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ORIGINAL COMMUNICATION

Clinical features, outcomes and prognostic factors of tuberculous meningitis in adults worldwide: systematic review and meta-analysis

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Abstract

Background Tuberculous meningitis (TBM) is one of the most life-threatening infectious diseases. We performed a systematic review and meta-analysis of the clinical features, outcomes, and prognostic factors for TBM in adults.

Methods PubMed, EMBASE, Cochrane CENTRAL, and Web of Science were searched for studies that reported the clinical outcomes and/or risk factors for death in adults with TBM between January 1990 and July 2018. A random-effects meta-analysis model was used to pool data on clinical features, outcomes, and risk factors for death.

Results Thirty-two studies that examined 5023 adults who had TBM met the inclusion criteria. Overall, the mortality was 22.8% [95% confidence interval (CI) 18.9–26.8] and the risk of neurological sequelae was 28.7% (95% CI 22.8–35.1). The major risk factors for death (OR > 2 and $P < 0.05$) were advanced stage of disease (OR = 6.06, 95% CI 4.31–8.53), hydrocephalus (OR = 5.27, 95% CI 2.25–12.37), altered consciousness (OR 3.33, 95% CI 1.51–7.36), altered sensorium (OR 3.31, 95% CI 2.20–4.98), advanced age (> 60 years; OR = 2.64, 95% CI 1.27–5.51), and cerebral infarction (OR = 2.35, 95% CI 1.63–3.38). The clinical features and diagnostic findings present in more than four-fifths of the patients were fever (86.3%, 95% CI 82.4–89.8) and low CSF/serum glucose ratio (80.6%, 95% CI 64.8–92.6).

Conclusions Adults with TBM have high rates of mortality. Clinicians should maintain a high clinical suspicion for patients who present with certain clinical features, and should pay more attention to prognostic factors.

Keywords Tuberculous meningitis · Clinical feature · Outcome · Prognostic factor · Meta-analysis

Introduction

Tuberculosis (TB) is a leading cause of death worldwide, and an estimated 10.0 million new TB cases occurred globally during 2017 [1]. TB commonly occurs in the lungs, but can also occur in other sites, including the meninges. Although TB meningitis (TBM) accounts for roughly 1% of all TB cases, it kills or disables nearly half of affected patients [2].

Several studies have examined the clinical features and outcomes of TBM in adults, and many studies have predicted outcomes based on clinical data. However, most of these were single-center studies, had small sample sizes, examined different populations, and used different diagnostic criteria and treatments [3, 4]. Worldwide data on the

Lan Wen and Maolin Li contributed equally to this work.

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clinical features, outcomes, and prognostic factors of TBM in adults are still inconclusive. A systematic evaluation using an evidence-based approach is necessary.

Thus, we conducted this systematic review and meta-analysis of the outcomes of adults diagnosed with TBM from 1990 onward. Our primary aim was to report the outcomes and identify risk factors associated with TBM, and to also identify the pooled frequencies of different clinical features.

Materials and methods

Search strategy

PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched to identify all relevant publications. The literature search was limited to English language studies published between January 1990 and July 2018. Two authors (L.W and T.X), independently reviewed the titles and abstracts of all studies, and excluded those that did not meet the selection criteria. Discrepancies were resolved by discussion until consensus was reached.

Study selection

All eligible studies were cohort studies that examined patients over 14 years old, and reported clinical outcomes (death, neurologic sequelae, recovery) and/or prognostic factors. The eligible studies should employ the diagnostic criteria dividing TBM patients into "definitive cases" and "clinically suspected cases". A definitive case had acid-fast bacilli in CSF, mycobacteria cultured from CSF, or a positive result in a mycobacterial nucleic acid amplification test. A clinically suspected case had (a) clinical symptoms that were consistent with TBM, (b) CSF laboratory results that were consistent with TBM, (c) brain imaging results that were consistent with TBM, (d) evidence of extra-neural tuberculosis, (e) diagnostic tests that excluded other aetiologies, and (f) a clinical response to anti-tuberculous treatment. Studies were excluded if they (i) were limited to TBM patients with a specific comorbidity or complication or (ii) examined TBM patients treated with an experimental anti-TB regimen.

Data extraction

Two investigators (L.W and X.Y.Y) independently extracted the data, and disagreements or uncertainties were resolved by discussion with a third reviewer (L.J.W). Any identified errors were re-examined and corrected. The following data were extracted when available: general characteristics (authors, publication year, study year, study design, geographic region); clinical features of patients (demographic data, clinical manifestations, imaging findings, cerebrospinal fluid results); patient outcomes (death, neurological sequelae, and prognostic factors).

Quality assessment

The methodological quality of the included studies was independently assessed by two study investigators (X.Y.Y and T.X) using the Newcastle–Ottawa Scale (NOS) [5]. NOS scores are summed, and used for quantitative comparison of study quality, as recommended by the Cochrane Non-Randomized Studies Methods Working Group [5]. Disagreements about quality assessment were resolved by discussion with a third study investigator (L.J.W).

Statistical analysis

The crude frequencies of clinical features, neurological sequelae, and mortality from TBM were first computed for each study, and then double-arcsine transformed using the Freeman–Tukey method [6]. Heterogeneity was tested using Cochran's Q statistic, and a p value below 0.1 indicated significant heterogeneity. The extent of heterogeneity was quantified using the I^2 statistic [7]. Because there was substantial heterogeneity among the included studies, a random-effects model was used to adjust for this prior to pooling the study-specific frequencies of clinical features, neurological sequelae, and mortality. For meta-analysis of mortality and neurological sequelae, a "leave-one-out" sensitivity analysis was used to assess the robustness of the pooled results [8]. This procedure determines whether a single study had a disproportional influence on the pooled results. Publication bias was checked by visual inspection of funnel plots, and tested for significance using Egger's regression test for funnel plot asymmetry and Begg's rank correlation test [9, 10]. Subgroup analysis was conducted to identify the diversity (heterogeneity) of the different studies in reported mortality due to TBM. A random-effects model was used to identify the risk factors for mortality. Generally, only risk factors that were investigated in at least three studies were used. All p values were two sided and a p value below 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 14.0 (STATA, College Station, TX).

