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ORIGINAL RESEARCH

Clinical Characteristics, Management, and Outcomes of Patients Living with HIV and Coinfected with *Talaromyces marneffei* and *Cryptococcus*: A Retrospective Case Series

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Background: *Talaromycosis* and *Cryptococcosis* are life-threatening opportunistic infections that occur in severely immunocompromised individuals. However, data on the clinical characteristics, management, and outcomes of patients with concurrent *Talaromyces marneffei* and *Cryptococcus* infections are limited.

Methods: We performed a retrospective review of the electronic medical records of patients living with human immunodeficiency virus (PLHIV) who were diagnosed with concurrent *Talaromyces marneffei* and *Cryptococcus* infection between January 2013 and December 2023. Risk factors for poor outcomes were determined through univariate and multivariate analyses.

Results: Most patients were male (72.3%) with advanced immunosuppression (median CD4 count: 15 cells/μL). Constitutional symptoms (91.5%) were most common, followed by gastrointestinal (55.3%) and respiratory symptoms (53.2%). Blood *cryptococcal* antigen testing was the most frequent method for detecting *Cryptococcus* in co-infected patients. The overall mortality rate was 29.8%. Cerebrospinal fluid (CSF) lactate dehydrogenase (LDH) >21.15 U/L was identified as an independent predictor of mortality (OR = 13.1, 95% CI: 1.27–135.76, p = 0.031).

Conclusion: Co-infection with *T. marneffei* and *Cryptococcus* in HIV patients is associated with nonspecific clinical presentations and high mortality. Elevated CSF LDH levels, particularly CSF LDH levels >21.15 U/L, are a significant risk factor for death. Early cryptococcal antigen screening and prompt antifungal therapy are crucial for improving outcomes in this population.

Keywords: *Talaromyces marneffei*, *Cryptococcus*, coinfection, fungal infection, HIV

Background

Human immunodeficiency virus (HIV) replication leads to the progressive loss of CD4+ T cells and immune disorders that cause Acquired Immune Deficiency Syndrome (AIDS). According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), approximately 40.8 million people were living with HIV (PLWH) globally. Despite advancements in the effectiveness of antiretroviral treatment, approximately 630,000 individuals died from AIDS-related illnesses, and 1.3 million new infections were reported by the end of 2024.[1] According to the surveillance data from the Chinese Center for Disease Control and Prevention (China CDC), a total of 1,355,017 PLWH were documented across 31 provinces of China, with advanced PLWH accounting for 44.6% and cumulative AIDS-related deaths reaching 91,437. Specifically, Guangxi Zhuang Autonomous Region, a region with a heavy HIV/AIDS burden, reported 123,200 prevalent cases.[2]

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PLWH in the early stage typically present with atypical clinical symptoms, and the majority of them remain undiagnosed during this period. It has been reported that in China, the rate of advanced HIV infections among newly diagnosed cases ranges from 35.5% to 42.1%, and these cases are often complicated by various opportunistic infections.[2]

Talaromyces marneffei is the only temperature-dependent dimorphic fungus of the *Talaromyces* genus that is prevalent in South Asian countries and South China (Guangxi, Guangdong, Yunnan, Hong Kong, etc.). *T. marneffei* causes disseminated and lethal fungal disease, which is known as *talaromycosis* and generally occurs in patients with late-stage AIDS.[3] *Cryptococcus* is a genus of opportunistic fungal pathogens, with two main species, *Cryptococcus neoformans* and *Cryptococcus gattii*, causing human *cryptococcosis*, which is characterized by high morbidity and high mortality. Even in developed countries, the 1-year mortality rate for patients infected with *Cryptococcus neoformans* exceeds 20%, especially in immunocompromised hosts.[4,5] Notably, *talaromycosis* and *cryptococcosis* are the most common OIs among AIDS patients in Southeast Asia, ranking second and third, respectively, after *tuberculosis*,[6] and are associated with a high incidence of OIs in advanced AIDS patients in Guangxi.[4,7] A missed diagnosis or misdiagnosis of either *talaromycosis* or *cryptococcosis* can be fatal and is one of the leading causes of death among AIDS patients.[8–10] Currently, the incidence of concurrent infections with *T. marneffei* and *cryptococcus* is unknown, and very few cases have been reported to date, posing unique diagnostic and therapeutic challenges for clinicians in the clinical setting.[11–13] Thus, the World Health Organization (WHO) recommends the routine screening for *talaromycosis* and *cryptococcosis* in endemic areas.[14,15]

In this study, the clinical information of PLWH coinfected with *T. marneffei* and *Cryptococcus* treated at the Fourth People's Hospital of Nanning from January 2013 to December 2023 was collected and retrospectively analyzed, and the clinical characteristics, management, and outcomes were summarized. This summary could serve as a reference for related clinical diagnosis and treatment.

Materials and Methods

Study Design and Ethics Statement

A retrospective study of PLWH treated at the Fourth People's Hospital of Nanning from January 2013 to December 2023 was conducted. Ethical permission was obtained from the Institutional Ethics Review Board of the Fourth People's Hospital of Nanning (2024–74). As the study was retrospective in nature, informed consent was waived by the committee.

The study inclusion criteria were as follows: adults older than 18 years, confirmed HIV infection, and concurrent diagnosis of *talaromycosis* and *cryptococcosis* within 14 days before enrollment through microbiological examinations (including cerebrospinal fluid India ink staining and/or serum capsular antigen detection). The exclusion criteria were *T. marneffei* infection without *Cryptococcus* infection and missing files or data.

Diagnostic Criteria for Talaromycosis and Cryptococcosis

The diagnosis of *talaromycosis* was defined by the isolation of *T. marneffei* from clinical samples (eg, blood, bone marrow, lymph nodes, sputum, skin scrapings, bronchoalveolar lavage fluid (BALF), and cerebrospinal fluid (CSF)) using standard culture techniques, or the specimens were subjected to staining with Gomori's methenamine silver (GMS) or periodic acid-Schiff (PAS) to assess the yeast-like morphology of T. marneffei, revealing characteristic intestinal-like cells featuring a septum.[16] Cryptococcosis was diagnosed if cultures of clinical specimens were positive for *Cryptococcus*, if the India ink stain was positive, or if elevated cryptococcal antigen titers were present in the clinical specimens.[17] Rapid and specific identification of *T. marneffei*/*Cryptococcus* by polymerase chain reaction (PCR)-based detection of specific sequences was used to diagnose *T. marneffei/Cryptococcus* infection.[16] HIV infection was confirmed by positive enzyme-linked immunosorbent assay (ELISA) and Western blot results.[18]

Data Collection Procedures

First, the patients' medical files were reviewed, and patients were assessed for eligibility. Sociodemographic data and details of clinical presentation, laboratory (including CD4+ count, C-reactive protein (CRP), white blood cells (WBC),

red blood cells (RBC), hemoglobin (HGB), platelets (PLT), neutrophils rate, procalcitonin (PCT), albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, lactic dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), serum ferritin, Aspergillus galactomannan), pathological and microbiological results, management, and outcomes were collected using a standardized form.

Second, according to the cryptococcal infection status and guidelines in China, patients received antifungal combinations (amphotericin B, voriconazole, fluconazole, itraconazole, and flucytosine) for 2–4 weeks as initial induction therapy, followed by consolidation therapy with fluconazole, itraconazole, or voriconazole.[16,17]

Third, the standardized forms of the selected patients were reviewed by 2 experts. Irregular antiretroviral therapy refers to not taking medication as prescribed, including missed doses, incorrect doses, or discontinuation without medical advice. Clinical outcomes were classified as follows: (1) survival, a sustained response to antifungal therapy (ie, absence of symptoms associated with blastomycosis and cryptococcosis and negative culture results); or (2) death, a patient's death during hospitalization; Patients in terminal condition at discharge (defined as imminent death within 24 hours).

Statistical Analysis

Statistical analysis was performed using SPSS software (version 27.0). Based on clinical outcomes, all patients were divided into a survival group and a death group. The normality of continuous data was assessed using the Shapiro–Wilk (S–W) test. Normally distributed continuous variables are expressed as mean ± standard deviation ($\bar{x} \pm s$), while non-normally distributed continuous variables are presented as median (interquartile range) [M (P25, P75)]. Categorical variables are reported as numbers and percentages. Continuous variables are expressed as mean ± standard error or M (Q25, Q75), and categorical variables as frequency and proportion. Categorical variables were analyzed using the χ^2-test or Fisher's exact test, and continuous variables were analyzed using the *t*-test or Mann–Whitney *U*-test. A two-tailed test was employed, and a P-value < 0.05 was considered statistically significant. Logistic regression was used to assess risk factors for death. All variables significant ($P \leq 0.05$) in the univariate analysis were considered potential predictors for the multivariate analysis.

Results

Baseline Characteristics and Clinical Presentation

A total of 47 patients with confirmed co-infection of *Talaromyces marneffei* and *Cryptococcus* were included in this study, comprising 33 survivors (70.2%) and 14 deaths (29.8%). The mean age of the cohort was 47.83 ± 2.21 years, with no significant difference between the two groups ($p = 0.762$). Males constituted the majority (72.3%), and sex distribution was comparable between survivors and non-survivors ($p = 0.927$). The most common occupation was farming (57.4%). Constitutional symptoms were nearly universal (91.5%), present in all deaths and 87.9% of survivors ($p = 0.173$). Other frequently reported symptoms included gastrointestinal (55.3%), respiratory (53.2%), and central nervous system involvement (44.7%), with no statistically significant differences between groups. Routine laboratory parameters—including complete blood counts, liver and renal function tests, inflammatory markers (C-reactive protein, procalcitonin, erythrocyte sedimentation rate), serum ferritin, admission CD4 count, Aspergillus galactomannan, and fungal (1,3)-β-D-glucan levels—did not differ significantly between survivors and deaths (all $p > 0.05$). However, cerebrospinal fluid (CSF) analysis revealed that lactate dehydrogenase (LDH) levels were significantly higher in the death group compared to survivors ($p = 0.012$). All patients received antifungal treatment. Initial induction therapy with amphotericin B combined with other antifungals was administered to 76.6% of patients, with no significant difference between survivors and deaths ($p = 0.593$). Consolidation therapy, however, differed significantly between groups ($p = 0.030$). Itraconazole was more frequently used in survivors (48.5%), while voriconazole was more common in deaths (21.4%). Antiretroviral therapy (ART) was administered to 66.0% of patients, with no significant association with mortality ($p = 0.394$). The results of the analysis of baseline characteristics and clinical presentation in the patients are summarized in Table 1.

Table 1 Baseline Characteristics and Presentation of 47 Patients with Co-Infection of *Talaromyces marneffei* and *Cryptococcus*

Patient Characteristics	Patients, n (%)			p-value
	All Patients n = 47	Survival Group n = 33	Death Group n = 14	
Age (years),(mean ± SD)	47.83 ± 2.21	48.27 ± 2.79	46.79 ± 3.56	0.762
Sex				0.927
Male, n (%)	34 (72.3%)	25(75.8%)	9(64.3%)	
Female, n (%)	13(27.7%)	8(24.2%)	5(35.7%)	
Length of hospital days, mean ± SD/, M(Q_{25},Q_{75})	21(14, 35)	26.3 ± 20.9	28.1 ± 24.3	0.803
Occupation				0.122
Farmer, n (%)	27 (57.4%)	19(57.6%)	8(57.1%)	
Unemployed persons, n (%)	8 (17.0%)	6(18.2%)	2(14.3%)	
Self-employed, n (%)	5 (10.6%)	3(9.0%)	2(14.3%)	
Other positions, n (%)	7 (14.9%)	5(15.2%)	2(14.3%)	
Constitutional symptom, n (%)	43 (91.5%)	29(87.9%)	14(100%)	0.173
Respiratory symptom, n (%)	25 (53.2%)	19(57.6%)	6(42.9%)	0.355
Circulatory symptom, n (%)	15 (31.9%)	10(30.3%)	5(35.7%)	0.716
Gastrointestinal symptom, n (%)	26 (55.3%)	19(57.6%)	7(50.0%)	0.633
Central nervous system symptom, n (%)	21 (44.7%)	14(42.4%)	7(50.0%)	0.875
Skin lesions, n (%)	18 (38.3%)	12(36.4%)	6(42.9%)	0.675
Oral lesions, n (%)	23 (48.9%)	16(48.5%)	7(50.0%)	0.924
Lymphadenopathy, n (%)	2 (4.3%)	1(3.0%)	1(7.1%)	0.523
WBC count, ×10^9/L, mean ± SD/, M(Q_{25},Q_{75})	4.3(2.9, 6.5)	4.7(2.9, 6.4)	4.9 ± 3.0	0.798
RBC count, ×10^{12}/L, mean ± SD/, M(Q_{25},Q_{75})	3.2(1.4, 4.9)	3.3 ± 0.8	3.1 ± 0.8	0.306
Platelets, ×10^9/L, M(Q_{25},Q_{75})	157.0(65.0, 279.0)	164(90.5, 305.0)	93.5(41.8, 277.5)	0.222
Hemoglobin, g/L, mean ± SD	89.9 ± 8.7	91.2 ± 4.2	84.9 ± 6.0	0.416
Neutrophils rate, %, M(Q_{25},Q_{75})	83.6(76.4, 88.3)	83.4(76, 88.2)	85.2(74.1, 93.6)	0.334
ALT, U/L, M(Q_{25},Q_{75})	31.1(18.0, 48.0)	33(21.9, 51.0))	21.7(10.3, 45.2)	0.089
AST, U/L, M(Q_{25},Q_{75})	53.0(33.0, 120.0)	55.1(33.5, 134.8)	37(15.9, 86.1)	0.213
Albumin, g/L, mean ± SD/, M(Q_{25},Q_{75})	28.0(9.0, 47.0)	29.2 ± 7.9	25.3 ± 8.4	0.139
Cr, mmol/L, M(Q_{25},Q_{75})	90.0(31.6, 492.1)	66.2(56.8, 77.8)	77.6(54.2, 143.7)	0.193
LDH, U/L, M(Q_{25},Q_{75})	328.0(227.0, 468.1)	328.0(242.8, 851.0)	282.1(192.5, 513.0)	0.657
C-reactive protein, mg/L, M(Q_{25},Q_{75})	44.0(19.0, 90.3)	53.5(32.8, 95.2)	33.2(5.2, 134.0)	0.515
ESR, mm/h, mean ± SD/, M(Q_{25},Q_{75})	69.2(15, 164)	71.5 ± 6.9	69.4 ± 15.3	0.882
PCT, ng/mL, M(Q_{25}, Q_{75})	0.5(0.2, 2.4)	0.4(0.2, 1.2)	2.4(0.1, 3.9)	0.374
Serum ferritin, ng/mL, M(Q_{25},Q_{75})	1089.2(641.1, 2040.5)	1113.4(620.2, 2374.3)	975.6(581.57, 1530.0)	0.519
Admission CD4 count, cells/μL, CD4, M(Q_{25},Q_{75})	15.0(9.0, 31.0)	15(8.5, 29.5)	16.5(8.0, 35.8)	0.926
Aspergillus galactomannan, ug/L, M(Q_{25},Q_{75})	4.8(0.6, 5.0)	4.8(0.4, 5.0)	5.0(1.7, 5.0)	0.422
Fungal glucan, pg/mL, M(Q_{25}, Q_{75})	126.7(73.6, 309.7)	116.1(39.6, 206.3)	139.4(112.4, 284.8)	0.828
CSF results (n = 37)				
Pressure, mmH_2O, M(Q_{25},Q_{75})	120.0(90.0, 230.0)	120.0(88.8, 197.5)	110.0(90.0, 280.0)	0.883
LDH, U/L, mean ± SD/, M(Q_{25},Q_{75})	22.3(13.7, 41.4)	20.7 ± 5.2	26.1 ± 6.7	0.012
Adenosine deaminase, U/L, mean ± SD	1.4(0.01, 6.0)	1.0 (0.7, 1.2)	1.01 (1.00, 2.01)	0.181
Protein. mg/L, mean ± SD/, M(Q_{25},Q_{75})	400.8(110.9, 2003.0)	276.3(223.2, 410.4)	435.7 ± 234.4	0.192
Glucose, mmol/L, M(Q_{25},Q_{75})	2.6(2.2, 2.9)	2.7(2.2, 3.0)	2.5(2.0, 2.8)	0.192
Chloride, mmol/L, mean ± SD/, M(Q_{25},Q_{75})	120.1(102.0, 130.3)	119.6 ± 6.2	121.5 ± 6.2	0.400
Cases with antifungal treatment	47	33(70.2%)	14(29.8%)	
Initial induction therapy				0.593
Without amphotericin B	10(21.3%)	6(18.2%)	4(28.6%)	
Amphotericin B+other antifungal drugs	36(76.6%)	27(81.8%)	9(64.3%)	

(*Continued*)

Table 1 (Continued).

Patient Characteristics	Patients, n (%)			p-value
	All Patients n = 47	Survival Group n = 33	Death Group n = 14	
Consolidation therapy				0.03
Itraconazole	17(36.2%)	16(48.5%)	1(7.0%)	
Fluconazole	19(51.4%)	14(42.4%)	5(35.7%)	
Voriconazole	5(10.6%)	2(6.1%)	3(21.4%)	
Receiving ART treatment	31(66.0%)	20(60.6%)	11(78.6%)	0.394
ART after hospitalization	13(27.7%)	10(30.3%)	3(21.4%)	0.791
ART before hospitalization	18(38.3%)	10(30.3%)	8(72.7%)	0.161
Regular	11(23.4%)	9(27.3%)	2(14.3%)	
Irregular	7(14.9%)	1(3.0%)	6(42.9%)	

Note: Lumbar puncture has not been conducted in 10 cases.
Abbreviations: WBC, white blood cell; RBC, red blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, Creatinine; LDH, lactic dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin; CSF, cerebrospinal fluid; M(Q25, Q75), interquartile range; SD, standard deviation.

Etiological Detection and Diagnostic Methods

Cryptococcus was most commonly detected in blood samples (85.1%), primarily via *cryptococcal* antigen screening (88.6% of those tested) and culture (43.2%). Among the 37 patients who underwent lumbar puncture, CSF testing was positive in 59.5%, with India ink staining (43.2%), culture (37.8%), and *cryptococcal* antigen screening (42.9%) as the main diagnostic methods. Concurrent positive India ink staining, culture, and antigen screening in CSF were observed in 16.2% of cases. *Talaromyces marneffei* was predominantly isolated from blood culture (63.8%), followed by sputum culture (25.5%) and swab cultures (17.0%). Co-detection of both pathogens in a single blood culture occurred in 17.0% of patients. Notably, 10 patients did not undergo lumbar puncture, and *cryptococcal* antigen testing was not performed in 11 blood samples. The results of the analysis of infection etiology in the patients are summarized in Figure 1 and Table 2.

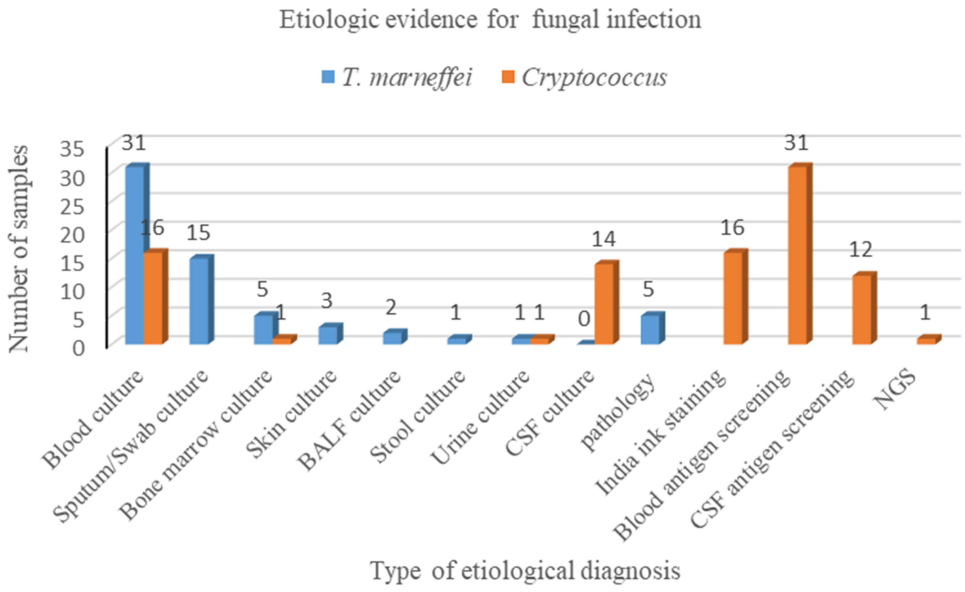

Figure 1 Number of etiological samples for T. marneffei and Cryptococcus.

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Table 2 Etiological Examination Characteristics

Items	n (%)
Specimens with positive etiological tests for *Cryptococcus*	
CSF	22(59.5%)
CSF India ink staining	16(43.2%)
CSF culture	14(37.8%)
CSF cryptococcal antigen screening	12(42.9%)
CSF India ink staining, culture, and cryptococcal antigen screening	6(16.2%)
Blood	40(85.1%)
Cryptococcal antigen screening	31(88.6%)
Culture	16(43.2%)
Bone marrow culture	1(2.1%)
Urine culture	1(2.1%)
Bronchoalveolar lavage fluid NGS	1(2.1%)
Specimens with positive etiological tests for *T. marneffei*	
Blood culture	30(63.8%)
Sputum culture	12(25.5%)
Swab cultures	8(17.0%)
Bone marrow culture	5(10.6%)
Skin culture	3(6.4%)
Bronchoalveolar lavage fluid culture	2(4.3%)
Stool culture	1(2.1%)
Pathology	5(10.6%)
Blood culture of *T. marneffei* and *Cryptococcus*	8(17.0%)

Note: Lumbar puncture has not been conducted in 10 cases, and blood cryptococcal antigen tests have not been conducted in 11 cases.

Treatment Patterns and Multivariate Analysis of Mortality

To assess the prognostic utility of CSF LDH in predicting in-hospital mortality among HIV patients co-infected with *Talaromyces marneffei* and *Cryptococcus*, receiver operating characteristic (ROC) curve analysis was performed (Figure 2). The area under the curve (AUC) for CSF LDH was 0.75 (95% CI: 0.58–0.93), indicating moderate discriminative ability (Figure 2). The optimal cutoff value for CSF LDH was determined to be 21.15 U/L, which yielded a sensitivity of 65% (95% CI: 0.47–0.84), specificity of 82% (95% CI: 0.59–1.00), positive predictive value (PPV) of 89% (95% CI: 0.76–1.00), and negative predictive value (NPV) of 50% (95% CI: 0.27–0.73). The overall diagnostic accuracy was 70% (95% CI: 0.53–0.84) (Table 3).

Variables included in the logistic regression analysis were selected based on clinical or statistical significance. CSF LDH and consolidation therapy were incorporated due to their significance in univariate analysis. Multivariate logistic regression analysis identified CSF LDH >21.15 U/L as an independent risk factor for mortality (OR = 13.1, 95% CI: 1.27–135.76, p = 0.031). In contrast, age, sex, and the type of consolidation therapy (fluconazole or voriconazole versus itraconazole) were not significantly associated with mortality in the adjusted model (Table 4).

Discussion

Our study delineates the clinical profile, management, and outcomes of HIV patients coinfected with *Talaromyces marneffei* and *Cryptococcus* in southern China. The key findings are as follows: First, patients presented predominantly with constitutional symptoms, followed by gastrointestinal and respiratory manifestations. Second, *Cryptococcus* was most frequently detected via blood antigen screening, while *T. marneffei* was primarily isolated from blood cultures; concurrent detection of both pathogens in a single blood culture occurred in a notable proportion (17.0%) of patients. Third, the overall mortality was high (29.8%), and an elevated CSF LDH level (>21.15 U/L) was identified as an independent predictor of death. This study expands our understanding of the clinical characteristics, management, and

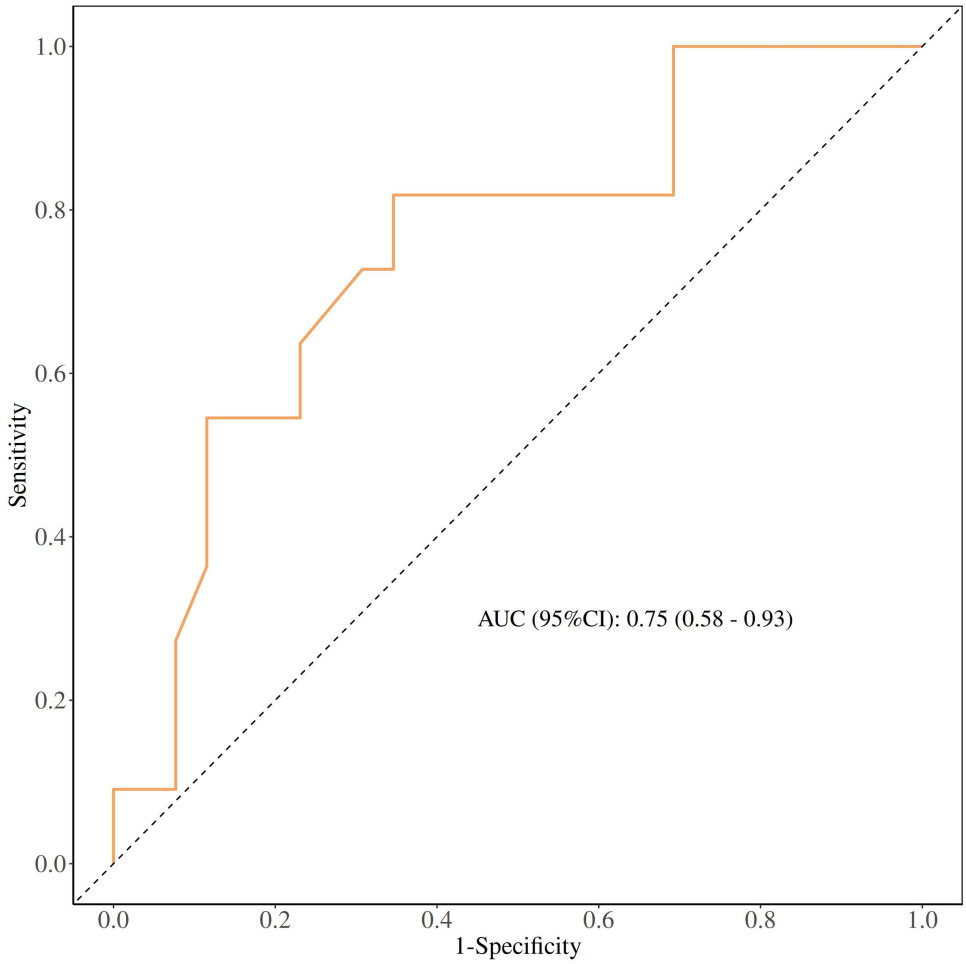

Figure 2 ROC curve. ROC curve was used to analyze the best cut-off value of LDH.

outcomes of coinfection with *T. marneffei* and *Cryptococcus* in PLHIV in southern China. Clinicians should take note of the possibility of concurrent infections with *T. marneffei* and other opportunistic pathogens.

T. marneffei infection typically occurs in individuals with advanced immunosuppression (CD4+ count < 100 cells/μL).[19] In such patients, concurrent opportunistic infections (OIs), including *cryptococcosis, tuberculosis*, and *Pneumocystis jirovecii pneumonia*, are common.[11,20–22] These OIs often share overlapping clinical features, complicating diagnosis and necessitating comprehensive diagnostic approaches. However, coinfections with *T. marneffei* and *Cryptococcus* are rarely reported, and their diagnosis and treatment are challenging in the clinical setting.[11] Only 10 human cases of concurrent infection with *T. marneffei* and *C. neoformans* have been reported, including 9 HIV-positive patients and 1 HIV-negative patient.[11–13] To our knowledge, this is the first case series report in which the clinical characteristics and outcomes of coinfection with *T. marneffei* and *Cryptococcus* in HIV-infected patients in southern China are described.[23]

Table 3 Diagnostic Performance of CSF LDH in Predicting Mortality in HIV Patients Co-Infected with *Talaromyces marneffei* and *Cryptococcus*

AUC (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Cut Off
0.75(0.58–0.93)	0.70(0.53–0.84)	0.65(0.47–0.84)	0.82(0.59–1.00)	0.89(0.76–1.00)	0.50(0.27–0.73)	21.15

Abbreviations: AUC, Area Under the Curve; CI, confidence interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

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Table 4 Multivariate Logistic Regression Analysis of Mortality in Patients with Coincident *T. marneffei* and *Cryptococcus*

Variable	Standard Error	Wald Value	P Value	OR	95% CI
Age	0.035	0.03	0.863	1.006	(0.94–1.05)
Sex					
Male	Ref				
Female	1.14	0.13	0.718	1.5	(0.16–14.24)
LDH ≤ 21.15 U/L	Ref				
LDH > 21.15 U/L	1.19	4.67	0.031	13.1	(1.27–135.76)
Consolidation therapy					
Itraconazole	Ref				
Fluconazole	1.56	2.15	0.14	0.10	(0.01–2.17)
Voriconazole	1.23	0.31	0.57	0.50	(0.05–5.65)

Note: The reference range for LDH is 0–40 U/L.
Abbreviations: CI, confidence interval; OR, Odds Ratio.

The clinical presentation in our cohort—constitutional, gastrointestinal, and respiratory symptoms being most frequent—aligns with prior reports of both *talaromycosis* and *cryptococcosis*.[6,17,24] Notably, central nervous system (CNS) symptoms, often highlighted in cryptococcosis,[11,12,25] were present in 44.7% of our patients but did not differ significantly between outcome groups. This underscores the nonspecific nature of symptoms in coinfected patients, emphasizing the critical role of laboratory diagnostics. In our study, when a blood culture for *T. marneffei* was positive in a coinfected patient, the most common test positive for *Cryptococcus* was a blood cryptococcal antigen test, followed by blood culture, CSF *cryptococcal* antigen test, and India ink staining in CSF. The finding that 17.0% of patients had both pathogens isolated from a single blood culture sample highlights the potential for concurrent bacteremia/fungemia and suggests that when one pathogen is identified, screening for the other is prudent. Despite guidelines recommending routine screening in endemic areas,[15] *cryptococcal* antigen testing is not universally implemented. Our findings reinforce the importance of early and simultaneous screening for both pathogens in severely immunocompromised HIV patients in endemic regions to avoid missed diagnoses and improve outcomes.

Amphotericin B is the preferred induction therapy for the treatment of cryptococcosis[26] and talaromyosis,[27] and the uncertainty of treatment is mainly related to the choice of drugs used during the consolidation period, which mainly include fluconazole, itraconazole, and voriconazole. Findings from a recent retrospective study indicated that in resource-poor settings, fluconazole following amphotericin B induction, an effective and well-tolerated regimen, may be an acceptable choice for the consolidation treatment of *C. neoformans* and *P. marneffei* coinfection.[11] In our study, amphotericin B-based induction therapy was used in most patients (76.6%) and was not associated with a survival difference. Patients treated with a combination of amphotericin B and other antifungal medications presented a greater survival rate than those who did not receive amphotericin B. Although the difference in induction and consolidation therapy between the groups was not statistically significant, most patients with coinfection who received amphotericin B as an induction therapy and itraconazole or fluconazole as a consolidation therapy obtained good outcomes. Fluconazole has poor in vitro and in vivo activity against *T. marneffe*i.[8] Conversely, itraconazole reaches negligible levels in CSF and is associated with a higher relapse rate during maintenance treatment of cryptococcal meningitis than with fluconazole.[28,29] Thus, the optimal azole therapy for one infection is suboptimal for the other.[11] Voriconazole has been revealed to exhibit potent in vitro activity and is used to treat multiple aggressive fungal infections with adequate safety and efficacy profiles.[12,30] Findings from numerous studies have indicated that voriconazole has good CSF levels and has been used to treat penicilliosis and central nervous system fungal infections, including cryptococcal meningitis, indicating that voriconazole may be appropriate for the treatment of coinfections with *T. marneffei* and *Cryptococcus*.[11,31–35] At present, no standard antifungal treatment for coinfection has been established, and a large amount of research data is still needed to clarify the optimal consolidation treatment regimen for patients with coinfection.

