Old age and hydrocephalus are associated with poor prognosis in patients with tuberculous meningitis

A retrospective study in a Chinese adult population

Hai-Jun Huang, MD, PhD; Ze-Ze Ren, MD; Yi-Ning Dai, MD; Yong-Xi Tong, MD; Dan-Hong Yang, MD; Mei-Juan Chen, MD; Yi-Cheng Huang, MD; Ming-Shan Wang, MD; Jia-Jie Zhang, MD; Wen-Yuan Song, MD; Hong-Ying Pan, MD.∗

Department of Infectious Diseases, Zhejiang Provincial People’s Hospital, No. 158 Shangtang Road, Hangzhou, Zhejiang Province, China.

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Correspondence: Hong-Ying Pan, Department of Infectious Diseases, Zhejiang Provincial People’s Hospital, People’s Hospital of Hangzhou Medical College, Department of Infectious Diseases, the Second Affiliated Hospital of Zhejiang Chinese Medicinal University, Hangzhou, Zhejiang Province, China.

Abstract
Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis with a very poor prognosis. We aimed at assessing risk factors related to the prognosis of patients with TBM.

Forty-five inpatients with TBM in our institution from January 2013 to December 2015 were enrolled retrospectively. The good or poor prognosis in the patients was defined, based on Glasgow Outcome Scale System at discharge. Patients with a GOS score less than 5 were defined as “poor prognosis.” Univariate and multivariate logistic regression analyses were performed to assess the predictors for TBM outcome.

Among 45 TBM patients, 35 (77.8%) and 10 (22.2%) were in good, poor prognoses, respectively. Old age, disturbance of consciousness, moderate to severe electroencephalogram abnormality, hydrocephalus, remarkable increase of protein (≥ 236 mg/dL) and white blood cell counts (≥ 243/μL) in cerebral spinal fluid were associated with poor prognosis. Multivariate analysis indicated that old age (odds ratio (OR) = 18.395, P = .036) and hydrocephalus (OR = 32.995, P = .049) were independent factors for a poor outcome of TBM.

In conclusion, old age and hydrocephalus are the predictors for poor prognosis of TBM. Patients with these risk factors should be treated promptly with a special care paid to improve their outcomes.

Abbreviations: ADA = adenosine deaminase, AIDS = acquired immune deficiency syndrome, CNS = central nervous system, CSF = cerebral spinal fluid, CT = computed tomographies, DALYs = disability-adjusted life years, EEG = electroencephalogram, GOS = Glasgow Outcome Scale, MRI = magnetic resonance imaging, OR = odds ratio, SD = standard deviation, TB = tuberculosis, TBM = tuberculous meningitis, V-P shunt = ventriculo-peritoneal shunt, WBC = white blood cells.

Keywords: logistic regression analysis, predictors, prognosis, tuberculous meningitis

1. Introduction

Tuberculosis (TB) is a major global health burden. In 2012, TB killed 1.3 million people worldwide.[1] In 2013, there were approximately 11 million prevalent TB cases worldwide.[2] Tuberculous meningitis (TBM) is the infection of the meninges by Mycobacterium tuberculosis. The infection site locates at the membranes which envelop the central nervous system (CNS). It is a very severe form of tuberculosis in terms of permanent sequelae and fatal ending.[3–5] It is commonly known that TBM carries a high morbidity and mortality.[6–8] In addition, serious neurological deficits such as cognitive impairment, hemiplegia, seizures, quadriplegia, and cranial nerve palsy commonly happened in TBM survivors.[4] Hence, a better understanding of the prognostic factors for TBM is essential for improving the life quality of patients.

Previous data have indicated that early diagnosis and in-time treatment is the most important issue related to the complications and mortality rates of TBM.[9–11] Nevertheless, with the advancement in molecular diagnosis, imaging techniques and newly developing anti-tuberculous (anti-TB) agents, recent studies related to TBM prognostic factors are still absent. In this study, we analyzed the risk factors associated with TBM prognosis, and planned to find out predictors for poor outcomes of TBM.

2. Methods

2.1. Patients and diagnosis of TBM

It was a retrospectively observational study, which enrolled consecutive patients with TBM admitted to Zhejiang Provincial People’s Hospital from January, 2013 to December, 2015. The
study protocol complied with the ethical guidelines of the Declaration of Helsinki. Written informed consents were waived as we used only data routinely collected during hospitalization.

