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Prognostic factors of adult tuberculous meningitis in intensive care unit: a single-center retrospective study in East China

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Abstract

Background: Tuberculous meningitis (TBM) is the most lethal form of tuberculosis worldwide. Data on critically ill TBM patients in the intensive care unit (ICU) of China are lacking. We tried to identify prognostic factors of adult TBM patients admitted to ICU in China.

Methods: We conducted a retrospective study on adult TBM in ICU between January 2008 and April 2018. Factors associated with unfavorable outcomes at 28 days were identified by logistic regression. Factors associated with 1-year mortality were studied by Cox proportional hazards modeling.

Results: Eighty adult patients diagnosed with TBM (age 38.5 (18–79) years, 45 (56 %) males) were included in the study. An unfavorable outcome was observed in 39 (49 %) patients and were independently associated with Acute Physiology and Chronic Health Evaluation (APACHE) II > 23 (adjusted odds ratio (aOR) 5.57, 95 % confidence interval (CI) 1.55–19.97), Sequential Organ Failure Assessment (SOFA) > 8 (aOR 9.74, 95 % CI 1.46–64.88), and mechanical ventilation (aOR 18.33, 95 % CI 3.15–106.80). Multivariate Cox regression analysis identified two factors associated with 1-year mortality: APACHE II > 23 (adjusted hazard ratio (aHR) 4.83; 95 % CI 2.21–10.55), and mechanical ventilation (aHR 9.71; 95 % CI 2.31–40.87).

Conclusions: For the most severe adult TBM patients of Medical Research Council (MRC) stage III, common clinical factors aren't effective enough to predict outcomes. Our study demonstrates that the widely used APACHE II and SOFA scores on admission can be used to predict short-term outcomes, while APACHE II could also be used to predict long-term outcomes of adult patients with TBM in ICU.

Keywords: Tuberculous meningitis, Prognostic factors, Intensive care unit

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Background

Tuberculosis is one of the top 10 causes of death, and the leading cause from a single infectious agent worldwide [1]. Tuberculous meningitis (TBM) is the most lethal form of tuberculosis, which accounts for approximately 1 % of all cases of active tuberculosis, and 5–10 % of extra-pulmonary tuberculosis cases [2, 3]. Mortality in adult patients with TBM reaches 30–60 % [4], and neurological sequelae were reported in more than 50 % of survivors [5]. Delayed diagnosis and treatment, higher Medical Research Council (MRC) disease severity stage, lower cerebrospinal fluid (CSF) lymphocyte cell count, and anti-tuberculosis drug resistance were reported to be associated with an unfavorable outcome in previous studies [6, 7]. Patients with TBM who had neurological complications frequently require admission to the intensive care unit (ICU) [8, 9]. However, studies on patients with TBM requiring ICU admission are scarce due to the limited access of patients to intensive care in developing countries. Therefore, we conducted this retrospective study on adult patients with TBM admitted to ICU in a tuberculosis endemic area. Our objective was to identify prognostic factors of unfavorable outcome in adult patients with TBM admitted to the ICU.

Methods

Design, setting, and participants

This was a single-center retrospective study on consecutive adult patients with TBM admitted to the medical ICU of Shandong Provincial Chest Hospital, Cheeloo College of Medicine, Shandong University, a 900-bed tertiary hospital located in Shandong Province, China, from January 2008 to April 2018.

Participants were included if they met the diagnostic criteria for TBM established by the expert consensus definition of 2010 [10]. According to the consensus definition, TBM patients were classified into three categories based on clinical information, CSF analysis, cerebral imaging, and evidence of tuberculosis elsewhere: definite TBM (microbiological identification or evidence from commercial nucleic acid amplification tests of CSF, or positive histological findings); probable TBM (diagnostic score of 10 or more points when cerebral imaging is not available, or 12 or above when cerebral imaging is available); and possible TBM (diagnostic score of 6–9 points when cerebral imaging is not available or 6–11 points when imaging is available). Patients were excluded if an alternative diagnosis was established, or if there were convincing signs of dual disease, or if a favorable outcome was observed in the absence of anti-tuberculosis therapy [10].

Data collection

Data were collected following the standardized methods for enhanced quality and comparability of TBM study guidelines [11]. Mental status at admission was staged based on the modified MRC criteria as: stage I: the Glasgow Coma Scale (GCS) score of 15 and the absence of neurological deficit; stage II: GCS of 11–14, or GCS of 15 associated with focal neurological sign; and stage III: GCS ≤ 10 [12]. The health status at admission was assessed by the acute physiology and chronic health evaluation (APACHE) II and sequential organ failure assessment (SOFA) scores [13, 14]. Immune deficiency was considered in the case of human immunodeficiency virus (HIV) infection, solid cancer, hematological malignancy, diabetes mellitus, steroid therapy, and/or chemotherapy. Initial anti-tuberculosis therapy consisted of a standard regimen with four drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. Data on adjunctive steroids and the use of invasive mechanical ventilation and neurosurgical interventions (external ventricular drainage) during the ICU stay were collected.

Outcomes

The primary endpoint was graded with the Glasgow Outcome Scale (GOS) 28 days after ICU admission as: 1: death; 2: vegetative state; 3: severe disability; 4: moderate disability; and 5: good recovery [15]. A favorable outcome was defined as GOS of 4–5, and an unfavorable outcome as GOS of 1–3 [16]. The second endpoint was overall mortality during a 1-year follow-up period.

