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Independent Risk Factors for In-Hospital Mortality in Non-HIV Adult Tuberculous Meningitis: A Large Retrospective Cohort Study from China

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Abstract

Background:

Tuberculous meningitis (TBM) represents the most severe form of tuberculosis and is associated with high short-term mortality, particularly in low- and middle-income countries. However, robust evidence identifying predictors of in-hospital mortality among non-HIV adult TBM patients remains limited.

Objective:

To identify independent clinical and laboratory predictors of in-hospital mortality among adults with TBM.

Methods:

We conducted a retrospective cohort study including adult patients with suspected TBM admitted to Changsha Central Hospital, Hunan Province, China, between October 1, 2013, and October 1, 2023. TBM cases were classified as definite, probable, or possible using standardized diagnostic criteria. In-hospital mortality was the primary outcome. Candidate predictors were initially screened using least absolute shrinkage and selection operator (LASSO) regression, followed by multivariable analysis with Firth-penalized logistic regression to address potential separation bias. Multicollinearity was assessed using variance inflation factors (VIF). Model discrimination and calibration were evaluated using the area under the receiver operating characteristic curve (AUC), bootstrap calibration, and the Hosmer–Lemeshow goodness-of-fit test.

Results:

A total of 1,346 adult patients were included (32.2% definite, 62.9% probable, and 4.8% possible TBM). The median age was 47 years (interquartile range [IQR], 30–62), and 68.0% were female. Overall in-hospital mortality was 12.26% (165/1,346). Multivariable analysis identified drug-induced hepatitis, hydrocephalus, renal failure, immunodeficiency, positive cerebrospinal fluid (CSF) tuberculosis antibody, elevated procalcitonin (PCT) levels, and advanced age as independent predictors of increased in-hospital mortality. Higher CSF glucose levels showed a protective trend. The final model included 16 predictors, demonstrated minimal multicollinearity (maximum VIF 4.0; mean VIF 1.28), and showed excellent performance (AUC 0.917; bootstrap mean absolute calibration error 0.014; Hosmer–Lemeshow p = 0.098).

Conclusion:

Among non-HIV adult patients with TBM, drug-induced hepatitis, hydrocephalus, renal failure, immunodeficiency, positive CSF tuberculosis antibody, elevated PCT levels, and advanced age are key independent predictors of in-hospital mortality. These findings may assist clinicians in identifying patients at higher risk of in-hospital mortality in high-burden settings.

Introduction

Tuberculosis remains a major global public health challenge, with a disproportionate burden in low- and middle-income countries. [1] Among extrapulmonary manifestations, tuberculous meningitis (TBM) is the most devastating, characterized by high mortality and substantial long-term neurological morbidity despite timely antimicrobial therapy and adjunctive corticosteroid treatment. [2–4] China is one of the countries with the most tuberculosis cases in the world. In 2023, it reported about 741,000 new cases, which is 6.8% of the global burden.[5, 6] Although pulmonary tuberculosis predominates, extrapulmonary disease constitutes 5–15% of cases, and central nervous system involvement occurs in approximately 0.5–3%, most commonly as TBM. [7–9]

Reported mortality rates for TBM in China range from 20% to 35%, underscoring its clinical severity. [2, 10]

Previous studies have identified several prognostic factors for TBM, including advanced age, disease severity at presentation, altered consciousness, hydrocephalus, immunodeficiency, and delayed diagnosis or treatment. [2, 10]

However, important gaps remain. First, many studies focus on long-term mortality or neurological sequelae, whereas in-hospital mortality—the outcome most directly influenced by early inpatient management—has received comparatively limited attention. [2, 11] Second, prior studies are frequently constrained by small sample sizes, limiting the ability to assess multiple interacting complications and biomarkers and increasing the risk of model instability. [3, 12, 13] Third, conventional regression approaches are often vulnerable to quasi-complete separation and overfitting, particularly when rare but clinically critical complications are included.

To address these limitations, we conducted a large, 10-year retrospective cohort study of non-HIV adult patients with TBM at a tertiary referral center in China. Our objectives were to systematically identify independent predictors of in-hospital mortality and to develop a robust prognostic model using modern penalized regression techniques. This represents one of the largest studies specifically targeting in-hospital mortality risk stratification in non-HIV adult TBM in a high-burden setting.

Methods

Study Design and Ethical Approval

This retrospective cohort study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Changsha Central Hospital, Affiliated to Hengyang Medical School, University of South China (Approval No. 20250122). Written informed consent was waived due to the retrospective nature of the study.

Changsha Central Hospital is a tertiary referral center for central nervous system tuberculosis, managing approximately 180 CNS tuberculosis cases annually.

Patients were identified from the electronic medical record system using International Classification of Diseases, 10th Revision (ICD-10) codes A17.0, A17.1, A17.8, and A17.9. All cases underwent detailed chart review. Between October 1, 2013, and October 1, 2023, consecutive admissions with suspected CNS tuberculosis were screened.

Exclusion criteria included concomitant non-tuberculous meningitis (e.g., cryptococcal meningitis), HIV co-infection, receipt of prior antitubercular treatment at other institutions or incomplete clinical data, and age younger than 18 years. After applying these criteria, a total of 1,346 adult patients were included in the final analysis.