Results

Study selection process and results

Figure 1 shows the study selection process and the results of the literature search. We screened 2569 articles by reading

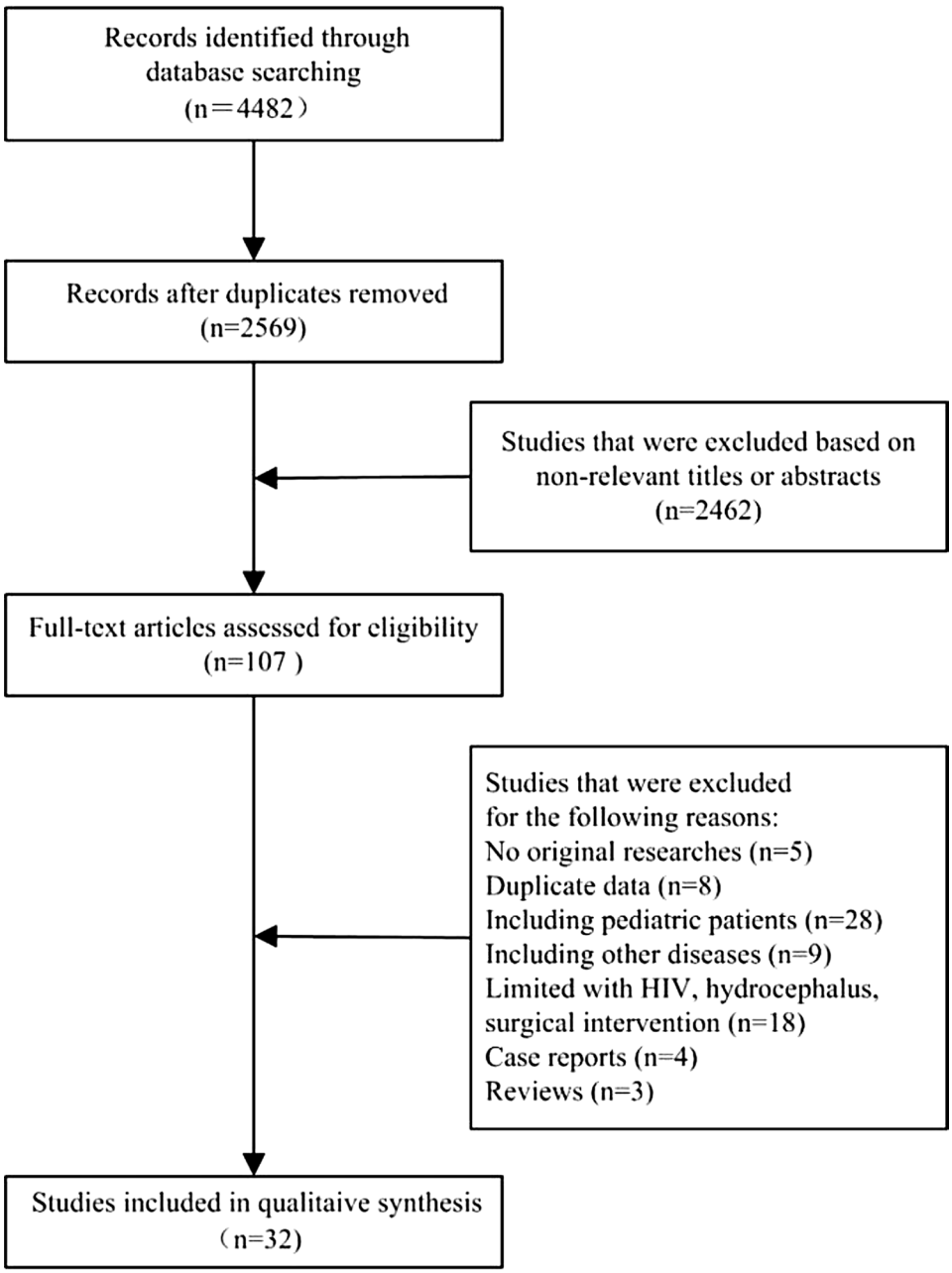


Fig. 1 Literature search and selection of TBM studies for the meta-analysis

the titles and abstracts, and assessed 107 articles in full-text form. After detailed assessments, we determined that 32 publications met the eligibility criteria. Twenty-nine studies provided data on mortality from TBM, and 21 reported prognostic factors for TBM.

Study characteristics

Table 1 summarizes the characteristics of the 32 studies. There were six prospective cohort studies and 26 retrospective cohort studies. Twenty-seven publications were single-center studies, and five were multicenter studies. Two studies were conducted in African, three in the Americas, two in the Eastern Mediterranean, six in Europe, seven in Southeast Asia, and 11 in the Western Pacific; the other study included patients from Europe, Africa, and the Eastern Mediterranean (Fig. 2). Thus, data on outcomes and risk factors for death had a worldwide coverage. Overall, there were 5023 patients, 57.9% of patients were male, and the mean age was 38.3 years (range 14–85).