In this study, we found a mortality rate of 29.8% in coinfected patients. The reported mortality rate is 40% among cryptococcal meningitis patients and 12.6% among talaromycosis patients.[21,36] It is speculated that the combined infection will cause the patient to be more dangerous. The clinical manifestations of patients with coinfections are atypical, the mortality rate is high, and the outcomes are very poor. Therefore, in patients with coinfections, early evaluation for risk factors for death and appropriate interventions, as well as the ability to identify protective factors, are very important to improve patient outcomes. Univariate and multivariate logistic regression analyses of risk factors for coinfection with *T. marneffei* and *Cryptococcus* showed that high LDH levels in the CSF were potential risk factors for poor outcomes and that regular ART before hospitalization was a potential protective factor. Guidelines in China recommend that ART should be initiated within 1–2 weeks of effective antifungal therapy for AIDS patients with talaromycosis. For patients with cryptococcal pneumonia, ART should be initiated within 2 weeks of effective antifungal therapy, whereas for patients with cryptococcal meningitis, antiviral therapy should be appropriately delayed, generally starting after 4–6 weeks. Therefore, screening for T. marneffei and Cryptococcus infection before antiviral treatment is particularly important. LDH is an enzyme that is widely present in a variety of cells in the body, and its high levels in serum may reflect tissue damage or cell death.[37] In some studies, a high level of LDH is correlated with the severity of *T. marneffei* infection and poor prognosis, and the LDH level can be used as an indicator of the severity of infection and the outcomes of patients.[38,39] In our study, the serum LDH level was elevated to varying degrees in almost all patients, indicating tissue damage and cell death. Although LDH levels in CSF were normal in almost all patients with coinfections, the difference between the groups was statistically significant, with a higher risk of death in patients with LDH >21.15 U/L.

This study has several important limitations. First, it is a single-center, retrospective study with a relatively small sample size, which limits the generalizability of our findings and estimates of outcomes. However, this is the first study of a large cohort of PLHIV coinfected with *T. marneffei* and *Cryptococcus* and the first comprehensive report of the clinical characteristics, management, and outcomes of coinfected patients. Second, because our study was based on the time of death or discharge from the hospital, the follow-up time was short; therefore, the recurrence and long-term outcomes of patients who received different consolidation regimens could not be fully evaluated. Third, the choice of antifungal therapy was not randomized; thus, factors influencing both therapeutic decisions and outcomes may have confounded the relationship between management and outcome.

Conclusion

In conclusion, coinfection with *Talaromyces marneffei* and *Cryptococcus* in HIV patients is characterized by nonspecific clinical presentations, a high mortality rate, and diagnostic complexity. We emphasize the importance of early and concurrent screening for both pathogens in endemic areas, utilizing blood cultures for *T. marneffei* and *cryptococcal* antigen tests. Furthermore, CSF LDH level emerges as a simple and independent prognostic marker; a value exceeding 21.15 U/L should alert clinicians to a significantly higher risk of mortality. The optimal antifungal consolidation regimen remains to be determined and warrants investigation in future prospective studies. Early diagnosis, vigilant monitoring of CSF LDH, and timely initiation of appropriate antifungal therapy are pivotal to improving outcomes in this vulnerable population.

Abbreviations

PLHIV, Patients living with human immunodeficiency virus; ART, Antiretroviral therapy; CSF, Cerebrospinal fluid; LDH, Lactate dehydrogenase; OR, Odds Ratio; CI, Confidence interval; HIV, Human immunodeficiency virus; AIDS, Acquired Immune Deficiency Syndrome; WHO, World Health Organization; OIs, Opportunistic infections; BALF, Bronchoalveolar lavage fluid; PCR, Polymerase chain reaction; ELISA, Enzyme-linked immunosorbent assay; ROC, Receiver operating characteristic; NGS, Next-generation sequencing.

Data Sharing Statement

Please contact the corresponding author for data requests.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Review Board of the Fourth People's Hospital of Nanning (No. 2024-74). The Institutional Review Board confirmed that the data had been anonymized or kept confidential. As this is a low-risk retrospective medical record review study, the Institutional Ethics Review Board of the Fourth People's Hospital of Nanning determined that obtaining consent to participate was not necessary and waived it.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The research was carried out without any financial or commercial ties that might be seen as having a conflict of interest, the authors disclose.

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