immunodeficiency virus (HIV) infection, CD4/CD8 < 0.5, percentage of CD4⁺ T cells < 42.8%, and length of time from onset to confirmation of diagnosis > 105 days were potential risk factors for poor prognoses. Length of time from onset to confirmation of diagnosis persisted as an independent predictor of all-cause mortality in multivariate analysis (odds ratio: 0.083, 95.0% confidence interval: 0.021–0.326, *P* < 0.001). However, the size of the lung lesions, dyspnea, thoracalgia, mediastinal lymphadenopathy, and pleural effusion did not significantly predict overall survival. There was no significant difference in prognosis according to the type of treatment.

Conclusions: *T. marneffe* infections involving the respiratory system are common. The critical determinants of prognosis are HIV infection, CD4/CD8, percentage of CD4⁺ T cells, type of treatment, and the time range from onset to confirmation of diagnosis. Rapid and accurate diagnosis is crucial for improving prognosis.

Keywords: *Talaromyces marneffe*; Respiratory system infection; Modes of transmission; Prognostic factors

Introduction

Talaromycosis is a deep fungal infection caused by *Talaromyces marneffe* (*T. marneffe*), which is an important endemic fungus in Southeastern Asia.^[1,2] Talaromycosis can involve the skin, respiratory system, digestive system, and reticuloendothelial system, leading to local or disseminated infections.^[3,4] This infection is known to have poor prognoses owing to its high recurrence and mortality rates, particularly in human immunodeficiency virus (HIV)-negative patients.^[2-5] In addition, *T. marneffe* infections with respiratory system lesions are often misdiagnosed as tuberculosis, and thus, patients receive long-term anti-tuberculosis treatment that in turn leads to refractory pneumonia, systemic spread, fatal complications (e.g., structural damage to the tracheal cartilage, severe tracheostenosis, and tracheal absence),^[6-8] and a high mortality rate. However, the determinants of

prognosis in *T. marneffe* infections with respiratory system lesions remain unknown, and few studies have investigated the reasons why *T. marneffe* infections with respiratory system lesions are commonly misdiagnosed as tuberculosis.

Previously, since *T. marneffe* infections were highlighted to involve the skin, involvements of other organs were overlooked. However, in recent animal studies, it was reported that rats become infected by inhaling aerosolized conidia from environmental sources rather than through the fecal-oral or transplacental routes.^[5-8] Therefore, the respiratory system maybe the first system to exhibit significant signs of infection. However, clinical evidences to prove this hypothesis in humans are lacking.

In this study, we aimed to investigate the characteristics and prognostic factors of *T. marneffe* infections with respiratory system lesions and explore the reasons for its

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Correspondence to: Prof. Jian-Quan Zhang, Department of Respiratory Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi 530021, China
E-Mail: jqzhang2002@126.com

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misdiagnosis in subtropical southern China, an endemic area for *T. marneffeii*. We also attempted to obtain clinical evidence that airborne transmission may be among one of the most important modes of transmission for *T. marneffeii* infections.

Methods

Ethical approval

This study was approved by the ethics committee of the First Affiliated Hospital of Guangxi Medical University at 2016 (No. 2016KY-E-044). Informed written consent was obtained from all of the patients in accordance with the Declaration of Helsinki of 1975, as revised in 2000.

Study design

Participant selection

This study retrospectively evaluated data from patients admitted at the First Affiliated Hospital of Guangxi Medical University between January 1, 2003 and January 1, 2015. Consecutive patients with confirmed diagnoses of *T. marneffeii* respiratory system infections involving the upper (pharynx and larynx) and/or lower respiratory tracts (trachea, bronchi, and lungs) were included. We excluded patients diagnosed with *T. marneffeii* infection that did not involve the respiratory system. Patient information, including demographics (sex and age), medical history (present history, comorbidities, and previous therapy), clinical presentation, auxiliary examination results (hematologic tests, serologic tests, immune status, imaging examinations, and pathologic and microbiologic tests), and treatment, were retrieved from medical records and summarized in the analysis. All patients were followed up to January 1, 2015 or the time of death. The outcomes were categorized as (1) effective when a sustained response after effective antifungal treatment was achieved (ie, resolution of talaromycosis-related symptoms and negative culture results); (2) relapse when a temporary clinical response with a subsequent relapse occurred; or (3) death.

Diagnostic criteria for *T. marneffeii* infections

T. marneffeii infections were diagnosed following the isolation of *T. marneffeii* from clinical specimens (eg, blood, bone marrow, lymph nodes, sputum, skin scrapings, or bronchoalveolar lavage fluid [BALF]) using standard culture techniques.^[1,2] Alternatively, the infection was diagnosed after *T. marneffeii* identification via light microscopy using cytology and histopathology specimens stained with periodic acid-Schiff or Wright-Giemsa.^[7-10] The yeast form of *T. marneffeii* had a characteristic morphology and a transverse septum.^[10] Positive *T. marneffeii* cultures were characterized by dimorphic fungi that grow as a mold at 25°C and as yeast at 37°C.^[1-4]

Enrollment criteria for *T. marneffeii* respiratory system infections

- (1) *T. marneffeii* respiratory system infections were directly diagnosed after *T. marneffeii* was identified in sputum,

BALF, and/or clinical samples from the upper or lower respiratory tracts at histopathology, cytology, and/or fungal culture.

- (2) When patients were diagnosed as *T. marneffeii* infection with an extrapulmonary etiology, the diagnosis of *T. marneffeii* respiratory system infections was based on abnormal chest radiography findings. These findings included new or changing pulmonary infiltrate with at least two of the following findings: fever, dyspnea, thoracalgia, cough, sputum production, leukocytosis, and purulent tracheal secretions. The diagnosis was confirmed after other diseases (eg, other bacterial or fungal pulmonary infections, lung cancer, non-infectious interstitial lung disease, pulmonary edema, pulmonary atelectasis, pulmonary embolism, and pulmonary eosinophil infiltration syndrome) were ruled out, and when improvement after treatment with antifungal agents alone is noted.

Exclusion criteria

Patients diagnosed with *T. marneffeii* infection that did not involve the respiratory system were excluded.

