

# Acute Ischemic Stroke in Tubercular Meningitis Patients Without Conventional Vascular Risk Factors: A Retrospective Case Control Study

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**Objective:** Ischemic stroke is a common complication in patients with tubercular meningitis (TBM). However, the risk factors for Ischemic stroke in TBM patients are not fully understood, especially in those patients without conventional vascular risk factors. The aim of the present study was to explore the clinical features and independent risk factors for tubercular meningitis-related Ischemic stroke (TBMRI).

**Methods:** Tubercular meningitis patients with acute Ischemic stroke without conventional vascular risk factors were recruited between July 2010 and July 2020 as the TBMRI group. Patients who solely had tubercular meningitis were recruited as the control group (TMB group). Demographic characteristics, clinical presentations, and cerebrospinal fluid (CSF) examinations were collected, and multiple logistic regression analysis was applied to analyse the independent risk factors for TBMRI.

**Results:** A total of 70 TBMRI patients and 70 TMB patients were enrolled. Most (82.86%) of the TBMRI patients experienced Ischemic stroke events within 3 months after the diagnosis of tubercular meningitis. The multiple logistic regression analysis revealed that variation in red blood cell distribution width (RDW-CV), mean platelet volume (MPV), C-reactive protein (CRP), CSF glucose and Modified Research Council Grade II (MRC Grade II) were independent risk factors for TBMRI. The AUC of the identification model was 0.808, with a sensitivity of 68.60% and a specificity of 84.30%.

**Conclusion:** This study revealed that RDW-CV, MPV, CRP, CSF glucose and MRC Grade II are potential independent risk factors for TBMRI. The identification model established in this study may help monitor TBM patients who are at high risk of developing TBMRI.

**Keywords:** tubercular meningitis, Ischemic stroke, tubercular meningitis-related Ischemic stroke, independent risk factor

## Introduction

Tubercular meningitis (TBM) remains a challenging illness with significant morbidity and mortality in developing countries. The main complications of TBM include stroke, hydrocephalus and tuberculoma formation.<sup>1</sup> It has been reported that the incidence of stroke in TBM patients is approximately 13–57%, and that stroke occurs more likely during the third stage of TBM,<sup>2,3</sup> Modified Research Council grade III referring to Modified Medical Research Council criteria. Stroke is also a major predictor of permanent disability.<sup>4</sup> Consequently, prevention of Ischemic stroke is of great

importance to TBM patients. However, the risk factors for Ischemic stroke in TBM patients are not fully understood, especially in those patients without conventional vascular risk factors.

In 1989, Teoh R. reported 2 patients with tubercular meningitis who suffered from rapid internuclear ocular palsy during anti-tuberculosis treatment and died within 14 days. The autopsy results of one of the patients revealed multiple intracranial infarction lesions with diffuse inflammatory infiltration of the basement artery accompanied by thrombosis, suggesting that tubercular meningitis might directly cause Ischemic stroke, namely, tubercular meningitis-related Ischemic stroke (TBMRI).<sup>5</sup> Since then, acute Ischemic stroke has been continuously reported in patients with TBM. However, most of these studies were radiological studies<sup>6–8</sup> and showed that the stage of TBM, basal meningeal enhancement, hydrocephalus, exudate and hypertension were related to stroke in TBM patients.<sup>2</sup> Only a few studies focusing on the clinical correlation of Ischemic stroke in TBM patients have been reported.<sup>9,10</sup> However, none of the risk factors were identified as independent risk factors in the retrospective analysis. The negative result of these studies may be related to their included subjects, some of whom had cerebral vascular risk factors, such as diabetes mellitus, hypertension and hyperlipidemia. It is well known that the exact mechanisms of stroke may differ between patients with or without conventional vascular risk factors. Therefore, we conducted this study to evaluate the clinical features and the independent risk factors for TBMRI. Patients with conventional vascular risk factors were excluded from our study to decrease the impact of atherosclerosis.

## Materials and Methods

Patients (>18 years of age) with a clinical or confirmed diagnosis of TBM attending the inpatient facilities of The First Affiliated Hospital of Guangxi Medical University, The Second Affiliated Hospital of Guangxi Medical University, Guangxi Zhuang Autonomous Region People's Hospital, Wuming Hospital affiliated with Guangxi Medical University and The Fourth People's Hospital of Nanning City were enrolled between July 2010 and July 2020. The study was approved by the Review Boards of the First Affiliated Hospital of Guangxi Medical University and local hospitals. Approval Number: 2022-E314-01. The written informed consent was waived because of the retrospective nature of our study. During the data collection, personally identifiable information such as names, addresses and phone numbers of the study participants were never recorded. The collected data were kept confidentially and used only for the purpose of the study.