The inclusion criteria were based on the following diagnostic standards of TBM\(^{[12,13]}\): symptoms and clinical signs of meningitis, for example, headache, fever, vomiting, photophobia, irritability, neck stiffness, focal neurological deficits, convulsions, altered consciousness, or lethargy; finding of active or previous extra-CNS tuberculosis infection; acid-fast bacilli seen in the cerebral spinal fluid (CSF); Mycobacterium tuberculosis cultured from the CSF; typical changes of CSF, including pleocytosis (>20 cells/μL), lymphocytes >60%, protein >1 g/L, and CSF to blood glucose ratio of <0.6; recall of recent exposure to tuberculosis; response to antituberculosis therapy. Criterion 1, 5, and 7 were necessary to define a case, while the other items were dispensable (at least 1 of them should be met). The diagnosis of TBM and the inclusion of each subject were approved by at least 2 experienced physicians in the Department of Infectious Disease, Zhejiang Provincial People’s Hospital. Children and adolescents whose ages were less than 18 years should be excluded.

### 2.2. Collection of clinical data

Data related to age, gender, comorbidities, clinical manifestations, treatments, and duration from onset to admission were collected. In addition, routine and biochemical analysis of CSF on admission were recorded, such as CSF pressure (in mm H2O), white blood cells (WBC) counts (μL), glucose (in mmol/L), protein (in mg/dL), chloride (in mmol/L), and adenosine deaminase (ADA) (in U/L). Furthermore, chest computed tomography (CT), electroencephalogram (EEG), brain CT or magnetic resonance imaging (MRI) were performed on every patient after admission, and the corresponding imaging data were documented. Hydrocephalus was diagnosed according to the results of brain CT or MRI.

### 2.3. Assessment of disease prognosis

Prognosis was determined prior to discharge using the Glasgow Outcome Scale (GOS).\(^{[14]}\) The GOS consists of 5 categories: patients would get 5 scores when they were in good recovery; those who were moderately disabled but still independent would be scored 4; subjects with severe disability but still conscious could reached to 3 scores; patients with vegetable state would be scored 2; dead patients would be scored 1. Disease prognosis was assessed independently by 2 investigators, and disagreements would be solved by a discussion.

All the patients were distributed into 2 groups: those with a GOS score of 5 were considered as “good prognosis,” while patients scored from 1 to 4 were allocated into the “poor prognosis” group.

### 2.4. Statistical analysis

All statistical analyses were performed using SPSS software (version 21.0). Categorical data were expressed as number (percentage) while measurement data were presented in the form of both “mean ± standard deviation” and “median (range)." The Student t test or \(\chi^2\) test was used for the comparison between groups with good and poor prognosis. Univariate and multivariate binary logistic regression analyses were conducted to evaluate risk factors associated with the prognosis of TBM. A P value of less than 0.05 was considered to be statistically significant.

### 3. Results

#### 3.1. Baseline characteristics

A total of 45 patients were included in this study. The clinical characteristics of the subjects are exhibited in Table 1. There were 30 males and 15 females, whose age ranged from 20 to 85 years. Twenty-nine patients were identified as extra-CNS tuberculosis, while 6 patients combined with Acquired Immune Deficiency Syndrome (AIDS). In this study, all 45 patients presented fever, while a proportion of subjects exhibited other different clinical symptoms, for example headache, nausea and vomiting, and disturbance of consciousness. Hydrocephalus was diagnosed in 6 patients through brain CT or MRI, and 3 of them received surgical intervention like ventriculo-peritoneal (V-P) shunt of CSF drainage. While hospitalized, 23 cases received antibiotics (except

### Table 1: Baseline characteristics of patients with TBM.

| Characteristics | Value* |
|-----------------|--------|
| Gender (male/female) | 30/15 |
| Age | 46.04 ± 17.01/45 (20–85) |
| Comorbidities | |
| Extra-CNS TB | 29 (64.4%) |
| Active extra-CNS TB | 5 (11.1%) |
| AIDS | 6 (13.3%) |
| Diabetes mellitus | 4 (8.9%) |
| Recent contact with TB | 7 (15.6%) |
| Symptoms | |
| Fever | 45 (100%) |
| Headache | 29 (64.4%) |
| Nausea and vomiting | 27 (60%) |
| Disturbance of consciousness | 11 (24.4%) |
| Clinical signs | |
| Neck stiffness | 39 (86.7%) |
| Kernig sign | 18 (40%) |
| Brudzinski sign | 18 (40%) |
| Babinski sign | 15 (33.3%) |
| Cranial nerve lesions | 15 (33.3%) |
| CSF parameters | |
| Pressure, mm H2O | 232.07 ± 85.66/210 (100–400) |
| WBC counts, μL | 243.78 ± 82.41/190 (59–830) |
| ADA, U/L | 6.67 ± 5.32/6 (1–26) |
| Protein, mg/dL | 133.74 ± 133.74/216.8 (80–830) |
| Glucose, mmol/L | 1.99 ± 0.69/1.8 (0.6–3.4) |
| Chloride, mmol/L | 110.69 ± 5.30/111 (100.4–118.4) |
| EEG | |
| Mild abnormal | 29 (64.4%) |
| Moderate to severe abnormal | 16 (35.6%) |
| Hydrocephalus | 6 (13.3%) |
| Treatment | |
| Antibiotics† | 23 (51.1%) |
| Corticosteroids | 16 (35.6%) |
| V-P shunt or CSF drainage | 3 (6.7%) |
| GOS | |
| 5 | 35 (77.8%) |
| 4 | 7 (15.6%) |
| 3 | 2 (4.5%) |
| 2 | 0 |
| 1 | 1 (2.2%) |

* Differences were considered statistically significant with a P value of less than 0.05.† Antibiotics refer to antibiotics other than antituberculosis drugs.
for antituberculosis drugs) to prevention and cure secondary infections. All patients received tuberculostatic therapy, while 16 cases have been given corticosteroids during their hospitalization. On discharge, 35 of the patients attained a good recovery, whereas the other 10 patients (22.2%) with a GOS score less than 5 were classified into the “poor prognosis” group. Univariate analysis indicated that old age (P = .001), disturbance of consciousness (P = .011), moderate to severe abnormality of EEG (P = .027), hydrocephalus (P = .022), increased CSF protein levels (≥ 236mg/dL) (P = .010), and increased CSF WBC counts (≥ 243 /μL) (P = .027) were associated with worse prognosis of TBM (Table 2). The application of corticosteroid seemed not to improve the outcome.

In the subsequent multivariate analysis, old age (OR = 18.395, P = .036) and hydrocephalus (OR = 32.995, P = .049) were observed to be independently associated with a poor outcome of TBM (Table 3). Increased level of CSF proteins seemed to be related to unfavorable prognosis (OR = 1.669, P = .731), but the P value (P = .057) indicated only borderline significance. However, there were no statistical associations between the prognosis of TBM with the other risk factors, for example the disturbance of consciousness, abnormality of EEG, and increased CSF WBC counts.

### 3.2. Predictive factors of TBM prognosis

The 35 patients with a GOS score of 5 were distributed into the “good prognosis” group, whereas the other 10 patients (22.2%) with a GOS score less than 5 were classified into the “poor prognosis” group. Univariate analysis indicated that old age (P = .001), disturbance of consciousness (P = .011), moderate to severe abnormality of EEG (P = .027), hydrocephalus (P = .022), increased CSF protein levels (≥ 236mg/dL) (P = .010), and increased CSF WBC counts (≥ 243 /μL) (P = .027) were associated with worse prognosis of TBM (Table 2). The application of corticosteroid seemed not to improve the outcome.

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### 4. Discussion

At the present time, TB is still a serious health burden worldwide, especially in less-developed regions.\[15\] The development of drug-resistant *Mycobacterium tuberculosis* and the AIDS epidemic particularly contribute to the increased prevalence of TB. Based on the 2010 disability-adjusted life years (DALYs) proposed by the Global Burden of Disease Study, TB is the 10th factor causing death, and the 13th factor of disability.\[16\] Despite the availability of effective chemotherapy, TB remains one of the top causes of death from infectious disease.\[11\]

TB is a very critical form of TB, and is often recognized as a medical emergency. Immune-suppressed patients, especially those with human immunodeficiency virus infection, are more likely to suffer disseminated TB with CNS involvement.\[17\] However, the diagnosis of TB is often obscured because of its nonspecific symptoms.\[11\] Thus, treatment is delayed, leading to a poor outcome. Understanding the risk factors related to the prognosis may improve its outcome. In this study, we investigated potential prognostic factors of TBM, in the purpose of timely intervention and offering more realistic expectations for patients and their relatives.

