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Risk Prediction Model for Isoniazid Dosing in Tuberculosis Meningitis Patients in Southwest China

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Purpose: Tuberculosis meningitis (TBM) has emerged as the most lethal type of disease. The prognosis of meningitis is often related to disease severity and early therapeutic intervention.

Methods: Patients were screened for primary TBM and received a quadruple regimen comprising isoniazid (standard dose of 300 mg/day and high dose of 600 mg/day), rifampin, ethambutol, and pyrazinamide. Further, the indices and prognosis factors of diseased patients were analyzed, using 12-month treatment mortality as the primary observation endpoint. Several predictors included demographic data, clinical presentation, ancillary tests, treatment changes, and isoniazid dose. The data were analyzed using a least absolute shrinkage, the selection operator regression, and multi-factor logistic regression.

Results: Among the selected TBM patients (n=119), 18 patients were dead at the end of December. A total of 68 influencing factors were screened, in which 5 clinical factors were included as potential prognostic factors, including older age, presence of nausea, high MRC grade, imaging suggestive of cerebral infarction, and dose of isoniazid (300 mg/day). The AUC value was recorded as 0.8316832. The validation set confirmed the model's robustness, with an AUC of 0.887 and good calibration performance. These findings highlight the model's potential for clinical application in optimizing isoniazid dosing. The model demonstrated the advantage of predicting the therapeutic outcome of patients.

Conclusion: In summary, the model could be suitable for evaluating the risk of death within 12 months in TBM patients towards assessing the severity and treatment needs of patients. The isoniazid dose is an important factor affecting the prognosis of these patients.

Keywords: tuberculosis meningitis, isoniazid dose, prediction model, risk predictors

Introduction

Tuberculosis meningitis (TBM), an extrapulmonary form of tuberculosis, has emerged as one of the most lethal types of disease, accounting for approximately 0.6–1.8% of tuberculosis cases with reported mortality rates of up to 30–50%.[1] The TBM prognosis is often closely related to the severity of the disease, early therapeutic interventions, and the optimum concentration of drugs crossing the blood-brain barrier (BBB).[2] Among various chemotherapeutics, isoniazid is considered an important drug against TBM due to its early antimicrobial effect and high permeability crossing BBB.

Currently, the World Health Organization (WHO) regimen has advised a quadruple therapeutic regimen for TBM consisting of isoniazid, rifampin, ethambutol, and pyrazinamide. The therapeutic regimen can be adapted from the pulmonary tuberculosis treatment procedure. In this context, the recommended dose of isoniazid should not exceed 5 mg/kg/day.[3] The WHO-prescribed dosage is much lower than the recommended dose of 10 mg/kg/day in the guidelines for TBM treatment in children.[4] Along this line, several reports indicated that lower isoniazid exposure or a lower dose of isoniazid of around 5 mg/kg/day than the recommended dose could be associated with a high risk of death in patients

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with TBM.[5,6] Accordingly, these studies with pharmacokinetic profiling suggested an increase in the isoniazid dosage.[7] Nonetheless, the optimal recommended dose of isoniazid to treat adults with TBM is currently inconclusive.

Motivated by these considerations, a prognostic model was developed for TBM to be designed specifically for children and adolescents.[8] Further, prognostic studies of TBM in adults identified several factors associated with 9-month mortality, including the Medical Research Council (MRC) grade, age, and dexamethasone usage.[9] Conclusively, these specific indicators would assist clinicians in monitoring and evaluating the severity and prognosis of TBM in patients.

Methods

Selection Criteria

The subjects for this prospective study were recruited from patients with central nervous system (CNS) tuberculosis (TB) admitted to the Affiliated Hospital of Zunyi Medical University between July 1, 2020, and December 31, 2021. It should be noted that this tertiary general hospital, a designated tuberculosis hospital in Guizhou Province, China, possessed a high TB prevalence area. Notably, the TBM patients aged 18–75 years old were primarily hailed from Southwest China. The patients with definite and probable cases of TBM provided signed informed consent. Inclusion criteria: i) Diagnosed with TBM based on accepted diagnostic criteria. ii) Aged 18–75 years. iii) Complete clinical data available. The exclusion criteria were set as follows: i) Patients who received prior tuberculosis treatment; ii) Patients who could not tolerate first-line tuberculosis treatment; iii) Patients who started tuberculosis treatment more than a week before this visit; iv) Patient samples with isoniazid and rifampicin-resistant strain that was found before or during treatment. v) Patient samples with alanine aminotransferase (ALT) or aspartate aminotransferase (AST)>2 upper limits of normal (ULN) at the beginning of treatment; and vi) Patient with human immunodeficiency virus (HIV) infection or severe underlying diseases and long-term immunosuppressive use. A total of 119 patients were included in the study and classified into three categories based on the most widely used and classic expert consensus on tuberculous meningitis: Definite tuberculous meningitis, Probable tuberculous meningitis, and Possible tuberculous meningitis.[10] External validation was performed to assess the generalizability and robustness of the prediction model. The validation set consisted of 72 independent patients who met the inclusion criteria but were not part of the training cohort. These patients were recruited from the same hospital during a different time frame (January 2022 to December 2022) to minimize temporal biases. The same inclusion and exclusion criteria were applied to ensure consistency between the training and validation datasets. For the validation cohort, demographic and clinical variables were collected prospectively, and the same model coefficients derived from the training set were used to calculate predicted probabilities for mortality risk. The validation metrics included the area under the receiver operating characteristic (ROC) curve (AUC), calibration plots to evaluate agreement between predicted and observed probabilities, and decision curve analysis (DCA) to assess clinical utility across different threshold probabilities. This study was approved by the Ethics Committee of Zunyi Medical University, which was registered with the Chinese Clinical Trial Registry (ChiCTR) under the registration number ChiCTR-OOC-17011408. This study was conducted in accordance with the Declaration of Helsinki.