Statistical analysis

Data were presented as median (range) or number (%). Patients' characteristics were compared according to primary outcomes, using Mann-Whitney tests for quantitative variables and Fisher's exact tests for categorical variables. Durations were calculated from the time of ICU admission. Univariate logistic regression analysis was performed to evaluate the relationships between variables and primary outcome. Variables associated with unfavorable outcome in univariate analysis ($P < 0.10$) were included in the multivariate model. Discriminations among the different scoring systems were tested using the area under the receiver operating characteristic (ROC) curves. The best cut-off points were that which maximized the sum of sensitivity and specificity. Survival outcomes were measured by the Kaplan-Meier survival curve, and the log-rank test was used to determine statistical difference. Univariate Cox proportional hazard regression model was performed to evaluate associations between variables and 1-year mortality. Variables associated with mortality in univariate analysis ($p < 0.10$) were entered into the multivariate model. $P < 0.05$ was

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Table 1 Baseline characteristics of the patients

Variables	All patients (*n* = 80)	Unfavorable outcome (*n* = 39)	Favorable outcome (*n* = 41)	*P* value
Demographic features				
Male sex	45 (56.3)	18 (46.2)	27 (65.9)	0.31
Age,years	38.5 (18–79)	44 (20–79)	36 (18–76)	0.31
Clinical features				
History of tuberculosis infection	7 (8.8)	5 (12.8)	2 (4.9)	0.26
Active extra-neural tuberculosis	41 (51.3)	20 (51.3)	21 (51.2)	> 0.99
Immune deficiency	15 (18.8)	10 (25.6)	5 (12.2)	0.16
Duration of symptoms, days	20 (3-365)	20 (6-365)	20 (3-365)	0.42
Length of ICU stay, days	12.5 (1-207)	9 (1-207)	15 (5-149)	0.03
Headache	59 (73.8)	31 (79.5)	28 (68.3)	0.31
Irritability	23 (28.8)	6 (15.4)	17 (41.5)	0.01
Nausea and vomiting	47 (58.8)	23 (59.0)	24 (58.5)	> 0.99
Fever (≥ 38.5℃)	60 (75.0)	28 (71.8)	32 (78.0)	0.61
Neck stiffness	67 (83.8)	32 (82.1)	35 (85.4)	0.77
Convulsions	15 (18.8)	9 (23.1)	6 (14.6)	0.40
Focal neurological deficits	43 (53.8)	20 (51.3)	23 (56.1)	0.82
Altered consciousness	70 (87.5)	33 (84.6)	37 (90.2)	0.51
Lethargy	68 (85.0)	32 (82.1)	36 (87.8)	0.54
GCS	3 (3–10)	3 (3–8)	3 (3–10)	0.06
APACHE II	23 (10–37)	26 (12–37)	20 (10–33)	0.003
SOFA	7 (3–13)	7 (4–13)	6 (3–11)	0.03
Laboratory results				
Positive culture in CSF	22 (27.8)	13 (34.2)[a]	9 (22.0)	0.32
Positive AFB in CSF	1 (1.3)	1 (2.8)[b]	0 (0.0)	0.47
Positive PCR in CSF	21 (26.9)	11 (29.7)[c]	10 (24.4)	0.62
CSF glucose, mmol/L	2.32 (0.33–12.60)	2.30 (0.33–12.60)	2.40 (0.40-5.00)	0.79
CSF/blood glucose ratio	0.32 (0.03–0.70)	0.33 (0.03–0.70)	0.30 (0.05–0.68)	0.82
CSF protein level, mg/L	1462 (299–3816)	1471 (299–3188)	1453 (464–3816)	0.31
CSF leukocyte, /μl	104 (2-1268)	108 (4-768)	102 (2-1268)	0.88
Peripheral blood leukocyte, /μl	10,045 (3420–40,400)	10,070 (3420–40,400)	9780 (3470–26,020)	0.36
Serum sodium, mmol/L	137 (107–158)	137 (117–158)	137 (107–154)	0.67
Cranial CT				
Hydrocephalus	45 (61.6)	25 (71.4) [d]	20 (52.6) [e]	0.15
Basal meningeal enhancement	10 (13.7)	5 (14.3) [d]	5 (13.2) [e]	> 0.99
Infarct	36 (49.3)	20 (57.1) [d]	16 (42.1) [e]	0.25
Tuberculoma	4 (5.5)	3 (8.6) [d]	1 (2.6) [e]	0.34
Pre-contrast basal hyperdensity	6 (8.2)	4 (11.4) [d]	2 (5.3) [e]	0.42
Mechanical ventilation	58 (72.5)	37 (94.9)	21 (51.2)	< 0.001
Surgical intervention	11 (13.8)	7 (17.9)	4 (9.8)	0.34

Data are presented as median (range) or numbers (percentages)

Abbreviations: *AFB* acid-fast bacilli, *APACHE* acute physiology and chronic health evaluation, *CSF* cerebrospinal fluid, *CT* computed tomography, *GCS* Glasgow coma scale, *ICU* intensive care unit, *PCR* polymerase chain reaction, *SOFA* sequential organ failure assessment

[a]Data missed in 1 case

[b]Data missed in 3 cases

[c]Data missed in 2 cases

[d]Data missed in 4 cases

[e]Data missed in 3 cases

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considered statistically significant. All analyses were conducted using SPSS 20.0 (IBM Inc., Armonk, NY, USA) software.

Ethical approval
This study was approved by the ethics committee of Shandong Provincial Chest Hospital and informed consent was waived.

Results

Patients' characteristics
Among the 151 patients with suspected TBM admitted to the ICU, 80 were included (Additional file 1). The baseline characteristics of the patients are summarized in Table 1. The median age was 38.5 (18–79) years and 45 (56 %) were males. All patients had MRC stage III illness on admission. HIV status was known in 71 and none were HIV-infected. Based on the consensus definition [10], 31 (39 %) patients were diagnosed with definite and probable TBM respectively, and 18 (22 %) patients with possible TBM. The median duration before ICU admission was 20 (3-365) days. Altered consciousness (87 %), lethargy (85 %), neck stiffness (83 %), fever (77 %) and headache (73 %) were the most common symptoms and signs.