In fact, a considerable number of studies have found numerous factors related to the outcome of TBM. Except for the prompt identification of disease and early anti-TB therapy,\[11,19\] advanced age, altered consciousness, presence of seizures, immunosuppression, diabetes mellitus, vasculitis, positive TB culture, or polymerase chain reaction of CSF and hydrocephalus

![Table 2](image)

Table 2

Univariate analysis of prognostic factors associated with TBM.

| Risk factors                  | Good prognosis (n=35) | Poor prognosis (n=10) | P value |
|------------------------------|----------------------|-----------------------|---------|
| Duration from onset to admission |                       |                       |         |
| >1 mo                        | 6 (17.1%)            | 5 (50%)               | .086    |
| 1 wk to 1 mo                 | 23 (65.7%)           | 3 (30%)               | .098    |
| <1 wk                        | 6 (17.1%)            | 2 (20%)               | 1.000   |
| Gender                       |                      |                       |         |
| Male                         | 25 (71.4%)           | 5 (70%)               | .375    |
| Female                       | 10 (28.6%)           | 5 (30%)               |         |
| Age (mean±SD)                | 41.86±14.63          | 60.70±17.28           | .001    |
| median (range)               | 42 (20–70)           | 61.5 (46–85)          |         |
| Comorbidities                |                      |                       |         |
| Extra-CNS TB                 | 22 (62.9%)           | 7 (70%)               | .967    |
| AIDS                         | 4 (11.4%)            | 2 (20%)               | .860    |
| Diabetes mellitus            | 2 (5.7%)             | 2 (20%)               | .441    |
| Fever                        |                      |                       |         |
| Body temperature > 39°C      | 8 (22.9%)            | 5 (50%)               | .202    |
| Body temperature < 39°C      | 27 (77.1%)           | 5 (50%)               |         |
| Headache                     | 23 (65.7%)           | 6 (60%)               | 1.000   |
| Nausea and vomiting          | 20 (57.1%)           | 7 (70%)               | .714    |
| Disturbance of consciousness | 5 (14.3%)            | 6 (60%)               | .011    |
| Neck stiffness               | 31 (88.6%)           | 8 (80%)               | .860    |
| Kernig sign                  | 11 (31.4%)           | 7 (70%)               | .067    |
| Brudzinski sign              | 12 (34.3%)           | 6 (60%)               | .272    |
| Babinski sign                | 9 (25.7%)            | 6 (60%)               | .099    |
| Cranial nerve lesions        | 10 (28.6%)           | 5 (50%)               | .375    |
| CSF pressure, mm H₂O         |                      |                       |         |
| ≥230                         | 17 (48.6%)           | 3 (30%)               | .496    |
| 180–230                      | 6 (17.1%)            | 3 (30%)               | .654    |
| <180                         | 12 (34.3%)           | 4 (40%)               | 1.000   |
| CSF protein, mg/dL           |                      |                       |         |
| ≥236                         | 13 (37.1%)           | 9 (90%)               | .010    |
| <236                         | 22 (62.9%)           | 1 (10%)               |         |
| CSF glucose, mmol/L          |                      |                       |         |
| ≥2                           | 2 (5.7%)             | 1 (10%)               | .714    |
| <2                           | 17 (47.1%)           | 7 (70%)               |         |
| CSF chloride, mmol/L         |                      |                       |         |
| ≥110                         | 22 (62.9%)           | 8 (80%)               | .526    |
| <110                         | 13 (37.1%)           | 2 (20%)               |         |
| CSF WBC counts (μL)          |                      |                       |         |
| ≥243                         | 9 (25.7%)            | 7 (70%)               | .027    |
| <243                         | 26 (74.3%)           | 3 (30%)               |         |
| ADA, U/L                     | ≥6.67                | 12 (34.3%)            | .098    |
| <6.67                        | 23 (65.7%)           | 3 (30%)               |         |
| Moderate to severe abnormality of EEG | 9 (25.7%) | 7 (70%) | .027 |
| Hydrocephalus                | 2 (5.7%)             | 4 (40%)               | .022    |
| Treatment                    |                      |                       |         |
| Antibiotics                  | 16 (45.7%)           | 7 (70%)               | .319    |
| Corticosteroids              | 10 (28.6%)           | 6 (60%)               | .145    |

**Table 3**

Independent prognostic factors associated with TBM.