Treatment and Follow-Up

The treatment procedure was performed as follows. Initially, patients were treated with a quadruple therapeutic regimen consisting of isoniazid, rifampin, ethambutol, and pyrazinamide. On the one hand, According to the 2019 Chinese Expert Consensus on Tuberculous Meningitis, isoniazid doses were assigned as either a standard dose of 300 mg/day or a high dose of 600 mg/day using the random table method. On the other hand, rifampicin was administered to patients weighing 50 kg or more at a dose of 600 mg, and a dose of 450 mg was administered to those weighing less than 50 kg. To this end, ethambutol at a dose of 0.75 g and pyrazinamide at a dose of 1.5 g were given. After a 3-month intensive treatment period, the administration of isoniazid and rifampicin was continued further for 9 months. The Tuberculosis Branch of the Chinese Medical Association of TBM Professional Committee referred to glucocorticoid usage, such as. Several glucocorticoids could be administered through different routes, such as intravenous administration of dexamethasone at a dose of 10 mg/day for 1 week and oral administration of prednisone at a dose of 30 mg/day for 1–2 weeks, and then

reducing the amount to 5 mg every week. N-acetyltransferase-2 (NAT2), the main metabolic enzymes of isoniazid, polymorphisms were detected as per previously reported methods.

The cut-off date for follow-up was December 31, 2022, corresponding with the completion of the anti-tuberculosis treatment by patients at the end of December. Further, the follow-up visits were conducted by the assigned research team monthly during treatment, either over the telephone or in person, while the patients visited the hospital outpatient clinic. It should be noted that the number of deaths due to TBM among the included cases was recorded at the end of March and December. The survivors underwent several evaluations for symptoms, including the cerebrospinal fluid examination and cranial imaging. The primary observation endpoint for analysis was the occurrence of a lethal outcome within 12 months of treatment. Further, the notified endpoint after the 12-month treatment period was used to analyze the changes among various indicators of patients who succumbed to the disease and the factors that affected their prognosis. In addition, the secondary indicators included changes in the clinical manifestations, laboratory tests, and imaging examinations of the patients.

Predictive Indicators

The predictive indicators in this study included demographic information, clinical manifestations of patients in the model, cerebrospinal fluid examinations, cranial imaging, CNS severity score (commonly used in CNS patients), and treatment-related, as well as prognosis-related variables. It should be noted that these predictive indicators were analyzed following the reported literature. Further, the doses of isoniazid and N-acetyltransferase 2 (NAT2) gene polymorphisms were also included as predictive factors in this study.

Notably, the sample size recruited for this study was based on the number of patients with TBM admitted to the hospital during the study period. The missing values for continuous variables were presented using the mean values. Contrarily, the missing values for categorical variables were presented using the mode. The demographic data, disease characteristics, and treatment characteristics were expressed as count information (%). The assignments involved in the risk factor screening and model construction were converted to measurement data. Moreover, the continuous variables were converted to categorical variables. The specific factors involved in prediction and the variable-specific conversion methods and cut-point value definitions are detailed in Supplementary Table 1.

Statistical Analysis

Data were analyzed using SPSS 26.0 (IBM Corp., NY, USA) and R software 4.2.2 (https://www.r-project.org/). The LASSO regression analysis was used to screen for covariates of prognostic risk factors associated with severity and mortality. Accordingly, the multiple logistic regression analysis was used to determine the risk factors associated with disability and death, constructing a prediction model. The odds ratios (ORs) and *P*-values with 95% confidence intervals (CI) were used as thresholds for significance assessments, considering a two-sided *P*-value of 0.05 as statistically significant. Among the selected predictive factors, the results that met the statistical criteria were included in the prediction model to assess risks associated with mortality.

The R software was used to develop a nomogram predictive model for disability and death events and visualize the model using a column chart. In addition, several multiple validation methods were employed to estimate the accuracy of the risk-prediction model. The ROC curve analysis was used to determine the predictive quality of the nomogram risk chart by distinguishing between true and false values. A decision curve analysis (DCA) was performed to determine the clinical utility of the model. Moreover, the calibration curves were plotted to evaluate the calibration performance of the models. External validation was conducted using an independent dataset to evaluate the model's generalizability and robustness. The final prognostic model was visualized using a nomogram and implemented as a web-based death risk calculator for clinical convenience.

Results

Patient Characteristics

A total of 147 patients with TBM were sought out for medical attention between June 2020 and December 2021. Among these selected patients, 141 subjects met the inclusion criteria and were recruited for further analysis in this study.

According to the exclusion criteria, a total of 22 patients were excluded, resulting in a total of 119 patients with CNS TB being subjected further in the study. The follow-up trials were conducted until the end of December, during which 18 patients died while 101 patients remained alive. Further details are shown in Figure 1.

The mean age of the CNS patients used for modeling was 42 years, in which males were 62 (52.1%) and females were 57 (47.9%). Most of the MRC classifications were grade I (N=83; 69.7%), with a few others being grade II (N=15; 12.6%) and III (N=21; 17.6%). According to the NAT2 gene polymorphism, the isoniazid fast acetylation type (FA), intermediate acetylation type (IA), and slow acetylation type (SA) were found to be 73 (61.3%), 34 (28.6%), and 12 (10.1%) patients, respectively. The NAT2 genotype distribution was IA > FA > SA, with the intermediate acetylator type being the most common. A detailed description is provided in Table 1.

Follow-Up Outcome

Among the 119 patients recruited with TBM for the study, 18 subjects died during the 12-month follow-up period, resulting in an overall mortality rate of 15.13%. Among 18 of them, 10 subjects (55.56%) were died within 3 months of diagnosis. The average overall survival time was 10.815±0.198 months (95% CI: 10.426–11.204). The detailed survival curves are shown in Figure 2.