Clinical features of patients

Table 2 summarizes the clinical data provided by the 32 studies. The most common symptoms were fever [86.3%, 95% confidence interval (CI) 82.4–89.8] and headache

Table 1 Characteristics of studies included in the meta-analysis

First author, year	Location	Type of study	Number of Patients (n)	Mean age (years)	Reported risk factors of mortality	Quality score[a]
Roj as-Echeverri et al. 1996	Mexico	Prospective cohort	24	Not reported	Not reported	8
Hosoglu et al. 1998	Turkey	Retrospective cohort	101	30.6	Advanced stage[b]	8
Karstaedt et al. 1998	South Africa	Retrospective cohort	56	Not reported	Age, advanced stage	6
Lu et al. 2001	China	Retrospective cohort	36	Not reported	Age, cerebral infarction, cranial nerve palsy, fever, headache, hydrocephalus, gender, seizure, advanced stage	7
Hosoglu et al. 2002	Turkey	Retrospective cohort	434	32.8	Altered consciousness, cranial nerve palsy, extra-cerebral TB, gender, seizure, advanced stage	7
Thwaites et al. 2002	Vietnam	Retrospective cohort	56	Not reported	Advanced stage	7
Chan et al. 2003	China	Prospective cohort	31	Not reported	Hydrocephalus	9
Sütlas et al. 2003	Turkey	Retrospective cohort	61	34.5	Not reported	6
AL-Edrus et al. 2007	Malaysia	Retrospective cohort	42	34.4	Advanced stage	8
Roca et al. 2008	Spain	Retrospective cohort	29	40.1	Not reported	7
Jau-Jiuan Sheu et al. 2009	China	Retrospective cohort	105	Not reported	Not reported	7
Chou et al. 2009	China	Retrospective cohort	43	Not reported	Not reported	7
Po-Chang Hsu et al. 2010	China	Retrospective cohort	108	54.9	Age, altered consciousness, cerebral infarction, definite TBM, extra-cerebral TB, fever, neck rigidity, advanced stage	8
Yasar et al. 2010	Turkey	Retrospective cohort	160	32.2	Alter sensorium, cerebral infarction, extra-cerebral TB, hydrocephalus, gender, seizure, advanced stage	7
Pawan Sharma et al. 2011	India	Retrospective cohort	158	32.0	Cranial nerve palsy	9
Ersöz et al. 2012	Turkey	Retrospective cohort	60	30.1	Not reported	7
Elizabeth Litta George et al. 2012	India	Retrospective cohort	98	Not reported	Cerebral infarctions, headache, hydrocephalus, advanced stage	7
Fernando Alarcón et al. 2012	Ecuador	Retrospective cohort	310	34.5	Altered consciousness, cerebral infarction, cranial nerve palsy, hydrocephalus, limb weakness, neck rigidity, seizure, advanced stage	7
Tushar Raut et al. 2012	India	Prospective cohort	80	30.1	Hydrocephalus	8
Chen et al. 2014	China	Retrospective cohort	38	56.5	Cerebral infarction	8
Kannikar Kongbunkiat et al. 2014	Thailand	Retrospective cohort	25	48.4	Not reported	7
Mohammad Wasay et al. 2014	Pakistan	Retrospective cohort	404	42.8	Cerebral infarction, hydrocephalus	8
Hakan Erdem et al. 2015	Albania et al	Retrospective cohort	507	37.7	Not reported	7
Jin Gu et al. 2015	China	Retrospective cohort	156	32.9	Definite TBM	8
Yahia et al. 2015	Qatar	Retrospective cohort	80	30.3	Alter sensorium, cranial nerve palsy, fever, headache, limb weakness, gender, seizure, advanced stage	7
Anurag Kumar Singh et al. 2016	India	Prospective cohort	141	29.7	Not reported	8

Table 1 (continued)

First author, year	Location	Type of study	Number of Patients (n)	Mean age (years)	Reported risk factors of mortality	Quality score[a]
Renu Gupta et al. 2016	India	Prospective cohort	391	27.8	Alter sensorium, definite TBM, cranial nerve palsy, extra-cerebral TB, fever, limb weakness, gender, neck rigidity, seizure, advanced stage	8
Hai-Jun Huang et al. 2017	China	Retrospective cohort	45	46.0	Not reported	8
Kunyi Li et al. 2017	China	Retrospective cohort	154	40.8	Age, altered consciousness, cerebral infarction, definite TBM, cranial nerve palsy, extra-cerebral TB, fever, headache, hydrocephalus, limb weakness, gender, neck rigidity, seizure, advanced stage	8
Alexander E. Merkler et al. 2017	America	Retrospective cohort	806	50.7	Not reported	8
Modi et al. 2017	India	Prospective cohort	209	30.4	Alter sensorium, altered consciousness, fever, hydrocephalus, advanced stage	8
Mihaja Raberahona et al. 2017	Madagascar	Retrospective cohort	75	35.4	Altered consciousness, cranial nerve palsy, gender, neck rigidity, seizure	7

[a]Quality score according to the Newcastle–Ottawa Scale; [b]advanced stage was defined as Medical Research Council stage 3

