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Research article

A nomogram to predict cryptococcal meningitis in patients with pulmonary cryptococcosis

Xiaoli Tan [a,1], Min Deng [b,1], Zhixian Fang [a], Qi Yang [a], Ming Zhang [a], Jiasheng Wu [c,d,**], Wenyu Chen [a,d,*]

[a] Department of Respiration, The Affiliated Hospital of Jiaxing University, Jiaxing, China
[b] Department of Infectious Diseases, The Affiliated Hospital of Jiaxing University, Jiaxing, China
[c] Department of Respiratory and Critical Care Medicine, Jiaxing Second Hospital, Jiaxing, China
[d] Department of Respiratory Diseases, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China

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ABSTRACT

Background: The most serious manifestation of pulmonary cryptococcosis is complicated with cryptococcal meningitis, while its clinical manifestations lack specificity with delayed diagnosis and high mortality. The early prediction of this complication can assist doctors to carry out clinical interventions in time, thus improving the cure rate. This study aimed to construct a nomogram to predict the risk of cryptococcal meningitis in patients with pulmonary cryptococcosis through a scoring system.

Methods: The clinical data of 525 patients with pulmonary cryptococcosis were retrospectively analyzed, including 317 cases (60.38 %) with cryptococcal meningitis and 208 cases (39.62 %) without cryptococcal meningitis. The risk factors of cryptococcal meningitis were screened by univariate analysis, LASSO regression analysis and multivariate logistic regression analysis. Then the risk factors were incorporated into the nomogram scoring system to establish a prediction model. The model was validated by receiver operating characteristic (ROC) curve, decision curve analysis (DCA) and clinical impact curve.

Results: Fourteen risk factors for cryptococcal meningitis in patients with pulmonary cryptococcosis were screened out by statistical method, including 6 clinical manifestations (fever, headache, nausea, psychiatric symptoms, tuberculosis, hematologic malignancy) and 8 clinical indicators (neutrophils, lymphocytes, glutamic oxaloacetic transaminase, T cells, helper T cells, killer T cells, NK cells and B cells). The AUC value was 0.978 (CI 96.2 %~98.9 %), indicating the nomogram was well verified.

Conclusion: The nomogram scoring system constructed in this study can accurately predict the risk of cryptococcal meningitis in patients with pulmonary cryptococcosis, which may provide a reference for clinical diagnosis and treatment of patients with cryptococcal meningitis.

* Corresponding author.
** Corresponding author.
E-mail addresses: wujiasheng@zjxu.edu.cn (J. Wu), 00135116@zjxu.edu.cn (W. Chen).
[1] These authors contributed equally to this work.

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1. Introduction

Pulmonary cryptococcosis (PC) is an invasive pulmonary fungal infection mainly caused by *CRYTOCOCCUS NEOFORMANS OR CRYPTOCOCCUS GATTII* [1]. The most common thin-section CT features of PC are pulmonary nodules/masses, which are poorly defined and located peripherally. Cavitations within nodules/masses are more prevalent in non-AIDS immunocompromised patients [36]. Studies have shown that patients with immunodeficiency have a higher rate of cryptococcal meningeal infectionsIn Sub-Saharan Africa (SSA), more than 90 % of pulmonary cryptococcal meningeal infections are related to HIV, and 19 % of AIDS-related deaths worldwide are caused by cryptococcal meningitis [7,8]. More importantly, patients with cryptococcal meningitis have poor clinical prognoses [9], with mortality rates as high as 20 %–60 % in patients with immunodeficiency [10]. The number of deaths due to cryptococcal meningitis among AIDS patients worldwide has reached 181,100 each year, and the number of non-AIDS patients who die of cryptococcal meningitis in developing countries is also increasing [8,11,12]. Compared with cryptococcal meningitis alone, cryptococcal meningitis combined with pulmonary infection has shown to be more difficult to treat and has a worse prognosis [9]. Cryptococcus can not only easily infect patients with immune insufficiency, but also healthy people with apparent normal immune function [2]. The lung and central nervous systems are the most invaded tissues and sites of this pathogen, which show no special symptoms in many cases and easily lead to missed diagnosis or misdiagnosis [3]. Pulmonary cryptococcosis can also spread and cause fatal complications [4,5], posing a significant threat to the central nervous system and respiratory system [5,6]. Understanding the clinical features of pulmonary cryptococcosis complicated with cryptococcal meningitis and exploring new methods for early diagnosis is of great clinical significance to improve the prognosis of patients.

Up to the recent decade, studies have conducted risk assessment of cryptococcosis and its complications, most of which focused on the comparison of clinical features and survival rates of cryptococcal disease between immunodeficiency patients and normal patients [9,13,14], analysis of risk factors for cryptococcal meningitis complicated with other diseases [15–17], or studies on blood-related biomarkers, etc. [18]. However, currently, there is no relevant research on the risk assessment system of pulmonary cryptococcosis complicated with cryptococcal meningitis.

A nomogram is a graphical tool based on regression models, commonly used to build predictive models [19]. The models can be employed to predict the probability of cancer metastasis, recurrence, patient survival rate, and the probability of some diseases [20–23], as well as for accurate diagnosis of pulmonary nodules before surgery [24]. Based on the retrospective analysis of patients with pulmonary cryptococcosis, the present study aims to use statistical methods to screen the influencing factors of cryptococcal meningitis in patients with pulmonary cryptococcosis, and to establish a nomogram to predict the probability of cryptococcal meningitis in patients with pulmonary cryptococcosis, which would be of clinical value for the timely diagnosis and early warning of meningeal infection complications of pulmonary cryptococcosis.

2. Materials and methods

2.1. Study population

The current study took the patients with pulmonary cryptococcus admitted to our hospital from 2008 to 2019 as the study population. According to the relevant guidelines of the Infectious Diseases Society of Chinese Medical Association and Infectious Diseases Society of America (IDSA) [25,26], in this study, pulmonary cryptococcosis (PC) was defined as the presence of pulmonary lesions in imaging examinations, with positive results in the alveolar lavage fluid or blood cryptococcal capsular antigen test. Among them, individuals who were cryptococcal capsular antigen-positive in the cerebrospinal fluid test or ink stain-positive PC were diagnosed with cryptococcal meningitis (CM). A total of 525 samples were collected, including 317 cases (60.38 %) with cryptococcal meningitis and 208 cases (39.62 %) without cryptococcal meningitis. In clinical diagnosis, imaging examinations, hematology examinations, pathogenic examinations and immune antibody examinations were carried out, and the immune status of patients and whether the disease had spread to the center or even the whole body were systematically evaluated. Patients were graded according to the severity of respiratory symptoms, and the treatment methods mainly included antifungal drug therapy, surgical therapy and combined therapy. Surgery would be considered if symptoms did not improve after adequate antifungal therapy, regardless of whether the patient's immune function was normal or not. This study has been approved by the Clinical Research Ethics Committee of the First Affiliated Hospital (IIT20210761A), and the Institutional Review Board waived written informed consent. In the process of data collection, a few data were missing in some cases. For these cases, we used the multiple imputation method to handle the missing data.

2.2. Statistical analysis

Statistical analysis was performed using SPSS V23.0 (IBM, USA) and R software (Version 3.6.1, R Foundation for Statistical Computing, Austria). The normal distribution of continuous variables were determined by the Kolmogorov-Smirnov test or Shapiro-Wilk test in SPSS. Continuous data were expressed as mean ± standard deviation or median (interquartile distance), and comparison between two groups was performed using the independent sample *t*-test. The non-normal continuous variables were presented as median and interquartile range (IQR), and the Mannu-Whiney *U* test was used for comparison between the two groups. Categorical data were expressed as numbers or percentages.

In univariate analysis, Student's t-test or Mann-Whitney *U* test was adopted for continuous variables, and Chi-square test or Fisher's exact test was used for categorical variables. Considering many independent variables of the regression model and potential collinearity problems, the LASSO regression model was employed to compress the regression coefficients of all variables by adding penalty

terms before multi-factor analysis and achieve the purpose of variable screening [27]. The cross-validation of the LASSO regression model was then conducted to screen out suspicious factors. Risk factors were identified by the binary logistic regression model, and a nomogram was used to construct a predictive scoring system for cryptococcal meningitis. Finally, the accuracy of the prediction model was verified by the receiver operating characteristic (ROC) curve and decision curve analysis (DCA). Taking different risk threshold probabilities as the abscissa, and the predicted number of people under corresponding threshold probabilities and the actual number of positives as the ordinate, the clinical impact curve was drawn, and the threshold probability that the prediction model could accurately predict was determined by the curve, so as to evaluate the clinical practicability of the prediction model ($P < 0.05$ was considered to indicate statistical significance).

3. Results

3.1. Description of the study population

This study involved 525 patients with pulmonary cryptococcosis with an age range of 49 ± 15 years, including 333 males (63.4 %) and 192 females (36.6 %), and the minimum and maximum ages were 6 and 89 years old, respectively. The average body mass index (BMI) was 22.96 ± 7.16 (range 1.87–56.41), the average onset time was 44 ± 82 days (range 1∼1095 days), and the length of hospital stay was 21 ± 18 days (range 1∼121 days). See Table 1 for the sample data statistics.

3.2. LASSO regression analysis

The 47 suspected variables in the univariate analysis that might influence cryptococcal meningitis were further screened using the LASSO regression model (Fig. 1A) and cross-validation (Fig. 1B). The minimum λ value corresponding to the simplest model was 0.006837. Based on the minimum λ value for variable screening, 32 factors affecting cryptococcal meningitis were obtained and included in the screening model. Among them, after the addition of the penalty item, the regression coefficients of variables such as hospital stay, BMI, HIV and white blood cell count were compressed to 0, and thus eliminated in the screening.

3.3. Logistic regression analysis

The 32 independent variables screened by LASSO regression model were further analyzed by logistic regression model (Table 2). There were 14 risk factors for pulmonary cryptococcosis with cryptococcal meningitis, including 4 clinical symptoms: fever (OR 19.657, 95 % CI 6.437–60.025), headache (OR 60.306, 95 % CI 15.279–238.02), nausea (OR 30.293, 95 % CI 5.244–174.985) and mental symptoms (OR 48.982, 95 % CI 4.671–513.666); 2 complications: tuberculosis (OR 4.934, 95%CI 1.014–24.009) and hematological malignancy (OR 103.311, 95%CI 4.835–2207.656); 8 blood test indicators: neutrophils (OR 0.88, 95%CI 0.82–0.944), lymphocytes, (OR 0.892, 95%CI 0.827–0.921), glutamic oxaloacetic transaminase (OR 1.069, 95%CI 1.024–1.116), T cells (OR 0.831, 95 % CI 0.738–0.935), helper T (OR 0.869, 95%CI 0.762–0.991), killer T (OR 0.83, 95%CI 0.7525–0.951), NK cells (OR 0.763, 95 % CI 0.634–0.917) and B cells (OR 0.695, 95 % CI 0.579–0.835). Every one unit increase in neutrophils, lymphocytes, T cells, helper T, killer T, NK cells and B cells within an appropriate range was a protective factor, while others were risk factors.

Among them, the regression coefficients of 7 indicators of neutrophil %, lymphocyte %, T cell %, helper T cell %, killer T cell %, NK cell %, B cell % were all <0, suggesting that the lower the value of these indicators, the higher the probability of cryptococcal meningitis. And the regression coefficients of other factors were >0, indicating the existence of factors such as fever, headache, nausea, psychiatric symptoms, tuberculosis and hematological malignancy, as well as the increase of glutamic oxaloacetic transaminase value, which predicted the increased probability of cryptococcal meningitis.

3.4. Construction of nomogram prediction model

On the basis of screening out the influencing factors of cryptococcal meningitis, these risk factors were incorporated into the nomogram model to construct a scoring system for meningeal infection prediction (Fig. 2A). Through the nomogram, the corresponding position of each parameter was perpendicular to the score axis to obtain the score corresponding to the parameter, and then all the parameter scores were added to obtain the total score of the prediction model. The probability of cryptococcal meningitis corresponding to each total score was shown in Table 3. Subsequently, the ROC curve was used to evaluate the performance of the prediction model. With 0.5 as the cut-off point, the AUC value obtained was 0.978 (CI 96.2 %∼98.9 %, Fig. 2B), revealing the high prediction accuracy of the model.

Table 1
Statistics and summary of research data.