Definition of *T. marneffeii* local respiratory system infection

T. marneffeii local respiratory system infections were defined as *T. marneffeii* infection limited to the respiratory system, including the upper (pharynx and larynx) and/or lower respiratory tracts (trachea, bronchi, and lungs).

Definition of disseminated *T. marneffeii* infection involving respiratory system

Disseminated *T. marneffeii* infections were defined as infections involving not only the respiratory system, but also other systems or tissues, such as the skin, lymph nodes, bone, bone marrow, liver, spleen, brain, thoracic cavity, pericardium, and other parts of the reticuloendothelial system.

Testing for the human immunodeficiency virus (HIV)

Patients' sera were tested in duplicate at our hospital and at the Guangxi Center for Prevention and Control using an enzyme-linked immunosorbent assay (Enzymun-Test Anti-HIV 1+2; Boehringer Mannheim GmbH, Diagnostica, Germany) and the particle agglutination test (Serodia-HIV; Fujirebio Inc., Tokyo, Japan). The patients were divided into two groups: HIV-positive and HIV-negative groups.

Statistical analysis

Measurement data of normal distribution were expressed as mean \pm standard deviation (SD) and data of non-normal distribution were expressed as median (interquartile range). The categorical variables were expressed as the number and percentage. The Pearson Chi-squared test or Fisher exact test Chi-squared (χ^2) analysis was used to analyze the antifungal treatment and outcomes in patients who have *T. marneffeii* infections with respiratory system lesion; the level of statistical significance was set at

$P < 0.05$. Survival curves were estimated using Kaplan-Meier analysis, and differences in survival rates between the two groups were compared using the log-rank test. Univariate analysis was performed to assess significant differences in age, recurrence, underlying diseases except HIV infection, white blood cell, neutrophils, lymphocytes, bilateral lung lesions, pleural effusion, mediastinal lymphadenopathy, dyspnea, thoracalgia, HIV infection, the time range from onset to confirmation of diagnosis, CD4/CD8 ratio, and CD4⁺ T-cell percentage on overall survival. Significant variables identified in the univariate analysis were evaluated further via multivariate analysis using Cox regression analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 25.0; SPSS Inc., Chicago, IL, USA). Two-tailed tests were used, and a $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Of the 126 patients diagnosed with *T. marneffei* infection during the study period, 63 (50.0%) patients with respiratory system infection were included in the analyses [Figure 1]. Of these, 30 and 33 were positive and negative for HIV, respectively. The infection involved the upper respiratory tract in seven (11.1%) HIV-positive patients. Thirteen (20.6%) patients had local *T. marneffei* pneumonia, of these, seven were HIV positive, one was undergoing glucocorticoid therapy, and one had diabetes. Of the 46 (73.0%) patients with disseminated *T. marneffei* infection,

19 were HIV positive, two had β -thalassemia, and two had hyperthyroidism. There were also single cases of diabetes, breast cancer, glucose-6-phosphate dehydrogenase deficiency, subacute thyroiditis, and chronic hepatitis B.

Respiratory system infections due to *T. marneffei* were observed in both infants and elderly patients. The mean age of patients overall was 39.5 ± 17.6 years (range, 1–72 years). The patients' birthplaces included Guangxi ($n = 60$), Hunan ($n = 1$), Guizhou ($n = 1$), and Shandong ($n = 1$). All patients were permanently residing in the Guangxi Province of China. Twenty-four (38.1%) patients were misdiagnosed as pulmonary tuberculosis and 5 (7.9%) as bacterial pneumonia. The median time from onset to confirmation of diagnosis was 105 days (range, 11–912 days).

Clinical features and laboratory findings

The common clinical and respiratory symptoms and signs included fever, cough, expectoration, and crackles, followed by thoracalgia, dyspnea, and respiratory failure [Table 1]. White sputum was the most common form of sputum. Yellowish and blood-streaked sputum were also observed, although no hemoptysis was identified. Sore throat, hoarseness, dysphagia, pharyngeal and laryngeal lumps, and/or mucosal ulcerations were the most common upper respiratory tract symptoms.

Mean white blood cell count was 15.9 ± 11.8 (range: $1.4\text{--}38.0$) $\times 10^9$ cells/L. Seven patients had white blood cell counts below 3.5×10^9 cells/L (one was HIV negative, six were HIV positive). Other findings were as follows:

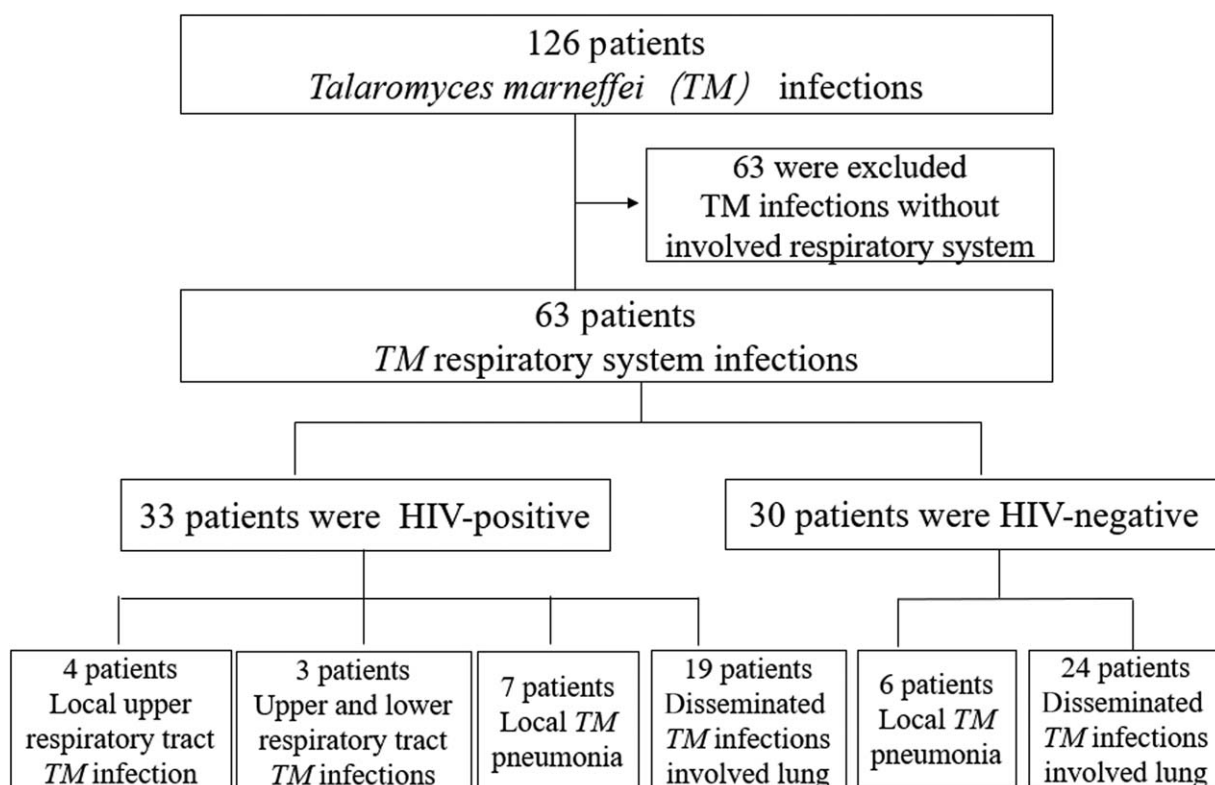


Figure 1: Enrollment, human immunodeficiency virus (HIV) infection status, and respiratory infection classification of the study.

Table 1: Clinical features of patients who have *Talaromyces marneffei* infections with respiratory system lesion (n = 63).

Characteristics	Patients, n (%)
Fever	63 (100.0)
Respiratory symptoms/signs	
Cough	53 (84.1)
Expectoration	46 (73.0)
White phlegm sputum	29 (46.0)
Yellowish sputum	17 (26.9)
Blood-streaked sputum	9 (14.3)
Thoracalgia	14 (22.2)
Dyspnea	12 (19.0)
Crackles	33 (52.4)
Respiratory failure	12 (19.1)
Sore throat	7 (11.1)
Hoarseness	4 (6.3)
Pharyngeal/laryngeal mucosal ulceration	6 (9.5)
Pharyngeal/laryngeal lump	4 (6.4)
Acataposis	2 (3.2)
Extrapulmonary symptoms/signs	
Swollen lymph nodes	51 (80.9)
Rashes or skin nodules	43 (68.3)
Pleural effusion	23 (36.5)
Splenomegaly	25 (39.7)
Hepatomegaly	24 (38.1)
Osteolysis	16 (25.4)
Pericardial effusion	9 (14.3)
Seroperitoneum	8 (12.7)
Pharyngeal and/or laryngeal lumps and/or ulcerations	7 (11.1)
Low density of brain nodule	1 (1.6)

decreased hemoglobin concentrations (mean: 89.8 ± 22.9 [range: 34.5–135.2] g/L); CD4⁺ lymphocyte percentage (median: 30.5% [13.1–38.8%]); CD8⁺ lymphocyte percentage (median: 28.7% [18.7–37.9%]); CD4⁺/CD8⁺ ratio (median: 0.9 [0.3–2.2]); and increased C-reactive protein concentrations and erythrocyte sedimentation rates. Twelve patients exhibited dyspnea and underwent blood gas analysis; the results showed that all 12 patients had type I respiratory failure with hypoxemia.

Endoscopy and high-resolution computed tomography

All the 63 patients underwent chest computed tomography (CT), and exhibited one or more abnormal characteristics in one or both lungs [Table 2]. The most common CT imaging findings were patchy exudates, fibrous cords, pleural effusion, ground glass opacities, and nodular lesions, followed by cavitory lesions, alveolar consolidation, miliary lesions, and tracheobronchial stenosis [Figure 2].

Seven patients underwent electronic and endoscopic nasopharyngoscopy that showed pharyngeal and laryngeal ulcers and/or lumps [Figures 3A–3C].

Thirty patients underwent fiberoptic bronchoscopy. Abnormal findings included inflammatory changes (24/30, 80.0%), tracheobronchial stenosis (8/30, 26.7%), and

Table 2: Local symptoms in *Talaromyces marneffei* infections with respiratory system lesion (n = 63).

Variables	Patients, n (%)
Upper respiratory tract	
Nasal endoscopic, electronic nasopharyngoscopy (n = 7)	
Pharyngeal/laryngeal ulcers and lump	3
Pharyngeal/laryngeal ulcers	4
Pharyngeal/laryngeal lump	4
Low respiratory tract	
Chest computed tomography (n = 63)	
Bilateral lung lesions	39 (61.9)
Unilateral lung lesions	24 (38.1)
Patchy exudation	53 (84.1)
Pleural effusion and/or pleural thickening	30 (47.6)
Fibrous cord	28 (44.4)
Ground glass opacities	22 (34.9)
Nodule lesions	17 (26.9)
Cavitory lesions	9 (14.3)
Alveolar consolidation	8 (12.7)
Miliary lesions	5 (7.9)
Fiberoptic bronchoscopy (n = 30)	
Inflammatory changes	24 (80.0)
Tracheobronchial stenosis	8 (26.7)
Nodule or mass in the trachea wall	6 (20.0)

nodules or masses in the tracheal wall (6/30, 20.0%) [Figures 3D–3F]. The nodules or masses were mostly multiple, white, and sub-mucosal. One patient underwent thoracoscopy, which revealed pleural adhesions and multiple small nodules on the visceral pleura.

Etiologic evidence for *T. marneffei* respiratory system infection

Forty-two (66.7%) cases were directly confirmed to be *T. marneffei* respiratory system infection via positive respiratory system specimen culture or cytologic/histopathologic analysis, as follows: sputum culture (14/63, 22.2%), BALF culture (17/30, 56.7%), cytologic lung brush inspection (16/30, 53.3%), lung histopathology (22/30, 73.3%), pharyngeal/laryngeal lesions (6/6), tonsil lesions (4/4), and histopathologic review of pharyngeal and laryngeal lesion specimens (7/7). Twenty-one patients were diagnosed with respiratory system talaromycosis without respiratory system etiology based on chest radiography findings, clinical symptoms, and the exclusion of other diseases, among these 21 patients with extrapulmonary etiology, the diagnosis was confirmed via samples from the skin (14/43, 32.6%); blood (37/63, 58.7%), purulent discharge (11/30, 36.7%), lymph nodes (6/28, 21.4%), bone marrow (13/36, 36.1%), and pleural membrane (1/1).