## Definition of TBMRI

Referring to the conception of cancer-associated Ischemic stroke,<sup>11,12</sup> the definition of TBMRI in the present study was defined as patients with tubercular meningitis (TBM) and acute Ischemic stroke without conventional vascular risk factors. According to American Heart Association diagnostic criteria for stroke,<sup>13</sup> acute Ischemic stroke was diagnosed as follows: patients who newly suffered from focal neurological deficits, such as fatigue or aphasia, who had weakness or numbness in one or both limbs, and who had brain MRI and/or CT that identified Ischemic lesions that were consistent with the neurological symptoms. Stroke severity was assessed by the National Institute of Health Stroke Scale (NIHSS).<sup>14</sup>

The conventional stroke risk factors were defined as follows: (i) hypertension (taking antihypertensive drugs, diastolic blood pressure  $\geq 90$  mmHg, or systolic blood pressure  $\geq 140$  mm Hg); (ii) diabetes (taking anti-diabetic drugs or random blood glucose level  $\geq 11.1$  mmol/L);<sup>15</sup> (iii) hyperlipidaemia (taking lipid-lowering drugs, low-density lipoprotein  $> 3.64$  mmol/L, serum total cholesterol  $> 5.72$  mmol/L or triglycerides  $> 1.70$  mmol/L);<sup>16</sup> and (iv) smoking and drinking, coronary artery disease, rheumatic heart valve disease, and atrial fibrillation (history of disease, or assessed by a cardiologist according to electrocardiogram and transthoracic echocardiography at admission).

The exclusion criteria for the TBMRI group were (i) patients with malignant tumor, HIV or *Treponema pallidum* infection, or autoimmune disease; (ii) patients with heart, kidney or liver failure; (iii) patients with bacterial, fungal pneumonia or sepsis; (iv) patients who took glucocorticoids and immunosuppressants in the last 3 months; (v) dead patients; and (vi) patients with incomplete clinical or imaging data.

## Diagnostic Criteria of Tubercular Meningitis

TBM was diagnosed according to a standard case definition published in 2010.<sup>17</sup> Patients were defined as having “definite” TBM if acid-fast bacilli were seen in the cerebrospinal fluid (CSF), *Mycobacterium tuberculosis* was cultured

from the CSF, or a CSF positive commercial nucleic acid amplification test was obtained. Patients were defined as having “probable” TBM if their diagnostic score was  $\geq 12$  (at least 2 points either from the CSF or cerebral imaging criteria) plus exclusion of alternative diagnoses. Patients were defined as “possible” TBM if their diagnostic score was 6 to 11 and if there was exclusion of alternative diagnoses.

The severity of meningitis was graded according to the modified British Medical Research Council criteria as follows: Stage I: prodromal phase with no definite neurological symptoms and a Glasgow coma scale score  $\geq 15$ ; Stage II: signs of meningeal irritation with slight or no clouding of the sensorium and minor (cranial nerve palsies), or no neurological deficit and a Glasgow coma scale score between 11 and 14; and Stage III: severe clouding of the sensorium, convulsions, focal neurologic deficits and involuntary movements and a Glasgow coma scale score  $\leq 10$ .<sup>18</sup>

Age-, sex- and living condition-matched acute TBM patients without radiological evidence of an infarct were recruited as the control group, which was also named the TBM group.

## Collection of Clinical Data

Data regarding the baseline demography, comorbidities (hypertension, diabetes mellitus, and HIV), clinical symptoms, signs, laboratory parameters, inflammatory markers, imaging examination (such as cranial CT, CT angiography, digital subtraction angiography, MRI, magnetic resonance angiography, diffusion-weighted MRI, chest CT or X-ray), details and duration of treatment (all patients received routine anti-tuberculosis treatment according to the recommendations of the World Health Organization (Fourth edition)) were obtained. CSF was examined for opening pressure, protein, cells, glucose, and bacteria. CSF was also tested by polymerase chain reaction (PCR) to detect mycobacterial deoxyribonucleic acid. India ink preparation of CSF was performed to exclude cryptococcal meningitis.