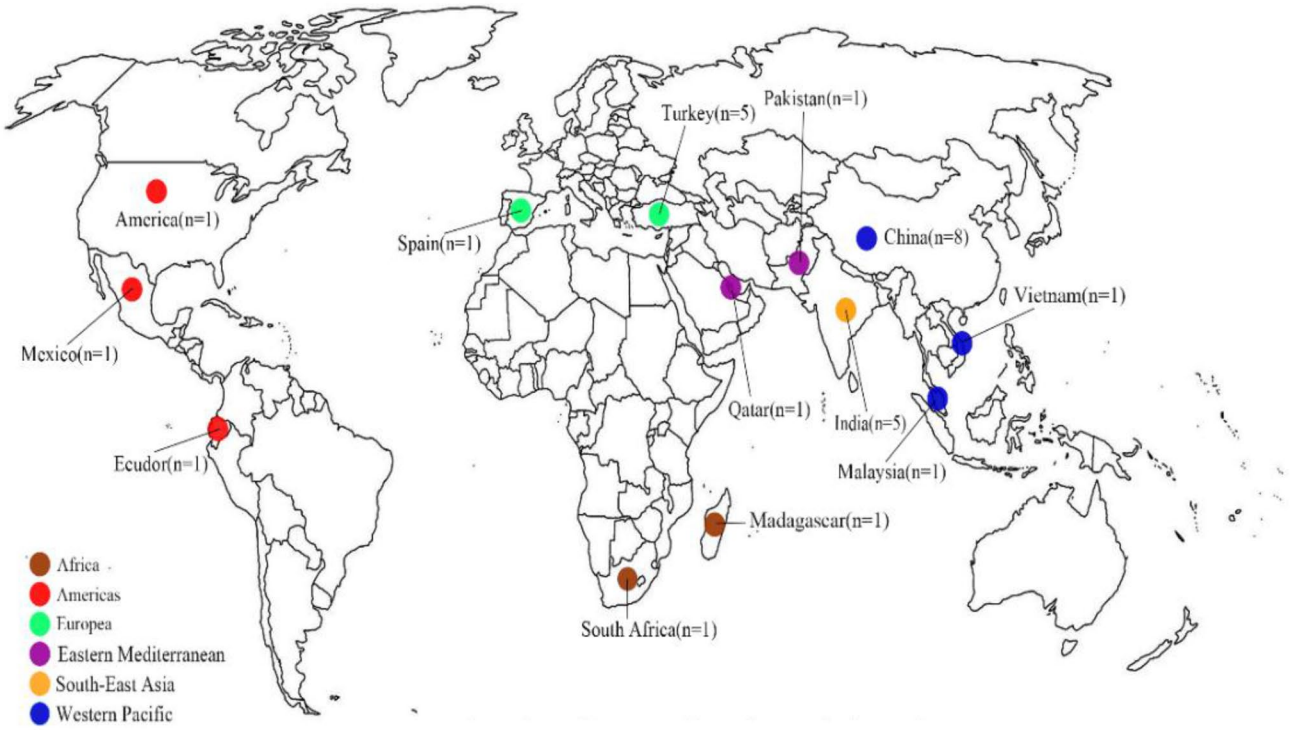
(78.8%, 95% CI 72.0–84.9), followed by altered consciousness (60.8%, 95% CI 55.2–66.3) and vomiting (59.0%, 95% CI 51.8–66.0). The most common clinical finding was neck rigidity (71.5%, 95% CI 63.8–78.7), followed by cranial nerve palsy (28.2%, 95% CI 22.1–34.7), and limb weakness (23.1%, 95% CI 17.0–29.8). Cerebrospinal fluid (CSF) results indicated significantly elevated white blood cell (WBC) counts ($> 100 \times 10^6$/L) in 69.7% of patients (95% CI 57.5–80.6), high protein (> 100 mg/dL) in 68.9% of patients (95% CI 59.7–77.4), high pressure (> 200 mmH_2O) in 63.6% of patients (95% CI 31.7–90.0), and low glucose (< 2.2 mmol/L) in 57.4% of patients (95% CI 33.9–79.3). There were large ranges of positive results from the CSF acid-fast bacilli smears (0–39.5%), cultures (9.9–80.7%), and nucleic acid amplification tests (10.0–67.5%). The most common imaging features were hydrocephalus (38.1%, 95% CI 32.8–43.5), cerebral infarction (22.7%, 95% CI 18.4–27.3), and tuberculoma (22.5%, 95% CI 16.2–29.5). In addition, 11 studies [11–21] reported the duration of symptoms before admission, and this ranged from 1–120 days. Four of these 11 studies [15, 17, 18, 20] reported symptoms lasting longer than 2 weeks before treatment in 37.9% (121/319) of these patients.

Mortality and risk of neurological sequelae

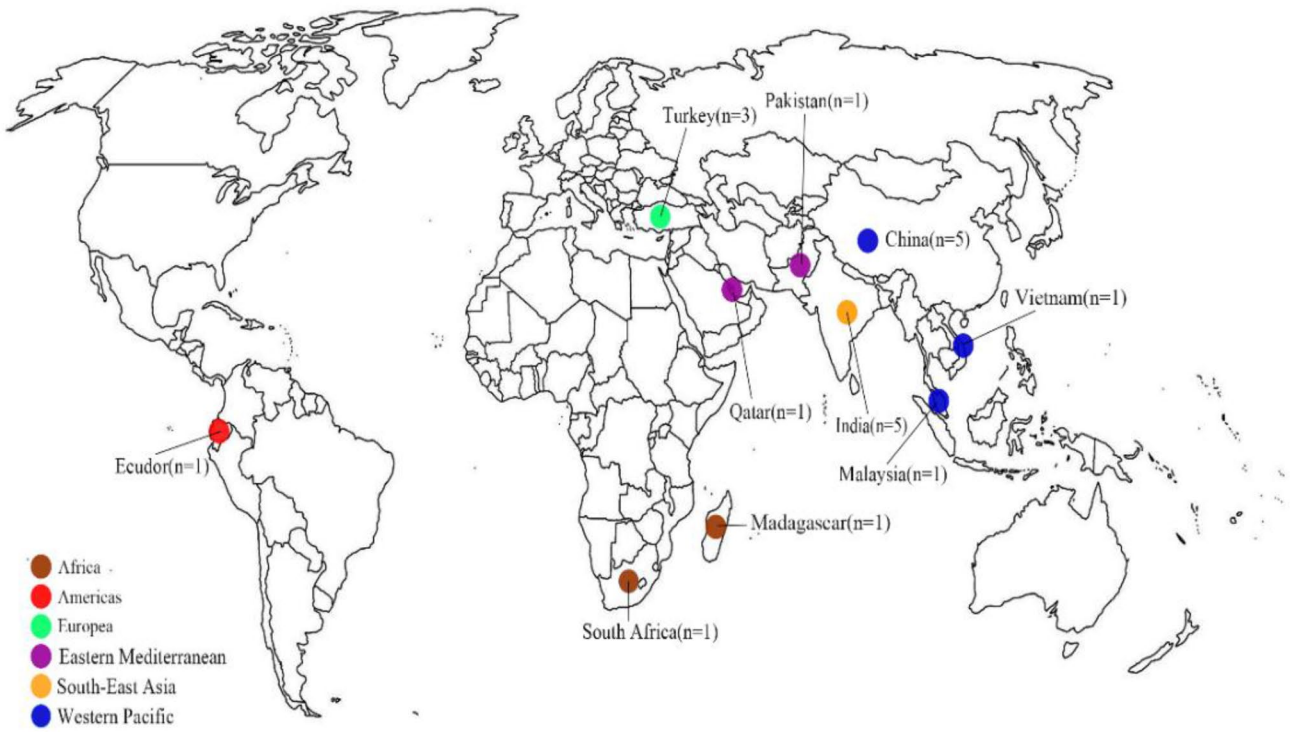
The pooled mortality from TBM was 22.8% (95% CI 18.9–26.8) and the pooled risk of neurological sequelae was 28.7% (95% CI 22.8–35.1) (Fig. 3). The "leave-one-out" sensitivity analysis (Online Supplementary Fig. 1.1–1.2) indicated the pooled mortality ranged from 21.4% (95% CI 18.0–25.9) to 23.6% (95% CI 19.7–27.6), and the pooled risk of neurological sequelae ranged from 26.5% (95% CI 21.6–31.7) to 30.0% (95% CI 23.9–36.4). Thus, no single study had a disproportional effect on the pooled results. Publication bias was not significant, based on visual inspection of funnel plots and the results of Begg's test and Egger's test (Online Supplementary Fig. 2.1–2.2).

