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Predicting the Risk of in-Hospital Mortality in Patients with HIV-Associated Talaromyces Marneffei Infection

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Abstract

Disseminated Talaromyces marneffei infection (formerly termed penicilliosis) is the third most common microbiologically confirmed opportunistic infection in Southeast Asia, with mortality of up to 30% despite antifungal therapy. There are restrictive clinical algorithms to predict treatment outcomes. A total of 513 patients with microbiology-confirmed HIV-associated talaromycosis were included in the analysis. Poor outcome was observed in 143/513 patients (27.9%). In the univariate logistic regression analysis, hepatomegaly and splenomegaly were protective factors. Shorter duration of illness, higher respiratory rates, dyspnea, AIDS-associated central nervous system syndromes, platelet counts <50,000 cells/mL, aspartate transaminase (AST) >300 U/L, alanine transaminase (ALT) >150 U/L, serum creatinine >110 µmol/L were predictors of poor outcome. In the multivariate logistic regression analysis, shorter days of illness, higher respiratory rates, platelet counts <50,000 cells/mL, AST >300 U/L and serum creatinine >110 µmol/L, active tuberculosis (TB) and/or ongoing TB induction treatment and AIDS-associated central nervous system syndromes were independent predictors of poor outcome. The prognostic scores ranged from 0 to 19, corresponding to a mortality risk of 0% to 100%. The internal validation showed acceptable discrimination (AUC=0.68) and calibration slope (0.93). The Brier score for model performance was 0.14. We developed a simple scoring system that can predict the risk of death in patients with HIV-associated talaromycosis based on routinely measured characteristics on admission. The scoring system will be further externally validated using other cohorts in the region.

Keywords: *Talaromyces marneffei, Invasive fungal infections, Mortality, Prognostic model, Vietnam.*

Introduction

Talaromyces marneffei (Tm) is a dimorphic fungus that can cause a life-threatening systemic infection in immunocompromised individuals living in or traveling to Southeast Asia and southern China [1, 2]. Rare before the HIV epidemic, talaromycosis has rapidly emerged in this region as a leading HIV-associated opportunistic infection and bloodstream infection [3, 4], accounting for 15% of HIV admissions annually [5-9]. The Tm mortality on antifungal therapy is up to 30% [5-10]. Despite its rapid emergence and significance, talaromycosis remains neglected [11].

[5] conducted a retrospective analysis in Ho Chi Minh City from 2004-2009 and identified injection drug use, absence of fever or skin lesions, high admission respiratory rates, and low platelet counts to be independent predictors of death. [6] evaluated 127 patients in Hanoi in 2012 and identified admission dyspnea, presence of ascites, and increased blood lactate

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dehydrogenase levels to be independent predictors of death. Other risk factors of Tm mortality included co-infection with tuberculosis or hepatitis C [7]. Pre-existing studies are limited by being single-center experience, having relatively small sample sizes, and generally lacking the robust statistical analysis and power to assess the risk of Tm death. Therefore, I aimed to develop a prognostic model and construct a simple clinical scoring system to assist clinicians in the rapid prognosis and timely management of patients at the bedside in order to reduce disease mortality.

Materials and Methods

Ethics Statement

We used the secondary dataset from a large retrospective study during 1996-2009 of patients with *Talaromyces marneffei* infections admitted to the Hospital for Tropical Diseases in Ho Chi Minh City, Vietnam [5]. The study dataset was permitted and provided by the principal investigator of the study in compliance with the principles in Good Clinical Practice and Helsinki Declaration. This study was approved by the Scientific and Ethical Committee of the Hospital for Tropical Disease, Ho Chi Minh City, Vietnam (approval number CS/ND/09/19) [5].

Study Setting, Design, and Population

The retrospective study included all patients hospitalized with talaromycosis from July 1996 to December 2009 at the Hospital for Tropical Diseases (HTD), Ho Chi Minh City, Vietnam. In brief, HTD is the biggest tertiary referral hospital for tropical diseases in southern Vietnam. Tm infection cases were searched and identified from microbiology records, which encompassed all culture data. In addition, hospital charts with a primary discharge diagnosis of penicilliosis, *P.marneffei* (formerly name of *T.marneffei*) were also searched. All patients were double-checked for duplicated records. Finally, a total of 513 patients were included in the study.

Study Definitions

Talaromycosis was defined as any disease condition that *Talaromyces marneffei* was isolated from blood, skin scrapings, lymph node, bone marrow and/or anybody's fluid samples [5, 12]. Isolation and identification of *Talaromyces marneffei* were performed in accordance with the standard culture techniques.

Clinical Outcomes and Candidate Predictors

In-hospital outcomes were classified as (i) death, (ii) worsening disease at hospital discharge (dramatically deteriorated clinical status and expected to die at home after discharge) (iii) improvement (iv) non-assessability (unchanged and without following doctor's advice). For study analysis, poor outcome was defined as death and worsening disease at discharge (died at home), good outcome was characterized as improvement and non-accessibility was manipulated as missing data.

Pre-defined covariables used in the model included age, sex, history of injection drug use, comorbidities, and clinical and laboratory characteristics at hospital admission. These covariates were preselected based on clinical experience and evidence from published literature [5-7].

Data Collection

We used the secondary data from a large retrospective Tm study during 1996-2009 of patients with *Talaromyces marneffei* infections admitted to the Hospital for Tropical Disease in Ho Chi Minh City, Vietnam [5]. For the primary data, clinical and laboratory information were collected and entered into separate case record forms, then gathered data were independently double-checked into database to ensure the data integrity.

Statistical Analysis

We performed a logistic regression analysis and developed a simple risk prediction model for HIV-associated talaromycosis, using data from a retrospective cohort [5]. Backward stepwise selection based on Akaike Information Criterion (AIC) was conducted to identify the strong independent predictors of Tm mortality in the final model. Multiple imputations using chained equation (MICE) was used for missing values of AST (19% missing) and serum creatinine (11% missing). Bootstrapping (500 times) was used for internal validation of the final model. We compared the modelling performance by the area under the ROC curve (AUC), calibration-in-the-large, and calibration slope of the logistic regression model [13]. Based on the coefficients of predictors, a simple prognostic score was developed to estimate the risk of death. All study analyses were conducted with statistical software R, version 4.1.1, and the companion R package MICE was applicable for multiple imputations [14, 15].

Results

Clinical Characteristics of Study Participants

The baseline clinical characteristics are presented in Table 1. The median age of patients was 28 years (interquartile range (IQR), of 25-32 years), and 82% of participants were male. Roughly 70% of participants had a history of intravenous drug use, and 20% of patients were receiving antiviral therapy. The major clinical characteristics of Tm patients included fever, malaise, pale skin and mucosa, skin lesions, hepatosplenomegaly, diarrhea, and dyspnea.

Table 1. Baseline Clinical Characteristics and Outcomes of Study Participants (N=513)

Characteristics	**Statistics***
Age, years	28 (25-32)
Male sex	421 (82)
History of intravenous drug use (yes)	332/485 (68)
Receiving ARV (yes)	103 (20)
Clinical Characteristics	
Days of illness	15 (7-30)
Fever	419 (82)
Malaise	239 (47)
Diarrhea	150 (30)
Weight loss	92 (18)
Pale	286/397 (72)
Skin lesions	346/487 (71)
Hepatosplenomegaly	286 (56)
Lymphadenopathy	131 (26)
Dyspnea	117/468 (25)
Laboratory Findings	
Hemoglobin level, g/dL	08 (06-9.8)
Absolute lymphocyte count, cells/µL	395 (232-696)
Platelet count, $x10^3$ cells/ µL	82 (42-150)
AST, U/L	122 (63-230)
ALT, U/L	60 (34-119)
CD4 cell count, cells/ µL	07 (4-24)
Radiological Findings	

Abnormal chest x-ray	357 (70)
Abnormal sonography	312 (60)
Hepatomegaly	197/312 (63)
Splenomegaly	176/312 (56)
Abdominal lymphadenopathy	159/312 (33)
Ascites	73/312 (23)
Positive Culture and Identification of *T.marneffei*	
Blood	395/472 (84)
Skin scrapings	186/195 (95)
Lymph nodes	17/20 (85)
Outcomes	
In-hospital death	101 (19.7)
Deteriorated and died at home	42 (8.2)
Good outcomes	370 (72.1)

*****Summary statistic is median (interquartile range, IQR) for continuous variables and frequency (%) for categorical variables

Most frequently seen laboratory abnormalities were anemia, thrombocytopenia, and elevated transaminase levels. Isolation of *T.marneffei* from clinical specimens with the highest sensitivities were obtained from skin scrapings, blood, and lymph node. The recent median CD4 count was 07 cells/µl (IQR, 4-24 cells/µl). In terms of radiological findings, 70% of patients had abnormal chest x-ray, and 60% had abnormal sonography findings.

Treatment and outcomes

Out of 513 patients, outcomes at discharge were an improvement in 347 (67.6%), death in 101 (19.7%), worsening in 42 (8.2%), and non-assessable in 23 (4.5%). Poor outcome was observed in 143/513 patients (27.9%).

Prognostic Modelling and Scoring System Development

In the univariate logistic regression analysis, hepatomegaly and splenomegaly were protective factors. Shorter duration of illness, higher respiratory rates, dyspnea, AIDS-associated central nervous system (CNS) syndromes, platelet counts <50,000 cells/mL, aspartate transaminase (AST) >300 U/L, alanine transaminase (ALT) >150 U/L, serum creatinine >110 µmol/L were predictors of poor outcome. In the multivariate logistic regression analysis, shorter days of illness, higher respiratory rates, platelet counts <50,000.

cells/mL, AST >300 U/L and serum creatinine >110 µmol/L, active tuberculosis and/or ongoing TB induction treatment, and AIDS-associated central nervous syndromes were independent predictors of poor outcome (Tables 2 and 3). The internal validation showed acceptable discrimination (AUC=0.68) and calibration slope (0.93) (Figure 1). The Brier score was 0.14. The prognostic scores ranged from 0 to 19, corresponding to a mortality risk of 0% to 100% (Table 4 and Figure 2).

Table 2. Multivariable Complete-Case Analysis (N=389)

Covariates	**Coefficient**	**OR**	**95% CI**	***P* value**
Days of illness [-7 days]	0.126	1.12	1.03 - 1.21	0.01
Respiratory rate [+10 breaths per minute]	1.094	2.99	2.09 - 4.42	< 0.01
Platelet count [-50 K/mm^3]	0.179	1.16	1.03 - 1.29	0.02
AST > 300 U/L	0.759	2.14	1.15 - 3.95	0.02

Creatinine > 110 µmol/L	1.185	3.27	1.85 - 5.83	< 0.01
Probable TB or TB on the first 2-months of treatment	0.993	2.70	0.86 - 8.28	0.08
CNS-associated syndromes	3.025	20.6	7.82 - 65.72	< 0.01

Table 3. Multivariable Analysis with Multiple Imputation (N=513)

Covariates	**Coefficient**	**OR**	**95% CI**	***P* value**
Days of illness [-7 days]	0.117	1.11	1.03 - 1.19	< 0.01
Respiratory rate [+10 breaths per minute]	1.033	2.81	2.02 - 3.90	< 0.01
Platelet count [-50 K/mm^3]	0.249	1.22	1.11 - 1.32	< 0.01
AST > 300 U/L	0.836	2.31	1.26 - 4.22	< 0.01
Creatinine > 110 µmol/L	0.920	2.51	1.50 - 4.20	< 0.01
Probable TB or TB on the first 2-months of treatment	1.159	3.19	1.16 - 8.72	0.02
CNS-associated syndromes	3.351	28.53	10.31 - 78.88	< 0.01

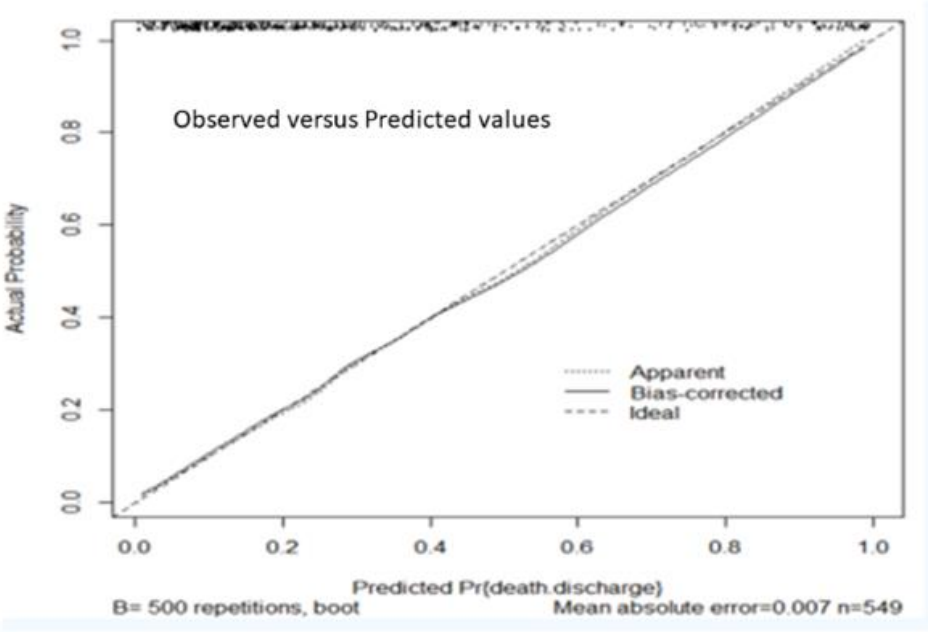

Figure 1. Calibration Plot Reveals Good Consistency between Predicted and Observed Values

Table 4. Risk Score to Predict Risk of Tm Mortality based on Complete-Case Analysis

Covariates	**Subcategory**	**Reference values**	**Sub-coefficient**	**Risk score**
Days of illness (days)	<7	-	0.474	1
	≥ 7	Reference	0	0
Respiratory rate (breaths per minute)	≤ 22	Reference	0	0
	>22 to ≤ 32	-	0.673	2
	> 32	-	2.360	5
Platelet count (K/mm^3)	< 50	-	0.496	1
	≥ 50	Reference	0	0
AST (U/L)	< 300	Reference	0	0
	≥ 300	-	0.765	2
Creatinine (µmol/L)	< 110	Reference	0	0

	≥ 110	-	1.053	2
Probable TB or TB on the first 2-months of treatment	No	Reference	0	0
	Yes	-	1.046	2
CNS-associated syndromes	No	Reference	0	0
	Yes	-	2.950	6
Intercept	-	-	- 2.741	-

