Heliyon 9 (2023) e20068

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Clinical features of HIV positive talaromycosis marneffei patients and development of a risk prediction model

Jiemei Cen [a,b], Jie Huang [c], Wen Zeng [a], Mianluan Pan [a], Ye Qiu [a], Jianquan Zhang [a,*]

[a] Department of Respiratory Medicine, the Eighth Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong 518033, China
[b] Department of Respiratory Medicine, the Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, 510630, China
[c] Guangxi Nanning Fourth People's Hospital, Department of Tuberculosis Ward, Nanning, Guangxi, China

ARTICLE INFO

Keywords:
HIV
Talaromycosis marneffei
Prediction model
Nomogram
Prognosis

ABSTRACT

Aims: The purpose of this study was to establish and verify a nomogram to predict the prognosis of patients with human immunodeficiency virus (HIV)-related talaromycosis marneffei and evaluate the prognosis.
Methods: We examined the acquired immune deficiency syndrome (AIDS) patients hospitalized in the Fourth People's Hospital of Nanning from 2018 to 2020 with an aetiological diagnosis of Talaromyces marneffei infection. Logistic regression analysis was used to identify the independent risk factors for relapse or death of the prognosis of Talaromyces marneffei infection. According to the regression coefficient, the corresponding nomograph prediction model was drawn.
Results: A total of 400 patients were included, including 321 males and 79 females. Recurrence or death occurred in 70 cases (17.5%). The area under the receiver operator characteristic curve (ROC) of the established model was 0.716 with good discrimination, calibration, and clinical effectiveness. The risks of age between 45 and 60 years old and <40 years old were successively higher than that of >60 years old, and the risks of G test <50 pg/ml and >100 pg/ml were higher than that of 50–100 pg/ml. Respiratory failure, decreased albumin and elevated total bilirubin are risk factors for relapse or death in HIV patients infected with Talaromyces marneffei.
Conclusion: This model can accurately predict the prognosis of HIV complicated with Talaromyces marneffei infection.

1. Introduction

Talaromyces marneffei, formerly known as Penicillium marneffei, is an invasive fungus and an important thermally pathogenic transition fungus causing systemic mycosis in Southeast Asia. It is commonly found in Southeast Asia and Guangxi, Guangdong, Fujian, and other places in South China [1]. It occurs mainly in immunocompromised populations, such as HIV patients, organ transplant patients, autoimmune diseases and haematologic malignancies, causing life-threatening disseminated infections [2,3]. In highly endemic countries such as Vietnam, Thailand and China, cases of talaromycosis marneffei (TSM), namely, with deep opportunistic pathogenic mycosis caused by Talaromyces marneffei, have surged from a rare infection to the most common AIDS-related infection, after tuberculosis, oral candida infection and pneumocystis pneumonia [2–4]. Talaromyces marneffei mainly invades organs and sites related to the monocyte–macrophage reticuloendothelial system. T. marneffei infections can be divided into disseminated and focal

* Corresponding author.
E-mail address: jqzhang2002@126.com (J. Zhang).

https://doi.org/10.1016/j.heliyon.2023.e20068
Received 17 March 2023; Received in revised form 2 September 2023; Accepted 11 September 2023
Available online 12 September 2023

types; focal type infections are often confined to the site of invasion, and the clinical manifestations are dominated by the symptoms of the original disease. The disseminated type often involves multiple tissues and organs. Common clinical manifestations of disseminated T. marneffei include fever, respiratory signs, anaemia, weight loss, skin lesions, lymphadenopathy, and hepatosplenomegaly. As overseas travel increases along with the use of chemotherapy and immunosuppression, TSM has become a global clinical challenge by spreading to nonendemic areas [5,6]. However, in recent years, there have been increasing reports of cases among non-HIV-infected patients [7]. In the past 20 years, Talaromyces marneffei (TM) has developed from a rare disease in HIV patients to a common co-infection in HIV patients, and studies have confirmed that TSM can increase the mortality of HIV patients and seriously threaten human life and health. However, studies on the prognosis of HIV/AIDS patients with TSM infection are still lacking. The purpose of the current study is to comprehensively analyse HIV-positive TSM patients' epidemiology, clinical and laboratory results, imaging, treatment and outcome, and summarization of the TSM prognosis risk factors through a clinical prediction model. Thus, to provide a simple method for predicting the prognosis of patients (see Fig. 12).

2. Methods

2.1. Study subjects and data collection

A large-scale retrospective cohort study was conducted in the Fourth People's Hospital of Nanning, Guangxi. HIV infection was diagnosed by ELISA and Western blot. The diagnosis of TSM was defined as a disease which TM was isolated from histopathology or specimens such as blood, bone marrow, bronchoalveolar lavage fluid (BAL), pleura and/or other body fluid samples. Patients lacking of prognostic and comorbidity information or relevant test data were excluded. Data on demographic characteristics, length of stay or survival in the hospital, routine blood test, G tests, GM tests, blood gas analysis, and treatment outcome were collected from the hospital electronic medical record system. We defined an adverse outcome as death at the hospital, deterioration, or recurrence after discharge. A good outcome was defined as improvement of clinical symptoms such as fever and skin lesions and/or fungal clearance in follow-up.

Ethics approval

The studies involving human participants were reviewed and approved by Ethics Committee of HIV/AIDS Clinical Treatment Center of Guangxi (Nanning) and the Fourth People's Hospital of Nanning and the reference number is Z20170148. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this manuscript.

2.1.1. Risk factors

We collected and analyzed the following factors: general information (gender, age, history of play), symptoms (fever, night sweats, chills, emaciation, anaemia, cough, sputum, digestive tract symptoms), physical examination (hepatomegaly, splenomegaly, rash, swollen lymph nodes, serous cavity effusion), laboratory tests (white blood cell count, red blood cells, platelets, haemoglobin, percentage of neutrophils and lymphocytes percentage, G test, $CD4^+$ cell count, albumin, liver enzymes, bilirubin, ESR, CRP, K+, creatinine, blood gas analysis), coinfection pathogen, antifungal therapy, antiretroviral therapy, and site of involvement (skin, lung, liver, spleen, lymph node).

2.1.2. Statistical analysis

Measurement data were expressed as the mean (standard deviation) and count data as frequency (percentage). The measurement data were analyzed by the Mann–Whitney *U* test, and the count data were analyzed by the $\chi 2$ test. Logistic regression analysis was used to screen the risk factors for Model A. The Akaike information criterion was used to screen the risk factors for Model B. All statistical analyses were performed by R Studio.

2.1.3. Construction and evaluation of prediction models based on risk factors

Based on the regression coefficients of independent variables, we established an individualized nomogram prediction model for the prognosis of TM infection as death or recurrence. The prediction model was evaluated from the perspectives of discrimination, correction and clinical validity. The discriminability of a predictive model refers to its ability to distinguish between patients who progressed to death or relapse from those who improved and is usually evaluated by calculating the area under the receiver operating characteristic (ROC) curve (AUC). Generally, a prediction model with an AUC of 0.5–0.75 is considered acceptable. The correction is usually calculated by calibration degree, which is the consistency between predicted and observed probability. A good calibration degree indicates that the accuracy of the prediction model is high. Otherwise, the model may overestimate or underestimate the risk of disease. In this study, calibration plot was drawn to evaluate the calibration degree of the model. We usually use ROC curves to find clinical trials of tangency, mainly taking specificity and sensitivity as equally important. However, egardless of which value is taken as the critical value, false-positive and false-negative will be encountered. It is better to avoid false-positive (misdiagnosis), and sometimes it is better to avoid false-negative (missed diagnosis). Since neither is inevitable, we need to find a way to maximize the net benefit. The decision curve analysis (DCA) can calculate the net benefit value of different critical points, so it can verify the clinical validity of the model.

3. Results

3.1. Demographics of the patients

In this study, 400 patients were enrolled, including 321 males and 79 females. A total of 212 (53.5%) were younger than 45 years old, 133 (39.5%) were between 45 and 60 years old, and 55 (16.25%) were older than 60 years old. A total of 234 patients (70.75%) had a prostitute history.

3.2. Diagnosis, treatment and outcomes of TSM

All patients underwent blood culture, but only 279 (69.75%) were positive, and 145 (127 (87.58%) were positive by bone marrow culture. Bronchoalveolar lavage fluid culture was performed in 13 patients (2 positive cases, 15.38%), and sputum culture and purulent secretion culture were performed in 245 patients (102 positive cases, 41.63%) and 2 patients (1 positive case, 50%) respectively. Among the anti-infection regimens, 17 cases (7.08%), 71 cases (29.58%), 24 cases (10%), 113 cases (47.08%) and 15 cases (6.25%) received polyenes, imidazoles, polyenes + imidazoles, polyenes + imidazoles, and polyenes + imidazoles respectively. Seventy patients (29.17%) relapsed or died.

3.3. Clinical features

Opportunistic infections (OIs) were diagnosed in 83 patients (34.58%). All coinfections were confirmed by aetiological examinations, including 17 cases (7.08%) of bacterial, 25 cases (10.42%) of fungal, 19 cases (7.92%) of viral and 22 cases (9.17%) of parasitic infections. The clinical characteristics of the patients are summarized in Table 2. The most common symptoms and signs were respiratory failure (366 cases, 91.5%), fever (316 cases, 79%), gastrointestinal symptoms (292 cases,73%), cough (257 cases, 64.25%), polyserositis (206 cases, 51.5%), expectoration (212 cases, 53%), emaciation (190 cases, 47.5%), cough (152 cases, 63.33%), and lymphadenopathy (190 cases, 47.5%). Others included night sweats, chills, headache, anaemia, hepatomegaly splenomegaly, and rash. The most frequently involved organs were the lung and pleura as shown in Table 1.

Regarding the laboratory examination, anaemia, hypoproteinaemia, leukopenia, elevated AST, lymphopenia, decreased $CD4^+$ T lymphocytes, hypokalaemia were very common as shown in Table 2. For treatment, 140 patients (35%) received ART; 27 (6.75%) patients, 110 (27.5%) patients, 41 (10.25%) patients, 194 (48.5%) patients, and 28 (7%) patients received polyene, triazole, polyene + imidazole + triazole, polyene + triazole, and imidazole + triazole as antifungals, respectively. After treatment, 70 (17.5%) patients experienced adverse outcome, namely, death, deterioration or recurrence as shown in Table 3.

3.4. *Construction of* the *nomogram*

The modelling and validation groups overlapped by 1/5 for better cohort fit, namely 80 of the 400 cases were randomly selected as the overlap between the modelling group and the validation group, and the remaining 320 cases were randomly divided into the modelling group and the validation group. As a result, modeling cohort and validation cohort included 240 cases each. Logistic regression was used to screen predictors to establish Model A, in which age (P = 0.0305), respiratory failure(P = 0.0383), G test(P =

Table 1
The clinical manifestation of all patients.

	number	percentage(%)
Fever	316	79
night_sweat	39	9.7
Chill	78	19.5
headache	62	15.5
emaciation	190	47.5
anemic_appearance	97	24.25
Cough	257	64.25
expectoration	212	53
respiratory failure	366	91.5
Gastrointestinal symptom	292	73
hepatomegaly	65	16.25
splenomegaly	85	21.25
Rash	96	24
lymphadenectasis	190	47.5
polyserositis	206	51.5
Pleural.involvement	144	36
skin.involvement	75	18.75
liver.involvement	120	30
spleen.involvement	174	43.5
lymphaden	130	32.5
lung.involvement	220	55

Table 2
The laboratory examination results of allpatients

	Number	percentage
WBC < 4X10*9/L	189	0.4725
RBC < 3.5X10*12/L	231	0.5775
PLT < 100X10*9/L	170	0.425
HGB < 110 g/L	324	0.81
N%		
< 50%	14	0.035
> 70%	331	0.8275
L%		
< 20%	344	0.86
> 40%	10	0.025
G_test		
< 50 ng/ml	92	0.23
50–100 ng/ml	59	0.1475
> 100 ng/ml	249	0.6225
$CD4^+$ cell count < 400 cells/μl	396	0.99
ALB < 35 g/L	382	0.955
AST > 40U/L	277	0.6925
ALT > 40U/L	176	0.44
Tbil > 23 μmol/L	61	0.1525
ESR > 15 mm/h	69.435	0.1735875
CRP > 10 mg/L	60.205	0.1505125
K < 3.5 mmol/L	162	0.405
Creatinine > 100 μmol/L	54	0.135

Annotation: WBC, white blood cell; RBC, red blood cell; PLT, blood platelet; HGB, hemoglobin; N%, neutrophilic granulocyte percentage; L%, lymphocyte percentage; G_test, 1, 3-beta-D glucan test; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Tbil, total bilirubin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; K, serum kalium.

Table 3
The treatment and outcomes of patients.

	number	percentage
ART	140	35%
Antifungal		
Polyene	27	6.75%
Triazole	110	27.50%
Polyene + Imidazole + Triazole	41	10.25%
Polyene + Triazole	194	48.5
Imidazole + Triazole	28	7%
death/deterioration/recurrence	70	17.50%

0.0305), albumin(P = 0.0386) and total bilirubin(P = 0.0004) were included in Model A and the P values of other parameters were over 0.05 (Fig. 1). While Model B screened predictors based on AIC (Akaike Information Criterion) step-based regression, and five factors including expectoration (P = 0.0399), red blood cells (P = 0.0342), albumin (P = 0.0069), total bilirubin (P = 0.0010) and pulmonary involvement (P = 0.0426) were included in Model B (Fig. 2). We then developed an individualized nomogram prediction model of TM infection and recurrence or progression to death. In Model A, the risk of older than 60 years was lower than that of younger than 45 years and 45–60 years. In the G test, the risk of less than 50 pg/ml and more than 100 pg/ml was higher than that of 50–100 pg/ml. With respiratory failure, decreased albumin, and increased total bilirubin, the odds of recurrence or death were increased, as was the probability of adverse outcome in Model A. In Model B, sputum production, elevated erythrocytes, decreased ALB, elevated total bilirubin and pulmonary involvement were high risk factors for adverse outcomes.

3.5. Validation of the nomogram

The validation of the models included discrimination, calibration and clinical validation. The ROC curve of the predicted probability was drawn, and the AUC values of the modelling group and the validation group were calculated. The AUC values of the five independent risk factors in the nomogram were calculated to verify the discrimination of the model. The difference was statistically significant (P < 0.05). The calibration plot was used to evaluate the discrimination. The AUC values of recurrence or death risk in Model A modelling group and validation group were 0.716 and 0.646, respectively (Fig. 3A–D and Fig. 4A–D), indicating that the nomogram prediction model had good recognition power. Calibration was evaluated by drawing a calibration plot. The P values of the modelling population and the validation population were 0.999 and 0.194, respectively, which are greater than 0.05, that is, there was no significant difference between the predicted curve and the observed curve, indicating that the calibration of the model was good

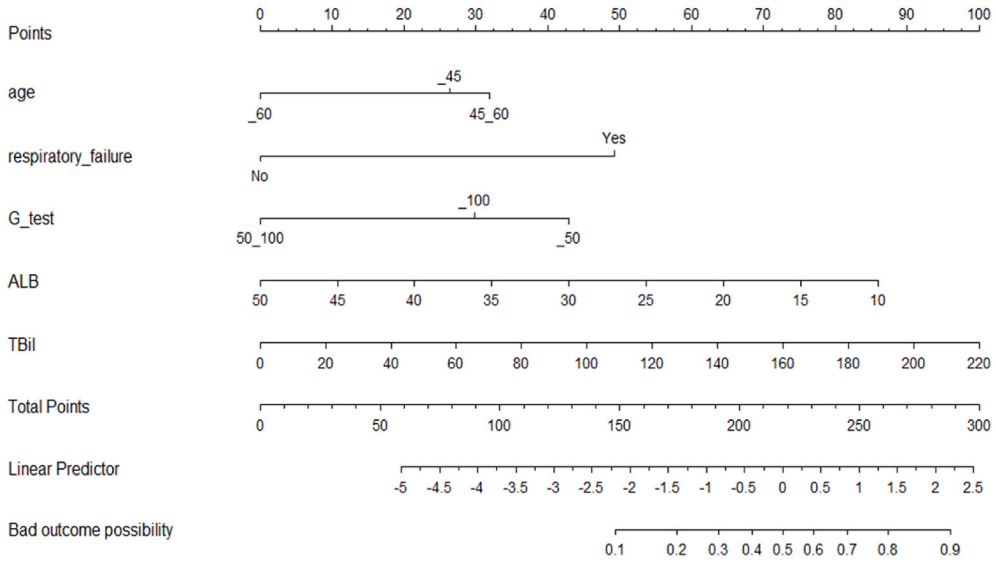

Fig. 1. The nomogram of model A.

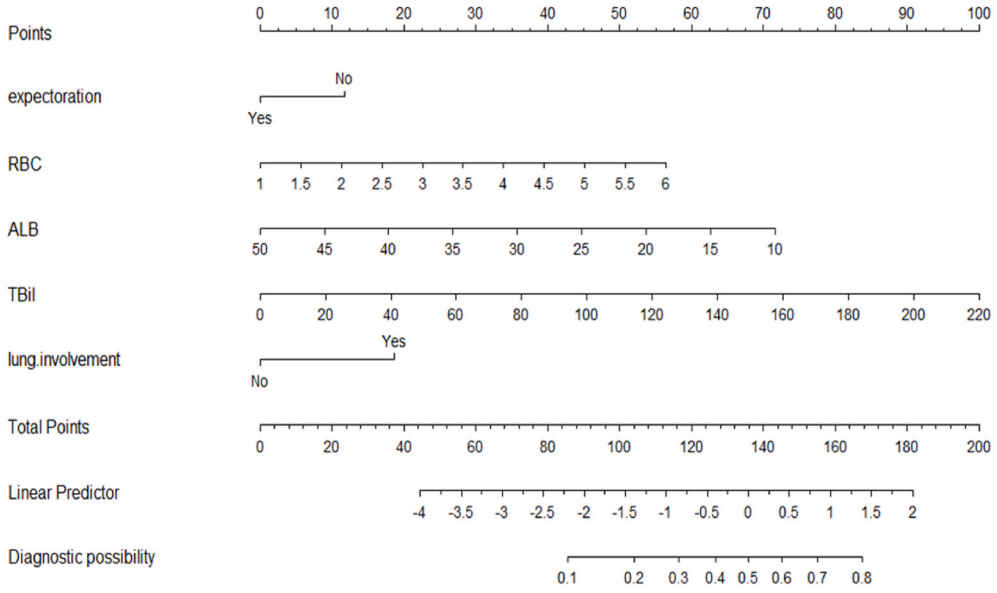

Fig. 2. The nomogram of model B.

(Fig. 7, Fig. 8). The AUC values of recurrence or death risk in Model B modelling group and validation group were 0.720 (cut-off 0.227) and 0.688 (cut-off 0.109), respectively (Figs. 5 and 6), indicating that the nomogram prediction model had good recognition power. In the calibration evaluation, the P values of the modelling population and the validation population were 0.974 and 0.148, respectively, which were greater than 0.05. The calibration curve of the nomogram showed that there was a high degree of consistency between Model A and Model B in the training and validation cohorts, and both the validation cohort and the modelling cohort indicated that the calibration degree of the model was good (Fig. 9, Fig. 10).The clinical applicability was verified by drawing the DCA curve. The X-axis is the threshold size, and the Y-axis is the net benefit of the model under different thresholds. In the modelling group, the clinical applicability of Model A was similar to that of Model B, however, in the validation group, the clinical applicability of model B was better than that of model A. Fig. 7 shows the decision curves of Model A and Model B for screening the clinical efficiency of recurrence or death after TSM infection. The clinical benefits of Model A and Model B were comparable. When the threshold was 0.24, the net benefits of Model A and B were 0.06 and 0.04, respectively, 6 and 4 patients received net benefits for every 100 people respectively. According to the above parameters, there was no statistically significant difference between Model A and Model B. However, the nomogram of Model A had a larger span of adverse outcomes than Model B (0.1–0.9), while Model B was only 0.1–0.8. Therefore,

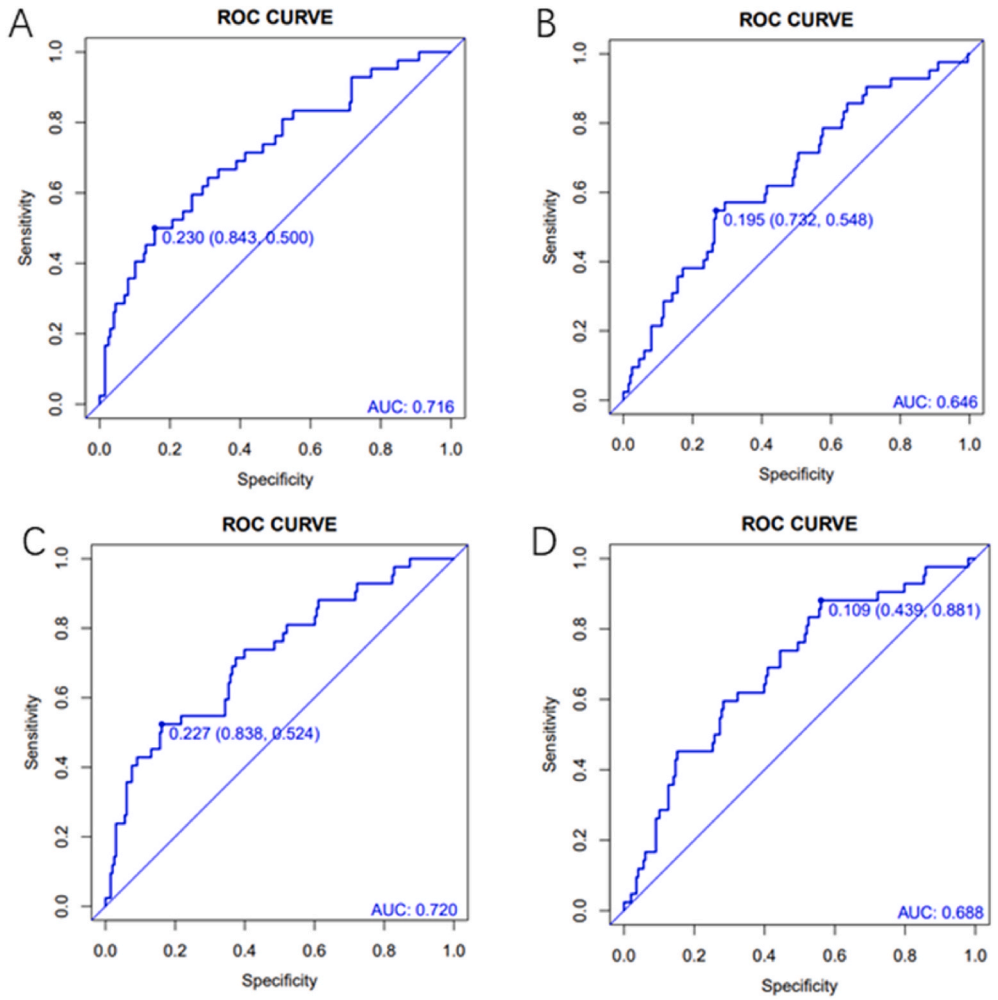

Fig. 3. A, B, C, D represent the ROC curve of the training group of model A, B, the validation group of model A, B respectively.

Model A was established as a more suitable model (see Fig. 11).

4. Discussion

TM is a temperature phase transition fungus, and disseminated TSM has insidious onset, complexity and high mortality [8]. In China, approximately 99% of TM infection reports come from the southern region: 43% from Guangxi Province and 41% from Guangdong Province. Eighty-eight percent of TM infections were found in people with HIV/AIDS [4]. Although tuberculosis is the main cause of death in HIV/AIDS patients in Guangxi [9], the number of TM coinfections has been increasing in recent years, and TM has become one of the main causes of death in HIV/AIDS patients [10,11].

Several small studies have reported the mortality of TSM in HIV/AIDS patients, focusing on the effect of HIV infection on the progression of TSM [12,13]. However, in addition to HIV infection, many factors may affect the prognosis of TSM in HIV/AIDS patients. In recent years, domestic and foreign scholars have studied the prognostic factors of AIDS complicated with TSM, such as creatinine, CRP, haemoglobin, platelets, liver function (ALT, AST, ALB), CD4+T lymphocytes, white blood cells, clinical symptoms and signs, age and comorbidities [14–17].However, most of the studys have not been comprehensively evaluated by analyzing one or several laboratory indicators or treatment regimens. To the best of our knowledge, this is the first study to comprehensively assess the risk factors for adverse prognosis in patients from general demographic characteristics, clinical manifestations, auxiliary examination results, treatment and other aspects. Simultaneously, a model with high identification and clinical validity was established, which provided a simple tool for the clinical assessment of patient prognosis.

In this study, we found that the clinical characteristics were nonspecific, which resulted in a delayed diagnosis or misdiagnosis. The most common laboratory results were leucocyte reduction, lower haemoglobin, albumin, and elevated liver enzymes, which implied bone marrow suppression and liver damage to a certain extent. This finding was closely related to the theory that TM spread spreads through the endothelial network. Due to a certain degree of bone marrow suppression, the above laboratory results may imply poor

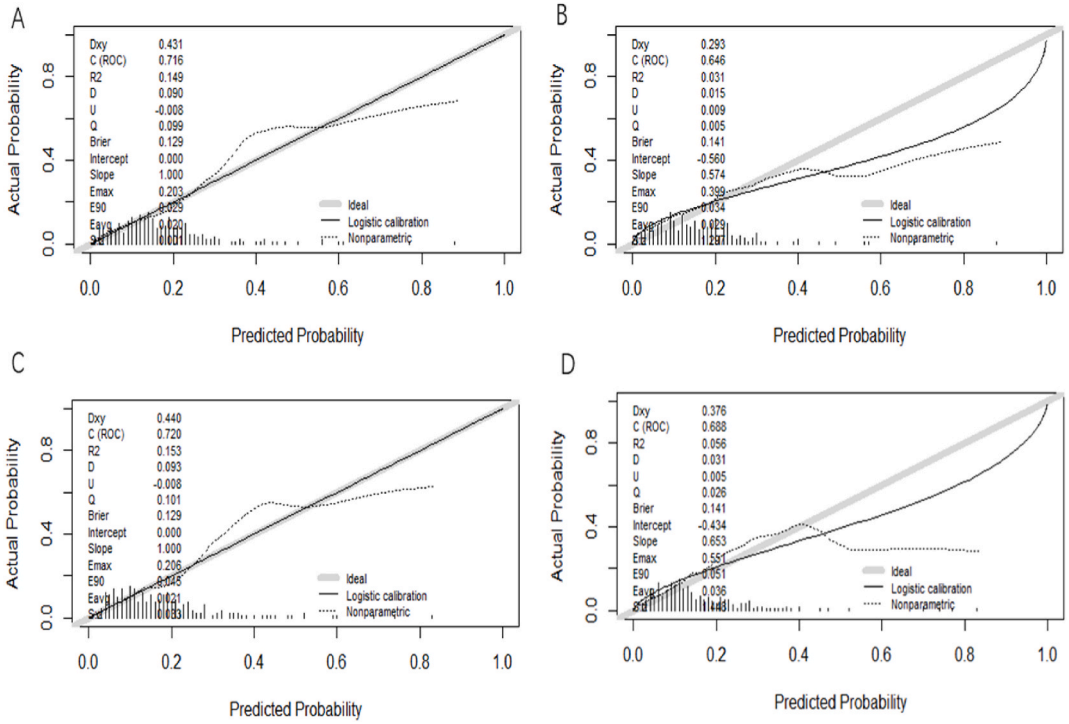

Fig. 4. A, B, C, D represent the calibration plot of the training group of model A, B, the validation group of model A, B respectively.

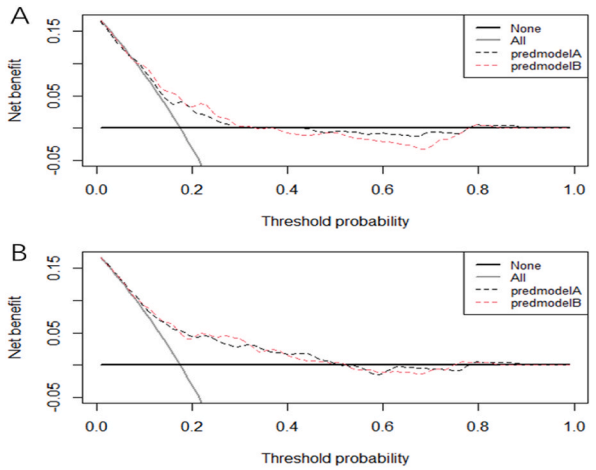

Fig. 5. The DCA curve of the training group of model A and model B.

prognosis.

In terms of treatment, Huang YT et al. revealed that induction therapy with voriconazole or itraconazole was associated with higher mortality than amphotericin B. They also confirmed the results of a 2017 randomized controlled trial in Vietnam, which showed the superiority of amphotericin B over itraconazole with less mortality [18]. In this study, although antifungal therapy was not included in the model, 113 and 119 patients received amphotericin B combined with itraconazole/voriconazole sequential therapy in the modelling group and the validation group, respectively, with lower adverse outcomes than other treatment regimens, namely with 13 patients (11.33%) and 14 patients (11.76%) in the two groups. These results showed that amphotericin B induction therapy plus itraconazole/voriconazole consolidation therapy has certain advantages in improving the prognosis of patients. Antiretroviral therapy (ART) plays an important role in HIV-positive patients with TSM. Yuanyuan Qin et al. [19] found that in HIV-positive patients with TSM, there was a significant difference in the death rate between early ART (within 2 weeks) and delayed ART (after 2 weeks). In this study, 140 patients (35%) received antiretroviral therapy, and all patients started antiretroviral therapy before the hospitalization.

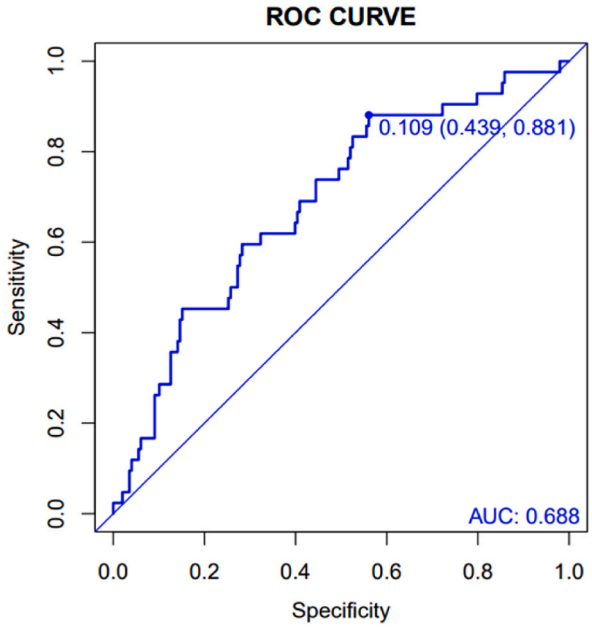

Fig. 6. The ROC curve of the validation group of model B.

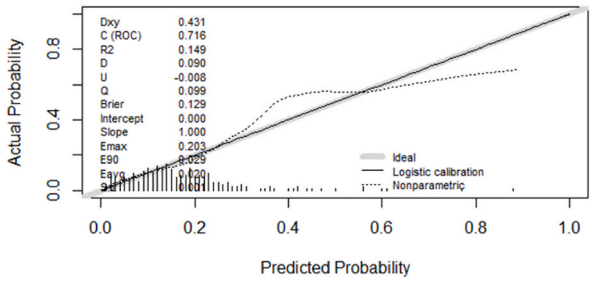

Fig. 7. The calibration plot of the training group of model A.

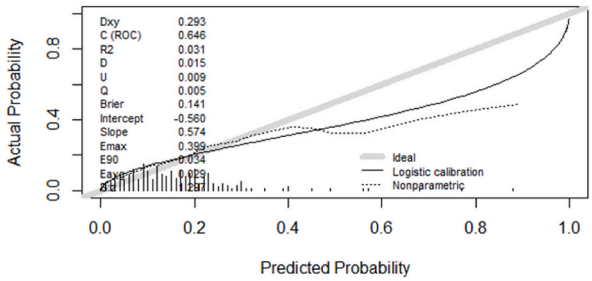

Fig. 8. The calibration plot of the validation group of model A.

However, the time of ART initiation was not recorded, and it was not known whether it was initiated before or within 2 weeks of the onset of TSM. In this study, the incidence of adverse outcomes was 19.02% in the modelling group of the no ART group, and 20.51% in the validation group, respectively, but the P value was greater than 0.05, and the difference was not statistically significant.

According to the model we constructed, age, respiratory failure, decreased albumin, and increased total bilirubin were significantly associated with death or recurrence in patients with TSM. This model has excellent discrimination, calibration and clinical validity, and can identify patients who are at low or high risk of death or recurrence.

However, there are limitations in this study. In the process of data analysis, a repeated random grouping method was used to divide patients into two groups with the largest area under the ROC curve and the largest calibration degree and clinical applicability of both

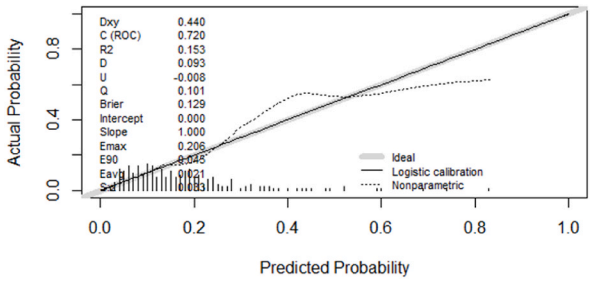

Fig. 9. The calibration plot of the training group of model B.

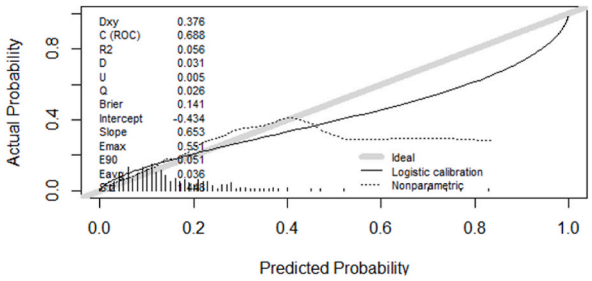

Fig. 10. The calibration plot of the validation group of model B.

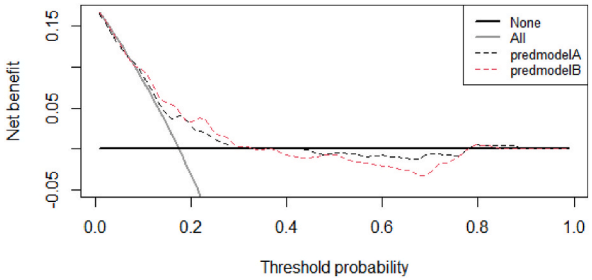

Fig. 11. The DCA curve of the training group of model A and model B.

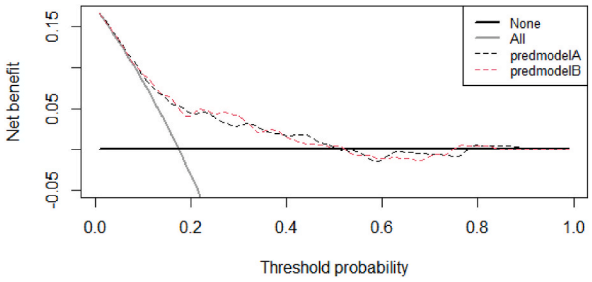

Fig. 12. The DCA curve of the validation group of model A and model B.

models. In addition, it was found that the larger the amount of data was, the larger the area under the ROC curve and the better the calibration degree and clinical applicability. Therefore, if the amount of data is larger, the model may be more accurate. This study was conducted by analyzing the clinical records of patients in the Fourth People's Hospital of Nanning, Guangxi. It was a single-centre retrospective study and was not validated in a prospective cohort, further research should include more study centers and add a prospective cohort to validate the model for stronger evidence.

5. Conclusion

The AUC of the model established in this study was 0.716. Among them, the risk of age 45–60 years old and <40 years old was successively higher than that of >60 years old, and the risk of G test <50 pg/ml and >100 pg/ml was higher than that of 50–100 pg/ml. Respiratory failure, decreased albumin and elevated total bilirubin are risk factors for relapse or death in HIV patients infected with TM. This model can accurately predict the risk of relapse or death of HIV complicated with TM infection, which is helpful to improve the early identification and screening of such high-risk patients.

Author contribution statement

Jianquan Zhang: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Jiemei Cen: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wen Zeng: Performed the experiments; Contributed reagents, materials, analysis tools or data.

Mianluan Pan: Contributed reagents, materials, analysis tools or data. </p>

Ye Qiu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data. </p>;

Jie Huang: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data. </p>.

Data availability statement

Data included in article/supplementary material/referenced in article.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Author contributions

JC, YQ, JZ conceived and designed the experiments; JC, WZ, JZ Performed the experiments; JC, JH, YQ, WZ, JZ, MP Contributed reagents, materials, analysis tools or data; JC, JH Analyzed and interpreted the data; JC wrote the paper. All authors have read and approved the manuscript.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We gratefully acknowledge our study group members for their work.