Subgroup meta-analysis of mortality

Table 3 summarizes the results of the subgroup meta-analysis of mortality. We determined region-specific mortality for TBM in the Western Pacific, Southeast Asia, the Eastern Mediterranean, the Americas, Africa, and Europe. Patients living in Africa (45.6%) had higher mortality than those in all other areas (15.4–26.4%). The follow-up time-specific mortality from TBM was 18.2% for the first 3 months, and



A Locations of countries on mortality and/or neurologic sequelae



B Locations of countries on predictors of mortality

Fig. 2 Locations of TBM studies that provided data on mortality and/or neurologic sequelae (**a**) and predictors of mortality (**b**)

Table 2 Clinical manifestations and diagnostic findings at admission

	Number of studies	Number of patients reporting	Proportion		Heterogeneity	
			(95% CI)	*P*	I^2,%	*P*
Demographics						
Sex/male	31	4917	57.9 (55.0–60.8)	< 0.001	70.7	< 0.001
Extra-cerebral TB	15	1896	44.9 (35.3–54.6)	< 0.001	93.9	< 0.001
Family history	6	1001	22.3 (7.7–41.7)	< 0.001	97.5	< 0.001
Immunosuppression[a]	15	1951	17.5 (12.3–23.4)	< 0.001	88.5	< 0.001
BCG vaccination	4	1014	35.8 (25.6–46.8)	< 0.001	90.6	< 0.001
HIV infection	23	3138	5.2 (2.0–9.5)	< 0.001	94.6	< 0.001
Clinical manifestations						
Headache	23	3055	78.8 (72.0–84.9)	< 0.001	94.4	< 0.001
Fever	23	3062	86.3 (82.4–89.8)	< 0.001	87.1	< 0.001
Neck rigidity	24	3379	71.5 (63.8–78.7)	< 0.001	95.4	< 0.001
Vomiting	16	2651	59.0 (51.8–66.0)	< 0.001	92.2	< 0.001
Altered consciousness	16	2723	60.8 (55.2–66.3)	< 0.001	87.2	< 0.001
Change in personality	6	591	25.8 (14.7–38.7)	< 0.001	90.7	< 0.001
Anorexia	3	744	59.0 (51.0–66.9)	< 0.001	76.2	0.020
Night sweats	5	1037	31.6 (22.7–41.3)	< 0.001	89.8	< 0.001
Weight loss	7	1213	26.4 (18.5–35.2)	< 0.001	90.2	< 0.001
Cranial nerve palsy	21	3092	28.2 (22.1–34.7)	< 0.001	92.7	< 0.001
Limb weakness	16	3221	23.1 (17.0–29.8)	< 0.001	94.3	< 0.001
Alter sensorium	7	1219	47.4 (40.7–54.2)	< 0.001	81.4	< 0.001
Vision impairment	6	1310	17.3 (9.7–26.5)	< 0.001	90.8	< 0.001
Diplopia	5	648	31.0 (16.7–47.5)	< 0.001	94.5	< 0.001
Ataxia	5	930	4.9 (2.2–8.5)	< 0.001	67.1	0.020
Seizure	22	4299	18.1 (14.0–22.6)	< 0.001	91.7	< 0.001
SIADH	4	559	13.9 (2.6–31.3)	< 0.001	91.8	< 0.001
Myelitis	5	180	7.9 (4.1–12.6)	< 0.001	0.0	0.560
TBM grade[b]						
Stage I	25	3555	26.6 (22.4–30.9)	< 0.001	86.3	< 0.001
Stage II	25	3585	47.3 (43.2–51.4)	< 0.001	81.4	< 0.001
Stage III	27	4074	26.4 (19.2–34.3)	< 0.001	96.5	< 0.001
Imaging findings[c]						
Hydrocephalus	28	3280	38.1 (32.8–43.5)	< 0.001	88.6	< 0.001
Cerebral infarction	25	3428	22.7 (18.4–27.3)	< 0.001	87.4	< 0.001
Tuberculoma	21	2975	22.5 (16.2–29.5)	< 0.001	94.3	< 0.001
Cerebral edema	8	1364	20.4 (15.4–25.9)	< 0.001	80.9	< 0.001
Leptomeningeal enhancement	13	1266	43.3 (28.3–58.9)	< 0.001	96.6	< 0.001
Basal enhancement	17	2211	28.5 (18.6–39.6)	< 0.001	96.4	< 0.001
Arachnoiditis	3	274	5.5 (1.2–12.2)	< 0.001	72.4	0.030
Vasculitis	3	681	7.1 (1.3–16.5)	< 0.001	89.2	< 0.001
Abscess	5	1037	3.1 (1.6–5.0)	< 0.001	39.3	0.160
Abnormal chest X-ray	10	1084	53.2 (42.1–64.2)	< 0.001	91.7	< 0.001
CSF and other laboratory results						
CSF protein > 100 mg/dL	5	780	68.9 (59.7–77.4)	< 0.001	83.4	< 0.001
CSF WBC > 100×10^6/L	6	1032	69.7 (57.5–80.6)	< 0.001	93.6	< 0.001
Lymphocyte-predominant CSF	8	1193	72.1 (60.4–82.5)	< 0.001	94.0	< 0.001
CSF glucose < 2.2 mmol/L	4	745	57.4 (33.9–79.3)	< 0.001	97.1	< 0.001
CSF pressure > 200 mmH_2O	3	371	63.6 (31.7–90.0)	< 0.001	97.3	< 0.001
Low CSF/serum glucose ratio	3	395	80.6 (64.8–92.6)	< 0.001	91.5	< 0.001
Positive CSF smear	17	2180	9.0 (4.1–15.3)	< 0.001	94.4	< 0.001

Table 2 (continued)

	Number of studies	Number of patients reporting	Proportion (95% CI)	*P*	Heterogeneity I^2,%	*P*
Positive CSF culture	21	2531	34.8 (23.8–46.7)	< 0.001	97.1	< 0.001
Positive NAAT result	16	1535	39.3 (26.6–52.7)	< 0.001	95.7	< 0.001
Elevated ESR	3	616	63.3 (48.0–77.3)	< 0.001	91.3	< 0.001
Positive PPD skin test	3	315	37.3 (28.8–46.3)	< 0.001	51.5	0.127

CSF cerebrospinal fluid, *WBC* white blood cell, *ESR* erythrocyte sedimentation rate, *BCG* Bacillus Calmette–Guerin, *NAAT* nucleic acid amplification test, *SIADH* syndrome of inappropriate secretion of antidiuretic hormone, *PPD* purified protein derivative

[a]Patients taking corticosteroids, immunosuppressants, or suffering from diabetes mellitus, alcoholism, malignancy, HIV infection, or other immunodeficiency disorders

[b]TBM grade was defined by the British Medical Research Council

[c]Detected by computed tomography or magnetic resonance imaging

24.7% for 3–9 months (similar to the death rate at more than 9 months). Two studies reported the causes of mortality [22, 23], and both reported the leading cause was elevated intracranial pressure (36/54).

Predictors of mortality

A total of 21 studies described factors associated with death from TBM (Table 4). These prognostic indicators were advanced age (> 60 years; odds ratio [OR] = 2.64, 95% CI 1.27–5.51), extra-cerebral TB (OR = 1.53, 95% CI 1.13–2.08), headache (OR = 0.33, 95% CI 0.17–0.65), altered consciousness (OR = 3.33, 95% CI 1.51–7.36), altered sensorium (OR = 3.31, 95% CI 2.20–4.98), hydrocephalus (OR = 5.27, 95% CI 2.25–12.37), cerebral infarction (OR = 2.35, 95% CI 1.63–3.38), and advanced stage of disease (OR = 6.06, 95% CI 4.31–8.53). Supplementary Fig. 3 shows forest plots for each of these risk factors.

Discussion

TBM is a life-threatening infectious disease worldwide, but there are limited data regarding the outcomes of patients with this disease. The present systematic review and meta-analysis provides comprehensive worldwide estimates of the outcomes and prognostic factors of TBM. Our meta-analysis of all available data on the outcomes of adults with TBM from 1990 onwards estimated that the pooled mortality of TBM was about 20%. Our subgroup meta-analysis indicated higher mortality for patients living in Africa than other areas, possibly because of the low level of economic development, limited access to health care, high prevalence of HIV/AIDS co-infection, and the growing problem of mycobacterial drug resistance in Africa [24]. However, only two studies reported the outcomes of patients with TBM in Africa, and these were retrospective cohort studies with small sample sizes and short follow-up times [21, 25]. Further high-quality prognostic studies that measure outcomes are needed to guide clinical interventions for TBM in Africa.

Our analysis of the follow-up time-specific mortality of TBM indicated that most deaths occurred during the first 3 months. This finding stresses the importance of early diagnosis and treatment, the most important factors affecting outcome [2]. We found that more than one-third of patients had symptoms longer than 2 weeks before admission. This emphasizes the need to educate primary care physicians so they maintain a high index of suspicion for TBM and perform rapid and specific diagnostic tests for this disease.

The CSF microbiological confirmatory examinations for *M. tuberculosis* include microscopy of acid-fast bacillus, cultures, and a nucleic acid amplification test (NAAT). Microscopy has low sensitivity, cultures have high sensitivity but are too slow for clinical decision-making, and NAAT has high sensitivity but is often unavailable in poor areas. Thus, the diagnosis of TBM remains a major clinical challenge, and there is great need for a rapid, sensitive, and simple diagnostic test [26]. Until such a test becomes available, clinicians should maintain high clinical suspicion for this disease, based on clinical data, routine CSF analysis, and neuroimaging signs, and should begin empirical treatment without waiting for confirmatory test results. The most common symptoms and diagnostic findings in our study were fever, headache, neck rigidity, lymphocyte-predominant CSF, and low CSF/serum glucose ratio.