Case Definitions and Outcome

TBM was classified as definite, probable, or possible according to the 2010 Marais consensus case definition. [14] Definite TBM was defined by the presence of clinical signs and symptoms of meningitis together with microbiological confirmation of *Mycobacterium tuberculosis*, including at least one of the following pieces of microbiological evidence available during the study period: positive acid-fast bacilli smear of cerebrospinal fluid (CSF), positive mycobacterial culture using the mycobacterial growth indicator tube (MGIT) system, positive CSF polymerase chain reaction (PCR) targeting the Mycobacterium tuberculosis complex (including GeneXpert MTB/RIF) [15-17], or positive CSF metagenomic next-generation sequencing for Mycobacterium tuberculosis. [18, 19]. Because all patients in this study underwent neuroimaging, probable TBM was defined as the presence of clinical features of meningitis together with a diagnostic score of ≥12 points, with at least 2 points derived from CSF or neuroimaging criteria. Possible TBM was defined as clinical features of meningitis with a total diagnostic score of 6–9 points (with neuroimaging) or 6–11 points (without neuroimaging). [14]

Definitions of Key Variables

In-hospital mortality was defined as death occurring during the index hospitalization. Drug-induced hepatitis was defined as an elevation of alanine aminotransferase (ALT) >5 × the upper limit of normal (ULN) without symptoms, or >3 × ULN with symptoms (e.g., nausea, vomiting, fatigue, right upper quadrant pain, or jaundice) during antitubercular therapy, after exclusion of other causes of liver injury (e.g., viral hepatitis, alcohol-related liver disease, or autoimmune hepatitis) by clinical evaluation and appropriate testing. [20, 21]

Hydrocephalus was defined as radiological evidence of ventricular dilatation on brain computed tomography (CT) or magnetic resonance imaging (MRI), typically with an Evans' index (ratio of maximal width of frontal horns to maximal width of inner skull) >0.3, or clinical/radiological signs of obstructive or communicating hydrocephalus secondary to basal exudates or cerebrospinal fluid (CSF) outflow obstruction. [4, 16, 22] This is a common complication in tuberculous meningitis (TBM), often confirmed by neuroimaging at admission or during hospitalization. [23, 24]

Renal impairment was defined as the presence of either acute kidney injury (AKI) during hospitalization or pre-existing chronic kidney disease (CKD). [25, 26] AKI was diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria: an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours, or ≥1.5 times baseline within 7 days, or urine output <0.5 mL/kg/h for ≥6 hours. [27, 28] Pre-existing CKD was identified from medical history or baseline estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (calculated using the CKD-EPI equation where data were available). [29, 30] Cases related to anti-tuberculous therapy, sepsis, or other causes were included.

Immunodeficiency was defined as secondary (non-HIV-related) immunosuppression, identified by any of the following criteria during admission or in the recent medical history: [31, 32]

- Ongoing systemic corticosteroid therapy for underlying diseases (equivalent to prednisone ≥15 mg/day or ≥0.3 mg/kg/day for at least 1 month, or higher doses for shorter periods if clinically significant);

- Use of other immunosuppressive agents (e.g., methotrexate, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, anti-TNF biologics, or chemotherapy) for conditions such as autoimmune diseases, organ transplantation, or malignancies;

- Laboratory evidence of impaired cellular immunity, such as reduced lymphocyte counts (total lymphocytes <1,000 cells/μL) or specific B- or T-cell subset reductions (e.g., CD4+ T-cells <500 cells/μL or CD19+ B-cells below institutional reference ranges), not attributable to HIV infection.

These criteria were based on clinical records and laboratory data, excluding primary immunodeficiencies and HIV-related causes, in line with definitions used in tuberculosis risk stratification guidelines and cohort studies.

Drug-resistant tuberculosis was defined as laboratory-confirmed resistance to at least one first-line anti-tuberculous drug (e.g., isoniazid, rifampicin, ethambutol, or pyrazinamide), identified by phenotypic drug susceptibility testing (DST) or genotypic methods (e.g., GeneXpert MTB/RIF or whole-genome sequencing). This included rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB; resistance to at least isoniazid and rifampicin), and pre-extensively drug-resistant TB (pre-XDR-TB; MDR/RR-TB with additional resistance to any fluoroquinolone), according to the latest World Health Organization (WHO) classifications. [33, 34]

Brain magnetic resonance imaging (MRI) findings were categorized based on contrast-enhanced T1-weighted sequences, T2-weighted/FLAIR sequences, and diffusion-weighted imaging (DWI) as follows,

adapted from standardized criteria in prior TBM literature: [4, 16, 35]

- Normal: No visible abnormalities attributable to TBM.

- Parenchymal lesions: Predominant involvement of the brain parenchyma, including tuberculomas (nodular or ring-enhancing lesions with or without caseation), granulomatous lesions, cerebral edema, or tuberculous abscesses (multiloculated enhancing masses with restricted diffusion on DWI), without overriding meningeal or complicated features.

-Meningeal enhancement: Predominant leptomeningeal or pachymeningeal gadolinium enhancement, typically in the basal cisterns, sylvian fissures, or cerebral convexity; may include ependymitis or basal exudates.

- Complicated: Predominant severe complications, such as hydrocephalus (ventricular dilatation with Evans' index >0.3 or signs of obstruction/communication), cerebral infarctions (hyperintense on DWI in basal ganglia or border zones due to vasculitis), venous sinus thrombosis (signal voids or filling defects on MR venography), hemorrhage, or extensive edema/infarct-abscess complexes.

- Spinal involvement: Extension to the spinal cord or meninges, including spinal meningeal enhancement, intramedullary tuberculomas, arachnoiditis, myelitis, or cord compression/edema (assessed if spinal MRI was performed).

These definitions were based on clinical records, neuroimaging reports, and standardized criteria.

Patients classified as possible TBM received empirical antitubercular therapy (standard HRZE regimen combined with adjunctive corticosteroids) and underwent repeated lumbar puncture with CSF analysis to seek microbiological confirmation. Unless an alternative diagnosis was established, antitubercular therapy was continued for the full treatment course. [4, 16]

The primary outcome was in-hospital mortality, defined as death occurring during the index hospitalization.

Statistical Analysis

Continuous variables are presented as medians with interquartile ranges (IQRs), and categorical variables are expressed as counts with percentages. Patients were categorized into in-hospital death and survival groups. Between-group comparisons were performed using the Wilcoxon rank-sum test for continuous variables and the χ^2 test or Fisher’s exact test for categorical variables, as appropriate.

To identify factors associated with in-hospital mortality, multivariable logistic regression models were constructed. Overall missingness was low (<10% across variables). Missing values were handled using multiple imputation with chained equations. Continuous variables were log-transformed when appropriate and subsequently standardized to z-scores prior to variable selection and model fitting. Candidate predictors were initially screened using least absolute shrinkage and selection operator

(LASSO) regression. Given the risk of quasi-complete separation in standard logistic regression, Firth-penalized logistic regression was applied to obtain finite and unbiased parameter estimates.

Multicollinearity among covariates was assessed using variance inflation factors (VIF). Model discrimination and calibration were evaluated using the area under the receiver operating characteristic curve (AUC), bootstrap resampling, and the Hosmer–Lemeshow goodness-of-fit test.

All statistical analyses, including variable selection, group comparisons, model fitting, and internal validation, were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *p*-value < 0.05 was considered statistically significant.

Results

Participant Demographics

As shown in Fig. 1, a total of 1,714 patients diagnosed with TBM were screened. After exclusion of 368 patients—including 19 with cryptococcal meningitis, 21 with HIV co-infection, 119 who had received prior treatment at other institutions or had incomplete data, and 209 who were younger than 18 years—1,346 adult patients were included in the final analysis. All included patients had complete in-hospital outcome data. Of these patients, 434 (32.2%) met the criteria for definite TBM, 847 (62.9%) for probable TBM, and 65 (4.8%) for possible TBM. The median age was 47 years (interquartile range [IQR], 30–62 years), and approximately 68% of the cohort were female. The overall in-hospital mortality rate was 12.26% (165 of 1,346 patients). Baseline demographic and clinical characteristics are summarized in Table 1.

Variables were retained based on their contribution to overall model performance, clinical plausibility, and stability during bootstrap resampling, rather than solely on p values.

Factors Associated with In-Hospital Mortality

Following variable selection using the least absolute shrinkage and selection operator (LASSO) regression, variables associated with in-hospital mortality were further evaluated using Firth-penalized multivariable logistic regression. To optimize the predictive performance of the model, certain variables (e.g., platelet count, cerebrospinal fluid glucose level, and aspirin use) were retained in the final model despite not reaching conventional statistical significance after multivariable adjustment ($p > 0.05$), based on their contribution to model stability or clinical relevance (Table 2). The final model incorporated 16 variables and showed no evidence of severe multicollinearity (maximum variance inflation factor [VIF] = 4.0; mean VIF = 1.28).

Significant risk factors ($p < 0.05$) included drug-induced hepatitis, hydrocephalus, renal failure, immunodeficiency, positive cerebrospinal fluid (CSF) tuberculosis antibody, elevated procalcitonin (PCT)

levels, and advanced age (Table 2). Higher CSF glucose levels showed a protective trend, although this did not reach conventional statistical significance (odds ratio 0.819, p = 0.059).

The model demonstrated excellent discriminative performance, with an area under the receiver operating characteristic curve (AUC) of 0.917 (Fig. 2), and good calibration, as indicated by a bootstrap mean absolute error of 0.014 and a Hosmer–Lemeshow goodness-of-fit test p-valuesof 0.098 (Fig. 3).

Neurological and Diagnostic Findings

All patients underwent lumbar puncture at admission. The median intracranial pressure was 150 mm H_2O (IQR, 120–190). CSF analysis revealed a median white blood cell count of 10 cells/μL (IQR, 9–50), protein concentration of 0.90 g/L (IQR, 0.58–1.38), and glucose level of 2.20 mmol/L (IQR, 2.20–3.27).

Brain magnetic resonance imaging showed abnormalities in 84.6% of patients, and hydrocephalus was observed in approximately 6.8% (91/1,346).

Treatment

Most patients received antitubercular regimens incorporating fluoroquinolones or linezolid (approximately 99.3%). Drug-resistant tuberculosis was identified in 5.60% of patients. Adjunctive corticosteroid therapy was administered to 1325 patients (98.4%).

Outcome

In-hospital death occurred in 165 patients, yielding an overall in-hospital mortality rate of 12.26%.

Discussion

In this large single-center retrospective cohort study, we characterized the clinical features of TBM among non-HIV adult patients in China and identified independent predictors of in-hospital mortality. This study focused on in-hospital mortality, an outcome most amenable to early inpatient intervention. The median age of 47 years is consistent with prior reports from China and other regions, underscoring that TBM continues to impose substantial morbidity and mortality even among relatively young adults.

Typical CSF abnormalities and a high prevalence of neuroimaging findings were observed, supporting their ongoing value as important adjunctive diagnostic tools. Nevertheless, microbiological confirmation was achieved in only 32.2% of cases, highlighting persistent diagnostic challenges in high-burden and resource-limited settings, where delayed or empiric treatment remains common.

The observed in-hospital mortality rate of 12.26% was relatively low compared with rates often ranging from 20% to 30% in previously reported non-HIV adult cohorts. [4, 23, 36] This difference may be partly explained by our strict exclusion of pediatric and HIV-positive patients—which may not have been as rigorously applied in some prior studies—as well as the widespread use of intensified antitubercular regimens incorporating fluoroquinolones or linezolid. Prior studies have suggested that such intensified

treatment strategies during the acute phase may improve outcomes and reduce mortality in severe TBM [37, 38], which may have contributed to the comparatively favorable prognosis observed in this cohort. The relatively lower mortality in our cohort may also reflect improvements in supportive care (e.g., early management of hydrocephalus and renal complications) at a specialized tertiary center. Consistent with existing literature, immunodeficiency, hydrocephalus, advanced age, and major complications—including renal failure and drug-induced hepatitis—were strongly associated with increased in-hospital mortality. [4, 22, 24]

Notably, positive CSF tuberculosis antibody emerged as an independent predictor of poor outcome, a finding that is relatively novel and warrants further investigation to clarify its biological significance and potential role in risk stratification.

Furthermore, elevated serum PCT levels also emerged as an independent predictor of poor outcome, consistent with prior evidence suggesting that it reflects heightened systemic inflammatory responses, secondary bacterial infection, or overall disease severity rather than TBM-specific pathology. [39, 40]

Drug-induced hepatitis, as a complication occurring during antitubercular therapy, likely reflects severe treatment-related hepatotoxicity that often accompanies clinical deterioration and multi-organ dysfunction during hospitalization, rather than serving as a baseline prognostic factor or implying a direct causal relationship with mortality. It should therefore be interpreted as a time-dependent marker of poor prognosis.

Strengths of this study include the large sample size and comprehensive clinical data. However, several limitations should be acknowledged, including the retrospective single-center design, exclusion of patients with incomplete data, and the absence of external validation. Although not designed as a formal prediction model under the TRIPOD framework, internal validation was performed to assess the robustness of the findings. Additionally, as a referral center, our cohort may include more severe cases, potentially limiting generalizability to primary care settings. Multicenter prospective studies are needed to validate and generalize these findings.

Conclusion

To our knowledge, this is one of the largest single-center studies specifically addressing in-hospital mortality in non-HIV adult TBM using penalized regression in a high-burden setting. Immunodeficiency, renal failure, positive CSF tuberculosis antibody, hydrocephalus, drug-induced hepatitis following antitubercular therapy, advanced age, and elevated PCT levels are independent risk factors for in-hospital mortality among non-HIV adult patients with TBM. The high discriminative performance of the model (AUC 0.917) supports its potential use for early risk stratification, pending external validation.

Table 1
Baseline demographic, clinical, and laboratory characteristics of patients with tuberculous meningitis, stratified by in-hospital survival status

Variable	Total (1346)	Survival (1181)	Death (165)	p
Demographics				
Age (years), median (IQR)	47 (30, 62)	46.00 (30, 61)	51.00 (33, 66)	**0.050**
Female, n (%)	915 (68.0)	797 (67.5)	118 (71.5)	0.342
Comorbidities and clinical features				
Hepatitis B, n (%)	137 (10.2)	120 (10.2)	17 (10.3)	1.000
Pulmonary tuberculosis type, n (%)				**0.359**
No pulmonary tuberculosis	300 (22.3)	269 (22.8)	31 (18.8)	
Hematogenous dissemination	415 (30.8)	354 (30.0)	61 (37.0)	
Primary pulmonary tuberculosis	3 (0.2)	3 (0.3)	0 (0.0)	
Secondary pulmonary tuberculosis	625 (46.4)	552 (46.7)	73 (44.2)	
Tuberculous pleurisy	3 (0.2)	3 (0.3)	0 (0.0)	
Cerebral infarction, n (%)	244 (18.1)	209 (17.7)	35 (21.2)	0.322
Drug-induced hepatitis, n (%)	103 (7.7)	16 (1.4)	87 (52.7)	**< 0.001**
Extrapulmonary tuberculosis, n (%)	442 (32.8)	395 (33.4)	47 (28.5)	0.237
Cerebral hemorrhage, n (%)	14 (1.0)	9 (0.8)	5 (3.0)	**0.023**
Epilepsy, n (%)	64 (4.8)	43 (3.6)	21 (12.7)	**< 0.001**
Hydrocephalus, n (%)	91 (6.8)	66 (5.6)	25 (15.2)	**< 0.001**
Immunodeficiency, n (%)	425 (31.6)	350 (29.6)	75 (45.5)	**< 0.001**
History of tuberculosis contact, n (%)	290 (21.5)	259 (21.9)	31 (18.8)	0.413
Hyponatremia, n (%)	383 (28.5)	318 (26.9)	65 (39.4)	**0.001**

Note: Data are n (%) for categorical variables and median (IQR) for continuous variables (all continuous variables were non-normally distributed). P-values were calculated using the χ^2 test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. For binary variables, only the positive category is shown. Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; PPD, purified protein derivative; ADA, adenosine deaminase; TB, tuberculosis; ESR, Erythrocyte sedimentation rate; PCR, Polymerase chain reaction; PCT, procalcitonin.

Variable	Total (1346)	Survival (1181)	Death (165)	p
Drug-resistant tuberculosis, n (%)	76 (5.6)	63 (5.3)	13 (7.9)	0.252
Coronary heart disease, n (%)	68 (5.1)	58 (4.9)	10 (6.1)	0.659
Hypertension, n (%)	124 (9.2)	103 (8.7)	21 (12.7)	0.128
Renal failure, n (%)	395 (29.3)	319 (27.0)	76 (46.1)	**< 0.001**
Laboratory findings				
Fibrinogen (g/L), median (IQR)	4.60 (2.90, 4.60)	4.60 (2.90, 4.60)	4.60 (2.83, 4.60)	0.389
Serum creatinine (μmol/L), median (IQR)	51.00 (36.00, 68.00)	50.00 (36.00, 66.00)	57.00 (41.00, 81.00)	**< 0.001**
CSF white blood cell count (×10⁶/L), median (IQR)	10.00 (10.00, 60.00)	10.00 (9.00, 50.00)	12.00 (10.00, 100.00)	**0.012**
Proportion of mononuclear cells in CSF, median (IQR)	0.68 (0.50, 0.69)	0.68 (0.50, 0.69)	0.67 (0.50, 0.69)	0.122
CSF chloride (mmol/L), median (IQR)	124.00 (115.00, 125.00)	124.70 (115.90, 125.00)	121.10 (113.00, 125.00)	**0.034**
CSF glucose (mmol/L), median (IQR)	2.20 (2.20, 3.26)	2.20 (2.20, 3.27)	2.20 (1.98, 3.21)	0.189
CSF protein (g/L), median (IQR)	0.90 (0.59, 1.44)	0.90 (0.58, 1.38)	0.96 (0.66, 1.86)	**0.010**
CSF ADA (U/L), median (IQR)	2.43 (2.43, 3.00)	2.43 (2.43, 3.00)	2.43 (2.43, 5.00)	0.061
Platelet count (×10⁹/L), median (IQR)	217.00 (149.00, 257.75)	217.00 (156.00, 261.00)	201.00 (125.00, 241.00)	**0.003**
ESR (mm/h), median (IQR)	20.00 (20.00, 40.00)	20.00 (20.00, 40.00)	20.00 (20.00, 46.00)	**0.017**
Hemoglobin (g/L), median (IQR)	115.00 (105.00, 126.00)	116.00 (105.00, 126.00)	110.00 (101.40, 119.00)	**< 0.001**
Indirect bilirubin (μmol/L),	5.50 (3.42, 6.40)	5.50 (3.40, 6.30)	5.50 (3.55, 6.43)	0.564

Note: Data are n (%) for categorical variables and median (IQR) for continuous variables (all continuous variables were non-normally distributed). P-values were calculated using the χ^2 test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. For binary variables, only the positive category is shown. Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; PPD, purified protein derivative; ADA, adenosine deaminase; TB, tuberculosis; ESR, Erythrocyte sedimentation rate; PCR, Polymerase chain reaction; PCT, procalcitonin.

Variable	Total (1346)	Survival (1181)	Death (165)	p
median (IQR)				
PCT (ng/mL), median (IQR)	0.04 (0.03, 0.09)	0.04 (0.03, 0.08)	0.05 (0.03, 0.28)	**< 0.001**
Diagnostic Tests				
CSF tuberculosis antibody positive, n (%)	173 (12.9)	148 (12.5)	25 (15.2)	0.414
CSF acid-fast bacilli smear positive, n (%)	7 (0.5)	6 (0.5)	1 (0.6)	1.000
PPD skin test reaction, n (%)				0.420
Negative	1240 (92.1)	1083 (91.7)	157 (95.2)	
Weak positive	32 (2.4)	29 (2.5)	3 (1.8)	
Positive	41 (3.0)	39 (3.3)	2 (1.2)	
CSF TB-PCR positive	41 (3.0)	36 (3.0)	5 (3.0)	1.000
Treatment				
Aspirin, n (%)	724 (53.8)	628 (53.2)	96 (58.2)	0.261
Fluoroquinolones, n (%)	1336 (99.3)	1171 (99.2)	165 (100.0)	0.482
Corticosteroid, n (%)	1325 (98.4)	1162 (98.4)	163 (98.8)	0.960
Linezolid, n (%)	866 (64.3)	770 (65.2)	96 (58.2)	0.094
Brain MRI findings, n (%)				0.224
Normal	207 (15.4)	187 (15.8)	20 (12.1)	
Parenchymal lesions	914 (67.9)	803 (68.0)	111 (67.3)	
Meningeal enhancement	125 (9.3)	107 (9.1)	18 (10.9)	
Complicated	73 (5.4)	59 (5.0)	14 (8.5)	
Spinal involvement	27 (2.0)	25 (2.1)	2 (1.2)	

Note: Data are n (%) for categorical variables and median (IQR) for continuous variables (all continuous variables were non-normally distributed). P-values were calculated using the χ^2 test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. For binary variables, only the positive category is shown. Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; PPD, purified protein derivative; ADA, adenosine deaminase; TB, tuberculosis; ESR, Erythrocyte sedimentation rate; PCR, Polymerase chain reaction; PCT, procalcitonin.

Variable	Total (1346)	Survival (1181)	Death (165)	p
Tuberculous meningitis diagnostic certainty, n (%)				0.219
Definite	434 (32.2)	384 (32.5)	50 (30.3)	
Probable	847 (62.9)	736 (62.3)	111 (67.3)	
Possible	65 (4.8)	61 (5.2)	4 (2.4)	

Note: Data are n (%) for categorical variables and median (IQR) for continuous variables (all continuous variables were non-normally distributed). P-values were calculated using the χ^2 test or Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. For binary variables, only the positive category is shown. Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; MRI, magnetic resonance imaging; PPD, purified protein derivative; ADA, adenosine deaminase; TB, tuberculosis; ESR, Erythrocyte sedimentation rate; PCR, Polymerase chain reaction; PCT, procalcitonin.

Table 2
Multivariable Firth penalized logistic regression analysis of factors associated with in-hospital mortality in patients with tuberculous meningitis

Variable	Odds Ratio (95% CI)	p value
PCT (per 1 SD increase)	1.28 (1.08–1.51)	**0.005**
Age (per 1 SD increase)	1.36 (1.05–1.76)	**0.019**
Platelet count (per 1 SD increase)	0.83 (0.67–1.04)	0.107
Hemoglobin (per 1 SD increase)	0.85 (0.70–1.05)	0.139
CSF glucose (per 1 SD increase)	0.82 (0.66–1.01)	0.059
Immunodeficiency (yes vs. no)	2.67 (1.62–4.48)	**< 0.001**
Pulmonary tuberculosis type (ref: No pulmonary TB)		
Hematogenous dissemination	1.67 (0.89–3.24)	0.110
Primary	15.13 (0.11–200)	0.196
Secondary	0.85 (0.46–1.62)	0.614
Tuberculous pleurisy	13.60 (0.10–167)	0.208
CSF tuberculosis antibody (positive vs. negative)	2.75 (1.45–5.09)	**0.002**
Drug-induced hepatitis (yes vs. no)	174.25 (86.9–377)	**< 0.001**
Hydrocephalus (yes vs. no)	4.26 (2.05–8.55)	**< 0.001**
Drug-resistant tuberculosis (yes vs. no)	2.33 (0.96–5.26)	0.062
Renal failure	3.17 (1.98–5.14)	**< 0.001**
PPD skin test reaction (ref: negative)	1.00	—
Weak positive	0.47 (0.05–2.70)	0.445
Positive	0.30 (0.04–1.60)	0.176
Strong positive	0.67 (0.10–2.89)	0.625
Aspirin (yes vs. no)	3.95 (0.89–19.6)	0.073
Brain MRI findings (ref: negative)	1.00	—
Parenchymal	2.02 (0.98–4.52)	0.057
Meningeal	2.13 (0.71–6.38)	0.176
Complicated	1.19 (0.35–3.83)	0.779
Spinal	4.08 (0.40–21.4)	0.196

Variable	Odds Ratio (95% CI)	p value
TBM diagnostic certainty (ref: Definite)	1.00	—
Probable	1.28 (0.76–2.21)	0.360
Possible	0.30 (0.05–1.24)	0.100

*Continuous variables (procalcitonin, platelet count, hemoglobin, and CSF glucose) were log(x + 1)-transformed to reduce skewness and subsequently standardized to z-scores (mean = 0, SD = 1) prior to model fitting. Age was standardized without log transformation. Odds ratios for continuous variables represent the change associated with a 1-standard deviation increase in the (transformed and) standardized variable. OR, odds ratio; CI, confidence interval; CSF, cerebrospinal fluid; PPD, purified protein derivative; MRI, magnetic resonance imaging; TBM, tuberculous meningitis; ref, reference category. Brain MRI findings: Categorized based on predominant feature as described in Methods. ref = Normal (no abnormalities); Parenchymal = primarily brain parenchyma involvement (e.g., tuberculomas, granulomas); Meningeal = leptomeningeal or pachymeningeal enhancement (e.g., basal cisterns); Complicated = severe complications (e.g., hydrocephalus, cerebral infarction, venous sinus thrombosis); Spinal = spinal extension (e.g., myelitis, arachnoiditis). In cases of multiple site involvement, the predominant abnormality (most extensive or clinically significant) determined the category. Due to small cell counts in rare subtypes (n = 3 for primary and pleurisy), estimates for these categories are imprecise and should be interpreted with caution.

Declarations

Ethics approval and consent to participate

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Changsha Central Hospital, Affiliated to Hengyang Medical School, University of South China (Approval No. 20250122). Written informed consent was waived by the Institutional Review Board due to the retrospective nature of the study and the use of fully anonymized data.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to institutional policies on patient data privacy and the retrospective use of clinical records. However, the data are available from the corresponding authors upon reasonable request and with permission of the Institutional Review Board of Changsha Central Hospital.

Competing interests

The authors declare that they have no competing interests.

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Authors'contributions

Authors' contributions QW and YZ contributed equally to this work and share first authorship. WZ and LC are co-corresponding authors. QW, YZ, WZ, and LC conceived and designed the study. QW, YZ, XX, HZ, JC, YF, JL, TZ, YO, GZ, WP, WZ, and LC were involved in identification and screening of eligible patients from medical records, data collection, and data curation. QW, YZ, XX, JC, YF, and JL performed statistical analysis and data interpretation. QW, YZ, WZ, and LC drafted the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