References

[1] N. Vanittanakom, C.R. Cooper Jr., M.C. Fisher, T. Sirisanthana, Penicillium marneffei infection and recent advances in the epidemiology and molecular biology aspects, Clin. Microbiol. Rev. 19 (1) (2006) 95–110.

[2] T.V. Nga, C.M. Parry, T. Le, N.P. Lan, T.S. Diep, J.I. Campbell, et al., The decline of typhoid and the rise of non-typhoid salmonellae and fungal infections in a changing HIV landscape: bloodstream infection trends over 15 years in southern Vietnam, Trans. R. Soc. Trop. Med. Hyg. 106 (1) (2012) 26–34.

[3] V.T. Son, P.M. Khue, M. Strobel, Penicilliosis and AIDS in Haiphong, Vietnam: evolution and predictive factors of death, Med Mal Infect 44 (11–12) (2014) 495–501.

[4] Y. Hu, J. Zhang, X. Li, Y. Yang, Y. Zhang, J. Ma, et al., Penicillium marneffei infection: an emerging disease in mainland China, Mycopathologia 175 (1–2) (2013) 57–67.

[5] P. Nenoff, D. Reinel, C. Krüger, H. Grob, P. Mugisha, A. Süß, et al., [Tropical and travel-related dermatomycoses : Part 2: cutaneous infections due to yeasts, moulds, and dimorphic fungi], Hautarzt 66 (7) (2015) 522–532.

[6] R.S. Ying, T. Le, W.P. Cai, Y.R. Li, C.B. Luo, Y. Cao, et al., Clinical epidemiology and outcome of HIV-associated talaromycosis in Guangdong, China, during 2011-2017, HIV Med. 21 (11) (2020) 729–738.

[7] J.F. Chan, S.K. Lau, K.Y. Yuen, P.C. Woo, Talaromyces (Penicillium) marneffei infection in non-HIV-infected patients, Emerg Microbes Infect 5 (3) (2016) e19.

[8] A.H. Limper, A. Adenis, T. Le, T.S. Harrison, Fungal infections in HIV/AIDS, Lancet Infect. Dis. 17 (11) (2017) e334–e343.

[9] Z. Zheng, Z. Tang, M. Lin, F. Liu, Z. Cui, W. Geng, [Feature analysis on patients died from co-infection of Mycobacterium tuberculosis and human immunodeficiency virus in Guangxi, from 2007 to 2012], Zhonghua Liuxingbingxue Zazhi 35 (6) (2014) 695–698.

[10] Y. Qiu, H. Liao, J. Zhang, X. Zhong, C. Tan, D. Lu, Differences in clinical characteristics and prognosis of Penicilliosis among HIV-negative patients with or without underlying disease in Southern China: a retrospective study, BMC Infect. Dis. 15 (2015) 525.

[11] Y. Qiu, J. Zhang, G. Liu, X. Zhong, J. Deng, Z. He, et al., Retrospective analysis of 14 cases of disseminated Penicillium marneffei infection with osteolytic lesions, BMC Infect. Dis. 15 (2015) 47.
[12] R. Kawila, R. Chaiwarith, K. Supparatpinyo, Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infection in Northern Thailand: a retrospective study, BMC Infect. Dis. 13 (2013) 464.
[13] M. Larsson, L.H. Nguyen, H.F. Wertheim, T.T. Dao, W. Taylor, P. Horby, et al., Clinical characteristics and outcome of Penicillium marneffei infection among HIV-infected patients in northern Vietnam, AIDS Res. Ther. 9 (1) (2012) 24.
[14] J. Zheng, X. Gui, Q. Cao, R. Yang, Y. Yan, L. Deng, et al., A clinical study of acquired immunodeficiency syndrome associated Penicillium marneffei infection from a non-endemic area in China, PLoS One 10 (6) (2015), e0130376.
[15] T. Le, M. Wolbers, N.H. Chi, V.M. Quang, N.T. Chinh, N.P. Lan, et al., Epidemiology, seasonality, and predictors of outcome of AIDS-associated Penicillium marneffei infection in Ho Chi Minh City, Viet Nam, Clin. Infect. Dis. 52 (7) (2011) 945–952.
[16] N.T.M. Thu, J.F.W. Chan, V.T. Ly, H.T. Ngo, H.T.A. Hien, N.P.H. Lan, et al., Superiority of a Novel Mp1p antigen detection enzyme immunoassay compared to standard BACTEC blood culture in the diagnosis of talaromycosis, Clin. Infect. Dis. 73 (2) (2021) e330–e336.
[17] D.R. Boulware, K.H. Hullsiek, C.E. Puronen, A. Rupert, J.V. Baker, M.A. French, et al., Higher levels of CRP, D-dimer, IL-6, and hyaluronic acid before initiation of antiretroviral therapy (ART) are associated with increased risk of AIDS or death, J. Infect. Dis. 203 (11) (2011) 1637–1646.
[18] T. Le, N.V. Kinh, N.T.K. Cuc, N.L.N. Tung, N.T. Lam, P.T.T. Thuy, et al., A trial of itraconazole or amphotericin B for HIV-associated talaromycosis, N. Engl. J. Med. 376 (24) (2017) 2329–2340.
[19] Y. Qin, Y. Zhou, S. Liu, Y. Lu, M. Liu, J. Yuan, et al., HIV-associated talaromycosis: does timing of antiretroviral therapy matter? J. Infect. 84 (3) (2022) 410–417.