| Variables                  | β    | SE   | OR    | P value |
|----------------------------|------|------|-------|---------|
| Age                        | 2.912| 1.390| 18.395| .036    |
| Disturbance of consciousness | 0.512| 1.492| 1.669 | .731    |
| CSF protein ≥ 236 mg/dL    | 3.214| 1.687| 0.040 | .057    |
| CSF WBC counts ≥ 243 /μL   | 0.700| 1.557| 0.497 | .653    |
| Moderate to severe abnormality of EEG | 0.335| 1.226| 1.398 | .785    |
| Hydrocephalus              | 3.496| 1.775| 32.995| .049    |

β = regression coefficient, CSF = cerebral spinal fluid, EEG = electroencephalogram, OR = odds ratio, SE = standard error, WBC = white blood cell.
have been reported to predict the unfavorable outcome.\textsuperscript{[20–23]} In addition, prognostic factors of neurological sequelae in patients with TBM include tuberculoma, focal neurological signs, and cranial nerve palsy.\textsuperscript{[5,22,24]} However, in recent years, the predictors of TBM might change with the development in diagnostic techniques and the accessibility of effective chemotherapy. Reviewing the published literature, recent prognostic analyses of TBM are relatively absent, especially in China. One research by Gu et al\textsuperscript{[21]} published in 2015 has indicated that advanced age, changes in consciousness, low Glasgow coma scale (GCS) score on admission and concomitant hydrocephalus are independent risk factors of TBM. But the study region is localized at Shanghai. Therefore, we performed a retrospective observational study in Hangzhou to identify predictors of TBM in a Chinese adult population.

In this study, the age of patients with favorable prognosis was 41.86 ± 14.63, significantly younger than patients with poor outcomes (mean age 60.70 ± 17.28). Cases with good outcomes had lower levels of CSF protein, WBC counts than cases with poor prognosis. Moreover, disturbance of consciousness, hydrocephalus, and moderate to severe abnormality of EEG were more prevalent in cases with unfavorable outcomes. Further multivariate analysis has demonstrated that old age and hydrocephalus are independent risk factors associated with the prognosis of TBM. Hence, we see that the results of this study agreed with the findings of previous studies.

Hydrocephalus is a quite common complication of TBM.\textsuperscript{[26]} Communicating hydrocephalus develops because of either overproduction of CSF or malfunctioning absorption of CSF in the subarachnoid space. Besides, the obstructive type of hydrocephalus is less common, which develops on account of the obstruction of the fourth ventricular outlets by inflammatory exudate. We believed that hydrocephalus in TBM carried a higher risk of poor prognosis. Therefore, the management of hydrocephalus is an essential issue. Mild hydrocephalus responds to medical therapy, whereas surgery should be required in case of raised intracranial pressure.\textsuperscript{[26]} However, the indications for V-P shunt, or CSF drainage is debatable, and the curative effect of surgical interventions remains controversial.\textsuperscript{[27–29]} Additional robust research exploring the optimal management for hydrocephalus in TBM is needed.

The limitation of this study was the relatively small sample size. Because it was based on a single-center infrmary, only 45 subjects were included. This might affect the stability of logistic model. Further multicenter large-scale prognostic studies in China are necessary for the better guidance of clinical decision making in TBM.

In conclusion, the study has found that TBM patients with advanced age and hydrocephalus had higher odds of a poor outcome. In clinical practice, physicians should pay more attention to those patients with old age or hydrocephalus.

References

\textsuperscript{[1]} Glaziou P, Sismanidis C, Floyd K, et al. Global epidemiology of tuberculosis. Cold Spring Harbor Persp Med 2015;5:a017798.

\textsuperscript{[2]} Dirlikov E, Raviglione M, Scano F. Global tuberculosis control: toward the 2015 targets and beyond. Ann Int Med 2015;163:52–8.

\textsuperscript{[3]} Kalita J, Miara UK, Ranjan P. Predictors of long-term neurological sequelae of tuberculous meningitis: a multivariate analysis. Eur J Neurol 2007;14:33–7.

\textsuperscript{[4]} Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004;351:1741–51.

\textsuperscript{[5]} Karstaedt AS, Valtchanova S, Barriere R, et al. Tuberculous meningitis in South African adult adults. QJM 1998;91:743–7.

\textsuperscript{[6]} Chin JH, Mateen FJ. (2013) Central Nervous System Tuberculosis: Challenges and Advances in Diagnosis and Treatment. Current infectious disease reports.

\textsuperscript{[7]} Lee HG, William T, Monen J, et al. Tuberculous meningitis is a major cause of mortality and morbidity in adults with central nervous system infections in Kota Kinabalu, Sabah, Malaysia: an observational study. BMC Infect Dis 2016;16:296.

\textsuperscript{[8]} Donald PR. The chemotherapy of tuberculous meningitis in children and adults. Tuberculosis 2010;90:375–92.

\textsuperscript{[9]} Hosoglu S, Geyik MF, Balk I, et al. Tuberculous meningitis in adults in Turkey: epidemiology, diagnosis, clinic and laboratory [corrected]. Eur J Epidemiol 2003;18:337–43.

\textsuperscript{[10]} Grygorczuk S, Panczewicz S, Zajkowska J, et al. Tuberculosis meningitis in 8-year observation of the Department of Infectious Diseases and Neuroinfections of the Medical Academy in Bialystok. Neurol Neurochir Polska 2004;38:31–6.

\textsuperscript{[11]} Lu CH, Chang WN, Chang HW. The prognostic factors of adult tuberculous meningitis. Infection 2001;29:299–304.

\textsuperscript{[12]} Maras S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis 2010;10:803–12.

\textsuperscript{[13]} Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. Lancet Neurol 2005;4:160–70.

\textsuperscript{[14]} Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975;1:480–4.

\textsuperscript{[15]} Kent SJ, Crowe SM, Yung A, et al. Tuberculous meningitis: a 30-year review. Clin Infect Dis 1993;17:987–94.

\textsuperscript{[16]} Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197–223.

\textsuperscript{[17]} Roshberg E, Sunderam G, Reichman LB, et al. Central nervous system tuberculosis with the acquired immunodeficiency syndrome and its related complex. Ann Intern Med 1986;105:210–3.

\textsuperscript{[18]} Thwaites G, Fisher M, Hemingway G, et al. British Infection Society/British Infection Society guidelines for the diagnosis and treatment of tuberculous of the central nervous system in adults and children. J Infect 2009;59:167–87.

\textsuperscript{[19]} Sheu JJ, Yuan RY, Yang CC. Predictors for outcome and treatment delay in patients with tuberculous meningitis. Am J Med Sci 2009;338: 134–9.

\textsuperscript{[20]} Erdem H, Ozuruk-Engin D, Tireli H, et al. Hamsi scoring in the prediction of unfavorable outcomes from tuberculous meningitis: results of Haydarpasa-II study. J Neurol 2015;262:890–8.

\textsuperscript{[21]} Hsu PC, Yang CC, Ye JJ, et al. Prognostic factors of tuberculous meningitis in adults: a 6-year retrospective study at a tertiary hospital in northern Taiwan. J Microbiol Immunol Infect 2010;43:111–8.

\textsuperscript{[22]} Hosoglu S, Geyik MF, Balk I, et al. Predictors of outcome in patients with tuberculous meningitis. Int J Tuberc Lung Dis 2002;6:64–70.

\textsuperscript{[23]} Kaur H, Sharma K, Modi M, et al. Prospective analysis of 55 cases of tuberculosis meningitis (TBM) in North India. J Clin Diagn Res 2015;9: DC15–9.

\textsuperscript{[24]} Pehlivanoglu F, Yasar KK, Sengoz G. Prognostic factors of neurological sequel in adult patients with tuberculous meningitis. Neurosciences 2010;15:262–7.

\textsuperscript{[25]} Gu J, Xiao H, Wu F, et al. Prognostic factors of tuberculous meningitis: a single-center study. Int J Clin Exp Med 2015;8:4487–93.

\textsuperscript{[26]} Raut T, Garg RK, Jain A, et al. Hydrocephalus in tuberculous meningitis: incidence, its prognostic factors and impact on the prognosis. J Infect 2011;66:330–7.

\textsuperscript{[27]} Sil K, Chatterjee S. Shunting in tuberculous meningitis: a neurosurgeon’s nightmare. Childs Nerv Syst 2008;24:1029–32.

\textsuperscript{[28]} Rameshkhar V. Management of hydrocephalus in patients with tuberculous meningitis. Neurol India 2009;57:368–74.

\textsuperscript{[29]} Lamprecht D, Schoeman J, Donald P, et al. Ventriculoperitoneal shunting in childhood tuberculous meningitis. Br J Neurosurg 2001;15:119–25.