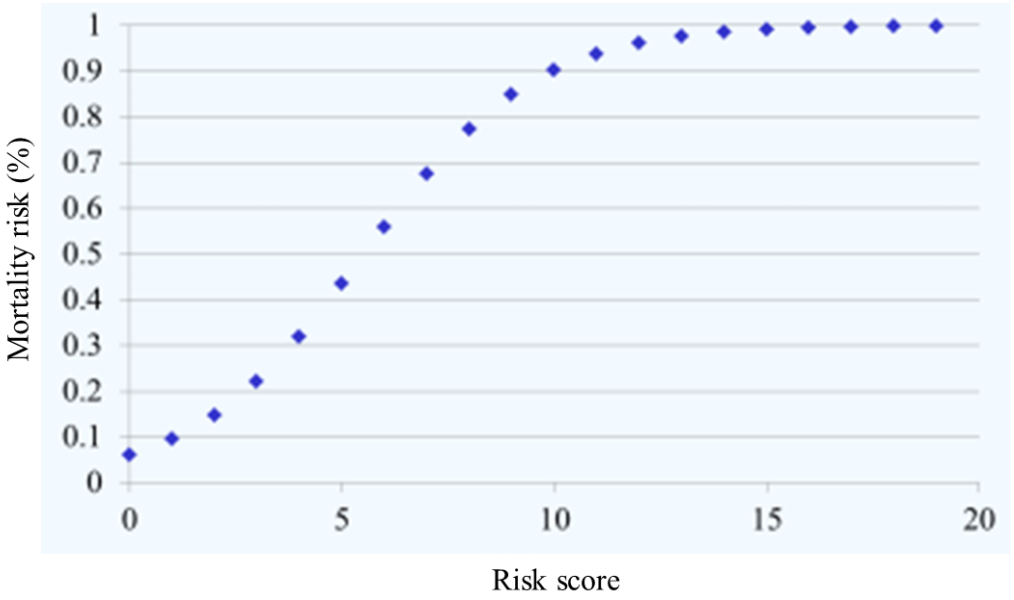

Figure 2. A Scoring Chart to Predict in-hospital Tm Mortality

Discussion

This study assessed the risk factors for poor outcomes in hospitalized patients with talaromycosis. Importantly, factors including shorter days of illness, higher respiratory rates, platelet counts <50,000 cells/mL, AST >300 U/L, serum creatinine >110 μmol/L, active tuberculosis and/or ongoing TB induction treatment, and HIV-associated CNS syndromes were independent predictors of Tm mortality. Previous Tm studies were restricted by being single-center experience, having relatively small sample sizes, and lacking advanced statistical analysis and power [5-7]. Despite several developed models to predict Tm risk of death, the previously reported prognostic models encompassed a plethora of covariates, which hampered its quick utility and convenience [17, 18]. Nonetheless, Qin Y *et al.* constructed and validated Tm prognostic model for mortality with only four strong predictors including age, liver transaminases, albumin and blood urea nitrogen [19]. Although Qin Y *et al.* report the developed model with area under the curve (AUC) of 0.793, the proposed Tm predictive model for death substantially lacked significant clinical predictors, for instance respiratory failure, tuberculosis and CNS-associated diseases previously reported as the strong predictor of Tm mortality [5, 7]. On this basis, we aimed to develop a robust prognostic model, a simple clinical algorithm, and a scoring system with only 07 robust clinical predictors to assist clinicians in the rapid prognosis and timely intervention of Tm patients. Our prediction model provides a useful tool to predict Tm mortality based on clinical and laboratory parameters routinely collected at hospital admission. The candidate predictors and outcomes were well predefined, and the model was well-developed and internally validated on the basis of standard statistical methodology to reduce the optimism effect [13, 16]. The final predictive model

revealed acceptable discrimination (AUC= 0.68) and good calibration values. Additionally, the Brier score used to measure model performance was 0.14 (acceptable range: 0 to 0.25) [20]. These parameters indicate our developed model has good prediction and performance values for Tm mortality and can be widely applicable in clinical practice.

We also simplified the final predictive model for Tm death to a risk scoring chart, allowing clinicians to make a rapid evaluation of patients' risk of severity and to aid physicians in decision-making. Despite a slight loss of precision [13], the scoring chart is easily comprehensible and applicable at the bedside. The risk score can be integrated into smartphones for quick utility. Using this Tm mortality risk score, clinicians can sort out patients at high risk of death based on routine clinical and laboratory parameters in the emergency department; therefore, they can rapidly determine who will require early and intensive interventions in order to minimize the talaromycosis-associated mortality.

Our study had several limitations. Firstly, there was a considerable percentage of missing data with regards to AST and creatinine values, regarding that these parameters were significant predictors of the final Tm mortality risk model. Secondly, our model was developed for hospitalized patients. Hence the study results could not be generalized to clinic-based outpatients. We only performed the internal validation, and there is a substantial need for further external validation.

Conclusion

We developed a simple scoring system that can predict the risk of death in patients with HIV-associated talaromycosis, based on routinely measured characteristics on hospital admission. The scoring system will be further externally validated using other cohorts in the region.

Financial Support and Sponsorship

The study was self-funded.

Conflicts of Interest

There is no conflict of interest.

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