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Figures

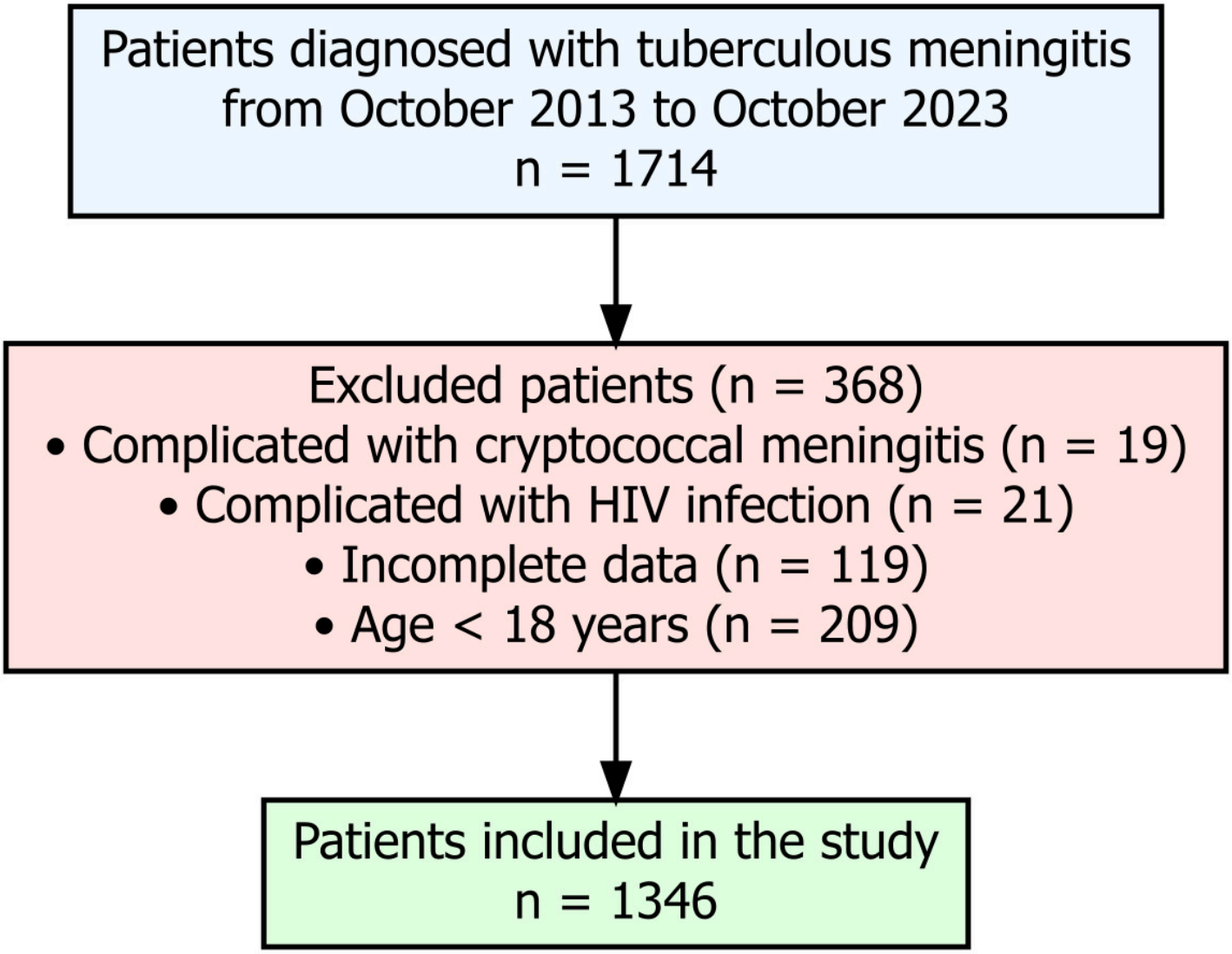


Figure 1

Flowchart of patient inclusion and exclusion in the study.