Variable Selection and Model Construction

To further assess the influence of various clinical factors on the survival of TBM patients, the LASSO regression method was employed to select variables from the 68 clinical factors. It was observed from the results that five clinical variables out of the 68 factors were identified as potential prognostic factors and were included in the model construction (Figure 3), including patient age, nausea symptoms, high MRC grade, imaging suggestive of cerebral infarction, and a standard dose of 300 mg/day of isoniazid. Although nausea is a nonspecific symptom, it may serve as an indirect marker of increased intracranial pressure, a common complication in TBM patients. These predominant variables were screened by LASSO regression as high-risk factors for death. These five variables were modeled as contributors to the risk of morbidity and mortality of TBM. Table 2 shows the odds ratios and corresponding confidence intervals for each predictive factor in the logistic regression model. Accordingly, a predictive model was constructed using these independent prognostic factors to estimate the probability of mortality risk. A simplified form of the model was presented as a nomogram (Figure 4). In addition to the well-established risk factors of older age and higher MRC grade for TBM,

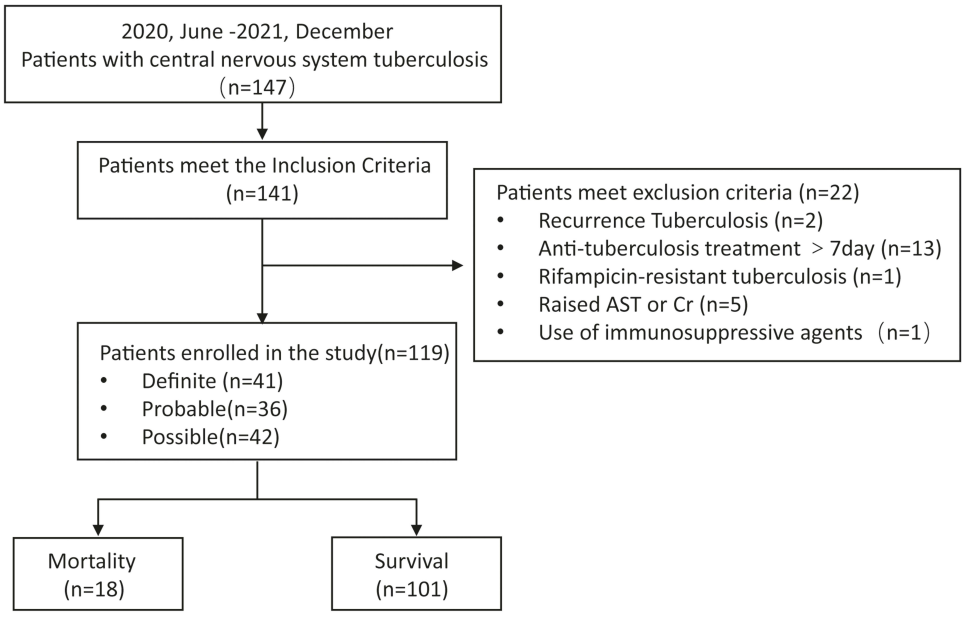

Figure 1 Flowchart for inclusion and exclusion of patients.

Table 1 A Summary Shows the Baseline Information of Patients

Variables	Total (n=119)	Survival (n=101)	Mortality (n=18)
Sex, n(%)			
Male	62 (52.10)	53 (52.48)	9 (50.00)
Female	57 (47.90)	48 (47.52)	9 (50.00)
Age (year), Mean±SD	42.13±19.21	40.26±18.72	52.61±19.02
Weight (kg), Mean±SD	52.57±7.96	52.64±8.13	52.08±6.93
Smoking, n(%)	38 (31.93)	32 (31.68)	6 (33.33)
Drinking, n(%)	31 (26.05)	28 (27.72)	3 (16.67)
Comorbidities, n(%)	50 (42.02)	40 (39.60)	10 (55.56)
MRC grade, n(%)			
Grade I	83 (69.74)	75 (75.26)	8 (44.44)
Grade II	15 (12.61)	11 (10.89)	4 (22.22)
Grade III	21 (17.65)	15 (14.85)	6 (33.33)
NAT2 genotype, n(%)			
FA	34 (28.57)	30 (29.70)	4 (22.22)
IA	73 (61.35)	62 (61.39)	11 (61.11)
SA	12 (10.08)	9 (8.91)	3 (16.67)
Diagnostic of TBM, n(%)			
Definite	41 (34.46)	34 (33.66)	7 (38.89)
Probable	42 (35.29)	31 (30.69)	5 (27.78)
Possible	36 (30.25)	36 (35.64)	6 (33.33)
INH Dose, n(%)			
300 mg/day	32 (26.89)	23 (22.77)	9 (50.00)
600 mg/day	87 (73.11)	78 (77.23)	9 (50.00)

the model of this study substantially highlighted a significant association between the use of isoniazid at a dosage of 300 mg/day (compared to 600 mg/day) and an elevated risk of mortality. Among the five prognostic factors selected by the model, the use of isoniazid at a dose of 300 mg/day indicated the greatest impact on the risk of death.

Model Evaluation

Further, the calibration curve of the final model, which could be estimated as the ideal indicator, was used to predict the probability of mortality risk for TBM. It was observed that the calibration curve demonstrated favorable agreement with

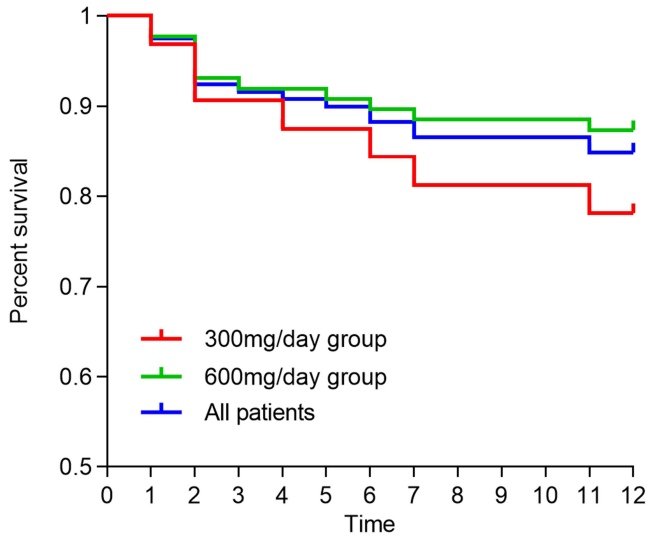

Figure 2 Survival curve for all the patients enrolled in this study.