The most common histopathologic findings were lymphocyte infiltration, neutrophil infiltration, and other components of a mixed inflammatory response, fibrosis, microabscess formation, and proliferation of inflammatory granulation tissue in HIV-negative patients. Meanwhile, pathologic non-reactive necrosis was observed in HIV-positive patients.

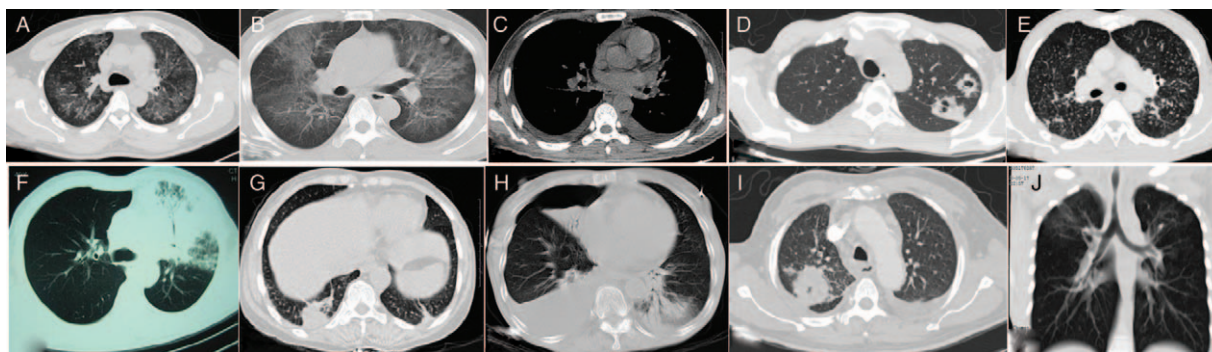


Figure 2: High-resolution computed tomography revealed pulmonary involvement in human immunodeficiency virus (HIV)-positive patients. (A) Patchy exudates, (B) nodular infiltrates, (C) pleural effusion, (D) cavitary lesions, and (E) miliary lesions. High-resolution computed tomography revealed pulmonary involvement in HIV-negative patients. (F) Patchy exudates, (G) fibrous cords, (H) pleural effusion, (I) cavitary lesions, and (J) tracheobronchial stenosis.

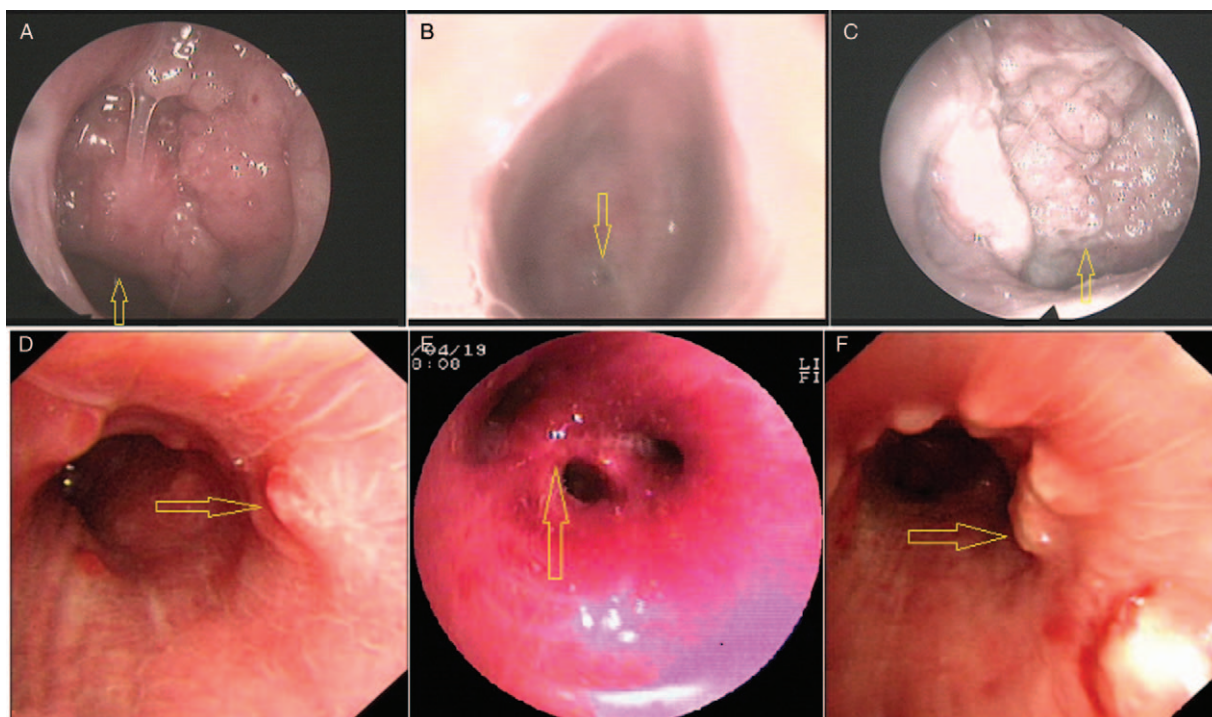


Figure 3: Electronic nasopharyngoscopy revealed nasopharyngeal lumps (A and C) and throat obstruction (B). Fiberoptic bronchoscopy revealed pulmonary involvement. Inflammatory changes at the trachea (D), tracheobronchial stenosis (E), and an irregular tracheal wall with numerous protrusions in the main trachea and the left and right principal bronchi (F). Arrow: abnormal findings.

Treatment and outcome

Seven of the patients did not receive antifungal therapy and had severe systemic inflammatory responses and died. Other patients received antifungal treatment based on susceptibility test results. Among the 56 patients who received antifungal therapy, 15 died during the first round of antifungal therapy due to worsened clinical conditions and organ failure. Eight patients relapsed due to improper withdrawal of antifungal therapy. Forty-one patients were effectively treated using intravenous amphotericin B ($0.6\text{--}1.0\text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) and fluconazole (400 mg/day) for 2 weeks, followed by oral itraconazole (400 mg/day) antifungal therapy [Table 3]. Treatment programs were

analyzed using Fisher exact test. There was no statistically significant difference in prognosis between different treatments.

Overall survival

We evaluated the capabilities of 15 variables to predict survival [Table 4]. Univariate analysis indicated that age ($P = 0.069$), underlying diseases except HIV infection, white blood cell, neutrophils, lymphocytes, bilateral lung lesions ($P = 0.068$), pleural effusion, mediastinal lymphadenopathy, and dyspnea were not significantly associated with overall survival. HIV infection, the time range from

Table 3: Treatment and outcomes in patients with *Talaromyces marneffe* infections with respiratory system lesion.

Variables	N	Effective, n	Relapse, n	Death, n
Amphotericin B followed by itraconazole*	17	13	2	2
Fluconazole	15	12	1	2
Itraconazole	4	2	0	2
Voriconazole	5	3	2	0
Caspofungin	1	1	0	0
Fluconazole + amphotericin B [†]	7	5	1	1
Amphotericin B	2	1	1	0
Fluconazole followed by itraconazole*	5	4	1	0
Treatment received*	56	41	8	7

Categorical data were analyzed using Fisher exact test as appropriate. * Sequential therapy. [†] Combination therapy. Drug dosage: Amphotericin B: 0.6–1.0 mg·kg⁻¹·d⁻¹; Fluconazole: 400 mg/day; Itraconazole: 400 mg/day; Voriconazole: 400 mg/day; Caspofungin: 50–70 mg/day. Treatment programs were analyzed using Fisher exact test ($\chi^2 = 14.6$, $P = 0.405$).

Table 4: Univariate and multivariate analyses of predictive factors of recurrence-free survival among patients with *Talaromyces marneffe* infections who have respiratory system lesions.

Factors	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
HIV infection	0.255	0.096–0.677	0.004	21.63	0–45.47	0.944
Age >60 years or <12 years	2.075	0.944–4.565	0.069			
With underlying diseases*	0.845	0.366–1.952	0.694			
Recurrence	1.154	0.500–2.663	0.737			
Bilateral lung lesions	2.333	0.938–5.801	0.068			
Pleural effusion	0.911	0.415–1.998	0.815			
Mediastinal lymphadenopathy	1.121	0.486–2.586	0.789			
Dyspnea	1.218	0.526–2.819	0.645			
Thoracalgia	0.704	0.264–1.876	0.482			
Duration of diagnosis >105 days [†]	0.092	0.037–0.228	<0.001	0.083	0.021–0.326	<0.001
WBC <4 × 10 ⁹ /L	0.918	0.265–3.177	0.893			
Neutrophils >6.3 × 10 ⁹ /L	0.980	0.131–7.330	0.984			
Lymphocytes <1.10 × 10 ⁹ /L	2.151	0.833–5.540	0.169			
CD4/CD8 <0.5	5.225	1.691–16.142	0.004	0.004	0–7.825	0.959
CD4% <42.80%	3.253	1.107–9.562	0.032	0.474	0.155–1.447	0.190

* Underlying diseases include undergoing glucocorticoid therapy, diabetes, β -thalassemia, hyperthyroidism, diabetes, breast cancer, glucose-6-phosphate dehydrogenase deficiency, subacute thyroiditis, and chronic hepatitis B, except HIV infection. [†] Duration of diagnosis means the time range from onset to confirmation of diagnosis. CI: Confidence interval; HIV: Human immunodeficiency virus; HR: Hazard ratio; WBC: White blood cell; CD4%: CD4⁺ T-cell percentage.

onset to confirmation of diagnosis, CD4/CD8 ratio, and CD4⁺ T-cell percentage were significantly associated with overall survival ($P < 0.05$) [Figures 4–6 and Table 4]. However, only the time range from onset to confirmation of diagnosis remained a significant independent predictor of all-cause mortality in the multivariate analysis (odds ratio: 0.083, 95% confidence interval: 0.021–0.326, $P < 0.001$).

Discussion

T. marneffe is an opportunistic fungal pathogen that poses a serious health threat to patients with acquired immunodeficiency syndrome (AIDS), particularly in southeastern Asia and southern China.^[1] Previously, HIV infection has been highlighted as a risk factor for *T. marneffe* infection, and the most common site of involvement is the skin.^[11] However, *T. marneffe* infection involved the respiratory

system in 50.0% of patients. Approximately 38.1% of patients were misdiagnosed as tuberculosis and received anti-tuberculosis treatment. These suggest that *T. marneffe* infection involving the respiratory system is not rare, but it is often overlooked and misdiagnosed as tuberculosis.

Recent studies have reported that the fungus is more frequently observed in bamboo rats' lungs than in other organs (lung specimens [100.0%], liver [83.3%], spleen [83.3%], burrows [8.2%], non-rat-associated sites [2.0%], and artificial bamboo rat farms [0]).^[6,7] Our data also showed that *T. marneffe* was more frequently isolated from the respiratory system (66.7%), particularly in BALF culture and lung and pharyngeal/laryngeal histopathology, than from other tissues, such as the skin, bone marrow, and lymph nodes. This suggests that the respiratory system may be the first and most commonly involved organ.

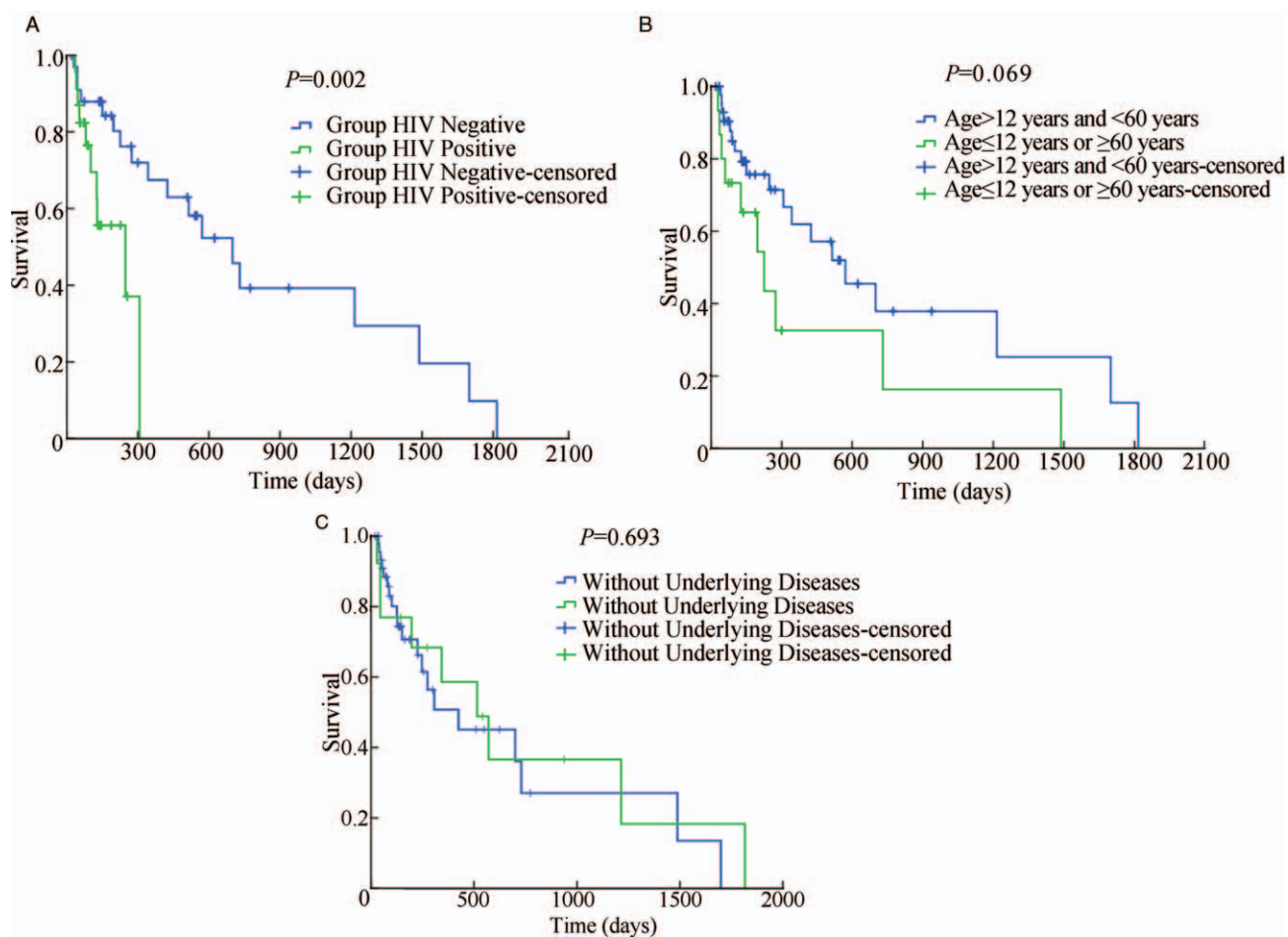


Figure 4: Survival curves. (A) Overall survival among human immunodeficiency virus (HIV)-positive and HIV-negative patients (log-rank test: $P = 0.006$). (B) Overall survival among patients aged >60 or <12 years, and ≥ 12 and ≤ 60 years (log-rank test: $P = 0.069$). (C) Overall survival among patients with underlying diseases and without underlying diseases except HIV infection (log-rank test: $P = 0.694$).

Inhaled aerosolized conidia from environmental sources may be an important mode of transmission for *T. marneffeii* infections.

Regarding overall survival, we found that respiratory conditions including pleural effusion, mediastinal lymphadenopathy, and dyspnea were not significantly associated with overall survival. Moreover, although the size of the lung lesions and age may tend to influence survival, they had no significant association with overall survival. This may be because of the limited number of cases in this study; in particular, there were few cases of severe pneumonia and large pleural effusion. Underlying diseases, aside HIV infection, may have minimal association with overall survival in the current study because only four patients (two with diabetes, one undergoing glucocorticoid therapy, and one with breast cancer) with underlying disease leading to immune compromise, were included in this study. However, the time from onset to confirmation of diagnosis, HIV infection, CD4/CD8 ratio, and CD4⁺ T-cell percentage were significantly associated with overall survival. This shows that HIV infections may be more closely associated with *T. marneffeii* infections than other diseases.^[12] Thus, comorbidities affecting the function and number of CD4⁺ T-cell may have a more pronounced effect

on prognosis than other conditions that do not. However, only the time from onset to confirmation of diagnosis remained a significant independent predictor of all-cause mortality and an independent risk factor of all-cause mortality in the multivariate analysis (odds ratio: 0.083, 95% confidence interval: 0.021–0.326, $P < 0.001$). In the present study, the median time from onset to confirmation of diagnosis was 105 days, and the longest diagnosis time was 912 days, which shows that the diagnosis of *T. marneffeii* infections is usually delayed. The infection was commonly misdiagnosed as tuberculosis, and patients received long-term anti-tuberculosis treatment. This may have caused the delayed diagnosis and emphasizes the importance of rapid and accurate diagnosis to improve prognosis.

T. marneffeii infection involving the respiratory system is often overlooked and misdiagnosed as tuberculosis owing to the following probable reasons. First, relevant literature and research on *T. marneffeii* infection with respiratory system lesions is limited. Secondly, *T. marneffeii* infection has been strongly emphasized as a common opportunistic infection of patients with AIDS, involving the skin. Thirdly, the signs and symptoms (fever, cough, expectoration, and crackles), lung imaging findings (catchy

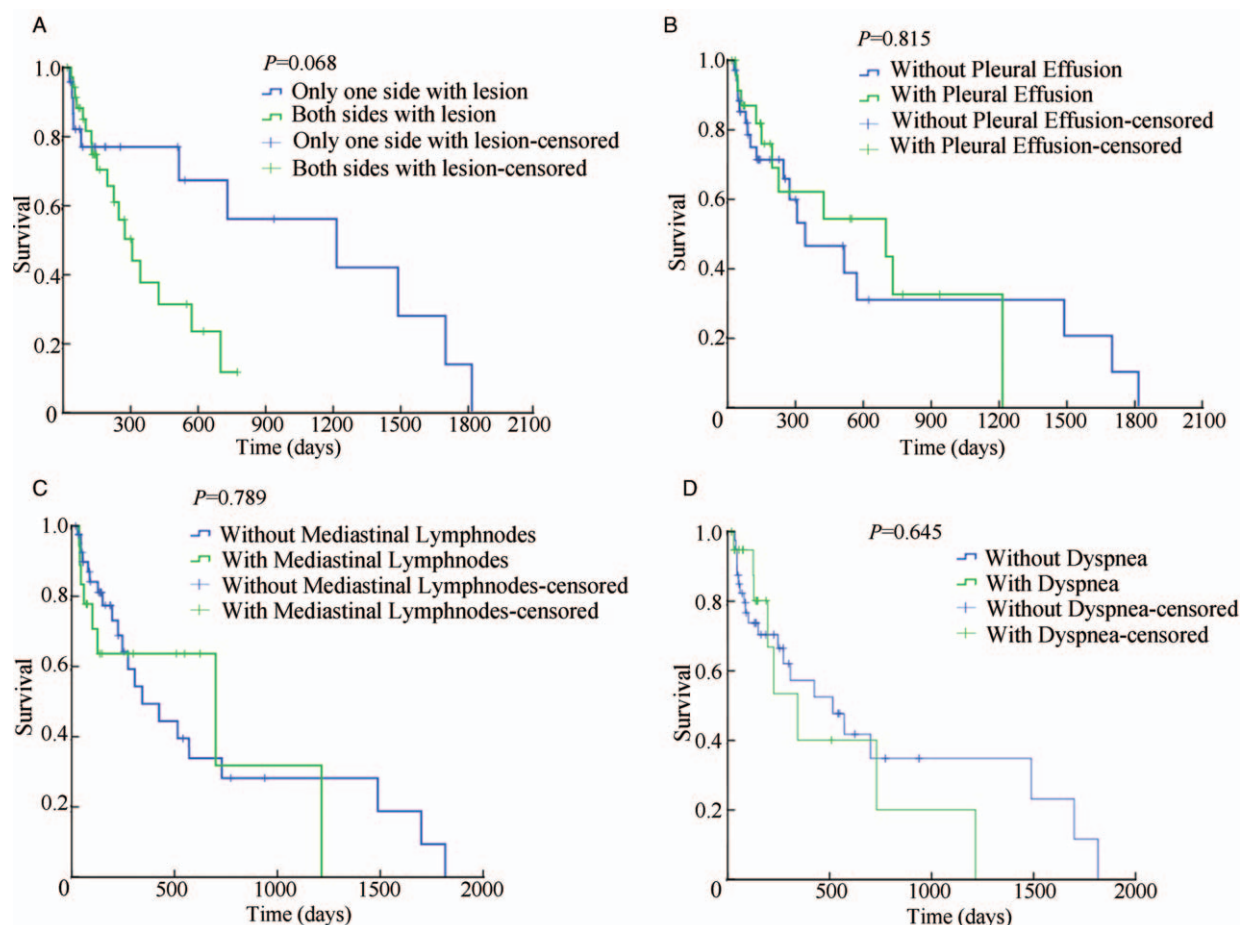


Figure 5: Survival curves. (A) Overall survival among bilateral lung lesions and unilateral lung lesions (log-rank test: $P = 0.068$). (B) Pleural effusion, (C) mediastinal lymphadenopathy, and (D) dyspnea were not significantly associated with overall survival.

exudates, fibrous cords, pleural effusion, ground-glass opacities, and nodular lesions, followed by cavitory lesions, alveolar consolidation, miliary lesions, and tracheobronchial stenosis), and endoscopy results (inflammatory changes, tracheobronchial stenosis, and nodules or masses in the tracheal wall), pathologic examination findings (lymphocyte infiltration, microabscess and granuloma formation, and non-reactive necrosis) are similar to those of tuberculosis. In addition, the absence of etiologic evidence during the early stages of the disease makes diagnosis challenging. Moreover, although endoscopy can provide accurate diagnosis as it can be used to obtain lung specimens for histopathology, cytology, and fungal culture, it is an unattractive procedure for patients.

Differential diagnosis from other bacterial and fungal pneumonias, such as tuberculosis, *Aspergillus* species, *Histoplasma capsulatum*, and *Cryptococcus neoformans*, is also crucial.

In this study, we found that *T. marneffei* respiratory system infection often disseminated to other systems including the lymph nodes, skin, thoracic cavity, spleen, liver, bone, and bone marrow. Thus, clinicians should consider *T. marneffei* respiratory system infection when treating an unusual clinical dissemination or frequent recurrence of

infection in patients with symptoms, and with lung imaging, endoscopy, and pathologic findings similar to those of tuberculosis. When treating patients who lack the primary basis for tuberculosis and who show poor response to anti-tuberculosis treatment, clinicians should also consider *T. marneffei* respiratory system infection. Respiratory system specimens are useful for establishing the etiologic basis. The use of endoscopy to obtain lung specimens for histopathology, cytology, and fungal culture should be emphasized as the most important modality for diagnosis. In addition, other modalities such as polymerase chain reaction (18S ribosomal DNA, MP1 gene, ITS1, and ITS4 DNA), enzyme-linked immunosorbent assay (Mp1p, MAbs 4D1, 8B11 and 8C3, and MAbs 8C3 for the detection of *T. marneffei* antigen), and G test/ GM test allow for rapid diagnosis of *T. marneffei*, and may reduce the time to diagnosis and improve the outcomes (including the reduction in infection-associated mortality).^[12-14] Furthermore, next-generation sequencing (NGS) can be combined with other modalities for rapid diagnosis of *T. marneffei*. NGS of infection provides a new perspective in the clinical approach to systemic fungi infections and has strong potential for providing rapid etiologic diagnosis.^[15,16]

Timely and effective treatment is essential. *T. marneffei* is highly susceptible to antifungal treatment, and the current

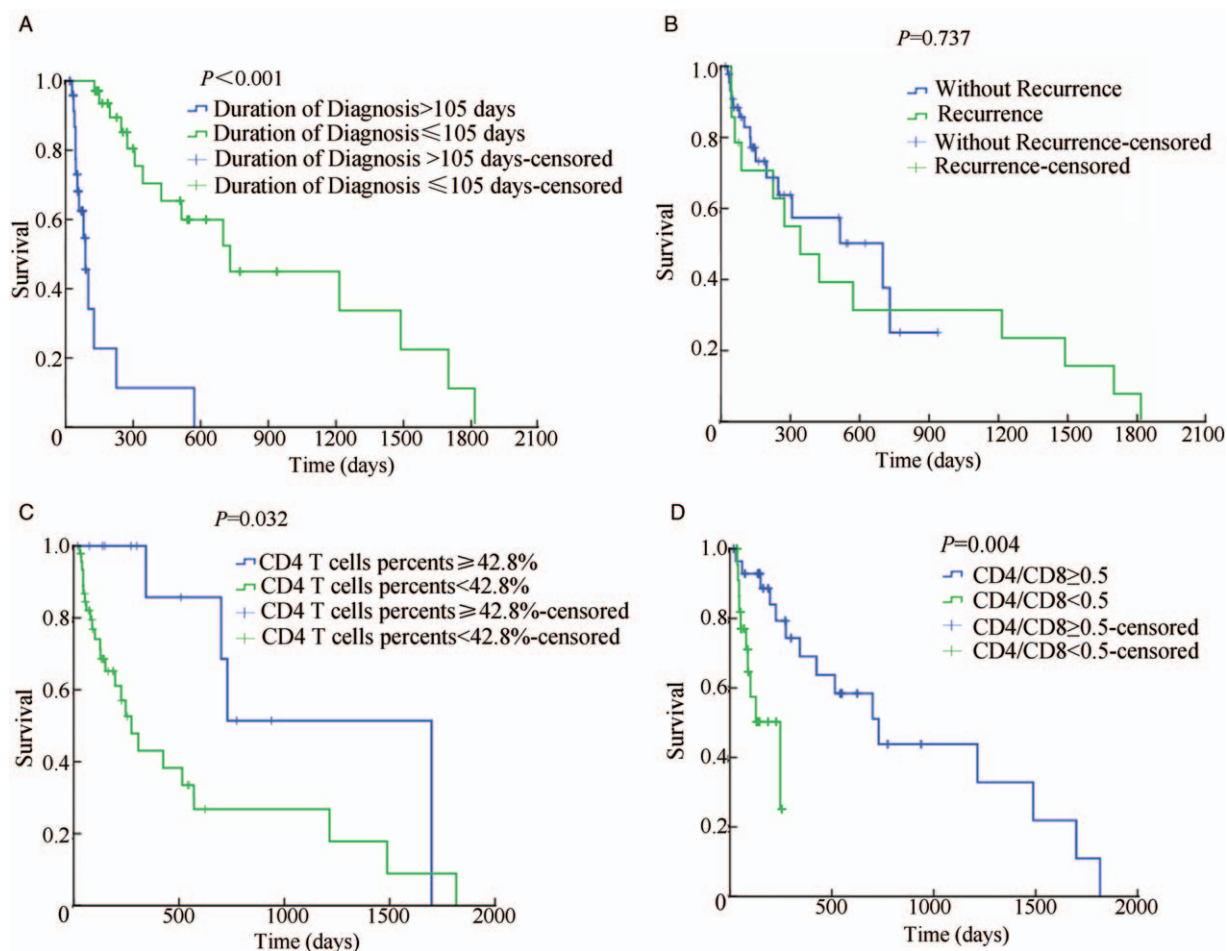


Figure 6: Overall survival among patients according to the duration of time from onset to confirmation of diagnosis (cut-off: 105 days; log-rank test: $P < 0.001$; A). Recurrence is not significantly associated with overall survival (B). Overall survival among patients according to a CD4⁺ T-cell percentage cut-off of 42.8% (log-rank test: $P = 0.032$; C). Overall survival among patients according to a CD4/CD8 ratio cut-off of <0.5 (log-rank test: $P = 0.004$; D).

recommended treatment for talaromycosis in HIV-positive patients is amphotericin B (0.6 mg/kg daily for 2 weeks), followed by oral itraconazole (200 mg twice daily for 10 weeks).^[1,2] In this study, the relapse rate was 14.3%, and the mortality rate was 26.9%. Most patients were effectively treated using intravenous amphotericin B and itraconazole (76.5%) or intravenous fluconazole (80.0%). Itraconazole, voriconazole, and caspofungin were also effective. Surprisingly, there was no statistically significant difference in the prognosis between the treatment modalities. This finding was consistent with those of previous in vitro research in Guangxi that reported no antagonistic effect in any of the antifungal combinations assayed for *T. marneffei*, including amphotericin B, itraconazole, micafungin, voriconazole.^[16,17] A retrospective study in Guangxi and a prospective study in Vietnam also showed that itraconazole and voriconazole are effective and well-tolerated in disseminated *T. marneffei* infection.^[1,17] However, individualized treatment and susceptibility testing should always be considered for an accurate treatment plan.

There are some limitations in our study. First, the number of cases was limited; thus large, multi-center research is needed for further understanding of the pathogenesis of

T. marneffei infection. Secondly, various adjuvant therapies were given to the patients; as such, we could not evaluate the optimal antifungal therapy for the infection. Despite these limitations, our results still offer valuable clinical information regarding patients with *T. marneffei* infection involving the respiratory system.

In conclusion, *T. marneffei* infections involving the respiratory system are common. HIV infection, CD4/CD8, percentage of CD4⁺ T, type of treatment, and the time from onset to confirmation of diagnosis are the major prognostic factors. The time from onset to confirmation of diagnosis is an independent risk factor of all-cause mortality. *T. marneffei* infections is commonly misdiagnosed as tuberculosis, and thus clinicians should consider *T. marneffei* infections in those with tuberculosis symptoms and with clinical findings, but have no tuberculosis etiology and do not respond to anti-tuberculosis treatment. Rapid and accurate diagnosis is crucial for improving prognosis.

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Conflicts of interest

None.

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