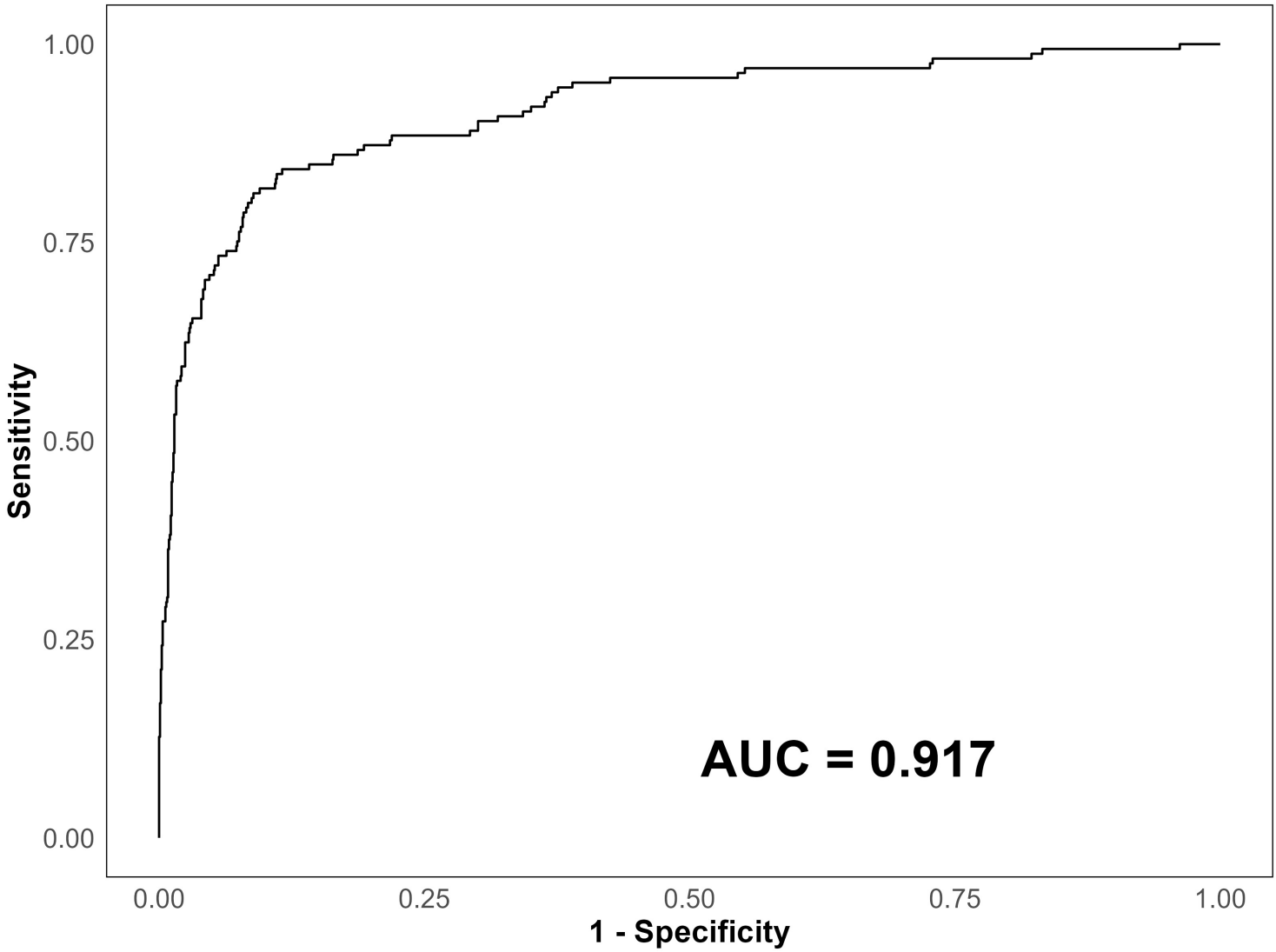


Figure 2

Receiver operating characteristic (ROC) curve of the prognostic model for predicting in-hospital mortality in patients with tuberculous meningitis (area under the curve [AUC] = 0.917).

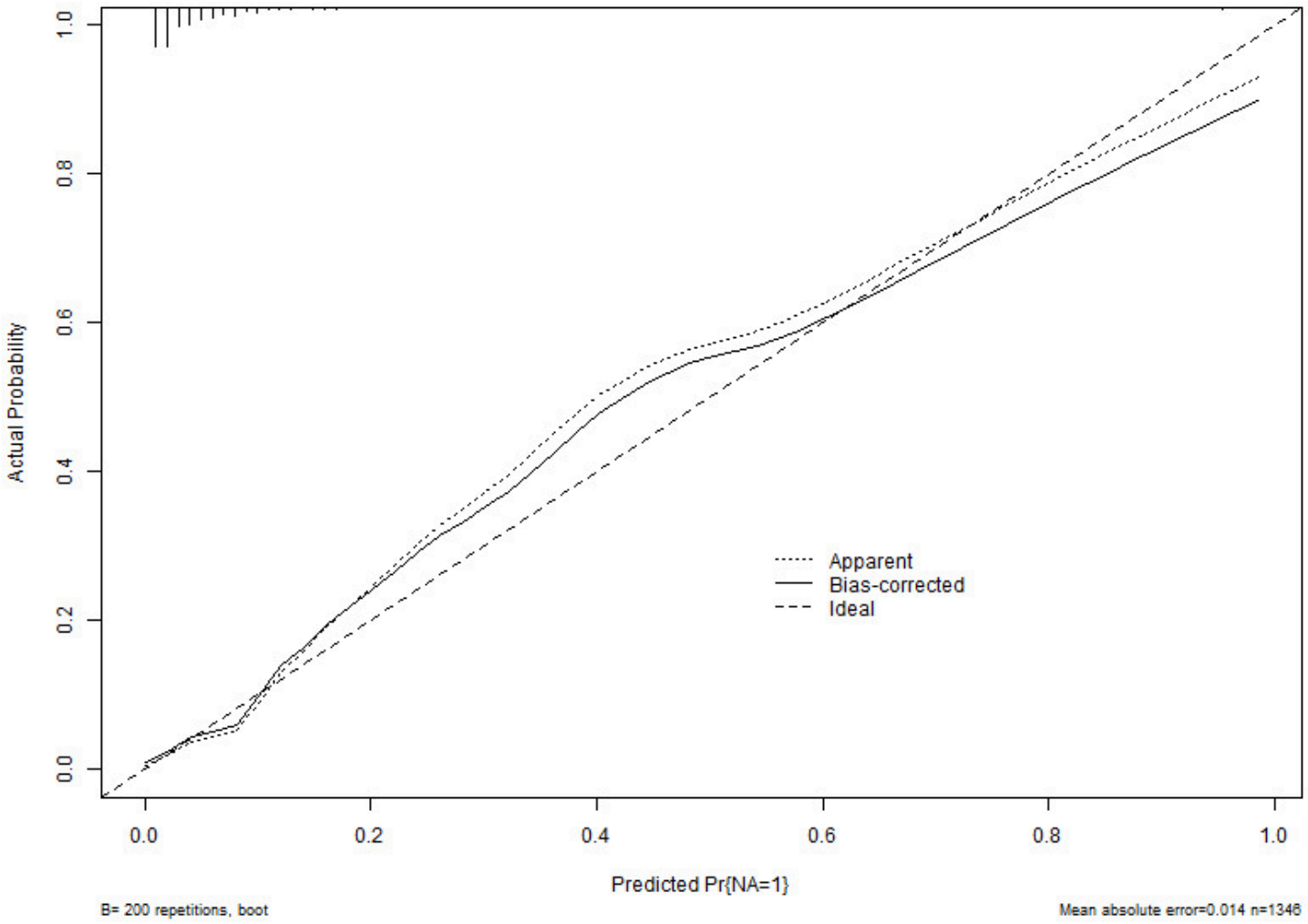


Figure 3

Calibration curve of the prognostic model for in-hospital mortality in patients with tuberculous meningitis using Bootstrap resampling (B=200). The mean absolute error was 0.014, and the Hosmer-Lemeshow goodness-of-fit test p-value was 0.098, indicating good agreement between predicted and observed outcomes. The diagonal line represents the ideal calibration (perfect prediction).