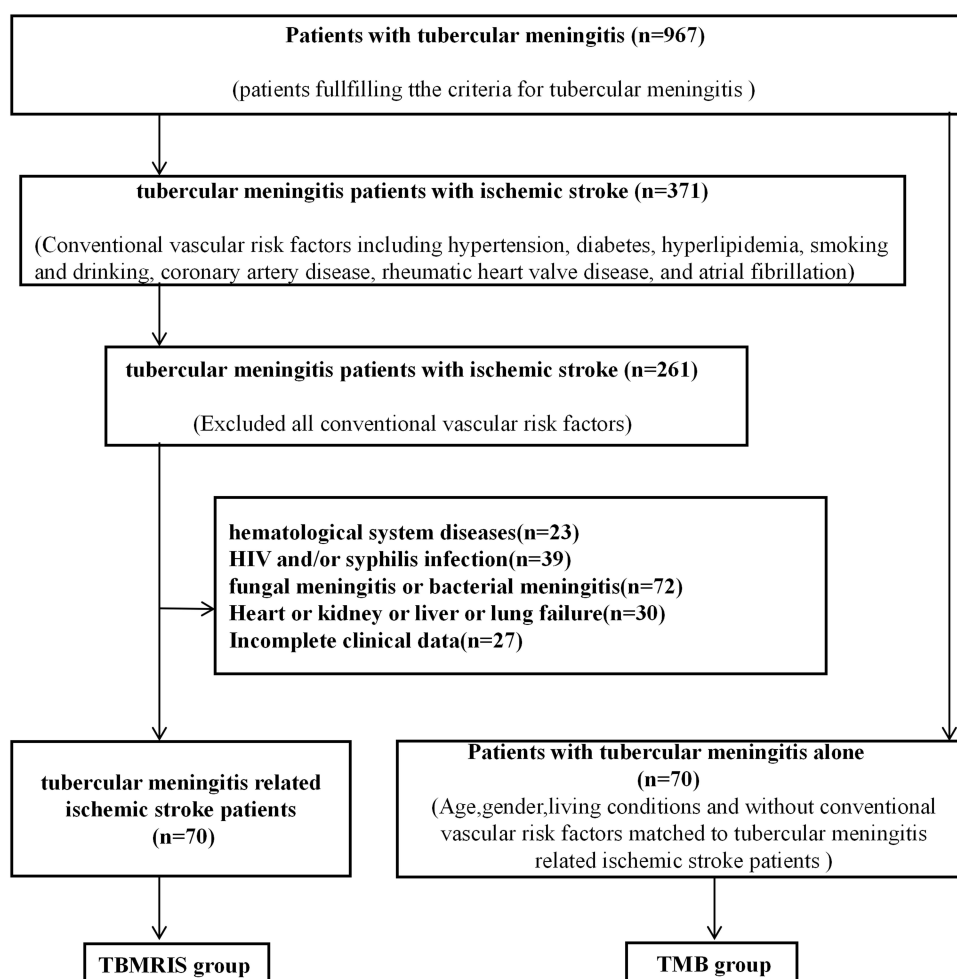
For the TBMRIS patients, the laboratory data were collected according to the following conditions: (i) data from the patients who were admitted for acute Ischemic stroke while they were diagnosed with TBM during the treatment of Ischemic stroke were collected within 48 hours after admission. (II) Data from the patients who were diagnosed with acute Ischemic stroke during the treatment of TBM were collected within 72 hours of the acute Ischemic stroke attack. All data were independently verified by three authors. This study was performed in accordance with the principles outlined in the Declaration of Helsinki and approved by the ethical committee and the institutional review board.

## Statistical Analysis

Statistical analyses were performed using SPSS 26.0.  $p < 0.05$  was considered statistically significant. Continuous variables are presented as the mean  $\pm$  standard deviation or median with interquartile range (IQR). Significance testing was carried out using Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for nonnormal data. The chi-square test or Fisher's exact test was used for categorical variables. All variables were initially tested by univariate analysis, and those with a  $P < 0.05$  were entered stepwise into a multivariate analysis by using the forward conditional method. To explore a reliable model to identify TBMRIS, we combined the independent risk factors for TBMRIS named the identification model. Moreover, ROC analysis was used to compare the area under the ROC curve (AUC) of the identification model with every independent risk factor using MedCalc version 15.8 software packages. The largest AUC variable and index (calculated by sensitivity and specificity) were called the reliable method to determine TBMRIS in this study.