Factors	Minimum	Max	Mean	Standard deviation	Lower quartile	Median	Upper quartile
Age(years)	6	89	48.71	14.88	38.00	49.00	60.00
The number of days in hospital(d)	1	121	21.24	18.17	9.00	18.00	28.00
BMI(kg/m^2)	1.87	56.41	22.96	7.16	18.30	22.61	25.32
Onset time(d)	1	1095	44.14	81.76	11.00	21.00	40.00

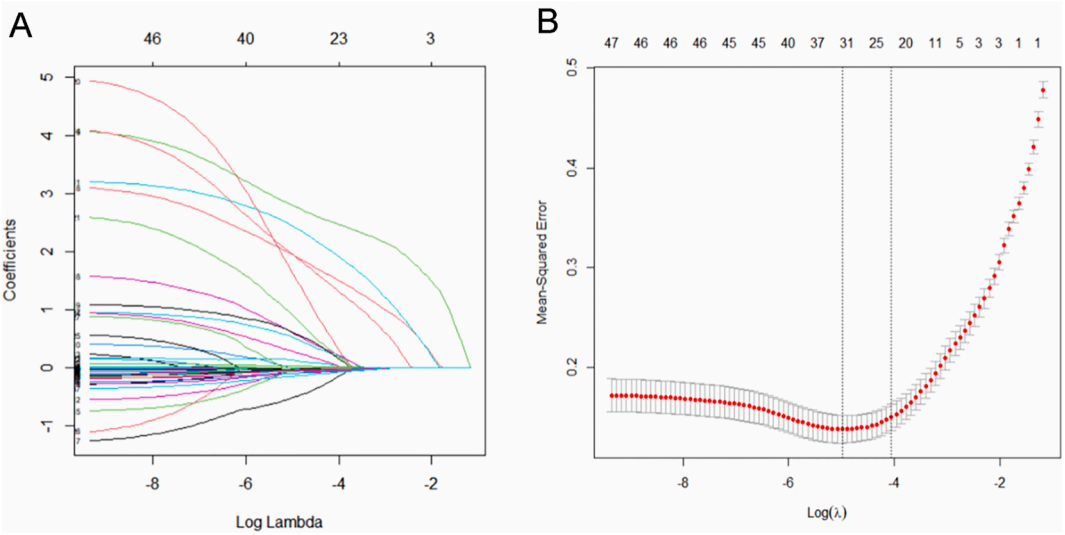

Fig. 1. Regression analysis of (A) influence factors based on Lasso for variable selection, and (B) cross validation of the regression model. Each curve in Fig. 1A represents the change trajectory of the coefficient of each independent variable, the coefficients of the unimportant variables tend to zero with the increasing of λ. For the cross validation, a confidence interval for the target parameter was obtained and marked by the two dotted lines, indicating two special ones of Lambda value.

With a cut-off point of 50 %, concurrent cryptococcal meningitis is generally considered to occur when a patient score is greater than 305. The statistical consistency of the scoring system was 97.8 % (confidence interval 96.2 %~98.9 %). POC model further verified the accuracy of the scoring system, and the prediction results were basically consistent with the standard curve, indicating that the prediction results were accurate (Fig. 2C).

The 14 risk factors were introduced into the nomogram to further investigate the net benefit of patients through the predictive scoring system. Decision curve analysis (DCA) results showed that the net benefit of patients using the nomogram predictive scoring system was higher than that of patients using any single factor alone (Fig. 2D).

Different probabilities of meningeal infection threshold were set through the model, and the influence curve was drawn (Fig. 2E). When the threshold probability $P < 0.6$, the number of high-risk people predicted by the model (red curve in the figure) was significantly higher than the actual number of infected people (blue curve in the figure). With the gradual increase of the threshold probability, the gap between the predicted number and the actual number of infected people gradually narrowed. And when $P > 0.6$, the two were completely consistent. This means that if the probability of cryptococcal meningitis predicted by the scoring system is greater than 60 %, i.e., the nomogram score is higher than 305, patients with pulmonary cryptococcosis are highly likely to develop cryptococcal meningitis with the prediction accuracy rate of 100 %.

To further verify the accuracy of the scoring model, another 30 % sample size (157 cases) was randomly selected for external validation. Among the validation samples, there were 5 cases of misdiagnosis and 6 cases of missed diagnosis, and 146 cases were accurately predicted, with an effective accuracy of 93 %. Hence, the prediction model was in line with expectations (Table 4).

4. Discussion

The clinical manifestations of pulmonary cryptococcosis are diverse, varying from asymptomatic pulmonary nodules to respiratory failure with diffuse infiltration and acute respiratory distress syndrome [28], with increased morbidity and mortality due to the tendency of pulmonary cryptococcosis to spread to the meninges or other sites [29]. Identifying the characteristic factors between patients with pulmonary cryptococcosis complicated with and without cryptococcal meningitis, and establishing a prediction model is of great guiding value for the clinical diagnosis and timely intervention of patients with pulmonary cryptococcosis complicated with cryptococcal meningitis.

This study conducted a retrospective study of 525 patients with pulmonary cryptococcosis. The sample data showed that the disease was more prevalent in middle-aged men (63.4 %), which is consistent with many research results [30]. The univariate results found that some clinical symptoms, including fever, headache, nausea, and weight loss, had significant differences between patients with and without cryptococcal meningitis, but BMI was no longer an independent risk factor in the multivariate regression analysis. Weight loss is a possible symptom of many diseases. Studies have shown that weight loss is significantly associated with cryptococcosis combined with other infections, and nutritional status significantly affects the treatment of AIDS patients infected with cryptococcosis [16]. Some patients with cryptococcosis do not show obvious symptoms at the initial stage of infection, and the above-mentioned clinical appearance can be used as an early warning signal for the spread of cryptococcal pulmonary to the central nervous system. Psychiatric symptoms are also an independent risk factor for cryptococcal meningitis, which is associated with cryptococcus infestation of the central nervous system [31]. Changes in mental status or neurological symptoms in patients with cryptococcosis suggest

Table 2
Multivariate logistic regression analysis of risk factors.

Factors		B	SE	Wald	Statistical significance	OR	OR(95%CI)	
							Lower limit	Upper limit
Age		−0.015	0.018	0.758	0.384	0.985	0.951	1.019
The number of days in hospital(d)		0.018	0.013	1.899	0.168	1.019	0.992	1.046
BMI(kg/m^2)		−0.053	0.035	2.279	0.131	0.949	0.886	1.016
Onset season				5.084	0.166			
	Summer	0.809	0.684	1.399	0.237	2.246	0.588	8.583
	Autumn	−0.008	0.66	<0.001	0.99	0.992	0.272	3.615
	Winter	−0.95	0.722	1.731	0.188	0.387	0.094	1.592
	Spring							
Other lung infections	Yes	−1.231	0.7	3.092	0.079	0.292	0.074	1.152
	No							
Fever	Yes	2.978	0.57	27.345	<0.001	19.657	6.437	60.025
	No							
Headache	Yes	4.099	0.7	34.249	<0.001	60.306	15.279	238.02
	No							
Nausea	Yes	3.411	0.895	14.531	<0.001	30.293	5.244	174.985
	No							
Cough	Yes	−0.518	0.506	1.047	0.306	0.596	0.221	1.606
	No							
Mental symptoms	Yes	3.891	1.199	10.533	0.001	48.982	4.671	513.666
	No							
Asymptomatic	No	1.035	0.764	1.836	0.175	2.816	0.63	12.594
	Yes							
Diabetes	Yes	0.914	0.595	2.357	0.125	2.494	0.777	8.011
	No							
Tuberculosis	Yes	1.596	0.807	3.909	0.048	4.934	1.014	24.009
	No							
Malignant tumor	Yes	1.213	1.346	0.812	0.368	3.362	0.24	47.003
	No							
Hematological malignancies	Yes	4.638	1.562	8.813	0.003	103.311	4.835	2207.656
	No							
Organ transplant	Yes	2.39	1.358	3.096	0.078	10.916	0.762	156.441
	No							
HIV	Yes	0.603	0.962	0.393	0.531	1.828	0.277	12.055
	No							
Capsular antigen	(+)	0.916	0.521	3.084	0.079	2.498	0.899	6.94
	(−)							
WBC(10^9/L)		−0.074	0.084	0.788	0.375	0.928	0.788	1.094
Neutrophils(10^9/L)		−0.128	0.036	12.746	<0.001	0.88	0.82	0.944
Lymphocytes(10^9/L)		−0.114	0.038	8.939	0.003	0.892	0.827	0.961
Hemoglobin(10^9/L)		0.009	0.01	0.874	0.35	1.009	0.99	1.029
PCV		−0.015	0.019	0.674	0.412	0.985	0.949	1.021
CRP(mg/L)		−0.008	0.007	1.173	0.279	0.992	0.979	1.006
Globulin(g/L)		−0.03	0.039	0.585	0.444	0.97	0.899	1.048
AST(U/L)		0.066	0.022	9.091	0.003	1.069	1.024	1.116
Creatinine(μmol/L)		−0.007	0.006	1.378	0.24	0.993	0.981	1.005
T cell(10^9/L)		−0.185	0.06	9.393	0.002	0.831	0.738	0.935
Auxiliary T(%)		−0.141	0.067	4.419	0.036	0.869	0.762	0.991
Lethal T(%)		−0.186	0.069	7.197	0.007	0.83	0.725	0.951
NK cells(%)		−0.271	0.094	8.282	0.004	0.763	0.634	0.917
B cell(%)		−0.364	0.094	15.128	<0.001	0.695	0.579	0.835
Constant(10^9/L)		42.025	8.571	24.042	<0.001	1.78291E+18		

Note: WBC - White blood cell count, AST - Aspartate aminotransferase.

that lumbar puncture or other methods should be used to detect and diagnose meningeal infection.

Patients with pulmonary cryptococcosis who have other underlying diseases are treated for a relatively long period of time, which will increase the risk of cryptococcus spreading to the meninges to a certain extent [2]. However, our study suggested that length of hospital stay was not an independent factor for cryptococcal meningitis. Underlying diseases increase the risk of cryptococcosis patients with other infections, mainly reflected in the patient's immune function, such as HIV infection, malignant tumors, organ transplantation, etc. [2]. Our study showed that tuberculosis ($P = 0.048$) and hematologic malignancy ($P = 0.003$) were independent risk factors for cryptococcal meningitis, suggesting that patients with pulmonary tuberculosis and hematologic malignancy should be screened for cryptococcal meningitis in advance. The pathogenesis of cryptococcal meningitis is complex, and the mechanism of diffusion from the lung to the central nervous system is not clear, which may be related to cellular immunomodulatory mechanisms with significant differences in indicators at the molecular level [32]. Pyrgos V et al. [33] found that cell-associated immunosuppression was the most important risk factor for cryptococcal meningeal infection in HIV-positive patients. We conducted a statistical analysis of

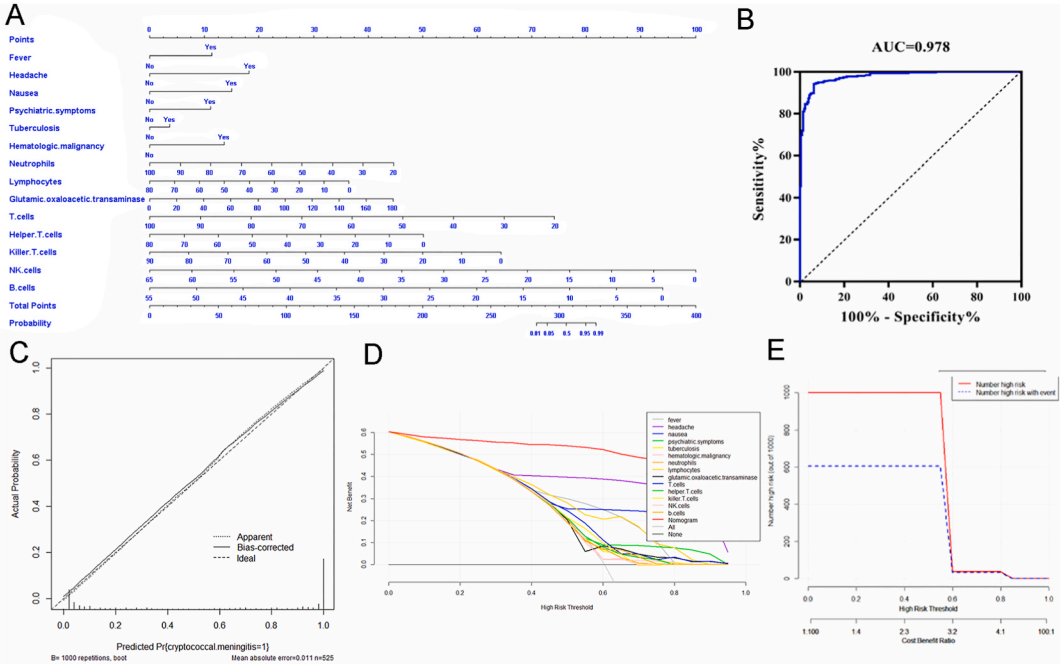

Fig. 2. Nomogram model to estimate the risk of meningeal infection in patients with pulmonary cryptococcosis. (A) The scores for all the parameters, and the risk probability corresponding to the total score, (B) Receiver operating characteristic (ROC) curve of the nomogram, AUI = area under the ROC curve, (C) Calibration of the evaluation for nomogram model, (D) Comparison of the net benefit for patients with predictive model by the decision curves analysis (DCA), (E) Clinical value under different risk threshold probability.

Table 3
The probability of meningeal infection corresponding to different scores.

Nomogram scoring total score	Probability of meningeal infection %
284	1.00 %
291	5.00 %
299	20.00 %
302	35.00 %
305	50.00 %
308	65.00 %
312	80.00 %
319	95.00 %
327	99.00 %

Table 4
Results of validation for prediction model based on 30 % of total sample quantity.

Factors		Meningeal infection prediction		Total
		No	Yes	
Meningeal infection actually	No	52	5	57
	Yes	6	94	100
Total		58	99	157

blood test indicators and found that some immune-related indicators had significant differences in meningeal infection. When the index values of neutrophil % and lymphocyte % are significantly decreased in patients, it indicates decreased immunity and is a risk factor of meningeal infection, which is similar to the results reported in other studies [16].

Screening of risk factors is a prerequisite for the establishment of prediction models. However, due to the large number of risk factors, it is difficult to make an accurate and systematic assessment only based on the subjective judgment of risk factors. The application of the nomogram scoring model can transform abstract influencing factor indicators into intuitive scores and visual graphics, which has great clinical practical value [19]. In the current study, we included 14 high-risk factors for cryptococcal meningitis to construct a nomogram, and the validation results of this prediction model showed that this model could accurately predict

patients at high risk of cryptococcal meningitis (>60 %). Based on this scoring system, clinicians can be guided to make timely predictions and intervention treatments. More than one million people are infected with cryptococcal meningitis globally every year, most of which spread from lung infection to meningeal infection. As the high mortality of cryptococcal meningitis requires great attention [34,35], the risk assessment system is conducive to the timely diagnosis and treatment of this disease, and is also of great significance to reduce the morbidity and mortality of pulmonary cryptococcosis complicated with cryptococcal meningitis. Nevertheless, there are also some defects and deficiencies in this study. On the one hand, this paper is based on a retrospective analysis of 525 patients with pulmonary cryptococcosis, but all of them came from the same hospital. On the other hand, there may be some limitations in the selection of influencing factors, and the estimation of risk factors is not perfect.

5. Conclusion

The present study retrospectively analyzed 525 patients with pulmonary cryptococcosis, identified 14 risk factors and clinical indicators for cryptococcal meningitis by univariate analysis, LASSO regression analysis and logistic regression analysis, and established a nomogram predictive scoring model. The model has been verified to have a high prediction accuracy for high-risk populations (the probability of patients with cryptococcosis complicated with cryptococcal meningitis is greater than 60 %), and it has great application value and guiding significance for the risk assessment of cryptococcal meningitis in patients with pulmonary cryptococcosis.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (IIT20210761A), and the Institutional Review Board waived written informed consent.

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Data availability statement

The datasets supporting the conclusions of this article are included within the article.

CRediT authorship contribution statement

Xiaoli Tan: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Min Deng:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Zhixian Fang:** Writing – review & editing, Methodology, Data curation. **Qi Yang:** Writing – review & editing, Investigation. **Ming Zhang:** Writing – review & editing, Methodology. **Jiasheng Wu:** Writing – review & editing, Writing – original draft, Data Curation, Resources. **Wenyu Chen:** Writing – review & editing, Funding acquisition, Conceptualization, Data Curation, Resources.

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.

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