CSF analysis revealed a typical pleocytosis of 104 (2-1268) cells/μl, elevated protein levels of 1462 (299–3816) mg/L, and low glucose levels of 2.32 (0.33–12.60) mmol/L. CSF cultures for *Mycobacterium tuberculosis* were positive in 22 (28 %) of the 79 patients' CSF specimens on which the test were performed, including one multidrug-resistant and three rifampicin-resistant strains (Table 2). CSF polymerase chain reactions (PCR) were positive in 21 (27 %) of 78 patients. Among cranial images, hydrocephalus was found in 45 (62 %) of 73 patients while infarcts were found in 36 (49 %). The median scores of GCS, APACHE II and SOFA were 3 (3–10), 23 (10–37), and 7 (3–13) respectively on admission.

First-line anti-tuberculosis therapy consisted of isoniazid (5–10 mg/kg, maximum 600 mg), rifampicin (10 mg/kg, maximum 600 mg), ethambutol (15 mg/kg, maximum 750 mg), and pyrazinamide (25 mg/kg, maximum 1500 mg) was initiated in all cases on admission. Four patients were secondarily detected with resistance to first-line drugs and switched to other drugs during their ICU stay. Adjunctive steroids were given to reduce inflammation in all patients on admission. Overall, 58 (73 %) patients received invasive mechanical ventilation and 11 (14 %) received lateral ventricular drainage during their ICU stay.

Outcomes
At 28 days, 39 (49 %) patients had unfavorable outcomes, including 29 (36 %) deaths. Variables including clinical and laboratory characteristics, and the three evaluating scores were independently analyzed in univariate logistic regression analysis. Only irritability, mechanical ventilation, APACHE II and SOFA scores showed statistical significance (Table 3). Multivariate logistic regression analysis identified three independent factors of unfavorable outcome (Table 4): APACHE II > 23 (adjusted odds ratio (aOR) 5.57, 95 % confidence interval (CI) 1.55–19.97), SOFA > 8 (aOR 9.74, 95 % CI 1.46–64.88), and the requirement of invasive mechanical ventilation (aOR 18.33, 95 % CI 3.15–106.80). One-year outcomes were available for 69 patients. Six patients died during the follow-up period, all of whom were from the unfavorable-outcome group. The 1-year overall mortality estimated by Kaplan-Meier analysis was 46 % (Fig. 1). The univariate Cox regression analysis is presented in Table 5. Multivariate Cox regression analysis identified two factors positively associated with 1-year mortality (Table 6): APACHE II > 23 (adjusted hazard ratio (aHR) 4.83; 95 % CI 2.21–10.55), and the requirement of mechanical ventilation (aHR 9.71; 95 % CI 2.31–40.87). Among 1-year survivors, functional independence (GOS of 5) was observed in 28/34 (82 %) cases. Of the 6 patients with functional dependence (GOS of 4), visual impairment was found in one case and reduced muscle strength was found in five cases.

In the ROC analysis (Fig. 2), the areas under the curve were: GCS 0.60 (95 % CI 0.46–0.73; $P = 0.17$), APACHE II 0.81 (95 % CI 0.70–0.91; $P < 0.001$), and SOFA 0.67 (95 % CI 0.54–0.80; $P = 0.01$). To obtain the strongest power of prediction, the cut-off points were 4 for GCS (sensitivity 0.80 and specificity 0.38), 23 for APACHE II (sensitivity 0.74 and specificity 0.82), and 8 for SOFA (sensitivity 0.43 and specificity 1.00) respectively. Kaplan-Meier survival curves for patients with APACHE II score ≤ 23 and > 23 are shown in Fig. 3, with $P < 0.001$. Patients stratified by SOFA (≤ 8 and > 8) yielded the similar result ($P < 0.001$; Additional file 2). There is no statistically significant difference between survival curves

Table 2 CSF cultures for *Mycobacterium tuberculosis*

	Favorable	Unfavorable
Positive cultures, n/N	9/41	13/38[a]
Drug-susceptibility test results available, n	7[b]	10[c]
No resistance	6	4
Rifampicin resistance	0	3
Multidrug resistance	0	1
Resistant to others	1	2

Abbreviations: *CSF* cerebrospinal fluid
[a]Data missed in 1 case
[b]Data missed in 2 cases
[c]Data missed in 3 cases

Table 3 Factors associated with outcome by univariate logistic regression analysis

Variable	Unfav	Fav	OR (95 % CI)	P Value	Variable	Unfav	Fav	OR (95 % CI)	P Value
Sex					Headache				
Male	18	27	0.44 (0.18–1.10)	0.08	Yes	31	28	1.80 (0.65–4.98)	0.26
Female	21	14			No	8	13		
Age, years					Irritability				
> 60	10	6	2.01 (0.65–6.20)	0.22	Yes	6	17	0.26 (0.09–0.75)	0.01
≤ 60	29	35			No	33	24		
Duration of Symptoms, days					Nausea and vomiting				
> 10	32	30	1.68 (0.58–4.89)	0.34	Yes	23	24	1.02 (0.42–2.48)	0.97
≤ 10	7	11			No	16	17		
ICU stay, days					Fever(≥ 38.5℃)				
> 15	12	18	0.57 (0.23–1.42)	0.23	Yes	28	32	0.72 (0.26–1.98)	0.52
≤ 15	27	23			No	11	9		
Immune deficiency					Neck stiffness				
Yes	10	5	2.48 (0.76–8.08)	0.13	Yes	32	35	0.78 (0.24–2.58)	0.69
No	29	36			No	7	6		
Old tuberculosis					Convulsions				
Yes	5	2	2.87 (0.52–15.75)	0.23	Yes	9	6	1.75 (0.56–5.49)	0.34
No	34	39			No	30	35		
Active extra-neuraltuberculosis					Focal neurologicaldeficits				
Yes	20	21	0.95 (0.39–2.30)	0.91	Yes	20	23	1.21 (0.50–2.93)	0.67
No	19	20			No	19	18		
Alteredconsciousness					Basal meningealenhancement				
Yes	33	37	0.60 (0.15–2.29)	0.45	Yes	5	5	1.10 (0.29–4.18)	0.89
No	6	4			No	30	33		
Lethargy					Hydrocephalus				
Yes	32	36	0.64 (0.18–2.20)	0.47	Yes	25	20	2.25 (0.85–5.94)	0.10
No	7	5			No	10	18		
GCS					Infarct				
≤ 4	32	29	1.89 (0.66–5.45)	0.24	Yes	20	16	1.83 (0.72–4.64)	0.20
> 4	7	12			No	15	22		
APACHE II					Tuberculoma				
≤ 23	13	29	0.21 (0.08–0.53)	0.001	Yes	3	1	3.47 (0.34–35.02)	0.29
> 23	26	12			No	32	37		
SOFA					MV				
≤ 8	23	39	0.07 (0.02–0.35)	0.001	Yes	37	21	17.62(3.74–82.93)	< 0.001
> 8	16	2			No	2	20		
Positive culture inCSF					Pre-contrast basalhyperdensity				
Yes	13	9	1.85 (0.68–5.02)	0.23	Yes	4	2	2.32 (0.40-13.55)	0.35
No	25	32			No	31	36		
Positive PCR in CSF					Surgical intervention				
Yes	11	10	1.31 (0.48–3.57)	0.60	Yes	7	4	2.02 (0.54–7.55)	0.29
No	26	31			No	32	37		

Abbreviations: *APACHE* acute physiology and chronic health evaluation, *CI* confidence interval, *CSF* cerebrospinal fluid, *Fav* favorable, *GCS* Glasgow coma scale, *ICU* intensive care unit, *MV* mechanical ventilation, *OR* odds ratio, *PCR* polymerase chain reaction, *SOFA* sequential organ failure assessment, *Unfav* unfavorable

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Table 4 Prognostic factors of unfavorable outcome by multivariate logistic regression

Variable	OR	95 % CI	P Value
APACHE II > 23	5.57	1.55–19.97	0.008
SOFA > 8	9.74	1.46–64.88	0.019
Mechanical ventilation	18.33	3.15–106.80	0.001

Abbreviations: *APACHE* acute physiology and chronic health evaluation, *CI* confidence interval, *OR* odds ratio, *SOFA* sequential organ failure assessment

for patients stratified by GCS $\leq$ 4 and > 4 (P = 0.38; Additional file 3).

When APACHE II, SOFA and mechanical ventilation were included in a model, the model showed good discrimination as evident by an AUC = 0.878 (95 % CI 0.805–0.950, P < 0.001; Additional file 4) and good calibration (Hosmer and Lemeshow test P = 0.904; Additional file 5).

Discussion

Our study found that both the APACHE II and SOFA scores on admission predicted short-term outcomes of adult patients with TBM in ICU. And the APACHE II scoring system was superior to SOFA in predicting 1-year outcomes. In addition, the requirement of invasive

mechanical ventilation was found to be independently associated with an unfavorable outcome.

In our study, the participants' characteristics differed significantly from those reported in previous studies conducted in other endemic areas [17, 18], but were similar to the one conducted in non-endemic area [4]. Most obviously, all the 80 patients presented with MRC stage III illness, and 58 (73 %) required invasive mechanical ventilation. These differences might be explained by selection bias of the most severe cases requiring ICU admission in this study, since the access to intensive care was low in China. Different factors such as older age, hydrocephalus, change in consciousness and higher MRC stage were reported to be associated with poor prognosis in patients with TBM [4, 19–21]. However, no clinical, laboratory or imaging factors were found to be associated with poor outcomes in our study cohort. This could be explained by the participants themselves, since they were the most severe cases who were more likely to develop hydrocephalus and comatose than those with MRC stage I or II illness.

Thirty-five patients in our cohort died, among whom 29 deaths were within 28 days. The 1-year overall mortality was 46 %, which was extremely high, but
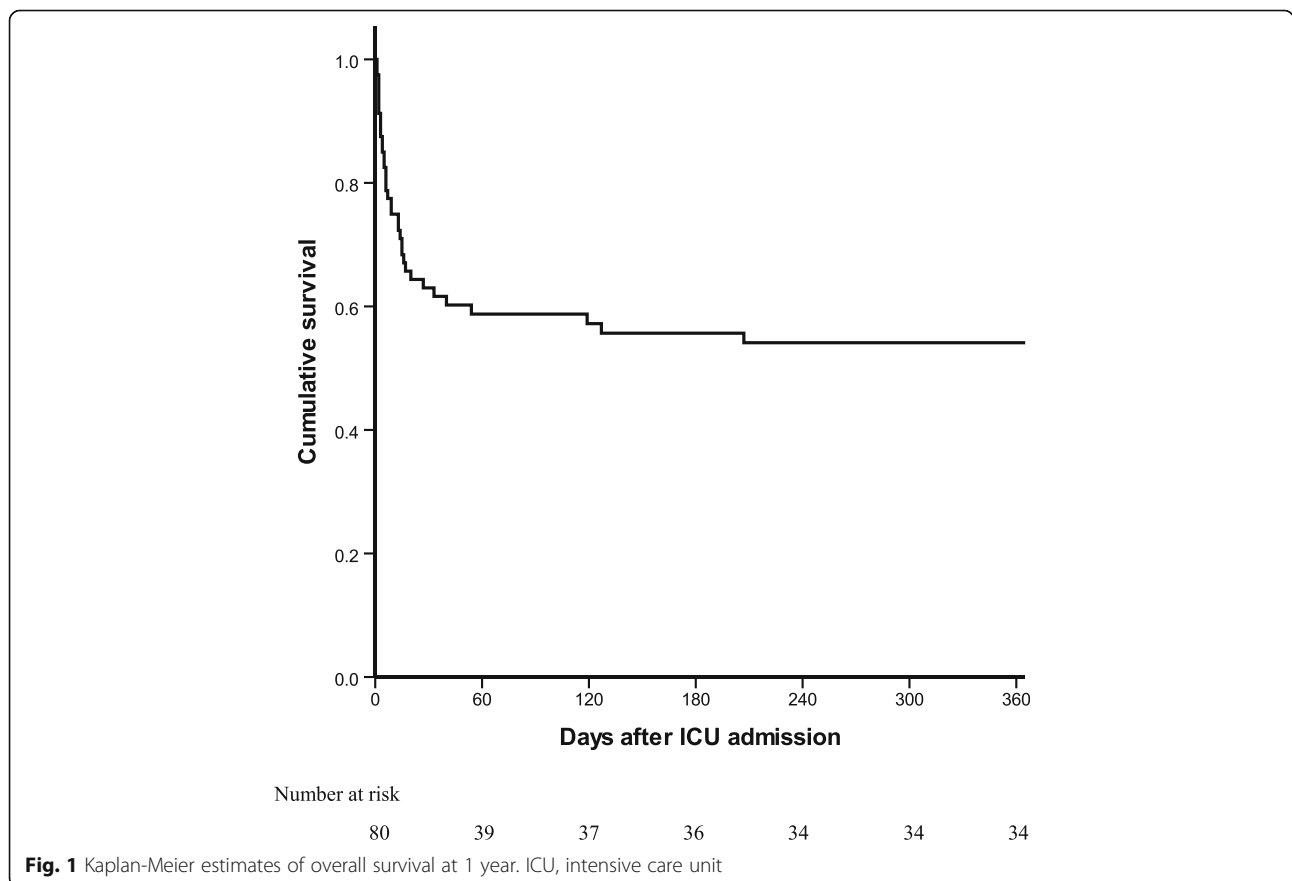

Fig. 1 Kaplan-Meier estimates of overall survival at 1 year. ICU, intensive care unit

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Table 5 Univariate Cox regression analysis of factors associated with 1-year mortality

Variable	HR	95 %CI	P value
Age	1.019	1.00-1.04	0.055
Male sex	0.470	0.24–0.92	0.027
Irritability	0.934	0.48–1.82	0.841
GCS	1.430	0.62–3.28	0.398
APACHEII	4.632	2.15–9.99	< 0.001
SOFA	3.646	1.85–7.19	< 0.001
MV	9.331	2.23–39.04	0.002

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *GCS* Glasgow coma scale, *APACHE* acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment, *MV* mechanical ventilation

comparable to a previous study [5]. In that systematic review and meta-analysis, the mortality rate was 64.8 % for patients with stage III TBM [5]. The phenomenon that most deaths (29/35) occurred early was consistent with a Madagascar cohort and a meta-analysis which consisted of 5752 adult TBM patients [22, 23].

Mechanical ventilation was reported to be required by 10-20 % of adult patients with TBM in all stages [24, 25]. For those admitted to ICU, this number increased to 70 % [4, 26]. In our study, 58 (73 %) patients received invasive mechanical ventilation during their ICU stay, of whom 37 (64 %) had an unfavorable outcome. Consistent with previous studies, the requirement of mechanical ventilation was associated with an unfavorable outcome [24, 25]. Those who needed mechanical ventilation were more critically ill because of associated sepsis and TBM-related or systemic complications, and had a higher mortality rate.

Hyponatremia is the most common electrolyte abnormality observed in hospitalized individuals and is associated with increased mortality [27]. For patients with TBM, the frequency of hyponatremia was reported to be about 40–50 % in different studies [28–30]. The relationship between hyponatremia and death was uncertain. It was reported to be certain in a tertiary care cohort [30]. However, hyponatremia didn't have a predictive value on the outcome of TBM in another prospective study [29]. In a study consisted of 1048 adult TBM patients, the authors used time-updated Glasgow coma score and plasma sodium measurements to dynamically predict the death, they found that plasma sodium values were higher

Table 6 Multivariate Cox analysis of factors associated with 1-year mortality

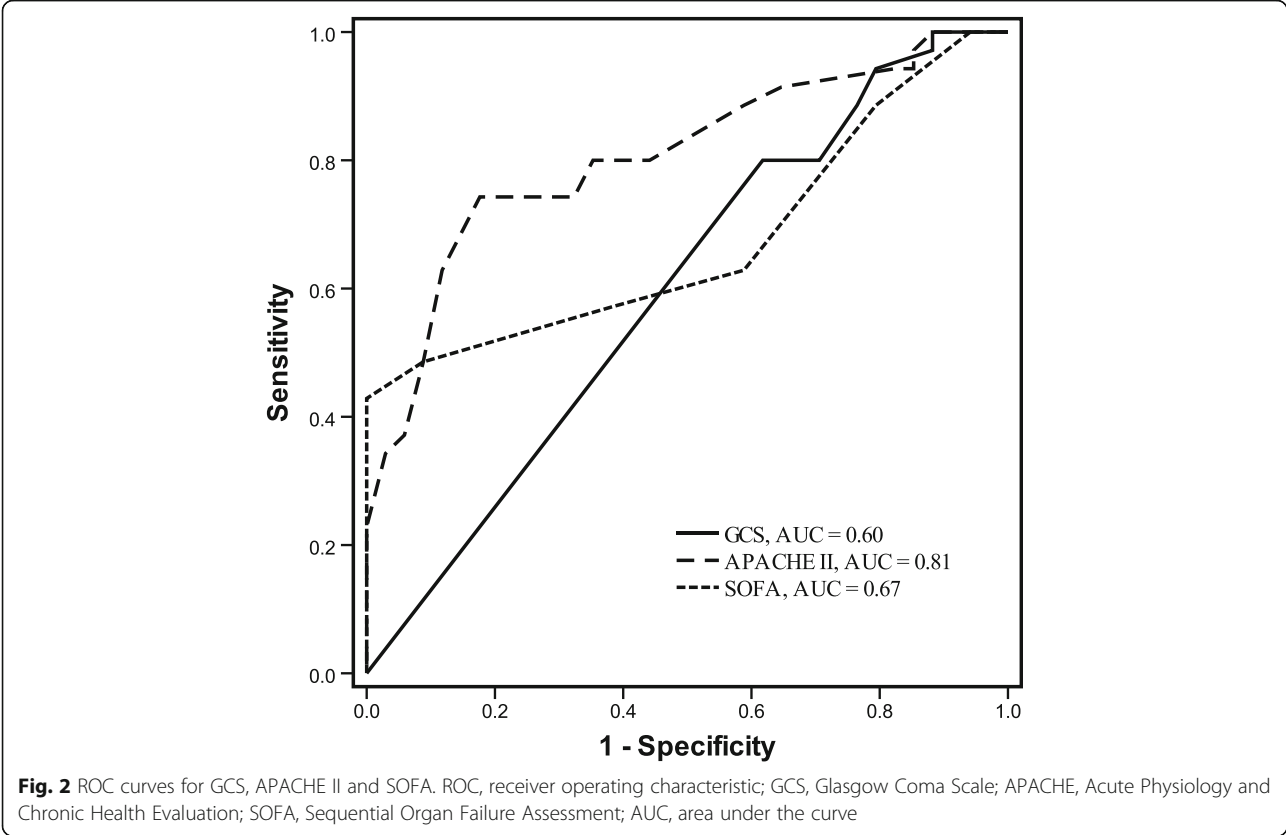| Variable	HR	95 % CI	P value
APACHE II > 23	4.83	2.21–10.55	< 0.001
Mechanical ventilation	9.71	2.31–40.87	0.002

Abbreviations: *HR* hazard ratio, *CI* confidence interval, *APACHE* acute physiology and chronic health evaluation
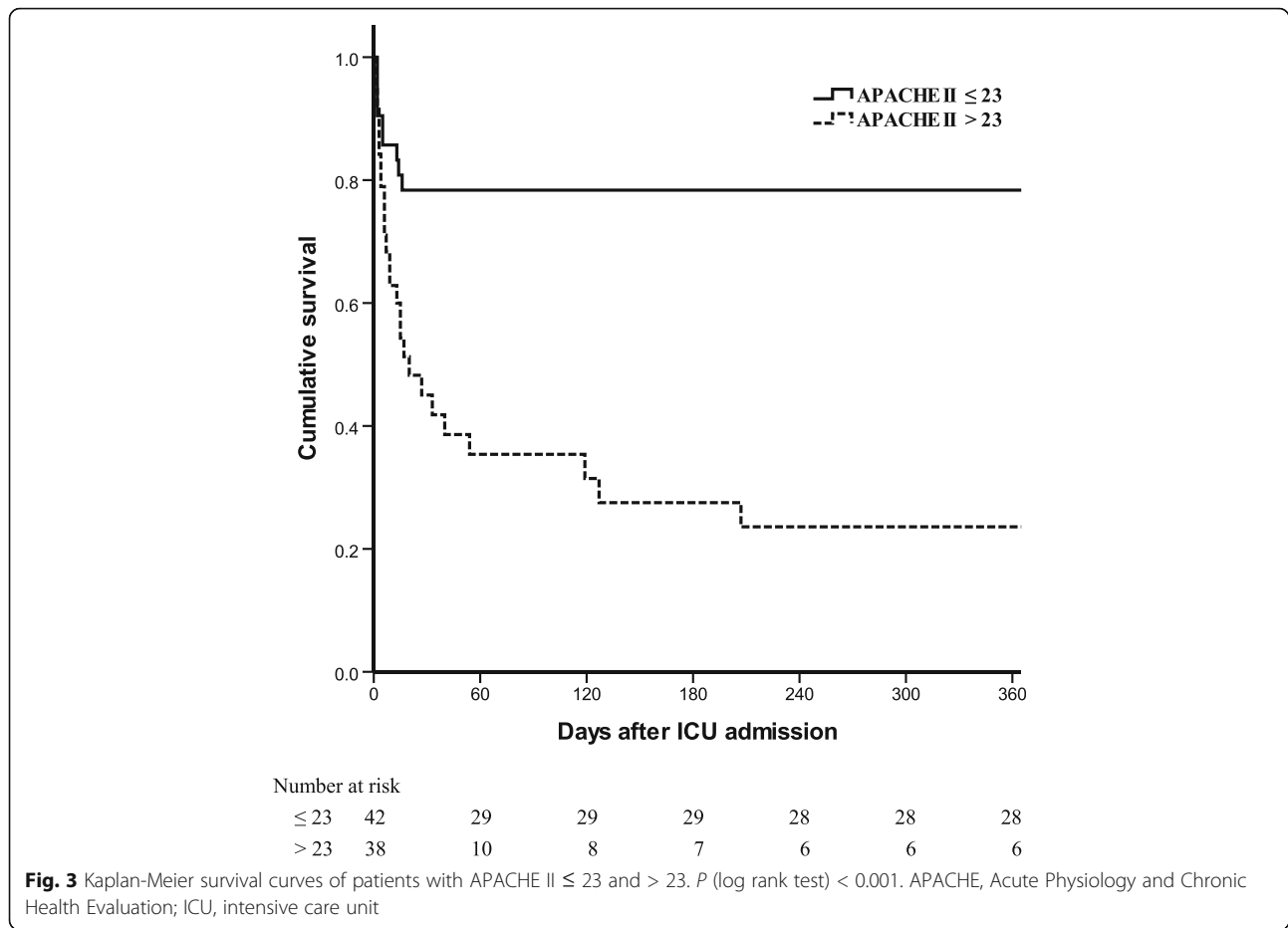
in HIV-infected survivors, with a less clear relationship between sodium and survival in HIV-uninfected patients [31]. We didn't observe an association of plasma sodium levels with death in our study cohort, too. So, more prospective studies need to be carried out in different patient populations to confirm the role of hyponatremia in TBM.