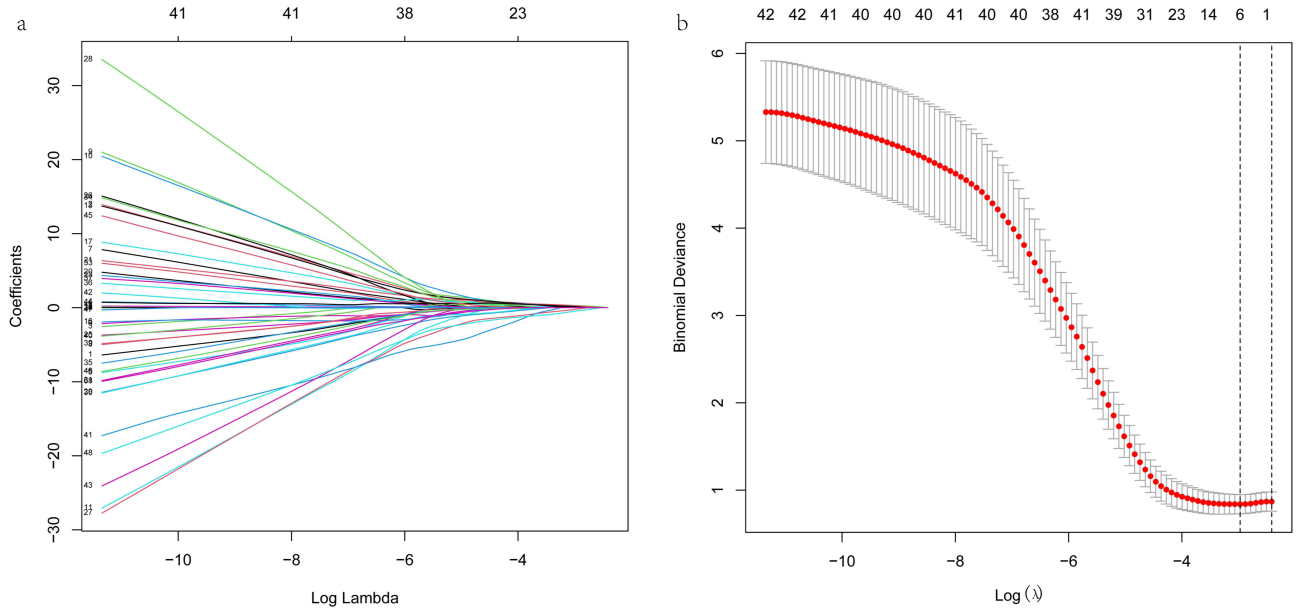

Figure 3 The LASSO regression of risk factors. (**a**) Coefficient distribution diagram with all 68 predictor coefficient paths meeting the screening requirements; (**b**) Coefficient distribution maps with all 68 predictor coefficient paths meeting the screening requirements; (**c**) Cross-validation curves with good lasso fit and lambda.min suggesting 5 predictors into the model construction.

the actual probability of mortality (Figure 5). According to the sensitivity and accuracy of the final model, the area under the receiver operating characteristic (ROC) curve (AUC) was calculated to be 0.83 (Figure 6). These findings indicated that the model possessed excellent predictive ability, discriminating well between the risk of survival and death within 12 months of TBM.

In the validation set, the model's performance was consistent with the training set. The AUC was 0.887 (95% CI: 0.808–0.965), confirming excellent discrimination (Figure 7). The calibration curve illustrated close agreement between predicted and actual probabilities, with both apparent and bias-corrected curves aligning with the ideal diagonal line (Figure 8).

Clinical Application

Typically, the DCA quantifies the net benefits of different threshold probabilities in the dataset. It should be noted that our model demonstrated good clinical applicability. As shown in Figure 9, the risk of death in patients could provide a net benefit using this research model. The results could be suitable for evaluating the risk of death in patients with TBM within 12 months. In the validation set, DCA demonstrated sustained clinical utility, with a higher net benefit within the

Table 2 A Summary Presents the Prediction Factors for Risk of Death in Tuberculosis Meningitis

Intercept and Variable	Prediction Model		
	β	Odds Radio (95%CI)	*P*-value
Intercept	−2.270	0.1033 (0.023–0.376)	0.001
Age (45–65)	0.335	1.3981 (0.318–5.877)	0.646
Age (65–75)	1.434	4.1958 (0.910–20.303)	0.066
Nausea	1.118	3.0574 (0.905–11.618)	0.081
MRC Grade (II)	1.130	3.0952 (0.592–15.014)	0.161
MRC Grade (III)	1.297	3.6570 (0.802–17.155)	0.091
Imaging of Cerebral Infarction	0.877	2.4036 (0.629–9.234)	0.193
Isoniazid Dose 300 mg/day	−1.532	0.2161 (0.054–0.777)	0.022

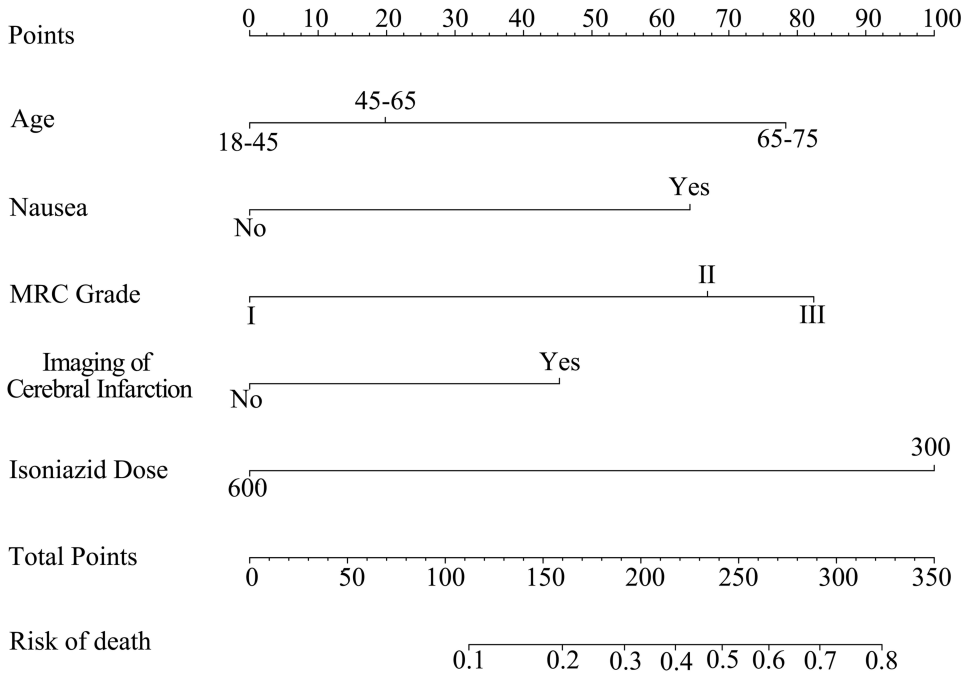

Figure 4 Nomogram for the final prognostic model.

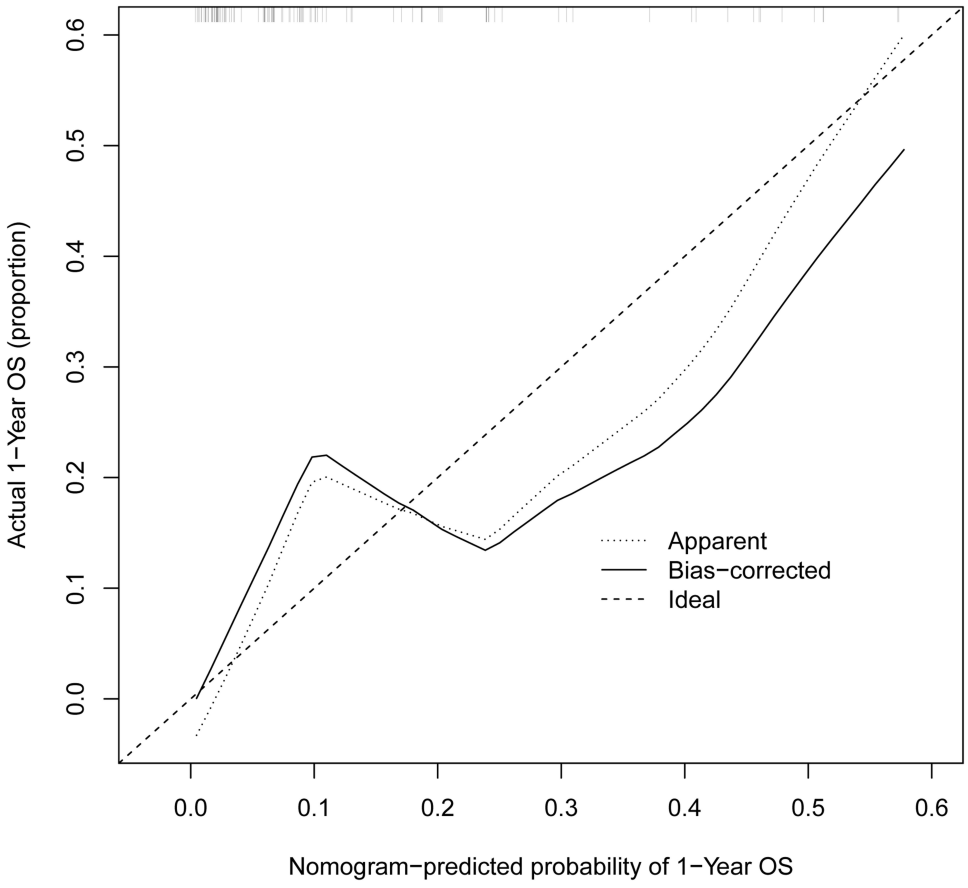

Figure 5 Calibration curves for final model.

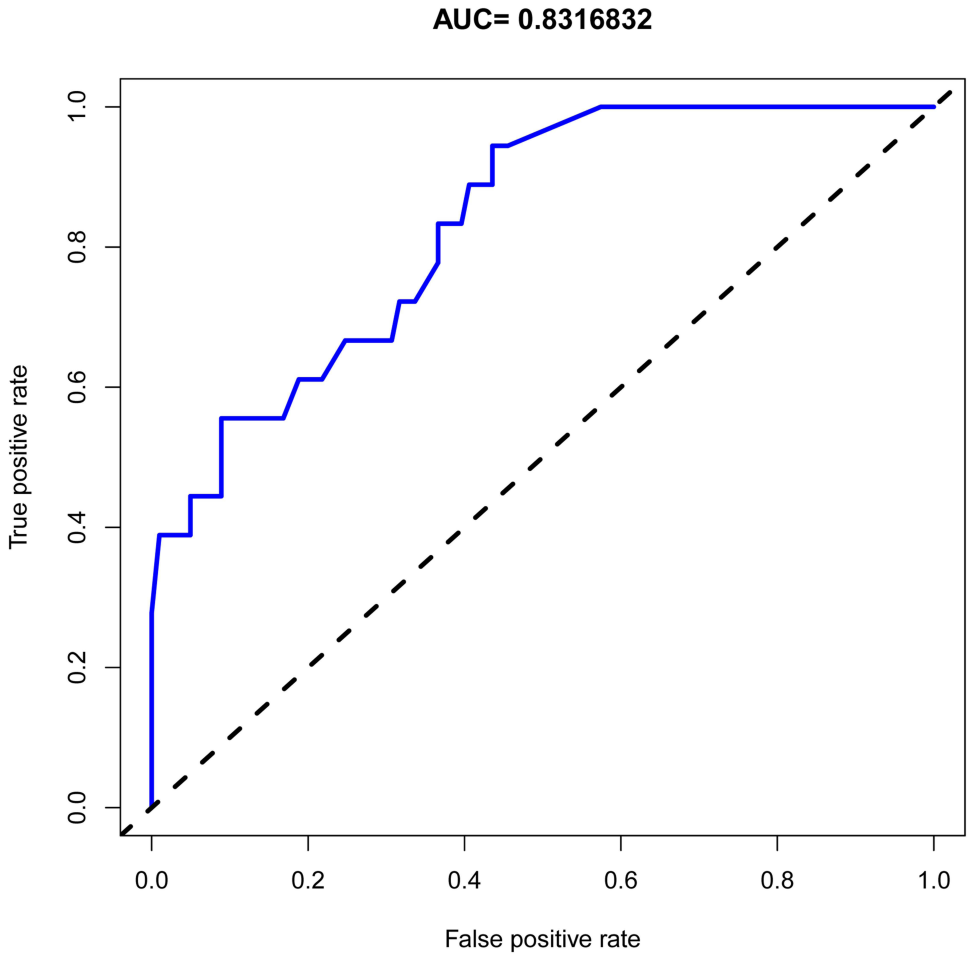

Figure 6 ROC curves for mortality rates of final prognostic model.

same threshold range as the training set (Figure 10). Notably, the model was simplified into a visual nomogram and developed into a user-friendly web-based application (https://hbwszhaoqun.shinyapps.io/nom-cuirongjun/).

