Supplementary Table 1 JBI critical appraisal table for analytical cross-sectional studies

REF.	1. Were the criteria for inclusion in the sample clearly defined?	2. Were the study subjects and the setting described in detail?	3. Was the exposure measured in a valid and reliable way?	4. Were objective, standard criteria used for measurement of the condition?	5. Were confounding factors identified?	6. Were strategies to deal with confounding factors stated?	7. Were the outcomes measured in a valid and reliable way?	8. Was appropriate statistical analysis used?	Overall appraisal: 1. Include 2. Exclude 3. Seek further info
Anselmo et al, 2017	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Bhatnagar et al, 2008	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Checkley et al, 2008	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Chusri et al, 2018	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Dendane et al,	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1

2013									
Erdem et al, 2015	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Ersoy et al, 2012	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Fong et al, 2023	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Goenka et al, 2018	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Handryastuti et al, 2023	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
He et al, 2021	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Hristea et al, 2012	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Imam et al, 2020	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Jipa et al, 2013	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Karabela et al, 2021	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Khan et al, 2017	?No	Yes	Yes	Yes	NA	NA	Yes	Yes	1

Kumar et al, 1999	Yes	Yes	Yes	?No	NA	NA	Yes	Yes	1
Lee et al, 2018	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Lu et al, 2021	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Luo et al, 2021	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Patel et al, 2010	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Solari et al, 2018	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Solomons et al, 2016	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Sunbul et al, 2005	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Thwaites et al, 2002	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Vibha et al, 2012	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Wang et al, 2022	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Wen et al, 2022	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1
Yang et al, 2020	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1

Zhang et al, 2014	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	1

Supplementary Table 2 Comparison of Thwaites (2002) to Modified Thwaites Scores

Parameter	Thwaites (2002)	Vibha (2012)
Age	(i) ≥ 36 years: *2 points*	(i) ≥ 26 years: *2 points*
	(ii) < 36 years: *0 points*	(ii) < 26 years: *0 points*
History of illness	(i) ≥ 6 days: *-5 points*	(i) ≥ 7 days: *-5 points*
	(ii) < 6 days: *0 points*	(ii) < 7 days: *0 points*
CSF analysis	A. CSF total white cell count (10^3/mL)	A. CSF total white cell count (10^3/mL)
	(i) ≥ 900: *3 points*	(i) ≥ 500: *3 points*
	(ii) < 900: *0 points*	(ii) < 500: *0 points*
	B. CSF % neutrophils	B. CSF % neutrophils
	(i) ≥ 75: *4 points*	(i) ≥ 83: *4 points*
	(ii) < 75: *0 points*	(ii) < 83: *0 points*
Blood white cell count (10^3/mL)	(i) ≥ 15 000: *4 points*	(i) ≥ 11 500: *4 points*
	(ii) < 15 000: *0 points*	(ii) < 11 500: *0 points*

Supplementary Table 3 Additional internal validation cohorts

Parameter	Luo (2021)	Lu (2021)	Yang (2020)
Sensitivity	79.5%	81.0%	97.0%
Specificity	90.9%	86.3%	81.0%

Supplementary Table 4 Chusri (2018)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Chusri et al, 2018	n=136 Location (years): Thailand (2002 - 2016) Gender (n): Male: 56.6% (77) Female: 43.4% (59) Age, median (range): TBM: 41 years (IQR 27-60) Non-TBM: 43 years (IQR 27-59) Comorbidities (n): HIV: 35.3% (48)	TBM Definite TBM was based on ≥ 2 of 3 of the following (1) Detection of acid-fast staining bacilli from CSF or brain tissue (2) Identification of *M.tuberculosis* from mycobacterial culture from CSF or brain tissue (3) Demonstration of M. tuberculosis DNA in CSF or brain tissue	With cut off score of 10: Sensitivity: 92.0% Specificity: 89.0% AUC of ROC • Overall: 0.956 • HIV infection: 0.766 • Diabetes mellitus: 0.582 • Duration of symptoms: 0.756 • Hydrocephal	Ideal diagnostic population: patients with non-suppurative meningitis.	Poor diagnostic yield of CSF ADA in TBM; as HIV-related neurological diseases can potentially raise CSF ADA level which can lead to false positives and negatives. CSF ADA as a biomarker may not be commonly evaluated; tests may not be readily available.

DM: 19.1% (26) Inclusion criteria: 1) at least 1 presenting symptom of fever, headache, seizure or depressed consciousness 2) at least 1 physical examination sign of fever, cervical stiffness, alteration of consciousness, cranial nerve palsy or plegia/paresis 3) CSF study showing at least 1 piece of evidence of white blood cells (WBCs) 5 cells/high power field (HP) which were <50%	Probable TBM diagnosis was based on the study's inclusion criteria with 3 criteria (1) Confirmation of extracranial TB with acid-fast staining, mycobacterial culture or detection of M. tuberculosis DNA (2) Clinical response with conventional anti-TB agents (3) Detection of acid-fast staining bacilli from CSF or brain tissue without confirmation from mycobacterial culture	us: 0.699 • CSF-ADA >10 IU: 0.832 PPV: 86.0% NPV: 93.0% Positive likelihood ratio: 7.74 Negative likelihood ratio: 0.0900	Studies were carried out retrospectively using patients' medical records, resulting in potential misclassification bias.

	polymorphonuclear leukocytes of all WBCs, glucose 60 mg/dL or CSF plasma glucose ratio 0.4, or protein 50 mg/dL. Exclusion criteria: Patients with brain abscess with or without parameningeal infection and bacterial meningitis with at least 1 of the following laboratory results: 1) conventional bacterial cultures 2) Streptococcus pneumoniae DNA and antigen detection from	or detection of *M.tuberculosis* DNA

	CSF and clinical specimens 3) serologic test or clinical response with conventional antibiotics without clinical subsequence of TBM. Subgroups: TBM: n=60 • TBM: n=55 • Probable TBM: n=5 Non-TBM: n=76 • Carcinomatous meningitis: n=26 • Lymphomatous/ leukaemic meningitis: n=24	

	• Lymphocytic meningitis: n=12 • Cryptococcal meningitis: n=11 • Histoplasmosis with meningitis: n=2 • Penicilliosis with meningitis: n=1 • Invasive aspergillosis with meningitis, n=1

Supplementary Table 5 endane (2013)

Study	Patient Population	Control (ref gold standard)	Outcome Data
Dendane et al, 2013	n=508 Location (years): Morocco (1999 - 2007) Gender (n): Male: 55.3% (281) Female: 44.7% (227) Age, median (range): TBM: 35 years (27-51) BM: 32 years (21-44) Subgroups: TBM: n=274 Bacterial meningitis (BM): n=234	TBM CSF isolation of *M. tuberculosis* or if patients had clinical meningitis with negative Gram stain, sterile culture and ≥ 1 of the following: (1) Extra-neurological TB (isolation of TB at lung, lymph or digestive tract) (2) Cranial CT scan consistent with hydrocephalus and basal meningeal enhancement (diagnosed by at least 1 radiologist) (3) Good response to anti-TB chemotherapy	Sensitivity: 88.0% Specificity: 95.0% AUC of ROC: 0.968

Supplementary Table 6 Ersoy (2012)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Ersoy et al, 2012	n=96 Location (years): Turkey (2000 - 2007) Gender (n): TBM, Male: 33.3% (10) TBM, Female: 66.7% (20) BM, Male: 65.2% (43) BM, Female: 34.8% (23) Age, mean ± SD: TBM: 30 years ± 27 Bacterial meningitis: 45 years ± 36 Subgroups: TBM: n=30	TBM *M. tuberculosis* isolated from CSF or clinical meningitis with negative Gram stain and sterile bacterial and fungal cultures plus ≥ 1 of the following: (1) Cranial tomographic or cranial magnetic resonance image consistent with tuberculoma or hydrocephalus (2) Chest radiograph or CT consistent with miliary or active TB (3) Good response to antituberculous treatment	Sensitivity: 95.5% Specificity: 100% AUC of ROC: 0.995	Does not include Brucella meningitis (excluded due to similarity to TBM); score may be less applicable in areas endemic for Brucella disease. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

Bacterial meningitis (BM): n=66

Supplementary Table 7 Goenka (2018)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments
Goenka et al, 2018	n=865 Location (years): South Africa (2010 - 2014) Gender (n): Male: 50.0% (44) Female: 50.0% (44) Age, median (range): TBM: 5.2 years (5 months-13.3 years) Unlikely TBM: 4.7 years (4 months-13.2 years) Comorbidities (n): TBM, HIV: 50.0% (11) Unlikely TBM, HIV: 35.0% (23)	TBM Positive CSF culture	With a cut off score of ≥4 Development group Sensitivity: 93.0% Specificity: 89.0% Test group Sensitivity: 100% Specificity: 93.0%	Score does not include radiological criteria; investigations can be done quickly with fast results and may be useful when a rapid diagnosis is needed. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

Inclusion criteria:

TBM: microbiologically confirmed TBM

Unlikely TBM: Negative CSF microscopy and culture and

- Did not receive anti-tuberculous treatment
- No death or neurologic sequelae
- Another CSF pathogen isolated

Subgroups:

Confirmed TBM: n=22

Unlikely TBM: n=66

and

Development group: n=60
Test group: n=28

Supplementary Table 8 Handryastuti (2023)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Handryastuti et al, 2023	n=167 Location (years): Indonesia (2011 - 2021) Gender (n): TBM, Male: 51.7% (44) TBM, Female: 48.3% (41) Non-TBM, Male: 63.4% (52) Non-TBM, Female: 36.6% (30) Age, (n): TBM: • <5 years: 63.5% (54) • 5-12 years: 18.9% (16) • 12-18 years: 17.6% (15) Non-TBM:	TBM CSF culture/gram stain + CT/MRI scan with contrast (1) Low CSF glucose and/or low CSF-serum glucose ratio with predominant mononuclear (MN) cells of CSF (2) Presence of basal meningeal enhancement and/or hydrocephalus on head CT scan	With a cut off score of ≥3 Sensitivity: 78.8% Specificity: 86.6% AUC of ROC: 0.890 With a cut off score of ≥ 2 Sensitivity: 61.2% Specificity: 75.2% AUC of ROC: 0.730 Overall Sensitivity: 47.1% Specificity: 95.1%,	Reference gold standard (CSF culture) was not routinely performed for every diagnosis of TBM. Paediatric study population; score has not been validated in an adult population. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias

• <5 years: 67.1% (55) • 5-12 years: 19.5% (16) • 12-18 years: 13.4% (11) Inclusion criteria Paediatric patients aged 3 months to 18 years hospitalised with a diagnosis of TBM or non-TBM from history, physical examination, blood work, chest X-ray imaging, CSF analysis and head CT/MRI examination Exclusion criteria Patients with any of the following • Congenital hydrocephalus • Leg paresis due to hypokalaemia • Other brain parenchymal	PPV: 90.9% NPV: 63.4%

	lesions such as tumours, vascular malformation or intracranial haemorrhage • History of trauma	
	Subgroups: TBM: n=85 Non-TBM: n=82	

Supplementary Table 9 He (2021)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
He et al, 2021	n=241 Location (years): China (2010 - 2016) Gender (n): Male: 64.3% (155) Female: 35.7% (86) Age, mean ± SD: 32.5 years ± 2.96 Inclusion criteria: BM: • Pathogenic bacteria separated from CSF • Clinical meningitis including the following: i) CSF	TBM CSF culture or AFB smear or commercial positive MTB nucleic acid amplification test	Sensitivity: 87.0% Specificity: 94.0% AUC of ROC: 0.962	Score does not include radiological criteria.

		lymphocytes and neutrophils and low glucose concentration (<50% in blood) ii) full recovery without antituberculosis chemotherapy 3 months after admission	
		Exclusion criteria: Patients with unclear diagnosis results, incomplete case data, TBM retreatment and whose course of disease was more than 1 month	
		Subgroups: TBM: n=141 Bacterial meningitis (BM):	

	n=100

Supplementary Table 10 Hristea (2012)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Hristea et al, 2012	n=591 Location (years): Romania (2001-2011) Gender (n): TBM: Male: 57.4% (58) Female: 43.6% (43) VM: Male: 59.6% (258) Female: 41.4% (175) Age, median (range): TBM: 38 years (1–78) VM: 23 years (2–84) Inclusion criteria:	TBM (Marais criteria:) Definite TBM (1) Positive CSF AFB smear (2) Positive CSF culture or commercial nucleic acid amplification test (NAAT) Probable TBM (1) ≥10 points (and cerebral imaging was not available), OR (2) ≥12 points (when cerebral imaging was available)	With cut off score of ≥6, Sensitivity: 92.0% Specificity: 94.0% AUC of ROC: 0.977	Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias. See Hristea et al, 2012; Jipa et al, 2017.

• Abnormal CSF findings of Pleocytosis ⩾ 5 cell/mm3 CSF protein ⩾ 50 mg/dl Positive culture for *M. tuberculosis* or acid-fast bacilli (AFB) on CSF smear Absence of other bacteria or fungi • Clear appearance of CSF, clinical symptoms of meningitis (fever, headache, vomiting, neck stiffness) • Full recovery without antibacterial and antifungal therapy	Possible TBM (1) 6–9 points (cerebral imaging not available), OR (2) 6–11 points (cerebral imaging available)

Exclusion criteria:

- Prior antibiotic treatment (possible pre-treated bacterial

	meningitis), malignancy, autoimmune disorders with CNS involvement and sarcoidosis, unless *M. tuberculosis* was isolated from a biological sample in the patient Subgroups: Viral meningitis (VM): n=433 Definite TBM: n=55 Probable TBM: n=46 Possible TBM: n=57		
Jipa et al, 2017	n=111 Location (years): Romania (2012-2015) Gender (n): TBM: Male: 64.5% (20) Female: 35.5% (11) VM:	TBM Positive CSF culture, GeneXpert MTB/RIF or both VM (1) Bacterial and other noninfectious causes of meningitis were	Specificity: 81.1% Sensitivity: 96.7% for differentiating TBM from VM With a cut off score of ≥6, TBM (n=31) versus VM (n=62): Sensitivity: 96.7%

Male: 37.1% (23) Female: 62.9% (39) Age, median (range): TBM: 38 years (30-54) VM: 34 years (23-46) Comorbidities (in TBM group): HIV: 45.2% (14) Exclusion criteria • Possible TBM • Prior antibiotic therapy • Malignancy • Autoimmune disorders with CNS involvement Subgroups: TBM: n=31	excluded (2) Viral cause was identified (3) Outcome was favorable under antiviral or supportive treatment CM Positive India ink stain, culture, and/or cryptococcal antigen assay.	Specificity: 81.1% AUC of ROC: 0.949 PPV: 75.0% NPV: 97.7% TBM (n=14) versus CM (n=18) in HIV-infected pts: Sensitivity: 86.6% Specificity: 27.7% AUC of ROC: 0.669 PPV: 50% NPV: 71.4% With a cut off score of ≥9, TBM (n=31) versus VM (n=62):

	• Definite: n=21 • Probable: n=10 Viral meningitis (VM): n=62 Cryptococcal meningitis (CM): n=18		AUC of ROC: NA Sensitivity: 51.6% Specificity: 100% PPV: 100% NPV: 77.9%		

Supplementary Table 11 Kumar (1999)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Kumar et al, 1999	n=204 Location (years): Lucknow, India (1994-1997) Age, median: TBM: 42.4 months Non-TBM: 39.0 months	TBM (1) Positive CSF culture or AFB smear (2) basal enhancement or tuberculoma on CT scan with clinical response to antituberculous	One or more predictor variables present Total n=100 TBM n=65 Non-TBM n=35 Sensitivity: 98.4%		Score does not include complex laboratory investigations and radiological criteria; may be useful in resource-poor

	treatment, with or without other antibiotics	Specificity: 43.5%	settings.
Inclusion criteria: • Children between the ages of 1 month and 12 years admitted with a diagnosis of meningoencephalitis on the basis of history, examination, and pleocytosis in CSF Exclusion criteria: • Final diagnosis could not be reached on the basis of the	Non-TBM (1) CSF was positive for bacterial culture/Gram stain (n=18) (2) Sustained response without antituberculous treatment (n=76)	Two or more predictor variables present Total n=59 TBM n=51 Non-TBM n=8 Sensitivity: 77.2% Specificity: 87.0% Three or more predictor variables present Total n=37 TBM n=36 Non-TBM n=1 Sensitivity: 54.5% Specificity: 98.3%	Score's clinical criteria are more consistent with later presentations of TBM. Score may not be as applicable to early TBM patients. Paediatric study population; score has not been validated in an adult population.

		diagnostic (gold standard) criteria either because the patient died early or because a CT scan could not be done or was non-confirmatory.		
Bhatnagar et al, 2008	Subgroups: TBM: n=110 Non-TBM: n=94 n=124 Location (years): India (2003 - 2004) Age range: 1 month - 12 years	TBM Clinical picture, CSF biochemistry (cell count, protein, sugar, ADA, , CSF TB culture, CT scan findings and response	Sensitivity: • TBM Stage I: 37.0% • TBM Stage II: 51.9%	Score with positive CSF-ADA (>8IU/l) Sensitivity: • TBM Stage I: 67.3%

Subgroups: TBM: n=72 Partially treated pyogenic meningitis: n=24 Aseptic meningitis: n=20 Febrile seizures: n=8	to therapy	• TBM Stage III: 81.7% Specificity • TBM Stage I: 58.1% • TBM Stage II: 61.7% • TBM Stage III: 66.2%	• TBM Stage II: 75.9% • TBM Stage III: 86.1% Specificity: • TBM Stage I: 73.2% • TBM Stage II: 78.2% • TBM Stage III: 83.1%	Score with positive CSF-ADA and negative CSF-CRP Sensitivity: • TBM Stage

	I: 76.5% • TBM Stage II: 83.1% • TBM Stage III: 88.9% Specificity: • TBM Stage I: 79.6% • TBM Stage II: 80.1% • TBM Stage III: 87.8%

Supplementary Table 12 Lee (2018)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Lee et al, 2018	Total n=98 Location (years): South Korea (2006 - 2015) Gender (n): TBM: Male: 68.1% (32) Female: 31.9% (15) VM: Male: 66.7% (34) Female: 33.3% (17) Age, median (range): TBM: 38 years (27.5-51.0) VM: 45 years (38.0-65.5)	TBM (1) Definite TBM: Positive CSF TB culture or MTB PCR (2) Probable TBM: clinical meningitis with extra-neural TB evidence or with neuroimaging findings suggestive of TBM (hydrocephalus or tuberculoma) (3) Possible TBM: good response with empirical TB medication after at least 6 months without evidence of other meningitis.	Sensitivity: 89.4% Specificity: 80.4% AUC of ROC: 0.901 PPV: 89.1% NPV: 80.8%	Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

Comorbidities, (n):

TBM:

- Hypertension: 14.9% (7)
- Diabetes mellitus: 6.38% (3)
- Chronic liver disease: 4.26% (2)
- Chronic kidney disease: 4.26% (2)
- Past TB history: 8.51% (4)
- Malignancy: 2.13% (1)
- HIV/AIDS: 6.38% (3)

VM:

- Hypertension: 11.8% (6)
- Diabetes mellitus:

11.8% (6)

- Chronic kidney disease: 1.96% (1)
- Past TB history: 5.88% (3)
- Malignancy: 1.96% (1)

Exclusion criteria:

- Received TB medication within 1 month prior to admission
- Underwent neurosurgical operation in the month before or the month following admission
- Patients who had not

undergone follow-up

Subgroups:

TBM: n=47

- Definite TBM n=7
- Probable TBM: n=6
- Possible TBM: n=34

Viral meningitis (VM): n=51

Supplementary Table 13 Lu (2021)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Lu et al, 2021	n=382 Location (years): China (2015 - 2018) Gender (n): TBM: Male: 47.8% (54) Female: 52.2% (59) VM: Male: 60.1% (86) Female: 39.9% (57) CM: Male: 62.3% (38) Female: 37.7% (23) BM:	TBM CSF positive for modified Ziehl-Neelsen stain or *M. tuberculosis* culture, and/or positive GeneXpert MTB/RIF. VM Confirmed viral aetiology or favourable outcome under supportive or antiviral treatment, after ruling out bacterial, tuberculous, fungal, and non-infectious causes of meningitis. CM CSF positive for India ink	With a cut off score of ≥5, Sensitivity: 85.8% Specificity: 87.7% AUC of ROC: 0.923 Additional validation cohort: With a cut off score of ≥5, Sensitivity: 81.0% Specificity: 86.3% AUC of ROC: 0.884 PPV: 83.3%	Primary focus was on early TBM presentation, score may perform differently with patients who present with late TBM features. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

Male: 61.5% (40) Female: 38.5% (25) Age, mean ± SD: TBM: 39.0 years ± 17.2 VM: 39.3 years ± 17.3 CM: 50.8 years ± 16.0 BM: 44.1 years ± 16.2 Inclusion criteria: Refer to control (ref gold standard) Exclusion criteria: ● Age under 18 ● Data was insufficient ● Pregnant mothers ● Patients treated for	stain or fungal culture, and/ or cryptococcal antigen. BM Bacteria isolated from CSF or Clinical meningitis with all of the following: (1) neutrophils dominant in CSF, (2) low concentration of glucose in CSF (< 50% of that in the blood), (3) sterile blood and CSF cultures, (4) full recovery (without anti-tuberculosis chemotherapy) 3 months after admission

	TBM but were not definite TBM patients • Patients with HIV positivity • If they had received more than 7 days of treatment for the current infection • If they have more than two types of microbial infection • If they underwent a neurosurgical operation during the month before admission	
Subgroups: TBM: n=113		

Viral meningitis (VM): n=143 Cryptococcal meningitis (CM): n=61 Bacterial meningitis (BM): n=65	
Additional validation cohort: Total n=114 TBM: n=63 VM: n=27 BM: n=14 CM: n=10	

Supplementary Table 14 Luo (2021)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Luo et al, 2021	n=174 Location (years): China (2017 - 2021) Gender, (n): TBM: • Male: 67.1% (51) • Female: 32.9% (25) BM: • Male: 70.4% (69) • Female: 29.6% (31) Age, median (range): TBM: 44 years (27-58) BM: 42 years (30-54) Inclusion criteria:	TBM Positive *M. tuberculosis* culture and/or positive GeneXpert MTB/RIF in CSF, with clinical symptoms and radiological characteristics suggestive of TBM. BM Isolation of bacteria from CSF using culture. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) was used for	With cut off score of 0.54, Sensitivity: 81.6% Specificity: 91.8% PPV: 88.6% NPV: 86.5% AUC of ROC: 0.949 Additional validation cohort: With cut off score of 0.54 Sensitivity: 79.5% Specificity: 90.9% PPV: 83.8% NPV: 88.3%	Calculation of score may not be intuitive and difficult to implement. CSF chlorine as a laboratory marker may not be commonly evaluated; tests may not be readily available. Score does not include non-bacterial meningitis (viral, fungal and autoimmune).

- Confirmed diagnosis of TBM/BM bacteria identification.

AUC of ROC: 0.923

Exclusion criteria:

- No confirmed diagnosis
- Anti-TB treatment within 2 weeks prior to enrollment

Subgroups:

TBM: n=76

Bacterial meningitis (BM): n=98

Additional validation cohort:

Total n=105

TBM n=39

BM n=66

Gender, (n):

TBM:

- Male: 66.7% (26)
- Female: 33.3% (13)

BM:

- Male: 65.0% (43)
- Female: 35.0% (23)

Age, median (range):

TBM: 45 years (29-59)

BM: 39 years (26-54)

Supplementary Table 15 Marais (2010)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Anselmo et al, 2017	n=300 Location (years): Brazil (2012 - 2013) Gender (n): TBM, Males: 70.0% (23) TBM, Females: 30.0% (10) Without TBM, Males: 55.0% (146) Without TBM, Females: 45.0% (121) Age, mean: 43 years Comorbidities (n): Total HIV: 49.7% (149) TBM, HIV: 60.0% (20)	TBM CSF culture and/or PCR, patients with culture and/or positive PCR in clinical specimens from outside the CNS (i.e. sputum, biopsy, bronchoalveolar wash) with neurological symptoms and CSF abnormalities who had improved after TB treatment, or autopsy and histopathological findings	With cut off score of ≥6, Sensitivity: 100% Specificity: 48.7% PPV: 24.1% NPV: 100% With cut off score of ≥8, Sensitivity: 84.9% Specificity: 77.2% AUC of ROC: 0.900 With reviewed Brazilian adjusted cut off score of ≥	CSF-PCR Sensitivity: 48.0% Specificity: 99.0% Original Marais cut-off may be less applicable in high-burden countries and should be lowered.	Score does not accurately distinguish between TBM and BME, see Erdem et al, 2015. Some studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias. See Imam et al, 2020; Erdem et al, 2015; Fong et al, 2023;

Without TBM, HIV: 48.0% (129) Inclusion criteria: Patients under investigation of TBM Exclusion criteria: Patients with any of the following • Severe intracranial hypertension • Coagulopathy • Conditions contraindicating lumbar puncture • Age<12 years Subgroups:	10 Sensitivity: 100% Specificity: 40.8% PPV: 17.3% NPV: 100% With reviewed Brazilian adjusted cut off score of ≥ 10 associated with CSF-PCR Sensitivity: 90.9% Specificity: 86.9% PPV: 46.2% NPV: 98.9%	Wang et al, 2022; Wen et al, 2022; Karabela, 2021.

	Confirmed TBM: n=33 Confirmed without TBM: n=267		
Imam et al, 2020	n=156 Location (years): Qatar (2007 - 2014) Gender (n): TBM: Male: 81.3% (65) Female: 18.8% (15) Controls: Male: 81.6% (62) Female: 18.4% (14) Age, mean ± SD: TBM: 30.3 years ± 8.90 Controls: 36.6 years ± 14.0	TBM Clinical criteria: cases suffering from fever, headache, meningism, altered sensorium or focal deficits on physical examination with ≥1 of the following in the absence of alternative diagnosis: (1) detection of acid-fast bacilli in CSF, or other sterile body fluids, or tissue under direct microscopy with Zeihl-Neelsen stain, or growth of such bacteria in culture, (2) positive CPR in CSF or	Using a cutoff of ≥6, All suspected TBM Vs controls: Sensitivity: 83.8%, Specificity: 85.5% AUC of ROC: 0.930 PPV: 85.9% NPV: 83.3% Subgroups Culture positive TBM vs bacterial: Sensitivity: 85.7%

Inclusion criteria TBM diagnosed using clinical, CSF criteria and clinical judgment. Controls: • Patients were diagnosed as having bacterial, viral or fungal if pathogenic bacteria, viral or fungal pathogens were isolated from the CSF. • Partially treated meningitis was diagnosed if: i) Clinical meningitis is	sterile body fluids (3) a history of close contact with an active pulmonary TB case (4) prior TB infection or family history of TB (5) characteristic findings suggestive of TB on brain imaging (basal meningitis, tuberculoma, etc.), (6) presence of pulmonary TB findings such as active infiltration, miliary pattern, or cavitation in pulmonary imaging, and (7) a favorable response to antituberculous therapy,	Specificity: 92.9% PPV: 93.8% NPV: 83.9% Culture Positive TBM Vs Nonbacterial: Sensitivity: 85.7% Specificity :81.3% PPV: 76.9% NPV: 88.6% Culture Positive TBM Vs Controls: Sensitivity: 85.7% Specificity: 85.5% PPV: 73.2%

	diagnosed. ii) And all the following: a) Excess neutrophils or lymphocytes in the CSF, (> 5 cells/uL). b) A low concentration of glucose in the CSF (< 50% of that in blood), c) Antibiotic administration prior to CSF drainage. d) Full recovery without anti-tuberculosis drugs.		NPV: 92.9%
•	Aseptic meningitis		

is diagnosed when CSF shows pleocytosis (> 5cell/uL), no pathogen is detected and no prior antibiotic history and a normal CSF glucose.

Exclusion criteria

- Chemical and iatrogenic meningitis due to intraventricular hemorrhage or post neurosurgical procedures

	Subgroups: TBM: n=80 • Culture proven: n=35 • Probable/possible TBM: n=45 Controls: n=76 • Aseptic: n=18 • Viral: n=23 • Bacterial: n=28 • Partially treated bacterial: n=3 • Fungal: n=4		
Karabela et al, 2021	n=20 Location (years): Turkey (2015-2019) Gender (n): Male: 80.0% (16)	TBM (1) *M. tuberculosis* isolation from CSF or clinical signs of meningitis (2) With negative Gram or Indian ink stain and	Sensitivity: 100%

	Female: 20.0% (4) Age, mean ± SD: 39.1 years ± 15.5 Inclusion criteria: • TBM Exclusion criteria: • Viral, brucellar, and fungal etiologies were excluded	negative culture for bacterial or fungal agents, in the presence of ≥1 of the following features: • Cranial imaging findings compatible with TB • Signs of accompanying pulmonary TB • Positive family history for TB • Close contact with an active TB case • Clinical response to antituberculous therapy	
Yang et al, 2020	n=103	TBM: *M. tuberculosis* isolated	Using a cutoff of ≥6,

Location (years): China (2012-2016) Gender (n): TBM: Males: 62.0% (36) Females: 38.0% (22) BM: Males: 73.0% (33) Females: 27.0% (12) Age, median (range): TBM: 52 years (19-75) BM: 42 years (16-70) Inclusion criteria: Patients with clinical and CSF features of community-acquired	from CSF: n=6 Clinical TBM features: n=52 BM: Bacteria isolated from CSF	Sensitivity: 97.0% Specificity: 56.0% AUC of ROC: 0.979 PPV: 74.0% NPV: 93.0%

meningitis who were ≥ 12 yo

Exclusion criteria:

- Meningitis in post-operative neurosurgical conditions, post-traumatic meningitis, parameningeal infections, brain abscess
- Chronic non-tb meningitis
- HIV positive patients

Subgroups:

	TBM: n=58 Bacterial meningitis (BM): n=45		
Wen et al, 2022	n=161 Location (years): China (2004-2019) Gender (n): TBM: Males: 60.5% (69) Females: 39.5% (45) BM: Males: 68.1% (32) Females: 31.9% (15) Age, mean ± SD: TBM: 44.5 ± 29.3 BM: 42.0 ± 28.0	TBM: Definite TBM: smear microscopy for AFB in CSF or MTB, which were cultured in CSF or a commercial positive MTB nucleic acid amplification test. BM: Pathogenic bacteria isolated from the CSF; or clinical meningitis with all of the following: lymphocytes and neutrophils in CSF; low glucose concentration in	Using a cutoff of ≥6, Sensitivity: 93.0% Specificity: 68.0% AUC of ROC: 0.954 PPV: 0.880% NPV: 0.800%

	Exclusion criteria: Insufficient data for a definitive diagnosis. Subgroups: TBM: n=114 Bacterial meningitis (BM): n=47	the CSF (< 50% of that in blood); sterile blood and CSF cultures; and full recovery (without anti-TB chemotherapy) 3 months after admission (these criteria were modified to full recovery at the time of discharge).	
Wang et al, 2022	n=30 Location (years): China (2006-2019) Gender, (n): Males: 53.3% (16) Females: 46.7% (14) Age, mean ± SD: 7.2 years ± 5.1	TBM: Presence of acid-fast bacilli (AFB) in cerebrospinal fluid (CSF) microscopy, CSF nucleic acid amplification test (NAAT, +), or *M.tuberculosis* cultured from CSF.	Using a cutoff of ≥6, Sensitivity: 100%

Erdem et al, 2015	n=484 Location: Turkey Gender (n): TBM, Male: 52.1% (99) TBM, Female: 47.9% (91) BME, Male: 54.1% (159) BME, Female: 45.9% (135) Age, median (range) TBM: 41 years (21-61) BME: 37 years (21-53) Inclusion criteria: BME: all of the following: • Presence of clinical symptoms consistent with	TBM: Clinical evidence of meningitis and microbiological confirmation of TBM, including culture, PCR analysis and Ehrlich-Ziehl-Neelsen staining from CSF	Using a cutoff of ≥6, Sensitivity: 96.8% Specificity: 3.06%

	either meningitis or meningoencephalitis • Presence of typical cerebro- spinal fluid (CSF) findings consistent with meningitis • Presence of positive culture or serological tests for brucellosis in the blood or in the CSF • Absence of an alternative neurological diagnosis
Subgroups:	

	TBM: n=190 Brucellar meningoencephalitis (BME): n=294		
Fong et al, 2023	n=113 Location (years): China (2009-2019) Gender (n): Anti-TBM treatment: Male: 76.0% (41) Female: 24.0% (13) Non-anti-TBM treatment: Male: 63.0% (37) Female: 37.0% (22) Age, median (range): Anti-TBM treatment: 39 years (32-51)	TBM Positive CSF culture (Ziehl-Neelsen staining) and nucleic acid amplification tests.	Using a cutoff of ≥6, Sensitivity: 66.7% Specificity: 84.8%

	Non-anti-TBM treatment: 43 years (27-58) Inclusion criteria Clinical entry criteria by Lancet: (headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy) Exclusion criteria: Patients with missing records, basic information, diagnostic details, TBSA results, or a large amount of laboratory examination data (more than four parameters for each	

	patient) Subgroups: Clinical resolution by anti-TBM treatment: n=54 Clinical resolution by non-anti-TBM treatment: n=59

Supplementary Table 16 Patel (2010)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Patel et al, 2010	n=148 Location (years): South Africa (2008-2009) Gender (n): Definite TBM: Male: 46.1% (18) Female: 53.9% (21) Non-TBM: Males: 29.6% (16) Females: 70.4% (38) Age, mean ± SD: Definite TBM: 33.5	TBM Positive CSF PCR or culture for *M. tuberculosis*.	AUC of ROC • LAM only: 0.740 • CPR≥6 + LAM: 0.800 • CPR ≥ 4: 0.860 • CPR ≥6: 0.860 • CPR ≥4 + LAM: 0.770 LAM antigen test + clinical index with cut off point ≥6: Sensitivity: 38.0% Specificity: 93.0%	LAM antigen test only: Sensitivity 14.0% Specificity 94.0% PPV 81.0% NPV 39.0% Used alone, negative LAM antigen test cannot exclude absence of TBM.	Carried out in South African study population with high HIV prevalence; score may perform differently in populations with lower HIV prevalence.

years ± 9.50 Non-TBM: 32.9 years ± 9.70 Exclusion criteria: ● No CSF ● Uncertain diagnosis Subgroups: Definite TBM: n=39 Probably TBM: n=55 Non TBM: n=54	PPV: 90.0% NPV: 47.0%

Supplementary Table 17 Solari (2018)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Solari et al, 2018	n=155 Location (years): Peru (2009-2012) <u>Comorbidities (n):</u> • Non TB meningitis (bacterial, viral, cryptococcal): 23.9% (37) • Non-meningeal infections (toxoplasmosis, severe sepsis w neurological impairment):16.	<u>TBM</u> Any of the following: (1) Positive AFB in smears, positive culture or positive PCR test for *M. tuberculosis* (2) Bacteriological evidence in other specimens: positive culture for *M. tuberculosis* in other body fluids or biopsies and a negative Gram staining and cultures for bacteria, negative cryptococcal latex	With cut-off of <1 point Sensitivity: 94.9% Specificity: 52.6% With cut-off of ≥3 points Sensitivity: 55.9% Specificity: 94.7% AUC of ROC: 0.870	42.4% (25) of TBM patients were diagnosed by bacteriological tests in CSF, or other body fluids while 57.6% (34) were diagnosed by "clinical plausibility" as determined by a database manager. Good clinical response to anti-TBM therapy is not clearly defined.	Score does not include radiological criteria due to inconsistent availability in resource-constrained settings. CSF ADA as a biomarker may not be commonly evaluated; tests may not be readily available.

	8% (26) • Miscellaneous (subarachnoid hemorrhage, metabolic encephalopathies): 21.3% (33)	agglutination test and negative culture for fungi in CSF (3) Clinical plausibility, defined as negative Gram staining and cultures for bacteria, a negative cryptococcal latex agglutination test and negative cultures for fungi in CSF and the decision of a national tuberculosis programme expert to initiate antituberculosis therapy and good clinical response (complete resolution of
<u>Inclusion criteria:</u> Had to have at least two of the following: headache, irritability, vomiting, fever, seizures, neurological deficit or altered consciousness, with no other explanatory medical condition. <u>Exclusion criteria:</u>		

• Patients who upon admission had already a defined diagnosis and had been put on treatment. • Patients who had a concomitant infection with 2 agents	the constitutional symptoms at one month after treatment initiation).	

Supplementary Table 18 Solomons A (2016)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Solomons et al, 2016	n=139 Location (years): South Africa (2010 - 2013) Gender (n): Male: 60.4% (84) Female: 39.6% (55) Age, median (range): TBM: 31 months (21-54) BM: 29 months (20-81) VM: 62 months (22-92)	TBM Clear CSF changes with pleocytosis 10-500/muL, increased protein > 1g/dl and decreased glucose < 2.2 mmol/L and CSF:serum < 50% with ≥ 2 of the following: (1) Recent contact with infectious TB source case or positive TST (2) CXR suggestive of TB (3) CT/MRI	Probable TBM score Sensitivity: 97.0% Specificity: 48.0%	3 variables were found to be significantly associated with TBM, see Table 17: Solomons B (2016). Overall outcome of a probable TBM score is better than Solomons B (2016) (3-variable predictive model), but may be of less use in resource-constrained settings due to radiological criteria.	Paediatric study population; score has not been validated in an adult population. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

	demonstrating
Inclusion criteria:	features of TBM
All children aged 3	(hydrocephalus,
months to 13 years	meningovascular
with clinically	enhancement,
suspected meningitis	infarction,
(fever, irritability,	granuloma)
lethargy, bulging	
fontanelle in children	BM
aged ,18 months,	(1) microscopy
nuchal rigidity, fever	and/or culture
with or without	confirmation of a
headache or	bacterial pathogen on
photophobia in	CSF
children aged 718	(2) purulent CSF with
months) confirmed	or without culture
using CSF analysis	confirmation of a
	bacterial pathogen on
	blood
Subgroups:	

	TBM: n=79 Bacterial meningitis (BM): n=10 Viral meningitis (VM): n=50	VM CSF PCR, or the clinical outcome was favourable with only supportive care and other causes of meningitis were excluded.		

Supplementary Table 19 Solomons B (2016)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Solomons et al, 2016	n=139 Location (years): South Africa (2010 - 2013) Gender (n): Male: 60.4% (84) Female: 39.6% (55) Age, median (range): TBM: 31 months (21-54) BM: 29 months (20-81) VM: 62 months (22-92) Inclusion criteria: All children aged 3 months to 13 years with clinically suspected meningitis (fever,	TBM Clear CSF changes with pleocytosis 10-500/muL, increased protein > 1g/dl and decreased glucose < 2.2 mmol/L and CSF:serum < 50% with ≥ 2 of the following: (1) Recent contact with infectious TB source case or positive TST (2) CXR suggestive of TB (3) CT/MRI demonstrating features of TBM (hydrocephalus, meningovascular enhancement, infarction, granuloma)	3-Variable Predictive Score Sensitivity: 79.0% Specificity: 78.0% AUC of ROC: 0.820	Paediatric study population; score has not been validated in an adult population. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

	irritability, lethargy, bulging fontanelle in children aged ,18 months, nuchal rigidity, fever with or without headache or photophobia in children aged 718 months) confirmed using CSF analysis Subgroups: TBM: n=79 Bacterial meningitis (BM): n=10 Viral meningitis (VM): n=50	BM (1) microscopy and/or culture confirmation of a bacterial pathogen on CSF (2) purulent CSF with or without culture confirmation of a bacterial pathogen on blood VM CSF PCR, or the clinical outcome was favourable with only supportive care and other causes of meningitis were excluded

Supplementary Table 20 Thwaites (2002)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Thwaites et al, 2002	n=251 (original population) Location (years): Vietnam (1997-2000) Gender (n): TBM: Males: 64.0% (91) Females: 36.0% (52) BM: Males: 78.0% (84) Females: 22.0% (24) Age, median (range): TBM: 34 years (16-64) BM: 41 years (17-70) Subgroups:	TBM: *M. tuberculosis* isolated from CSF OR clinical meningitis with negative gram and India ink stains, plus sterile bacterial anti fungal cultures, plus ≥ 1 of the following: (1) Cranial CT scan consistent with tuberculous meningitis (hydrocephalus, oedema, basal meningeal enhancement) (2) Chest radiograph consistent with active pulmonary tuberculosis (3) Good response to antituberculosis chemotherapy BM Pathogenic bacteria isolated	Original population Sensitivity 97.0% Specificity: 91.0% AUC of ROC: 0.990 Test data population Sensitivity: 86.0% Specificity: 79.0%		Originally formulated with a study population that did not include patients with non-bacterial meningitis (viral, fungal and autoimmune). Score does not perform well in patients with CM. In one study, all patients with CM (n=12) were

	TBM: n=143 + 42 BM: n=108 + 33 Exclusion criteria: Does not meet diagnostic criteria fully Normal CSF glucose n=75 (test data population for internal validation) Subgroups: TBM: n=42 Bacterial meningitis (BM): n=33	from CSF fluid OR clinical meningitis with all of the following: (1) Lymphocytes and neutrophils in CSF (2) Low concentration of glucose in CSF (<50% of that in blood) (3) Sterile blood and CSF cultures (4) Full recovery without antituberculosis chemotherapy 3 months after admission		wrongly classified as TBM. See Checkley et al, 2008. Score includes age as a criterion, which yields different outcomes in different populations. In one study, exclusion of this criterion produced improved outcomes. See Vibha et al,
Imam et al, 2020	n=156 Location (years): Qatar (2007 - 2014) Gender (n): TBM:	TBM (1) Clinical criteria: cases suffering from fever, headache, meningism, altered sensorium or focal deficits on physical examination.	Using a cutoff of ≤4, all suspected TBM vs controls: Sensitivity: 97.5%	

Male: 81.3% (65) Female: 18.8% (15) Controls: Male: 81.6% (62) Female: 18.4% (14) Age, mean ± SD: TBM: 30.3 years ± 8.9 Controls: 36.6 years ± 14.0 Inclusion criteria TBM • Clinical criteria: cases suffering from fever, headache, meningism, altered sensorium or focal deficits on physical	(2) CSF criteria: including any of: lymphocytic pleocytosis (> 20 cells/ uL, > 50% lymphocytes), decreased glucose (less than 50% of blood glucose) and increased protein levels in the CSF (> 0.5 g/L). and ≥1 of the following: (1) detection of acid-fast bacilli in CSF, or other sterile body fluids, or tissue under direct microscopy with Zeihl-Neelsen stain, or growth of such bacteria in culture, (2) detection of M. tuberculosis DNA in CSF or in other sterile body fluids or in tissue with PCR, (3) a history of close contact	Specificity: 40.8% AUC of ROC: 0.80 PPV: 63.4% NPV: 93.9% Subgroups Culture positive TBM vs bacterial: Sensitivity: 100% Specificity: 80.7% PPV: 85.4% NPV: 100% Culture Positive TBM vs	2012. Score does not distinguish between TBM and partially treated BM effectively, but may be improved with inclusion of T-SPOT.TB or MRI results. See Zhang et al, 2014. Some studies were carried out retrospectively using patients'

examination. • CSF criteria: including any of: lymphocytic pleocytosis (> 20 cells/ uL, > 50% lymphocytes), decreased glucose (less than 50% of blood glucose) and increased protein levels in the CSF (> 0.5 g/L). • In addition, subjects should have any of the following: (i) detection of acid-fast bacilli in CSF, or other sterile body fluids, or tissue under direct microscopy with Zeihl-Neelsen stain, or growth of such bacteria in	with an active pulmonary TB case (4) prior TB infection or family history of TB (5) Characteristic findings suggestive of TB on brain imaging (basal meningitis, tuberculoma, etc.), (6) presence of pulmonary TB findings such as active infiltration, miliary pattern, or cavitation in pulmonary imaging, and (7) a favorable response to antituberculous therapy, (8) no alternative diagnosis is available.	Nonbacterial: Sensitivity: 100% Specificity: 80.7% PPV: 45.5% NPV: 100% Culture Positive TBM vs Controls: Sensitivity: 100% Specificity: 40.8% PPV: 43.8% NPV: 100%		medical records resulting in potential misclassification bias. See Imam et al, 2020; Erdem et al, 2015; Sunbul, 2005; Vibha et al, 2022; Karabela et al, 2021; Khan et al, 2017; Zhang et al, 2014.

culture,

(ii) detection of *M. tuberculosis* DNA in CSF or in other sterile body fluids or in tissue with PCR,

(iii) a history of close contact with an active pulmonary TB case

(iv) prior TB infection or family history of TB

(v) Characteristic findings suggestive of TB on brain imaging (basal meningitis, tuberculoma, etc.),

(vi) presence of pulmonary TB findings such as active infiltration, miliary pattern, or

cavitation in pulmonary imaging, and

(vii) a favorable response to antituberculous therapy,

(viii) no alternative diagnosis is available.

Controls

- Patients were diagnosed as having bacterial, viral or fungal if pathogenic bacteria, viral or fungal pathogens were isolated from the CSF.
- Partially treated meningitis was diagnosed if:

  i) Clinical meningitis is diagnosed.

ii) And all the following:

a) Excess neutrophils or lymphocytes in the CSF, (> 5 cells/uL).

b) A low concentration of glucose in the CSF (< 50% of that in blood),

c) Antibiotic administration prior to CSF drainage.

d) Full recovery without anti-tuberculosis drugs.

- Aseptic meningitis is diagnosed when CSF shows pleocytosis (> 5cell/uL), no pathogen is detected and no prior antibiotic history and a normal CSF glucose.

Exclusion criteria

- Chemical and iatrogenic meningitis due to intraventricular hemorrhage or post neurosurgical procedures

Subgroups:

TBM: n=80

- Culture proven: n=35
- Probable/possible TBM: n=45

Controls: n=76

- Aseptic: n=18
- Viral: n=23
- Bacterial: n=28
- Partially treated bacterial: n=3

	• Fungal: n=4		
Karabela et al, 2021	n=20 Location (years): Turkey (2015-2019) Gender (n): Male: 80.0% (16) Female: 20.0% (4) Age, mean ± SD: 39.1 years ± 15.5 Inclusion criteria: • Suspected TBM Exclusion criteria: • Viral, brucellar, and fungal etiologies were excluded	TBM *M. tuberculosis* isolation from CSF or clinical signs of meningitis with negative Gram or Indian ink stain and negative culture for bacterial or fungal agents, in the presence of ≥1 of the following: (1) Cranial imaging findings compatible with TB (2) The signs of accompanying pulmonary TB (3) Positive family history for TB (4) Close contact with an active TB case (5) Clinical response to antituberculous therapy	Sensitivity: 100%
Khan	n=72	TBM	With cut off

et al, 2017	Location (years): Pakistan (2011-2013) Gender (n): TBM: Male: 64.0% (27) Female: 36.0% (15) PM: Male: 53.0% (16) Female: 47.0% (14) Age, mean ± SD: TBM: 33.1 years ± 19.1 PM: 37.9 years ± 22.5 Inclusion criteria: • Clinically diagnosed TBM, based on duration of the illness, previous	Clinical diagnosis was based on the duration of the illness, previous exposure to TB, previous history of TB, physical examination, blood culture and radiological findings (such as basal enhancement, hydro-cephalus and presence of tuberculomas on CT).	score of ≤3.5, Sensitivity: 95.0% Specificity: 23.5% AUC of ROC: 0.666

	exposure to TB, previous history of TB, physical examination, blood culture and radiological findings (such as basal enhancement, hydro-cephalus and presence of tuberculomas on CT).		
Zhang et al, 2014	Subgroups: TBM: n=42 Pyogenic meningitis (PM): n=30 n=211 patients Location (years): China (2007-2012) Gender (n): TBM: Male: 56.4% (62) Female: 43.6% (48)	TBM (1) Positive mycobacterial/acid-fast stain (2) Clinical manifestations of meningitis (fever, headache, vomiting, disturbances of consciousness) (3) Elevated WBCs, ESR,	With cut off score of ≤4: TBM vs BM (total): Sensitivity: 98.2%, Specificity: 43.6%

	positive rate of T-SPOT	
BM: Male: 65.3% (66) Female: 34.7% (45)	(4) Favourable response to antituberculous therapy	PPV: 65.9% NPV: 95.8%
		Subgroups
Age, mean ± SD: TBM: 43.7 years ± 16.1 BM: 39.4 years ± 15.9		TBM vs BM (partially treated): Sensitivity: 98.2% Specificity: 24.2%
Exclusion criteria: (i) incidence of intracranial infection secondary to CNS surgery (ii) incidence of primary or secondary immunodeficiency disease (iii) a history of mental illness.		PPV: 68.3% NPV: 88.9%
		TBM + BM (initially treated): Sensitivity:
Subgroups: TBM: n=110		

	Bacterial meningitis (BM): n=101 • BM (partially treated): n=66 • BM (initially treated): n=35		98.2% Specificity: 82.9% PPV: 94.7% NPV: 93.5%
Yang et al, 2020	n=103 Location (years): China (2012-2016) Gender (n): TBM: Males: 62.0% (36) Females: 38.0% (22) BM: Males: 73.0% (33) Females: 27.0% (12) Age, median (range):	TBM: M. *tuberculosis* isolated from CSF or clinical TBM features BM: Bacteria isolated from CSF	Specificity: 36.0%

TBM: 52 years (19-75)

BM: 42 years (16-70)

Inclusion criteria:

Patients with clinical and CSF features of community-acquired meningitis who were >= 12 yo

Exclusion criteria:

- Meningitis in post-operative neurosurgical conditions, post-traumatic meningitis, parameningeal infections, brain abscess
- Chronic non-tb meningitis
- HIV positive patients

Subgroups:

	TBM: n=58 BM: n=45			
Vibha et al, 2012	n=590 Location (years): India (2004-2008) Gender (n): TBM: Males: 47.6% (100) Females: 52.4% (110) BM: Males: 86.7% (322) Females: 13.3% (58) Age, median (range): TBM: 26 years (13-82) BM: 22 years (13-86) Subgroups:	TBM: *M. tuberculosis* isolated from CSF OR clinical meningitis with negative gram and India ink stains, plus sterile bacterial anti fungal cultures, plus ≥ 1 of the following: (1) Cranial CT scan consistent with tuberculous meningitis (hydrocephalus, oedema, basal meningeal enhancement) (2) Chest radiograph consistent with active pulmonary tuberculosis (3) Good response to antituberculosis chemotherapy BM Pathogenic bacteria isolated	Unmodified Thwaites criteria: Sensitivity: 98.1% Specificity: 87.9% PPV: 81.8% NPV: 98.8% Thwaite's without age: Sensitivity: 97.1% Specificity: 94.7% PPV: 91.1% NPV: 98.4%	Modified Thwaites cut offs: Age >26 years Blood total leukocyte count <11,500 History of illness ≥7 days CSF leukocyte count <500 cells CSF neutrophils

TBM: n=210 BM: n=380 Inclusion criteria: Patients with clinical and CSF features suggestive of community acquired meningitis of age ≥12 years were included (patients of lesser age are admitted in paediatrics department as a hospital policy). Exclusion criteria: Any of the following: • Meningitis in post operative neurosurgical condition or post traumatic meningitis or parameningeal infections or brain abscess.	from CSF fluid OR clinical meningitis with all of the following: (1) Lymphocytes and neutrophils in CSF (2) Low concentration of glucose in CSF (<50% of that in blood) (3) Sterile blood and CSF cultures (4) Full recovery without antituberculosis chemotherapy 3 months after admission	Modified Thwaites criteria: Sensitivity: 95.7% Specificity: 97.6% PPV: 95.7% NPV: 97.6%	<83%

		• Chronic meningitis other than tuberculous meningitis. • Patients with a positive HIV result.	
Sunbul et al, 2005	n=126 Location:: Turkey Gender (n): TBM: Males: 26.1% (6) Females: 73.9% (17) BM: Males: 65.0% (67) