



Analysis of clinical characteristics and prognosis of talaromycosis (with or without human immunodeficiency virus) from a non-endemic area: a retrospective study

Qian Shen¹ · Lingyan Sheng¹ · Junli Zhang² · Jian Ye³ · Jianying Zhou¹

Received: 23 July 2020 / Accepted: 27 July 2021 / Published online: 5 August 2021
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Abstract

Purpose *Talaromyces marneffe* (TM) is a pathogenic fungus endemic in Southeast Asia and human immunodeficiency virus (HIV)-positive populations, but studies related to non-endemic areas and HIV-negative populations are still limited. Therefore, this study aims to provide more additional evidence for clinical work of talaromycosis.

Methods To collect clinical information of patients with talaromycosis admitted to hospitals in Zhejiang Province, China from January 1, 2010 to May 31, 2020, retrospectively analyzed clinical characteristics and prognosis, COX multivariate regression analysis was used for survival analysis.

Results A total of 92 patients were enrolled, including 76 males, 73 HIV-positive patients, with an average age of 40.1 ± 13.0 . Compared to HIV-positive group, the negative group had higher admission age (47.7 ± 14.6 vs 38.1 ± 11.9 , $p=0.003$) and lower proportion of male (89.0% vs 57.9%, $p=0.004$), there was no significant difference in imaging of lungs. There were significantly more HIV-positive patients in those with pleural effusion (100% vs 69.4%, $p=0.001$). COX multivariate regression analysis suggested pleural effusion (HR = 3.220; 95% CI 1.117–9.287; $p=0.030$) and HIV infection (HR = 0.057; 95% CI 0.009–0.370; $p=0.003$) which were independent predictors of prognosis in patients with talaromycosis.

Conclusions In non-endemic areas, clinical symptoms, signs, and laboratory tests of patients with talaromycosis are similar to those in endemic areas. Patients with pleural effusion have lower survival rate, HIV-infected people are less likely to relapse, and there is no significant correlation between extent of lung involvement and survival of infected patients.

Keywords *Talaromyces marneffe* · Talaromycosis · Non-endemic Area · Human Immunodeficiency Virus · Clinical characteristics · Prognostic analysis

Qian Shen and Lingyan Sheng contributed equally.

✉ Jianying Zhou
zjyhz@zju.edu.cn

¹ Department of Respiratory Medicine, The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China

² Department of Liver Infection, The Affiliated Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China

³ Department of Respiratory Medicine, The Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China

Introduction

Talaromyces marneffe (TM) is an opportunistic pathogenic fungus which can cause systemic disseminated infections. It is the only known dimorphic fungus in *Talaromyces* at present [1, 2].

TM was originally isolated from a bamboo rat in Vietnam (1956) by Capponi and Sureau [3]. Since the first case of natural human infection reported in 1973 [4], more and more talaromycosis cases are reported. The vast majority of infected people are Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) patients or other immunodeficiency patients with CD4⁺ T cells < 100/μL. Therefore, TM is endemic in Southeast Asia and South Asia, which are AIDS-endemic areas, mainly including Vietnam, India, Thailand, southern provinces of

China (especially Guangxi, Guangdong) and Hong Kong of China [5–7].

Although talaromycosis is an endemic epidemic fungal disease, there are more and more infected patients in non-endemic areas and HIV-negative populations. Even HIV-negative infections with normal immune function have appeared [8]. However, studies on talaromycosis in non-endemic areas and HIV-negative populations are still limited. Therefore, more research is needed on people infected with TM (with or without HIV) in non-endemic areas.

In China, talaromycosis are mainly prevalent in individual southern provinces such as Guangdong, Guangxi, and Yunnan, and Zhejiang is a non-endemic province in East China. This study collected clinical information of patients with talaromycosis admitted to hospitals (mainly The First Affiliated Hospital, School of Medicine, Zhejiang University) in Zhejiang Province, China from January 1, 2010 to May 31, 2020, then retrospectively analyzed and summarized their clinical characteristics, compared differences in clinical characteristics and prognosis of HIV-positive and negative patients, and compared against patients in endemic areas, which could provide more references and suggestions for related clinical diagnosis and treatment.

Methods

Patients

To collect clinical information of adult patients (≥ 18 years old) from several hospitals in Zhejiang Province, China (mainly The First Affiliated Hospital, School of Medicine, Zhejiang University, the rest included The Affiliated Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, The Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University and Cangnan People's Hospital) with confirmed talaromycosis from January 1, 2010 to May 31, 2020. These patients were divided into two groups: HIV-positive and HIV-negative group.

Inclusion criteria: adult patients (≥ 18 years of age) who had been determined to be infected with TM (with or without HIV) through pathogen culture or gene sequencing or microscope observation;

Exclusion criteria: patients with TM infections were determined by pathogen culture or gene sequencing or microscope observation, but it was not possible to determine whether they were HIV-infected.

Diagnostic criteria for talaromycosis:

- 1) Using standard culture techniques to isolate and culture TM from clinical specimens. Such clinical specimens mainly include blood, bone marrow, sputum, bronchoalveolar lavage fluid (BALF), skin secretions, skin biopsy

specimens, cerebrospinal fluid, etc. [9, 10]. The key evidence of the positive culture result is the thermal dimorphism of the pathogen, that is, the form of mycelium at 25°C coupling with brick red pigment and the form of yeast at 37 °C.

- 2) After Wright staining, Giemsa staining or periodic acid Schiff staining of cytology and histopathology specimens, the special yeast form and diaphragm of TM are directly observed with the microscope [11].
- 3) Polymerase Chain Reaction (PCR), Next Generation Sequencing (NGS) and other genetic testing methods specifically suggest that TM is positive.

Clinical information

Through the hospital's electronic information system, the patient's inpatient medical records were reviewed.

In this study, the patient's diagnosis of talaromycosis was mainly through pathogen culture and NGS. Pathogen culture and result judgment were completed by the hospital laboratory and NGS was carried out by sending out clinical specimens to specialized testing institutions. The imaging data used in this research all came from the hospital imaging system, and data were all based on patients' first non-contrast chest computed tomography (CT) after admission. The radiology reading work in the hospital was completed by the radiologist and subsequently reviewed by the respiratory physician.

The discharge outcome was defined as follows: (1) Effective: there was a stable and lasting recovery response after treatment with antifungal drugs. That was, the symptoms related to talaromycosis disappeared or the pathogen was negative again; (2) Recurrence: there was a temporary recovery response after treatment with antifungal drugs, but then symptoms related to talaromycosis appeared again, and the pathogen test was positive; (3) Death; (4) Lost to follow-up. Regarding the time of follow-up, all patients who did not have a death event were followed up to May 31, 2020, mainly through the patient's hospital visit records, hospitalization records and follow-up telephone calls.

Statistical analysis

All data in this study were statistically analyzed using SPSS 20.0 software (IBM SPSS Inc., Chicago, Illinois, USA). Continuous variables with normal distribution were expressed as mean \pm standard deviation (SD). The Kolmogorov–Smirnov test was used to determine whether the normal distribution condition was met. If $p > 0.05$, then the normal distribution was met, and the t test was used for comparison between groups. If the normal distribution was not met, non-parametric rank sum test was used for comparison between groups. The count data

was expressed in terms of frequency and percentage, and Chi-square test or Fisher exact test was used for comparison between groups. Independent predictors related to prognosis were analyzed by COX multivariate regression analysis. All statistical analyses used a two-sided test and $p < 0.05$ was considered statistically significant.

Results

A total of 92 adult patients (≥ 18 years old) with confirmed talaromycosis and basically complete clinical data from January 1, 2010 to May 31, 2020 were enrolled. There were 73 cases in the HIV-positive group and 19 cases in the HIV-negative group. Patients were mainly from The First Affiliated Hospital, School of Medicine, Zhejiang University, and 5 cases (two HIV-negative and three HIV-positive) were from The Affiliated Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, 2 cases were from The Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University, and one was from Cangnan People's Hospital. Among these patients, 6 cases were definitely with a history of exposure to TM endemic areas, others' permanent residences were nearly all in Zhejiang Province. But the travel history of some patients was unavailable.

Clinical baseline information of patients with talaromycosis

92 cases with talaromycosis had an admission age range of 18–74 years old, with an average of 40.1 ± 13.0 . The admission age of HIV-negative group was significantly higher than the HIV-positive group (47.7 ± 14.6 vs 38.1 ± 11.9 , $p = 0.003$). Of the 92 patients, 76 were male (82.6%) and 16 were female (17.4%). The proportion of male in the

HIV-positive group was significantly higher than HIV-negative group (89.0% vs 57.9%, $p = 0.004$) (Table 1).

There were 56 patients (60.9%) with other comorbidities, and the proportion of patients with comorbidities in the HIV-negative group was significantly higher than HIV-positive group (84.2% vs 54.8%, $p = 0.019$). The detailed comorbidities can be seen in Supplemental Table 1. HIV-positive patients themselves had varying degrees of immunodeficiency, while in HIV-negative group, there was one patient each (6.3%) with liver or kidney transplantation, two patients (12.5%) with rheumatoid arthritis and one patient (6.3%) with systemic lupus erythematosus (SLE).

With regard to the clinical symptoms and signs of TM infected people (Table 2), the most common clinical signs and symptoms of 92 patients were fever (75 cases, 81.5%), lymphadenopathy (74 cases, 80.4%) and cough (58 cases, 63.0%). Specifically, the proportions of patients with cough (84.2% vs 57.5%, $p = 0.032$), expectoration (78.9% vs 38.4%, $p = 0.002$) and abnormal pulmonary breathing sounds (73.7% vs 46.6%, $p = 0.035$) in the HIV-negative group were significantly higher than HIV-positive group, and the proportion of fever (86.3% vs 63.2%, $p = 0.047$) and splenomegaly (58.9% vs 10.5%, $p < 0.001$) in the HIV-positive group was significantly higher than the HIV-negative group.

Laboratory tests and chest CT results of patients with talaromycosis

In terms of laboratory test results (Table 3), the counts of white blood cell (WBC) (10.7 ± 8.4 vs 4.1 ± 2.7 , $p = 0.003$), lymphocytes (1.4 ± 1.1 vs 0.4 ± 0.4 , $p < 0.001$) and platelets (PLT) (270.3 ± 189.2 vs 121.4 ± 104.7 , $p = 0.001$) in HIV-negative group were significantly higher than HIV-positive group. The average values of these three indicators were all much lower than normal. Moreover, alanine aminotransferase (ALT) (66.8 ± 71.2 vs 34.3 ± 36.4 , $p = 0.016$) and aspartate aminotransferase (AST) (140.9 ± 176.2 vs

Table 1 Clinical baseline data of patients infected with TM

Items	All <i>n</i> (%)	HIV-positive <i>n</i> (%)	HIV-negative <i>n</i> (%)	<i>p</i> value
Cases	92	73	19	/
Admission age	40.1 ± 13.0	38.1 ± 11.9	47.7 ± 14.6	0.003
Age range	18–74	18–74	24–72	/
Male	76 (82.6)	65 (89.0)	11 (57.9)	0.004
Occupation	86 (93.5)	69 (94.5)	17 (89.5)	0.786
Smoking history	22 (23.9)	17 (23.3)	5 (26.3)	1.000
Drinking history	14 (15.2)	12 (16.4)	2 (10.5)	0.779
Comorbidity	56 (60.9)	40 (54.8)	16 (84.2)	0.019
History of co-infection	77 (83.7)	60 (82.2)	17 (89.5)	0.677
History of immunosuppressive agents or hormone use	14 (15.2)	5 (6.8)	9 (47.4)	<0.001

Table 2 Clinical symptoms and signs of patients infected with TM

Items	All <i>n</i> (%)	HIV-positive <i>n</i> (%)	HIV-negative <i>n</i> (%)	<i>p</i> value
Cases	92	73	19	/
Fever	75 (81.5)	63 (86.3)	12 (63.2)	0.047
Severity of fever				
Low	8 (10.7)	5 (7.9)	3 (25.0)	/
Medium	16 (21.3)	14 (22.2)	2 (16.7)	/
High	38 (50.7)	33 (52.4)	5 (41.6)	/
Unknown	13 (17.3)	11 (17.5)	2 (16.7)	/
Respiratory symptom				
Cough	58 (63.0)	42 (57.5)	16 (84.2)	0.032
Expectoration	43 (46.7)	28 (38.4)	15 (78.9)	0.002
Dyspnea	18 (19.6)	13 (17.8)	5 (26.3)	0.611
Gastrointestinal symptom				
Abdominal pain	14 (15.2)	13 (17.8)	1 (5.3)	0.318
Diarrhea	17 (18.5)	14 (19.2)	3 (15.8)	0.994
Weight loss	41 (44.6)	36 (49.3)	5 (26.3)	0.072
Skin lesions	45 (48.9)	39 (53.4)	6 (31.6)	0.090
Bone and joint pain	3 (3.3)	2 (2.7)	1 (5.3)	1.000
Lymphadenopathy	74 (80.4)	58 (79.5)	16 (84.2)	0.888
Hepatomegaly	7 (7.6)	7 (9.6)	0	0.358
Splenomegaly	45 (48.9)	43 (58.9)	2 (10.5)	<0.001
Abnormal pulmonary breathing sounds	48 (52.2)	34 (46.6)	14 (73.7)	0.035

Low: ~38°C; Medium: ~39°C; High: ~41°C

The proportion of fever with different degrees is the percentage of fever cases

Table 3 Laboratory tests of patients infected with TM

Items	All <i>n</i> (%)	HIV-positive <i>n</i> (%)	HIV-negative <i>n</i> (%)	<i>p</i> value
Cases	92	73	19	/
Hb (g/L)	98.1 ± 21.4	97.8 ± 20.4	99.2 ± 25.2	0.797
WBC (×10 ⁹ /L)	5.5 ± 5.2	4.1 ± 2.7	10.7 ± 8.4	0.003
Lymphocytes (×10 ⁹ /L)	0.6 ± 0.7	0.4 ± 0.4	1.4 ± 1.1	<0.001
Lymphocytes (%)	12.8 ± 9.5	11.8 ± 8.7	16.4 ± 11.8	0.104
Neutrophils (%)	79.9 ± 12.7	81.2 ± 11.6	75.2 ± 15.8	0.068
PLT (×10 ⁹ /L)	152.2 ± 139.4	121.4 ± 104.7	270.3 ± 189.2	0.001
Creatine (μmol/L)	75.9 ± 76.6	71.7 ± 38.1	92.1 ± 152.6	0.103
ALT (U/L)	60.1 ± 66.7	66.8 ± 71.2	34.3 ± 36.4	0.016
AST (U/L)	123.2 ± 163.8	140.9 ± 176.2	55.1 ± 72.6	0.041
Albumin (g/L)	28.0 ± 6.1	27.8 ± 5.9	28.9 ± 6.9	0.502
ALP (U/L)	186.9 ± 218.6	191.9 ± 233.8	167.6 ± 150.2	0.668
CRP (mg/L)	75.5 ± 62.3	73.7 ± 61.1	83.1 ± 68.9	0.579
ESR (mm/h)	53.0 ± 33.9	52.8 ± 33.9	54.1 ± 35.0	0.903
CD4+ T cells (%)	10.8 ± 13.7	5.5 ± 6.4	34.9 ± 12.1	<0.001

Hb hemoglobin, ALP alkaline phosphatase, ESR erythrocyte sedimentation rate

55.1 ± 72.6, *p* = 0.041) in the HIV-positive group were significantly higher than HIV-negative group. The percentage of CD4⁺ T cells was 5.5 ± 6.4 (%) in the HIV-positive group

(*n* = 59) and 34.9 ± 12.1 (%) in the negative group (*n* = 13). There was a significant difference between the two groups (*p* < 0.001).

In the chest CT images of 92 patients (Table 4), there were two in the HIV-positive group who had completely normal images at the time of admission. The remaining 90 patients all had abnormalities of varying degrees and types, and the typical chest CT images of several abnormal types could be seen in Fig. 1. Among them, high-density plaques/stripes (70 cases, 77.8%), pulmonary nodules (59 cases, 65.6%), hilar/mediastinal lymphadenopathy (47 cases, 52.2%) and pleural effusion (30 cases, 33.3%) were the most common presentations. There were no significant differences between the HIV-positive group and the HIV-negative group in all kinds of abnormal changes and extent of lung involvement ($p > 0.05$).

Diagnosis and treatment of patients with talaromycosis

92 patients included in this study all identified talaromycosis by means of pathogen culture or NGS, a total of 6 cases (6.5%) were diagnosed by NGS, and the remaining 86 cases (93.5%) were diagnosed by traditional pathogen culture, details can be seen in Supplemental Table 2. In terms of diagnostic interval, the average time of 89 patients was 8.4 ± 5.5 days, and there was no significant difference between two groups (7.7 ± 3.8 vs 11.3 ± 9.1 , $p > 0.05$).

Regarding the treatment plan (Table 5), except for one patient in each of the two groups who were discharged from the hospital without any treatment, the remaining 90 patients all received antifungal treatment. It was found that the proportion with selecting amphotericin B (11.1% vs 0, $p = 0.049$) or voriconazole (44.4% vs 12.5%, $p = 0.006$) alone in HIV-negative group was significantly higher than

Table 4 Chest CT images among patients infected with TM

Items	All <i>n</i> (%)	HIV-positive <i>n</i> (%)	HIV-negative <i>n</i> (%)	<i>p</i> value
Cases	92	73	19	/
Normal	2 (2.2)	2 (2.7)	0	1.000
Abnormal	90 (97.8)	71 (97.3)	19 (100)	
Abnormal types				
Unilateral	15 (16.7)	13 (18.3)	2 (10.5)	0.644
Nodule	59 (65.6)	46 (64.8)	13 (68.4)	0.767
High-density plaque/strip	70 (77.8)	52 (73.2)	18 (94.7)	0.091
Cavity	8 (8.9)	4 (5.6)	4 (21.1)	0.100
Mass	3 (3.3)	3 (4.2)	0	0.848
Interstitial lesions	1 (1.1)	1 (1.4)	0	1.000
Pleural effusion	30 (33.3)	21 (29.6)	9 (47.4)	0.144
Pericardial effusion	11 (12.2)	10 (14.1)	1 (5.3)	0.517
Hilar/mediastinum lymphadenopathy	47 (52.2)	35 (49.3)	12 (63.2)	0.283
Emphysema	15 (16.7)	12 (16.9)	3 (15.8)	1.000

The percentage of abnormal manifestations of lung CT imaging was the percentage of abnormal cases

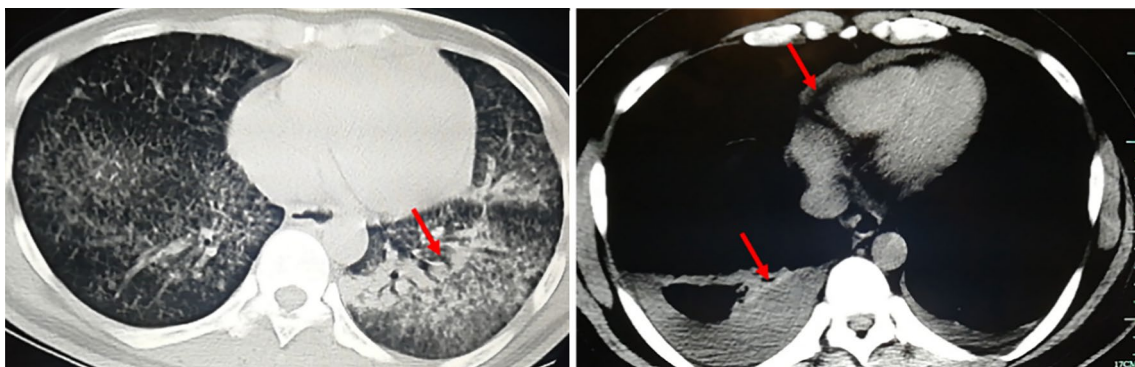


Fig. 1 Chest CT images among patients infected with TM (from left to right: high-density plaque/strip; pleural effusion + pericardial effusion)

Table 5 Treatment Schemes for patients infected with TM

Items	All n (%)	HIV-positive n (%)	HIV-negative n (%)	p value
Cases	92	73	19	/
Cases with antifungal treatment	90 (97.8)	72 (98.6)	18 (94.7)	0.878
Fluconazole	4 (4.4)	2 (2.8)	2 (11.1)	0.371
Amphotericin B	2 (2.2)	0	2 (11.1)	0.049
Itraconazole	4 (4.4)	2 (2.8)	2 (11.1)	0.371
Voriconazole	17 (18.9)	9 (12.5)	8 (44.4)	0.006
Amphotericin B + Voriconazole	17 (18.9)	16 (22.2)	1 (5.6)	0.201
Amphotericin B + Itraconazole	21 (23.3)	20 (27.8)	1 (5.6)	0.093
Voriconazole + Itraconazole	2 (2.2)	2 (2.8)	0	1.000
Amphotericin B + Itraconazole + Voriconazole	13 (14.4)	12 (16.7)	1 (5.6)	0.410
Amphotericin B + Itraconazole + Voriconazole + Fluconazole	1 (1.1)	1 (1.4)	0	1.000
Others	9 (10.0)	8 (11.1)	1 (5.6)	0.792

Others: In the HIV-positive group, including 2 cases of fluconazole + amphotericin B, 1 cases each of fluconazole + voriconazole/nystatin/itraconazole, 1 case of nystatin, 1 case each of amphotericin B + fluconazole + voriconazole/itraconazole; in HIV-negative group, including 1 case caspofungin

HIV-positive group, and there was no significant difference between two groups in the remaining treatment options ($p > 0.05$).

The average hospital stay of 92 patients was 20.0 ± 10.9 days, and there was no significant difference in the length of hospitalization between two groups (19.7 ± 10.3 vs 20.9 ± 13.0 , $p > 0.05$). The total number of lost to follow-up was 13 cases (14.1%), including 11 cases in the HIV-positive group (15.1%) and 2 cases in the HIV-negative group (10.5%). The lost to follow-up rate in both groups reached more than 10%, and the effective rate of treatment in the HIV-positive group was significantly higher than that in the HIV-negative group (77.4% vs 41.2%, $p = 0.004$) (Table 6).

Clinical characteristics and prognosis of patients with talaromycosis under different imaging characteristics

The data of chest CT images in this study were all based on patients' first non-contrast chest CT after admission, it is meaningful to explore clinical characteristics and prognosis of patients with talaromycosis under different imaging characteristics. When calculating the prognostic-related differences between groups, relapse-related analysis removed both lost and dead cases, and the rest only removed lost to follow-up cases.

In the unilateral/bilateral lung involvement groups (Table 7), there were 90 patients with lung involvement, 15 patients were with unilateral involvement (16.7%), and 75 patients were with bilateral involvement (63.3%). There was no significant difference in clinical symptoms and signs, laboratory test results and chest CT images between two groups ($p > 0.05$). But the recurrence rate of patients with unilateral

Table 6 Follow-up of patients infected with TM

Items	All n (%)	HIV-positive n (%)	HIV-negative n (%)	p value
Cases	92	73	19	/
Discharge outcome				
Effective	55 (69.6)	48 (77.4)	7 (41.2)	0.004
Recurrence	10 (12.7)	6 (9.7)	4 (23.5)	0.097
Death	14 (17.7)	8 (12.9)	6 (35.3)	0.075
Lost to follow-up	13 (14.1)	11 (15.1)	2 (10.5)	0.891
Length of hospital stay/days	20.0 ± 10.9	19.7 ± 10.3	20.9 ± 13.0	0.683

When calculating the prognostic-related differences between two groups, relapse-related analysis removed both lost and dead cases, and the rest only removed lost to follow-up cases

Table 7 Corresponding clinical characteristics and prognosis in patients with unilateral/bilateral lung involvement

Items	All <i>n</i> (%)	Unilateral <i>n</i> (%)	Bilateral <i>n</i> (%)	<i>p</i> value
Cases	90	15	75	/
Admission age	40.4 ± 13.0	37.7 ± 9.7	40.9 ± 13.5	0.389
Male	74 (82.2)	10 (66.7)	64 (85.3)	0.175
HIV infection	71 (78.9)	13 (86.7)	58 (77.3)	0.644
Smoking history	22 (24.4)	2 (13.3)	20 (26.7)	0.443
Drinking history	14 (15.6)	2 (13.3)	12 (16.0)	1.000
Comorbidity	53 (58.9)	9 (60.0)	44 (58.7)	0.924
History of co-infection	75 (83.3)	10 (66.7)	65 (86.7)	0.129
History of immunosuppressive agents or hormone use	14 (15.6)	3 (20.0)	11 (14.7)	0.897
Fever	73 (81.1)	12 (80.0)	61 (81.3)	1.000
Respiratory symptom				
Cough	56 (62.2)	9 (60.0)	47 (62.7)	0.846
Expectoration	42 (46.7)	7 (46.7)	35 (46.7)	1.000
Dyspnea	18 (20.0)	4 (26.7)	14 (18.7)	0.724
Skin lesions	44 (48.9)	8 (53.3)	36 (48.0)	0.706
Lymphadenopathy	73 (81.1)	11 (73.3)	62 (82.7)	0.630
Abnormal pulmonary breathing sounds	47 (52.2)	6 (40.0)	41 (54.7)	0.299
Splenomegaly	44 (48.9)	7 (46.7)	37 (49.3)	0.850
Hepatomegaly	7 (7.8)	2 (13.3)	5 (6.7)	0.725
WBC ($\times 10^9/L$)	5.6 ± 5.2	5.5 ± 6.3	5.6 ± 5.0	0.953
Lymphocytes (%)	12.7 ± 9.6	15.9 ± 11.7	12.1 ± 9.0	0.153
Creatine ($\mu\text{mol/L}$)	76.3 ± 77.5	76.3 ± 51.9	76.3 ± 82.0	0.999
Lymphocytes ($\times 10^9/L$)	0.6 ± 0.7	0.7 ± 0.5	0.6 ± 0.7	0.766
PLT ($\times 10^9/L$)	153.7 ± 140.5	186.0 ± 166.8	147.3 ± 135.0	0.332
ALT (U/L)	60.7 ± 67.3	54.9 ± 38.8	61.9 ± 71.8	0.716
AST (U/L)	123.1 ± 165.1	96.1 ± 83.9	128.5 ± 176.8	0.492
Albumin (g/L)	28.0 ± 6.0	30.2 ± 6.9	27.5 ± 5.8	0.123
ALP (U/L)	188.6 ± 220.7	275.5 ± 375.2	171.2 ± 173.5	0.095
CRP (mg/L)	75.4 ± 62.6	63.0 ± 61.3	78.0 ± 63.0	0.401
ESR (mm/h)	53.6 ± 34.1	54.2 ± 29.6	53.4 ± 35.2	0.938
CD4+T cells (%)	10.8 ± 13.8	10.1 ± 13.1	11.0 ± 14.0	0.848
Diagnostic interval/days	8.4 ± 5.5	9.7 ± 5.7	8.2 ± 5.5	0.324
Discharge outcome				
Effective	54 (69.2)	7 (53.8)	47 (72.3)	0.323
Recurrence	10 (12.8)	5 (38.5)	5 (7.7)	0.021
Death	14 (17.9)	1 (7.7)	13 (20.0)	0.509
Lost to follow-up	12 (13.3)	2 (13.3)	10 (13.3)	1.000
Length of hospital stay/days	20.0 ± 11.0	23.4 ± 12.5	19.3 ± 10.6	0.190

lung involvement was significantly higher than those with bilateral involvement (38.5% vs 7.7%, $p=0.021$).

In the group with/without pleural effusion (Supplemental Table 3), a total of 92 cases were included in the analysis. A total of 30 patients (32.6%) had pleural effusion and 60 patients (67.4%) were without pleural effusion. The proportion of HIV-positive patients in patients with pleural effusion was significantly higher than those without pleural effusion (100% vs 69.4%, $p=0.001$), and the albumin in laboratory results was lower (24.5 ± 5.4 vs 29.7 ± 5.6 , $p < 0.001$), the

C-reactive protein (CRP) value was higher (94.3 ± 63.7 vs 66.1 ± 60.0 , $p=0.043$).

In the group with/without nodular lesions (Supplemental Table 4), a total of 92 cases were included in the analysis. There were 61 patients (66.3%) with nodular lesions and 31 patients (33.7%) without nodular lesions. Patients with nodular foci on lung imaging were more prone to have cough (70.5% vs 90.2%, $p < 0.038$) and surface lymphadenopathy (70.5% vs 61.3%, $p=0.001$), while the incidence of dyspnea was lower (13.1% vs 32.3%, $p=0.029$).

Survival analysis of patients with talaromycosis

During the follow-up time of all patients, 11 cases were lost to follow-up in the HIV-positive group and 2 cases were in the HIV-negative group. The time span of this study was 10 years, so the lost cases were not included in the survival analysis.

In this study, COX regression analysis was used to determine the independent predictors of prognosis of talaromycosis. In all 92 patients, a total of 79 patients were included in this analysis, including 10 patients with recurrence (12.7%) and 14 patients with death (17.7%). In the study of independent predictive factors for patients' survival, factors with $p < 0.1$ (HIV infection, comorbidities, diagnostic interval, lymphadenopathy, creatinine, nodules, pleural effusion) were included in multivariate regression by univariate regression analysis. The result showed that pleural effusion (HR = 3.220; 95% CI: 1.117–9.287; $p = 0.030$) was an independent predictor of survival in patients with talaromycosis. Similarly, it was concluded that HIV infection (HR = 0.057; 95% CI: 0.009–0.370; $p = 0.003$) was an independent predictor of recurrence-free in patients with talaromycosis (Table 8).

Discussion

In this study, HIV/AIDS patients are still the main part of TM infected population in non-endemic area. Yongxuan Hu et al. [1] retrospectively analyzed 668 cases of talaromycosis reported in Mainland China from 1984 to 2009, and found that 99.4% of the cases were from cities in southern China, of which Guangxi accounted for 42.8% and Guangdong accounted for 40.6%, 87.7% of the cases were combined with HIV infection. It can be concluded that the distribution of talaromycosis in non-endemic areas is similar to the overall situation in endemic areas. Moreover, younger males from HIV-positive populations in non-endemic areas are the main population of talaromycosis, which is consistent with a previous literature reported in Thailand [12]. This conclusion is also in line with the current situation of HIV/AIDS prevalence among young males.

In China, as the migration population increases year by year, the disease has traveled far beyond the original areas like Guangdong and Guangxi. 21 other provinces and cities in China have reported cases [13]. This study included 6 cases with definite history of exposure to TM endemic areas, while most others are permanent residences of Zhejiang Province.

Therefore, it is justifiable that talaromycosis is no longer case in Zhejiang Province, and it is worthy of attention.

The comorbidities explored in this study did not show any primary immunodeficiency, but HIV-negative patients also included several cases with acquired immunodeficiency. These patients could suffer from severe immunodeficiency due to taking immunosuppressive agents or hormones, which is consistent with the results of previous studies [14, 15]. In HIV-negative populations, there were three patients without comorbidity. In addition to two patients with a history of tuberculosis, the others' immune function was completely normal and had no relevant history. Such patients are rare in talaromycosis, in 2018, a study suggested that only four cases of talaromycosis were reported in non-endemic areas. Therefore, future studies on genetics and other levels in this special population may need to be more in-depth to fully understand talaromycosis [8, 16].

The findings of clinical symptoms, signs, and laboratory tests in this study were basically consistent with the description of related research in endemic areas [12, 17]. Some previous studies tried to explore the differences in clinical manifestations between HIV-positive and negative populations, but some small differences were usually ignored [18, 19]. This study is the first large retrospective study in this area (non-endemic areas), the significant differences in clinical manifestations between the two groups could provide some constructive references for clinical work.

In this study, 92 patients were included to determine talaromycosis by pathogen culture or NGS, without serological diagnosis. Studies have shown that in practical clinical applications, the beta-D-glucan test and GM (Galactomannan) test have a certain role in monitoring and auxiliary diagnosis of talaromycosis [20, 21]. They were applied in the treatment and follow-up of these patients. Previous study also showed that adult immunodeficiency caused by anti-IFN- γ autoantibodies could explain many previous HIV-negative Asian infected patients. Since these patients had no remaining symbiotic diseases, whether anti-IFN- γ autoantibodies could enter the clinic in the future as a screening indicator for TM infection in HIV-negative population is still to be studied [22]. In addition, an antibody test for TM Mp1p based on ELISA (Enzyme Linked Immunosorbent Assay) has been developed previously, and the results proved that about 80% of the HIV-positive TM infections could respond specifically [23], and there are still many research on serological diagnosis of TM. If the fungal infection can be directly diagnosed by serological testing in the

Table 8 COX multivariate regression analysis for the prognosis of people infected with TM

Prognosis	Items	HR	95% Confidence Interval		P value
			Lower limit	Upper limit	
Recurrence-free	HIV infection	0.057	0.009	0.370	0.003
Survival	Pleural effusion	3.220	1.117	9.287	0.030

future, there is no doubt that it is a milestone for the diagnosis of talaromycosis.

The imaging data in this study were all based on patients' first chest CT after admission, but the time intervals between admission and CT-scanning were not consistent. Previous studies have shown that in patients with talaromycosis in the lungs, the size of the lung lesions and pleural effusion are not associated with recurrence-free survival [24]. The result in this study was consistent with it. Moreover, when patients are suspected of being infected with TM and their lung images suggest the presence of pleural effusions, screening for HIV infection is required. Previous studies have explored pleural effusions of HIV-negative patients with talaromycosis. Laboratory analysis of hydrothorax showed that it was characterized by neutrophil-based light yellow pleural effusion, and high neutrophil count and IL-23 may prompt talaromycosis [25]. This can be considered in actual work based on pleural effusion as an auxiliary reference for diagnosis of HIV-positive talaromycosis.

Previous study suggested that the total mortality rate of talaromycosis in endemic areas is 22.7% [12]. In this study, the mortality rate was 15.2% in the existing information, which was lower than the value reported in the literature, despite certain censored data. But this may also be related to factors such as strict supervision of HIV-positive people. This study suggests that pleural effusion is related to patient's survival, there is no similar study before, and the follow-up can be continued to explore the reliability and stability of this conclusion by increasing the sample size. In actual clinical work, patients with pleural effusion should be alert to the possibility of death and follow-up should be strengthened. This study suggests that the recurrence rate of HIV-positive patients is lower. This may be related to the strict supervision of these patients. People with HIV-negative infection often have secondary immunodeficiency, more comorbidities, and poor basic conditions, which may also be related to this result.

Of course, this study still has some limitations. Firstly, the number of infections is still not comparable with those in the endemic areas, which may prevent some variables from being revealed. Secondly, all patients have a hospital admission span of up to 10 years, there is a hospital bias, and related laboratory testing techniques are different in each time period. Some data are missing, such as whether the patient has a history of exposure to TM endemic areas. In addition, most of the patients in this study are HIV/AIDS patients, and there are certain limitations of follow-up due to objective reasons such as privacy protection. Finally, because this study is a retrospective study, some of the correlations mentioned in the text can only provide as references. However, as the first large retrospective study in Zhejiang Province, it still attracts attention to talaromycosis in endemic areas and provides several practical suggestions for

clinical work, and it is also necessary to increase sample size further to make conclusions more convincing.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s15010-021-01679-6>.

Acknowledgements We acknowledge The Affiliated Hangzhou First People's Hospital, School of Medicine, Zhejiang University, The Affiliated Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University and Cangnan People's Hospital for providing partial data

Author contribution SQ and ZJY conceived the ideas; SLY, ZJL and YJ collected the data; SLY and SQ analyzed the data and wrote manuscript; SQ and ZJY led the writing and reviewing.

Funding Not applicable.

Availability of data and material Data and material are submitted in this study and electronic supplementary material.

Code availability Not applicable.

Declarations

Conflict of interest Not applicable.

Ethics approval The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to and the appropriate ethical review committee approval has been received.

Consent for participate Not applicable.

Consent for publication Informed consent was obtained from patients for publication of this report and accompanying images.

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