Discussion

In this study, a prediction model was established to determine the risk of death within 12 months after diagnosis based on the recruited subjects with TBM in southwestern China, including isoniazid dose as a predictor. Along this line, several predominant factors, namely increasing patient age, nausea symptoms, high MRC grade, imaging suggestive of cerebral infarction, and a dose of 300 mg/day of isoniazid, were found to be significant predictors of patient mortality risk. Among these factors, a standard dose of isoniazid (300 mg/day) showed a significant impact on the risk of death.

Indeed, these notified prognostic risk variables that were widely recognized as prognostic factors in the eventual model have already been reported in previous studies. Nevertheless, this model provided additional insights into the importance of predicting the risk of death and the influence of risk factors on mortality in newly diagnosed patients with TBM. In contrast to the heterogeneity of TB treatment regimens, the recruited subjects in this study used homogenized TB and glucocorticoid therapy based on the quadruple first-line anti-tuberculosis drug regimen, including isoniazid, rifampin, ethambutol, and pyrazinamide, which was recommended by the World Health Organization (WHO). Nevertheless, it should be noted that the study population substantially varied after administering isoniazid. Some patients were administered isoniazid at a dose of 300 mg/day, which was consistent with the other studies (5 mg/kg/d, maximum 300 mg/d). All patients were treated with dexamethasone, and none were treated with quinolones during the intensive phase.

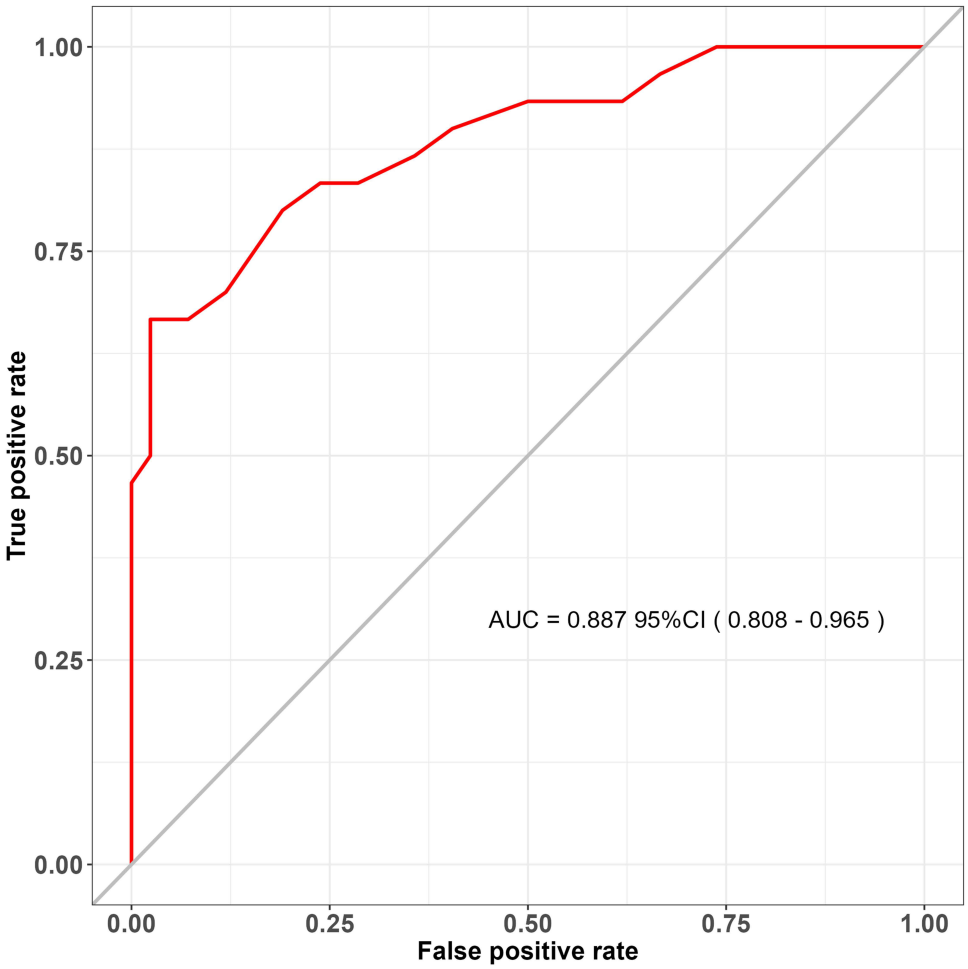

Figure 7 ROC curves for mortality rates of final prognostic model in validation set.

Recent studies indicated that standard dose isoniazid exposure in patients with TBM might be associated with an increased mortality rate.[11] In this context, the pharmacogenomic studies demonstrated an association between the dose of isoniazid in anti-TB therapy and treatment outcomes in TB patients. These studies highlighted the role of isoniazid metabolism by NAT2 in determining its rate, further influencing treatment outcomes.[12] Considering the importance of isoniazid in the treatment of TBM,[13] an increasing number of studies have focused on the treatment outcomes of isoniazid for TBM.

Regardless of the NAT2 gene type, standard dose exposure to isoniazid at 300 mg/day was associated with a high risk of death. Particularly, a higher dose of isoniazid (5 mg/kg/day) could be required for patients with fast metabolism to reach the minimum dose of isoniazid Cmax in the cerebrospinal fluid to kill *Mycobacterium tuberculosis*.[14–16] Accordingly, the dose should be increased in the peak blood concentration of isoniazid, ie, below 2 μg/mL. Considering the ratio of BBB permeability,[17] it was estimated that a dose of 10 mg/kg/day could achieve an effective EC50 in the cerebrospinal fluid of patients with TBM. Along this line, several clinical studies demonstrated that increasing the dose of isoniazid could effectively improve the etiology of tuberculosis without an increase in the risk of hepatotoxicity.[18,19] Currently, the WHO-recommended dose of isoniazid for adults of 300 mg/day may be ineffective in treating TBM.[20] The findings of this study suggested that a high dose of isoniazid could be beneficial for patients, emphasizing its importance as an important prognostic factor. Nevertheless, it would be better to monitor isoniazid blood concentration to guarantee drug safety profiling.