The difficulty of early diagnosis and the high rates of death and disability from TBM emphasize the importance of prevention. We found that only one-third of the patients in the included studies received BCG vaccinations. Although BCG vaccination can reduce the incidence of TBM meningitis in children [27], its effect in adults remains uncertain. However, a recent study demonstrated the long-term efficacy of BCG vaccination against TB in general [28]. Our study found that an

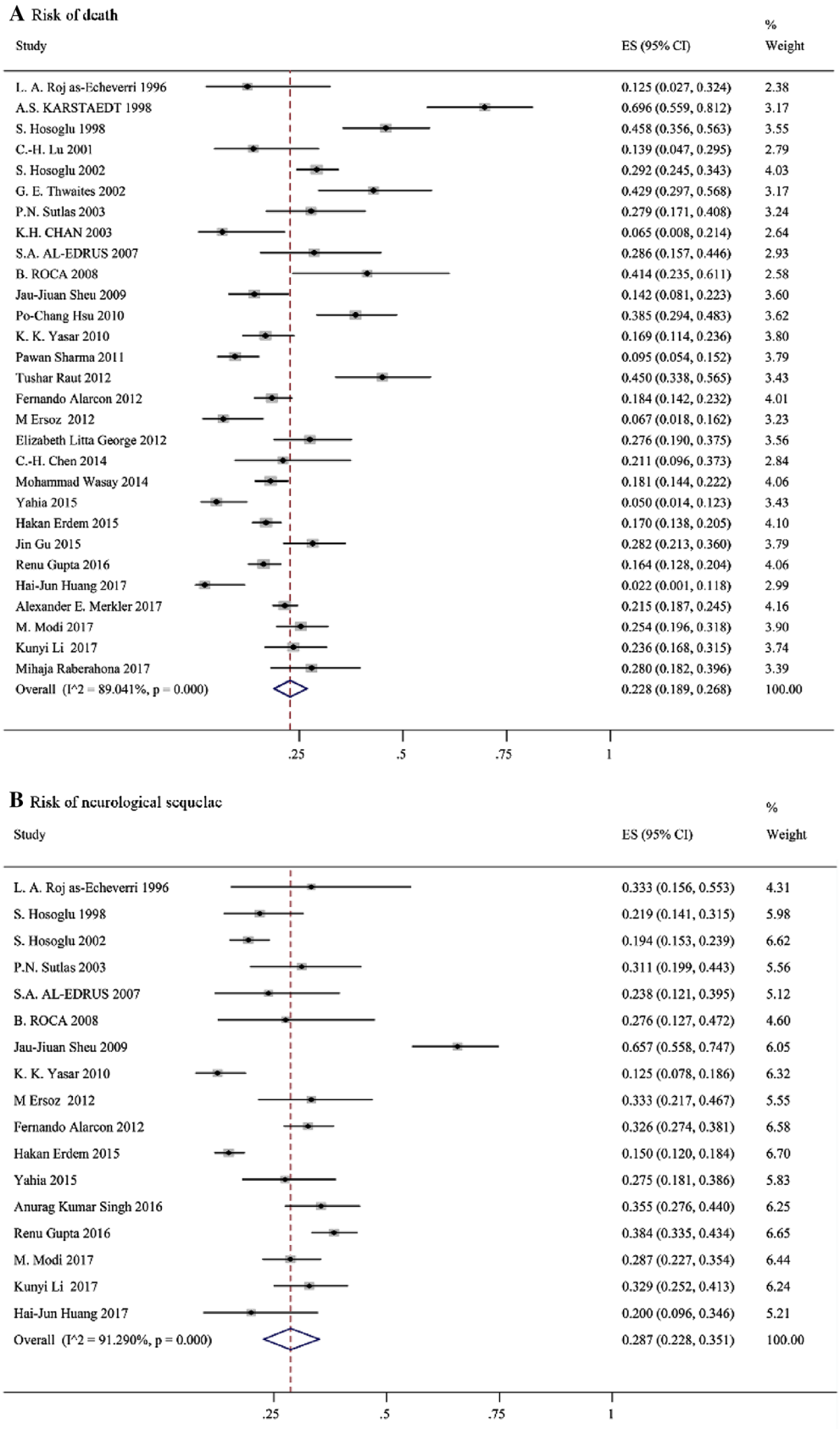


Fig. 3 Risk of death (**a**) and neurological sequelae (**b**) in studies of TBM

Table 3 Subgroup analyses of mortality from TBM

Subgroups	Categories	Studies (*n*)	ES (95% CI)	Heterogeneity I^2 (%)
Location	Americas	3	20.0 (17.6–22.6)	4.5
	Africa	2	45.6 (37.1–54.2)	95.7
	Eastern Mediterranean	2	15.4 (12.3–18.8)	91,0
	Western Pacific	10	21.0 (13.8–29.3)	84.5
	Europe	6	26.4 (16.4–37.3)	89.2
	Southeast Asia	5	23.3 (14.2–33.9)	91.6
	Mixed regions[a]	1	17.0 (13.8–20.5)	–
Sex	Male	7	18.3 (12.2–25.4)	77.6
	Female	7	18.4 (15.2–21.7)	0.0
Diagnosis	Definitive	4	36.1 (16.4–58.4)	92.1
	Clinically suspected	4	21.0 (16.1–26.3)	33.6
Follow-up time	0–3 months	15	18.2 (13.1–23.9)	91.5
	3–9 months	9	24.7 (17.9–32.2)	90.8
	9 months–8 years	9	24.6 (19.0–30.7)	82.3
Study type	Prospective cohort	5	20.9 (11.4–32.3)	88.6
	Retrospective cohort	24	23.1 (18.8–27.7)	89.6

ES effect size

[a]Mixed regions included Europe, Africa, Eastern Mediterranean

Table 4 Predictors of mortality from TBM

	Systematic review and/or meta-analysis						
	Number			Odds ratio		Heterogeneity	
Risk Factor	Studies	Patients (*n*)	Model	(95% CI)	*P* value	I^2,%	*P* value
Demographics characteristics							
Age > 60 years	4	340	Random	2.64 (1.27–5.51)	0.009	27.7	0.246
Male	7	1316	Random	1.07 (0.81–1.42)	0.623	0.0	0.723
Extra-cerebral TB	5	1233	Random	1.53 (1.13–2.08)	0.006	0.0	0.789
Definite TBM	4	795	Random	2.00 (1.02–3.91)	0.043	65.8	0.032
TBM grade							
Stage I	12	1639	Random	0.22 (0.14–0.35)	< 0.001	19.6	0.251
Stage II	12	1639	Random	0.62 (0.37–1.04)	0.070	73.8	< 0.001
Stage III	14	2129	Random	6.06 (4.31–8.53)	< 0.001	29.9	0.138
Clinical manifestations							
Headache	4	354	Random	0.33 (0.17–0.65)	0.002	0.0	0.607
Fever	6	964	Random	0.72 (0.47–1.11)	0.138	0.0	0.519
Neck rigidity	5	1024	Random	1.91 (0.64–5.69)	0.248	83.0	< 0.001
Altered consciousness	6	1276	Random	3.33 (1.51–7.36)	0.003	80.6	< 0.001
Cranial nerve palsy	8	1624	Random	1.55 (0.74–3.25)	0.249	75.6	< 0.001
Limb weakness	4	921	Random	3.15 (0.96–10.35)	0.059	84.6	< 0.001
Alter sensorium	4	840	Random	3.31 (2.20–4.98)	< 0.001	0.0	0.615
Seizure	8	1626	Random	1.29 (0.73–2.26)	0.380	55.9	0.026
Image findings[a]							
Hydrocephalus	8	1259	Random	5.27 (2.25–12.37)	< 0.001	79.3	< 0.001
Cerebral infarction	8	1279	Random	2.35 (1.63–3.38)	< 0.001	17.0	0.296
Tuberculoma	6	1245	Random	0.94 (0.41–2.14)	0.874	81.7	< 0.001

[a]Detected by computed tomography or magnetic resonance imaging

immunocompromised state, including HIV coinfection, occurred in nearly one-fifth of patients. An immunocompromised state could reduce the immune response to *M. tuberculosis*, and TBM patients who are immunocompromised have increased morbidity and mortality [29, 30]. Active interventions for patients who are immunocompromised and enhancement of their immune systems may help prevent or treat TBM.

Our results indicated the risk factors associated with death from TBM were advanced stage of disease and certain demographic characteristics (advanced age, extra-cerebral TB, definite TBM), clinical features (absence of headache, altered consciousness, altered sensorium), and imaging findings (hydrocephalus, cerebral infarction). The British Medical Research Council (BMRC) staging of TBM only considers clinical manifestations, including neurological signs and state of consciousness, and clinicians have used this system to assess the severity and prognosis of TBM since 1948 [31]. Unsurprisingly, we found that advanced-stage disease is strong prognostic factor, in that it is associated with a sixfold increased risk of mortality. In addition to advanced stage, we also found that extra-cerebral TB and definite TBM (which indicates a higher microbial load and a more serious condition) are associated with mortality. The greater mortality in older patients could be explained by their poorer natural defense mechanisms and the presence of more comorbidities. A surprising result was that absence of headache was associated with greater mortality; this could be because absence of headache could delay the diagnosis, or it could be simply be because coma patients who have advanced disease cannot complain of headaches.

Hydrocephalus occurred in nearly two-fifths of our TBM patients, and a patient with hydrocephalus had an approximately fivefold greater probability of death. Thus, appropriate management of hydrocephalus is essential. Hydrocephalus can be communicating or non-communicating. Communicating hydrocephalus is more common and can respond to medical therapy; however, for those who fail medical therapy, rapid intervention is required. For non-communicating hydrocephalus, prompt surgery is required to improve outcome [32]. The main challenge for surgeons is the selection of patients for ventriculo-peritoneal shunting (VPS) or endoscopic third ventriculostomy (ETV). Further research is needed to determine the indications and efficacies of these two procedures [3, 33].

Cerebral infarction occurred in one-fifth of our patients, and was associated with an approximately twofold increased risk of death. A recent randomized trial of HIV-uninfected adults who had TBM suggested that aspirin reduces new infarcts and stroke-associated deaths because of its anti-thrombotic and anti-inflammatory effects [34]. Further large-scale randomized trials are needed to confirm the safety and efficacy of long-term aspirin use in these patients.

Only two of the studies that we examined reported causes of death, and they both indicated that elevated intracranial pressure (ICP) was the major cause. Hydrocephalus is the most common cause of raised ICP, in addition, metabolic abnormalities, such as hyponatremia, hyperthermia, and hypercapnia, could cause cerebral edema and elevated intracranial pressure. Thus, close clinical monitoring of TBM patients should include correction of abnormalities in gas exchange and tissue oxygenation, precise fluid and electrolyte management, and adequate temperature control [33]. Systemic complications, such as sepsis and pneumonia, were responsible for nearly one-third of all deaths in the included studies, and these could be considered as potentially preventable. However, very few studies examined the association of systematic complications with outcomes, so future studies are needed for this important topic.

Study heterogeneity is a major limitation of our results. This is because we included many different types of studies that examined different populations, used different imaging methods and anti-TB treatments, and had different follow-up times. In addition, the diagnostic criteria of TBM and the definitions of some clinical manifestations were not standardized among the included studies. Although we performed subgroup analyses to identify the sources of heterogeneity, significant heterogeneity remained after this analysis. Second, although we included 32 studies in our meta-analysis, there were usually no more than five studies that examined any individual risk factor, thus limiting our statistical power to detect publication bias. Third, we did not assess the prognostic factors for neurological sequelae, because the definition of disability was not uniform among the included studies and because there was no inter-observer reproducibility. Fourth, the included studies had very limited data on the causes of death, thus indicating the need for more prospective studies and further detailed analysis. Fifth, the included studies had very limited focus on some "candidate prognostic factors", and we could not assess these factors.

Conclusion

Our systematic review and meta-analysis examined the clinical characteristics, outcomes, and prognostic factors of adults with TBM. The results indicate high rates of mortality and disability from TBM in adults. Because CSF microbiological confirmatory examination has low sensitivity, clinicians should maintain a high clinical suspicion for this disease based on the clinical features identified in the present study. High-quality prospective studies are needed to assess the impact of different interventions that focus on prognostic factors.

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