GCS was used to assess the mental status of patients with TBM and low GCS scores were reported to be associated with an unfavorable outcome in numerous studies [32–35]. In our study, GCS had no association with unfavorable outcomes, which might be explained by the relatively lower GCS scores of the patients with MRC stage III illness on admission. Irritability displayed a better association with favorable outcomes in univariate analysis, partially due to its relationship with a relatively higher GCS score.

APACHE II and SOFA were the most common used scoring systems to evaluate the disease severity of patients in ICU [13, 14]. To our knowledge, few studies have used APACHE II in patients with TBM [16], and none has used SOFA. In the previous study, APACHE II showed a good predictive value as GCS and superior to MRC for discharge outcomes of adult patients with TBM [16]. To obtain the greatest power in prediction based on ROC curve analysis, the cut-off points chosen for GCS, APACHE II and SOFA were 4, 23 and 8 respectively in our study. The results showed that only APACHE II had both acceptable sensitivity and specificity. In univariate and multivariate logistic regression analyses, APACHE II and SOFA were independently associated with an unfavorable outcome. APACHE II > 23 was identified as predictor of 1-year mortality by multivariate Cox regression analysis. These two scoring systems were based on physiological variables other than levels of consciousness or neurological deficits, on which the GCS was based. Therefore the use of APACHE II and SOFA would be more suitable for assessing the prognosis of patients with TBM, especially for those admitted to ICU.

Imran and collegues have derived a simple bedside score (MASH-P) including variables baseline modified Barthel index (M), age (A), stage (S), hydrocephalus (H) and papilledema (P), which can be used easily at bedside to predict 6-month mortality in tuberculous meningitis [36]. However, the model needs external validation to assess its performance in different settings. In our study cohort, a model including APACHE II, SOFA and mechanical ventilation also showed good discrimination and good calibration. However, it also needs external validation and further assessment since there were duplicate indices between the two scoring systems such as GCS scores, mean arterial pressure and creatinine. APACHE II itself had a good predictive value on the outcome of

Fig. 2 ROC curves for GCS, APACHE II and SOFA. ROC, receiver operating characteristic; GCS, Glasgow Coma Scale; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; AUC, area under the curve

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Fig. 3 Kaplan-Meier survival curves of patients with APACHE II ≤ 23 and > 23. *P* (log rank test) < 0.001. APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit

TBM (area under the ROC curve = 0.81), so we would suggest using APACHE II alone instead of the three-factor model to reduce the workload of clinicians.

Our study has some strengths. First, no study was conducted on adult patients with TBM admitted to ICU in China. Second, participants included in our study were the most severe TBM cases of MRC stage III - a group which was not previously reported separately. Moreover, we used validated guidelines and consensus definitions to include participants and report data.

Our study was limited by its retrospective design. All data were collected from a single medical center and the sample size was not large enough. Most patients only took cranial CT scans, which lack sensitivity for TBM-associated cerebrovascular or inflammatory complications. The present results may not be applied to a less severe population since we focused on the most severe TBM cases of stage III admitted to the ICU.

Conclusions

For the most severe adult TBM patients of MRC stage III, common clinical factors aren't effective enough to predict outcomes. Our study demonstrates that the widely used APACHE II and SOFA scores on admission can be used to predict short-term outcomes, while APACHE II could also be used to predict long-term outcomes of adult patients with TBM in ICU.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-021-02340-3.

Additional file 1: Figure S1. The flow diagram of patient enrollment.

Additional file 2: Figure S2. Kaplan-Meier survival curves of patients with SOFA ≤ 8 and > 8.

Additional file 3: Figure S3. Kaplan-Meier survival curves of patients with GCS ≤ 4 and > 4.

Additional file 4: Figure S4. ROC curves for the final model including APACHE II, SOFA and mechanical ventilation.

Additional file 5: Figure S5. The calibration plot of the final model.

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Authors' contributions
BF, YS, XZ, DS, YZ and WR conceived of and designed this study. XF, MS, JX and WZ contributed to the acquisition and analysis of data. BF and XF interpreted the data and drafted the manuscript. All authors revised the manuscript for important intellectual content. All authors reviewed, discussed, and approved the final manuscript.

Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the ethics committee of Shandong Provincial Chest Hospital and informed consent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. World Health Organization. Global tuberculosis report 2019. Available at: http://www.who.int/tb/publications/global_report/en/. Accessed 20 Dec 2019.
2. Torok ME. Tuberculous meningitis: advances in diagnosis and treatment. Br Med Bull. 2015;113(1):117–31.
3. Thwaites G, Fisher M, Hemingway C, et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009;59(3):167–87.
4. Cantier M, Morisot A, Guérot E, et al. Functional outcomes in adults with tuberculous meningitis admitted to the ICU: a multicenter cohort study. Crit Care. 2018;22(1):1-8.
5. Wang MG, Luo L, Zhang Y, et al. Treatment outcomes of tuberculous meningitis in adults: a systematic review and meta-analysis. BMC Pulm Med. 2019;19(1):200.
6. Thao LTP, Heemskerk AD, Geskus RB, et al. Prognostic Models for 9-Month Mortality in Tuberculous Meningitis. Clin Infect Dis. 2018;66(4):523–32.
7. Heemskerk AD, Nguyen M, Dang H, et al. Clinical outcomes of patients with drug-resistant tuberculous meningitis treated with an intensified antituberculosis regimen. Clin Infect Dis. 2017;65(1):20–8.
8. Verdon R, Chevret S, Laissy JP, et al. Tuberculous meningitis in adults: review of 48 cases. Clin Infect Dis. 1996;22(6):982–8.
9. Sonneville R, Gault N, de Montmollin E, et al. Clinical spectrum and outcomes of patients with encephalitis requiring intensive care. Eur J Neurol. 2015;22(1):6–16.
10. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis. 2010;10(11): 803–12.
11. Marais BJ, Heemskerk AD, Marais SS, et al. Standardized methods for enhanced quality and comparability of tuberculous meningitis studies. Clin Infect Dis. 2017;64(4):501–9.
12. Thwaites GE, Tran TH. Tuberculous meningitis: many questions, too few answers. Lancet Neurol. 2005;4(3):160–70.
13. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
14. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med. 1996;22(7):707–10.
15. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975;1(7905):480–4.
16. Chou CH, Lin GM, Ku CH, et al. Comparison of the APACHE II, GCS and MRC scores in predicting outcomes in patients with tuberculous meningitis. Int J Tuberc Lung Dis. 2010;14(1):86–92.
17. 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(17):1741–51.
18. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. N Engl J Med. 2016;374(2):124–34.
19. Wen L, Li M, Xu T, et al. Clinical features, outcomes and prognostic factors of tuberculous meningitis in adults worldwide: systematic review and meta-analysis. J Neurol. 2019;266(12):3009–21.
20. Huang H, Ren Z, Dai Y, et al. Old age and hydrocephalus are associated with poor prognosis in patients with tuberculous meningitis. Medicine. 2017;96(26):e7370.
21. Modi M, Sharma K, Prabhakar S, et al. Clinical and radiological predictors of outcome in tubercular meningitis: a prospective study of 209 patients. Clin Neurol Neurosurg. 2017;161:29–34.
22. Raberahona M, Rakotoarivelo RA, Razafinambinintsoa T, et al. Clinical features and outcome in adult cases of tuberculous meningitis in tertiary care hospital in Antananarivo, Madagascar. Biomed Res Int. 2017;2017: 9316589.
23. Anna MS, Jayne E, Thomas HAS, et al. Treatment outcomes in adult tuberculous meningitis: a systematic review and meta-analysis. Open Forum Infect. 2020;7(8):ofaa257.
24. Qureshi HU, Merwat SN, Nawaz SA, et al. Predictors of inpatient mortality in 190 adult patients with tuberculous meningitis. J Pak Med Assoc. 2002;52(4): 159–63.
25. Misra UK, Kalita J, Betai S, et al. Outcome of tuberculous meningitis patients requiring mechanical ventilation. J Crit Care. 2015;30(6):1365–9.
26. Misra UK, Kalita J, Bhoi SK. Spectrum and outcome predictors of central nervous system infections in a neurological critical care unit in India: a retrospective review. Trans R Soc Trop Med Hyg. 2014;108(3):141–6.
27. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med. 2009;122(9):857–65.
28. Ameet K, Jay S, Owais H, et al. Frequency of hyponatremia in patients of tuberculosis bacterial meningitis in a tertiary care hospital. Cureus. 2021; 13(3):e13888.
29. Misra UK, Kalita J, Bhoi SK, Singh RK. A study of hyponatremia in tuberculous meningitis. J Neurol Sci. 2016;367:152–7.
30. Misra UK, Kalita J, Kumar M, et al. Complications of tuberculous meningitis and their effect on outcome in a tertiary care cohort. Int J Tuberc Lung Dis. 2020;24(11):1194–9.
31. Le TPT, Marcel W, Dorothee A. H, et al. Dynamic prediction of death in patients with tuberculous meningitis using time-updated Glasgow Coma Scale and plasma sodium measurements. Clin Infect Dis. 2020;70(5):827–34.
32. Li K, Tang H, Yang Y, et al. Clinical features, long-term clinical outcomes, and prognostic factors of tuberculous meningitis in West China: a multivariate analysis of 154 adults. Expert Rev Anti Infect Ther. 2017;15(6):629–35.

33. Morgado TC, Kinsky M, Carrara H, et al. Prognostic value of computed tomography-evident cerebral infarcts in adult patients with tuberculous meningitis and hydrocephalus treated with an external ventricular drain. World Neurosurg. 2013;80(6):e255–60.
34. George EL, Iype T, Cherian A, et al. Predictors of mortality in patients with meningeal tuberculosis. Neurol India. 2012;60(1):18.
35. Gu J, Xiao H, Wu F, et al. Prognostic factors of tuberculous meningitis: a single-center study. Int J Clin Exp Med. 2015;8(3):4487–93.
36. Imran R, Hardeep SM, Ravindra KG, et al. Derivation of a bedside score (MASH-P) to predict 6-month mortality in tuberculous meningitis. J Neurol Sci. 2020;415:116877.

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