In addition to dose, this study explored other predictive factors, such as older age and a high MRC score, which were consistent with the results of modeling the risk of death within 6 and 9 months of diagnosis in patients with TBM.[21]

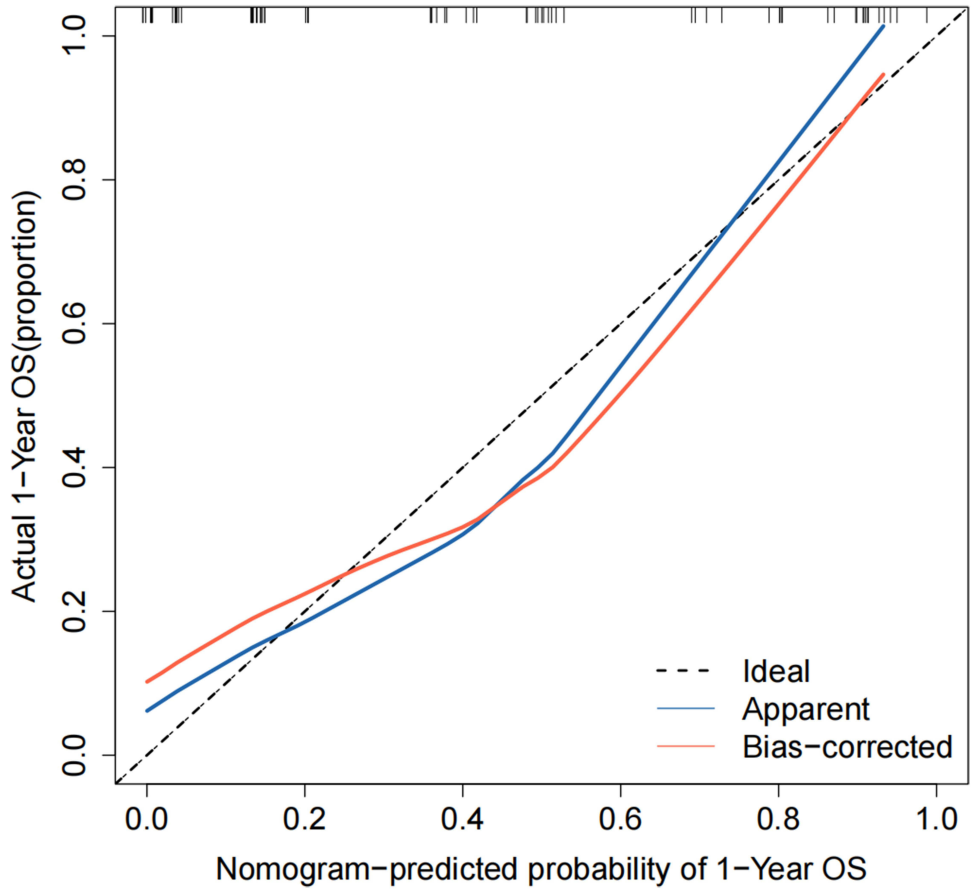

Figure 8 Calibration curves for final model in validation set.

Patients with TBM were acquainted with using the improved MRC grading standard to evaluate disease severity and prognosis. A higher MRC score could be an independent risk factor for ischemic stroke.[22] Moreover, age, TBM severity classification, and imaging indications of infarction were other predictors of poor prognosis, which were independent risk factors for the long-term survival of patients with TBM.[23] Finally, the designed model was based on the predictive index of the MRC grade, including senility, cerebral infarction, nausea symptoms, and isoniazid dose, to assess the severity and risk of patient death. It should be noted that this model demonstrated an enhanced ability to distinguish between patients who died due to TBM. Contrarily, the surviving patients might have better predictive ability than using MRC alone as a prognostic assessment. Although nausea is a nonspecific symptom, it was included in the model as a potential indicator of increased intracranial pressure, which is a critical factor in TBM prognosis.

The model's accessibility is significantly enhanced through its presentation as a nomogram and its implementation as a web-based application. These tools simplify complex statistical calculations, allowing for rapid and intuitive risk assessments in clinical settings. The web-based application, in particular, offers a user-friendly interface that can be accessed globally, facilitating its adoption in resource-limited settings where TBM is prevalent. Together, these features provide a practical pathway for integrating the model into routine clinical practice, ultimately improving decision-making and patient outcomes. Compared to existing TBM prediction models[21] that predominantly focus on demographic and clinical severity scores, our model uniquely incorporates isoniazid dosing as a prognostic factor. This inclusion addresses an essential gap in TBM management, as previous models often overlook the variability in drug exposure and its critical role in treatment outcomes. For instance, studies have highlighted the importance of optimizing isoniazid dosing to achieve adequate cerebrospinal fluid concentrations, which is vital for effective TBM treatment. By integrating this variable, our model provides a more comprehensive tool for clinical decision-making, enabling personalized treatment strategies that consider both disease severity and pharmacological factors.

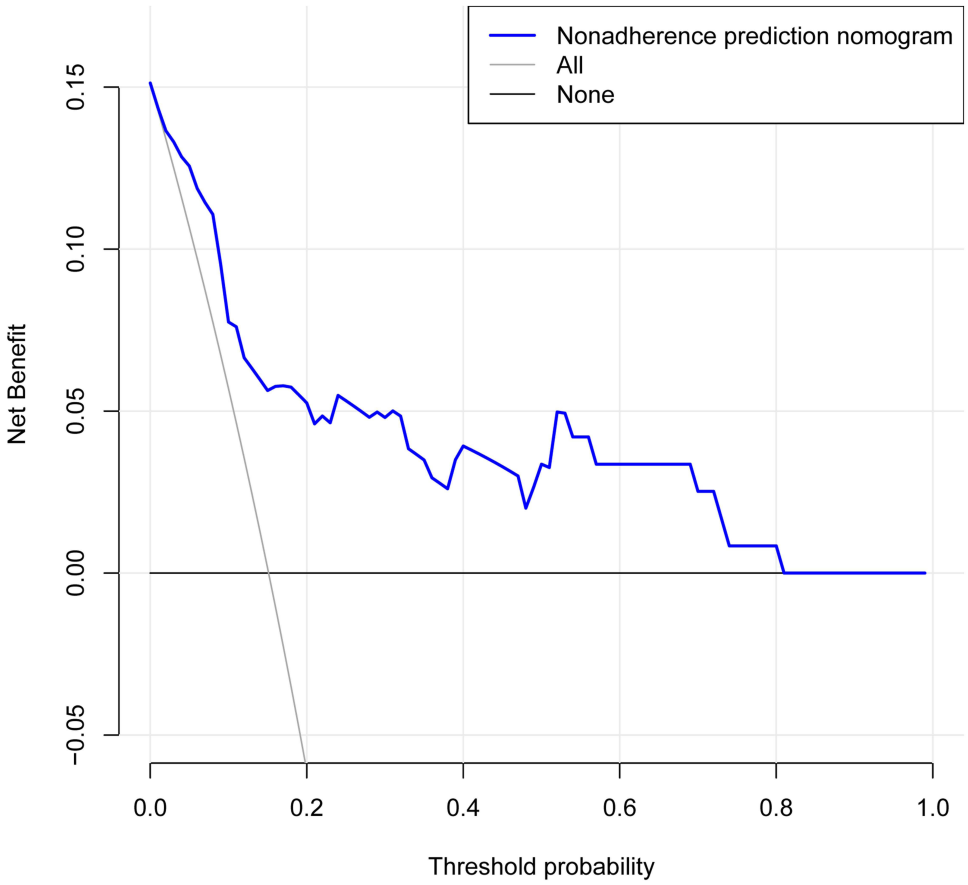

Figure 9 DCA for evaluating the clinical value of the model.

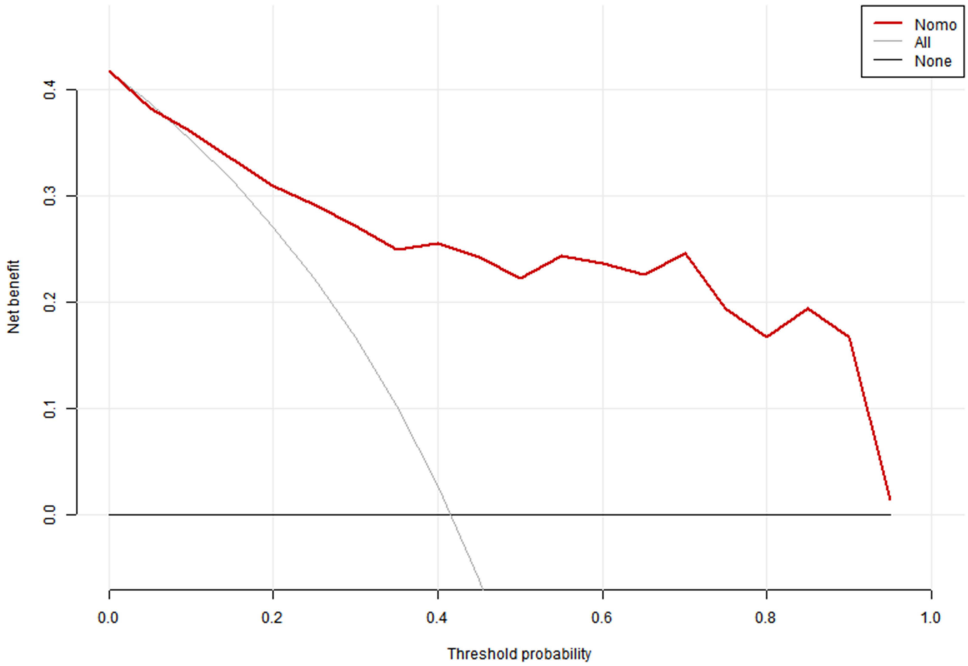

Figure 10 DCA for evaluating the clinical value of the model in validation set. The two gray lines represent the extreme scenarios where all patients either experience death or do not experience death. The blue line represents the calibration plot of the model established in this study.

This study has several limitations. First, while the external validation confirmed the model's generalizability to a different population, it was still limited to a single region and healthcare system. Validation across multiple centers with diverse demographic and clinical characteristics is needed to further enhance the model's applicability. Second, the relatively small sample size in both the training and validation datasets may limit the model's robustness, particularly in capturing less common clinical scenarios. Expanding the dataset to include a larger and more heterogeneous population could improve the model's performance and reliability. Third, although isoniazid dosing was incorporated as a unique factor, pharmacokinetic data such as serum drug concentrations were not included, which might limit the precision of the dosing recommendations. Future research should integrate pharmacokinetic and pharmacodynamic data to refine the model further. Lastly, the study did not assess long-term safety outcomes, such as hepatotoxicity associated with high-dose isoniazid. Prospective studies with extended follow-up are warranted to evaluate the balance between efficacy and safety.

Conclusion

In summary, our model was developed for newly treated adult patients with TBM. The prognostic factors in the model could be widely recognized indicators, possessing excellent ability to identify the severity of the disease and the prognosis of death. These factors could be helpful for individual treatment and prognostic management of patients. The model was simplified in the form of a column-line graph and web calculator, which were more intuitive and convenient for clinical use. Patients with a high risk of death were more likely to be identified early, suggesting serious illness or requiring additional medical support. Together, the dose of isoniazid emerged as a significant prognostic factor influencing the overall survival of patients, offering crucial guidance for clinical decision-making regarding the dosage of isoniazid in the treatment of TBM.

Data Sharing Statement

None of the data generated or analyzed (including figures and tables) during this study have been submitted elsewhere or are included in this published article. Supplementary figures and tables for this study can be found in the Supplementary Material. All the datasets are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

It was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical University (KLLY- 2021-022).

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We thank all the doctors and nurses who worked on the treatment of the patients in this study. This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-3591762/v1

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 in 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 authors declare that they have no competing interests in this work.

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