## Results

In this study, a total of 967 patients had a diagnosis of TBM. Among these, 371 patients had a diagnosis of Ischemic stroke, and 301 patients were excluded, including 110 patients with traditional stroke risk factors, 23 patients with hematological system diseases, 39 patients with HIV and/or syphilis infection, 72 patients with fungal meningitis or bacterial meningitis, 30 patients with heart, kidney, liver or lung failure, and 27 patients with incomplete clinical data. Finally, 70 patients aged 21–88 years (median 59.50 [IQR 18], 46 males, 24 females) who met the TBMRIS criteria were enrolled. In the TBM group, 70 patients were included who were aged 46–75 years (median 54.00 [IQR 13], 42 males, 28 females) (Figure 1). A comparison of the presenting clinical features in TBMRIS and TBM is presented in Table 1. Significant differences were not found in age, sex, diagnostic category, extracranial tuberculosis or living



**Figure 1** Flowchart of the screening of patients with tubercular meningitis-related Ischemic stroke.

**Abbreviations:** TBM RIS, tubercular meningitis-related Ischemic stroke; TMB, tubercular meningitis.

conditions between the two groups ( $p > 0.05$ ) (Table 1). The two groups of patients shared similar tubercular meningitis manifestations: headache, fever, meningeal irritation, vomiting, and altered mentation.

In the TBM RIS group, 10 (14.29%) patients were first hospitalized for Ischemic stroke, were diagnosed with tubercular meningitis during hospitalization and initiated anti-tuberculosis treatment. Sixty (85.71%) patients presented with tubercular meningitis as the initial manifestation and were diagnosed with Ischemic stroke during anti-tuberculosis treatment. Among the TBM RIS group, 58 (82.86%), 8 (11.43%) and 4 (5.71%) patients experienced Ischemic stroke in the first 3 months, 4–6 months and more than 6 months, respectively.

The infarctions of the TBM RIS' patients were scattered and unevenly distributed. The anatomical locations that were most often involved were the basal ganglia area, followed by the frontal lobe, parietal lobe, radiative crown area and side ventricle horn. Subsequently, locations such as the occipital lobe, temporal lobe, cerebellum, and brainstem were less involved (Table 2 and Figure 2).

Compared to the TMB group, the TBM RIS group had lower levels of red blood cell (RBC) count, mean platelet volume (MPV), and cerebrospinal fluid (CSF) glucose ( $p < 0.05$ ) (Table 3). The variations in red blood cell distribution width (RDW-CV), D-dimer, and C-reactive protein (CRP) in TBM RIS were significantly higher than those in the TMB group ( $p < 0.05$ ) (Table 2). Significant differences were also found in the Modified Research Council (MRC) Grade between the two groups ( $p < 0.05$ ) (Table 3). Furthermore, multiple logistic regression analysis revealed that variation of RDW-CV (odds ratio [OR]:1.261, 95%confidence interval [CI]:1.056–1.506,  $p < 0.05$ ), MPV (OR:0.657, 95% CI:0.464–

**Table 1** General Data

Characteristic	TBMRIS (n=70)	TBM (n=70)	P value
Age(years), median (IQR)	59.50 (18)	54.00 (13)	0.289
Gander, n (%)			0.484
Male	46 (65.7)	42 (60.0)	
Female	24 (34.3)	28 (40.0)	
Diagnostic category, n (%)			0.831
Definite	45 (64.3)	43 (61.4)	
Probable	15 (21.4)	18 (25.7)	
Possible	10 (14.3)	9 (12.9)	
Extracranial tuberculosis, n (%)			0.642
Yes	58 (89.2)	60 (85.7)	
No	12 (17.1)	10 (14.3)	
Living conditions, n (%)			0.699
City	19 (27.1)	17 (24.3)	
Countryside	51 (72.9)	53 (75.7)	

**Abbreviations:** TBMRIS, tubercular meningitis-related Ischemic stroke; TBM, tubercular meningitis; IQR, interquartile range.

**Table 2** The Distribution of Cerebral Infarction Lesions in TBMRIS Patients

Location	Basal Ganglia Region	Frontal Lobe	Parietal Lobe	Corona Radiata	Occipital Lobe	Temporal Lobe	Thalamus	Centrum Semiovale	Occipital Lobe	Insular Lobe	Pons	Ependymal
Unilateral	23	5	1	3	2	3	3	0	1	2	1	1
Bilateral	27	12	9	6	6	2	1	3	2	0	1	1

**Abbreviation:** TBMRIS, tubercular meningitis-related Ischemic stroke.

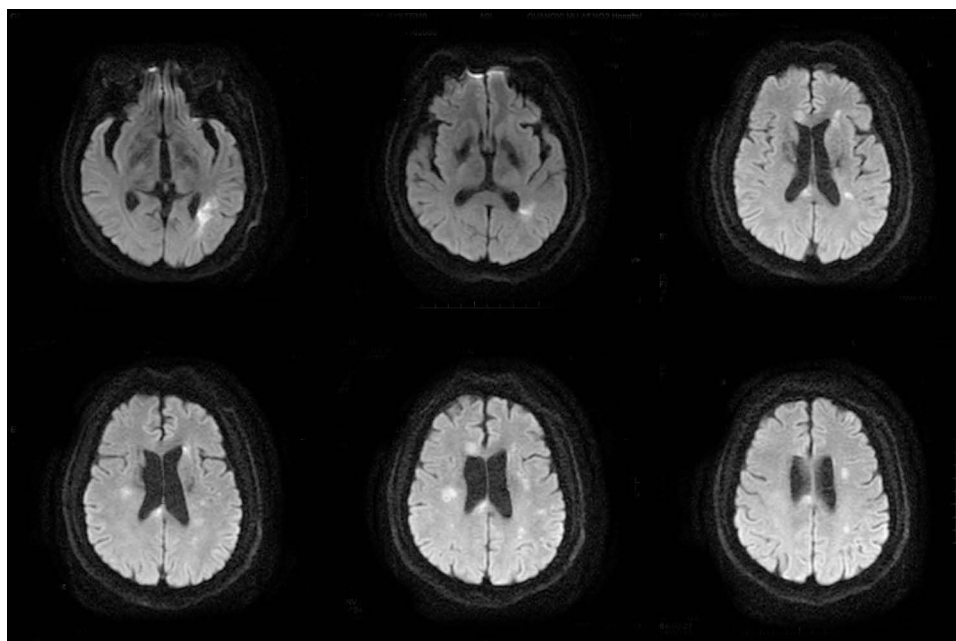
0.930,  $p < 0.05$ ), CRP (OR:1.012, 95% CI:1.001–1.023,  $p < 0.05$ ), Glucose (OR:0.500, 95% CI:0.309–0.809,  $p < 0.05$ ), and MRC Grade II (OR:3.578, 95% CI:1.441–8.886,  $p < 0.05$ ) were independent risk factors for TBMRIS (Table 4).

Compared to the AUC of RDW-CV, MPV, CRP, glucose, and MRC grade II, the AUC of the identification model was the largest (AUC=0.808, sensitivity 68.60%, specificity 84.30%, Index 0.529), which means that the combined model had the greatest predicting ability for TBMRIS (Table 5 and Figure 3).

## Discussion

Stroke is one of the main causes of mortality and long-term physical and cognitive impairment in China.<sup>19</sup> In addition to conventional vascular risk factors, such as hypertension, diabetes, long-term smoking and drinking and hyperlipidaemia, recent studies have found that inflammation is closely connected to cerebral infarction.<sup>20–22</sup> In clinical terms, tuberculosis is a common chronic inflammatory disease. Although tuberculosis meningitis comprises 1% of the incident cases of tuberculosis, it remains the most serious form of extrapulmonary tuberculosis.<sup>1,23</sup> The occurrence of stroke has been reported in up to 57% of TBM patients,<sup>3,24</sup> with mortality approximately three times higher in TBM patients with stroke than in patients without stroke.<sup>3</sup> In the present study, most TBMRIS patients (82.86%) developed Ischemic stroke within 3 months after the diagnosis of TBM. This finding suggests that TBMRIS was likely to develop during the intensive inflammatory response period that occurred in active TBM patients. This is consistent with the results of previous studies.<sup>2,25</sup> In addition, there were 10 (14.29%) patients who were hospitalized for acute Ischemic stroke and who had a confirmed diagnosis of TBMRIS, indicating that measures should be taken to screen out TBM. Significant differences in the Modified Research Council (MRC) grade were also found between the TBMRIS group and TBM group, and the multivariate analysis showed that MRC Grade II was an independent risk factor for TBMRIS. As





**Figure 2** Typical neuroimaging of a patient with acute Ischemic stroke and active tuberculosis meningitis. Images are from a male in his 50s who had acute Ischemic stroke without conventional stroke risk factors and who was initially diagnosed with active tuberculosis meningitis during the treatment of Ischemic stroke. Six MRI diffusion-weighted images show multiple high-signal lesions in multiple arterial regions of the brain.

Anuradha<sup>26</sup> found that patients with MRC grade III were more likely to have acute cerebral infarction events, in which TBM patients with conventional vascular risk factors were included, the finding in the present study, in which patients with conventional vascular risk factors were excluded, suggested that ischemic stroke may occur at early stage in patients with TBM without conventional vascular risk factors, indicating that clinicians should pay more attention to the prevention of ischemic stroke from patients with TBM without conventional vascular risk factors.

Previous studies have suggested that atherosclerosis aggravation may be the main cause of stroke in patients with conventional vascular risk factors. Therefore, in TBM patients, it was difficult to determine whether stroke was caused by TBM or atherosclerosis. In our study, patients with conventional vascular risk factors were excluded, reducing the effects of atherosclerosis. The multivariate analysis showed that variations of RDW-CV, MVP, CRP, CSF glucose and MRC Grade II were independent risk factors for TBMRIS, implying that these independent risk factors alone or in combination promoted the development of TBMRIS through different kinds of pathways.

The unveiling of independent risk factors for TBMRIS is an important issue because the pathogenesis that is induced by independent risk factors may influence the choice of management, stroke prognosis, and risk of recurrence. In some previous studies, inflammatory changes in the vessels of the circle of Willis are the most likely reason for vascular complications in tubercular meningitis. Exudative basal meningitis results in vasospasm with or without secondary thrombosis. These changes jeopardize arterial blood flow, causing Ischemic stroke in the early stage of the disease.<sup>27,28</sup> However, to date, the underlying pathogenesis of vasospasm in tubercular meningitis-related Ischemic stroke has not been entirely elucidated. First, in the present study, the TBMRIS group had elevated plasma C-reactive protein and lower cerebrospinal fluid glucose than the TMB group, which implies that the immune response to tuberculosis infection may be more intensive in TBMRIS patients than in TMB patients.<sup>29,30</sup> Moreover, a lower MPV was also found in the TBMRIS group. As platelets are known to change their structure and function from inactive to active platelets owing to physiologic signals<sup>31</sup> and MPV reflects platelet size and activity, increases or decreases in MPV can represent various inflammatory processes and diseases.<sup>32</sup> Previous studies have investigated that the MPV is correlated inversely with the C-reactive protein concentration, suggesting that a lower MPV implies a more intensive inflammatory response.<sup>33–36</sup> In addition, plasma levels of C-reactive protein are an independent risk factor for vasospasm severity,<sup>37,38</sup> the more intensive immune response to a tuberculosis infection may induce a more severe vasospasm in the TBMRIS group.

**Table 3** Comparison of the Laboratory Data Between the TBMRIS Group and the TBM Group

Characteristic	TBMRIS (n=70)	TBM (n=70)	P value
WBC( $10^9/L$ ), median (IQR)	8.53 (4.09)	7.20 (4.31)	0.053
Hb(g/L), (mean $\pm$ SD)	109.58 $\pm$ 22.64	114.26 $\pm$ 18.27	0.181
RBC( $10^9/L$ ), (mean $\pm$ SD)	3.96 $\pm$ 0.72	4.23 $\pm$ 0.70	0.041
RDW-CV(%), median (IQR)	15.25(3.13)	13.40(3.02)	0.000
MCV(fL), median (IQR)	87.22(10.40)	84.60(14.25)	0.156
HCT, median (IQR)	0.85(0.17)	0.846(0.14)	0.533
MCH(pg), median (IQR)	28.24(4.34)	27.80(5.45)	0.674
MCHC(g/L), (mean $\pm$ SD)	322.64 $\pm$ 14.72	327.23 $\pm$ 20.75	0.086
NEU( $10^9/L$ ), median (IQR)	6.29(3.40)	5.44(3.59)	0.074
NEUR(%), median (IQR)	77.70(12.97)	75.25(10.73)	0.386
LYM( $10^9/L$ ), median (IQR)	1.03(0.79)	1.05(0.94)	0.595
LYMR(%), median (IQR)	12.40(11.69)	14.81(8.19)	0.095
NLR, median (IQR) ratio	6.23(6.82)	5.04(3.92)	0.118
MONO( $10^9/L$ ), median (IQR)	0.59(0.45)	0.50(0.41)	0.261
MONOR(%), median (IQR)	7.30(5.46)	7.65(4.98)	0.777
LMR, median (IQR)	1.76(2.23)	2.02(1.90)	0.245
PC, ( $10^9/L$ ), (mean $\pm$ SD)	268.48 $\pm$ 96.66	247.70 $\pm$ 110.54	0.238
Platelet volume indices			
MPV (fL), median (IQR)	8.33(1.70)	8.86(1.60)	0.009
MPV/PC, median (IQR)	3.39(1.82)	3.72(2.68)	0.064
PDW(%), median (IQR)	0.15(0.05)	0.15(0.06)	0.723
PDW/PC, median (IQR)	5.32(3.84)	5.77(4.79)	0.451
FIB(g/L), median (IQR)	3.41(1.44)	3.26(1.58)	0.116
D-dimer( $\mu$ g/mL), median (IQR)	1.98(1.58)	1.65(1.79)	0.020
CRP(mg/mL), median (IQR)	20.50(58.40)	13.20(35.85)	0.011
ESR(mm/h), median (IQR)	37.00(46.00)	36.00(48.00)	0.663
SF( $\mu$ g/mL), median (IQR)	595.60(579.39)	148.35(612.48)	0.103
CSF examination			
pressure(cm H <sub>2</sub> O), median (IQR)	143.50(153)	150.00(105)	0.562
WBC ( $10^9/L$ ), median (IQR)	99.00(167.50)	100(234.00)	0.830
Glucose(mmol/L), median (IQR)	1.87(1.09)	2.61(1.01)	0.000
Chloride(mmol/L), median (IQR)	115.45(12.90)	115.10(14.25)	0.435
Protein (mmol/L), median (IQR)	1102.30(1009.75)	886.40(1167.06)	0.214
MRC Grade n(%)			0.003
I	24(34.3%)	44(62.9%)	
II	29(41.4%)	17(24.3%)	
III	17(24.3%)	9(12.9%)	
GCS score	14.50(4)	15.00(1)	0.052

**Abbreviations:** WBC, white blood cells; Hb, hemoglobin; RBC, red blood cells; RDW-CV, red blood cell distribution width; MCV, mean corpuscular volume; HCT, haematocrit value; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; NEU, neutrophil count; NEUR, neutrophil percentage; LYM, lymphocyte count; LYMR, lymphocyte percentage; NLR, neutrophil-to-lymphocyte ratio; MONO, monocyte count; MONOR, monocyte percentage; LMR, lymphocyte-to-monocyte ratio; PC, platelet count; MPV, mean platelet volume; PDW, platelet distribution width; FIB, fibrinogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SF, serum ferritin; CSF, cerebrospinal fluid; MRC, Modified Research Council; GCS, Glasgow Coma Score.

In addition, in the present study, the TBMRIS group had elevated variation in RDW-CV levels. Previous studies have found that elevated variations in RDW-CV levels are common in TBM patients.<sup>39</sup> Elevations in the RDW-CV levels suggests that the patients' red blood cell life is shortened and red blood cell rupture is increased, so that substances such as hemoglobin and ferrous ions that are released into blood circulation can directly combine with NO to stimulate the generation of oxygen free radicals and ultimately activate a variety of inflammatory factors including C-reactive

**Table 4** Multivariate Logistic Regression Analysis

Factors	$\beta$	SE	Wals	Df	OR	95% CI	P value
RBC( $10^9/L$ )	-0.249	0.275	0.820	1	0.780	0.455–1.336	0.365
RDW-CV(%)	0.232	0.091	6.531	1	1.261	1.056–1.506	0.011
MPV (fL)	-0.420	0.177	5.607	1	0.657	0.464–0.930	0.018
D-dimer( $\mu g/mL$ )	0.003	0.095	0.001	1	1.003	0.833–1.208	0.975
CRP(mg/mL)	0.012	0.006	4.256	1	1.012	1.001–1.023	0.039
Glucose (mmol/L)	-0.693	0.245	7.988	1	0.500	0.309–0.809	0.005
MRC Grade			7.993	2	1.032	0.896–1.190	0.018
II	1.275	0.464	7.547	1	3.578	1.441–8.886	0.006
III	0.952	0.611	2.426	1	2.590	0.782–8.576	0.119
Constant	1.841	2.437	0.571	1	6.306		0.450

**Abbreviations:** RBC, red blood cells; RDW-CV, red blood cell distribution width; MPV, mean platelet volume; CRP, C-reactive protein; MRC, Modified Research Council; CI, confidence interval.

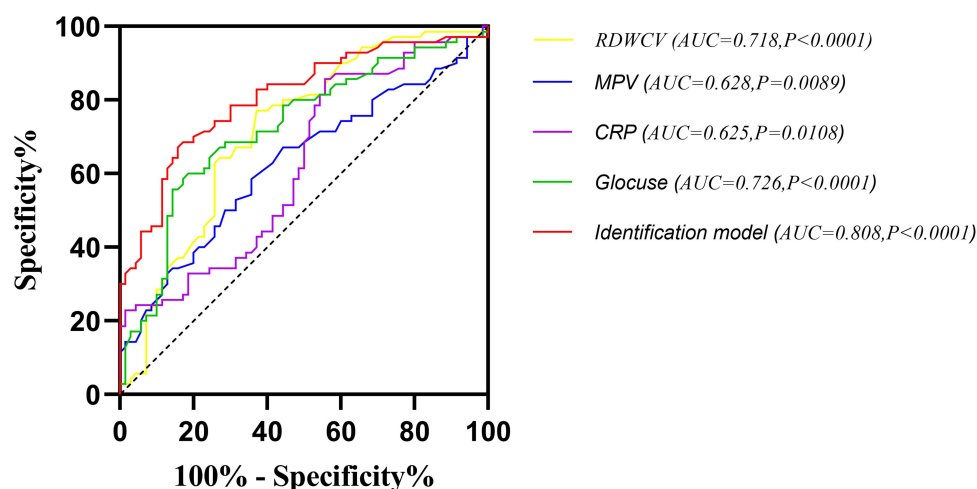
**Table 5** ROC Analysis of Independent Risk Factors and the Identification Model of TBRIS

Factors	AUC	95% CI	Sen (%)	Spe (%)
RDW-CV(%)	0.718	0.633–0.803	77.10	62.90
MPV (fL)	0.628	0.535–0.721	58.60	64.30
CRP(mg/mL)	0.625	0.532–0.718	85.70	44.30
Glucose(mmol/L)	0.726	0.641–0.811	58.60	82.90
Identification model	0.808	0.736–0.881	68.60	84.30

**Abbreviations:** RDW-CV, red blood cell distribution width; MPV, mean platelet volume; CRP, C-reactive protein; AUC, area under ROC curve; CI, confidence interval; Sen, sensitivity; Spe, specificity.

protein.<sup>40</sup> In summary, in the present study, the more intensive immune response to tuberculosis infection in the TBMRIS group may initially induce more active platelet activation, then a more severe vasospasm, with or without thrombosis, and ultimately the development of TBMRIS.

In the present study, the multivariate logistic regression analysis revealed that variations in RDW-CV, MVP, CRP, CSF glucose and MRC Grade II were independent risk factors for TBMRIS, indicating that these parameters could be

**Figure 3** The analysis of ROC curve and area under curve.

**Abbreviations:** RDW-CV, red blood cell distribution width; MPV, mean platelet volume; CRP, C-reactive protein.



used as potential biomarkers for TBMRI. However, these biomarkers are also commonly found in systemic inflammation and other diseases. Considering that the development of TBMRI may be caused by the combined effects of variation of red blood cell distribution width, mean platelet volume, C-reactive protein, CSF glucose and Modified Research Council Grade II, we calculated the TBMRI Index (0.529). The area under the ROC curve of the TBMRI Index was highly accurate (0.808), which suggests that the independent risk factors together promoted the development of TBMRI, and this also illustrates that the index of TBMRI equaling to 0.529 had the most power to predict the TBM patients who were at higher risk for TBMRI.

The strengths of our study were the multicentre enrolment and the study's comparison with TBM patients without conventional vascular risk factors. Our study also has limitations. Due to the retrospective nature of the study, this study included some uncontrollable settings, and the findings need to be confirmed by future studies with large sample randomized control trials.

## Conclusion

In conclusion, our results show that RDW-CV, MVP, CRP, CSF glucose and MRC Grade II are independent risk factors for TBMRI. These independent risk factors alone or in combination promoted the development of TBMRI. We found that the more intensive immune response to tuberculosis infection in the TBMRI group contributed to the initiation of platelet activation and to the development of vasospasm, which are attributed to the pathogenesis of TBMRI. The identification model established in this study may assist clinicians in identifying TBM patients at high risk of developing TBMRI. The findings in the present study should be further validated in more prospective larger studies.

## Data Sharing Statement

The datasets generated and analyzed in this study will be available by the corresponding authors upon reasonable request.

## Ethical Approval

This project fully considered and protected the rights and interests of the study objects. It meets the criteria of Ethical Review Committee. The Medical Ethics Committee of The First Affiliated Hospital of Guangxi Medical University has approved the protocol.

## Informed Consent

The written informed consent was waived because of the retrospective nature of our study.

## Acknowledgments

We would like to thank Prof. Li for her guidance on statistical methods. We are grateful for the advice and discussions with our colleagues Junli Liang and Jinyu Liang as well as the anonymous reviewers.

## 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.

## Funding

This study was supported by National Natural Science Foundation of China (NSFC 82260243); the Foundation of National Key R&D Program of China (2018YFC 1311300); and Guangxi Medical and Health and Appropriate Technology Development and Promotion Application Project (Nos. S2021101 and S2020013).

## Disclosure

The authors report no conflicts of interest in this work.

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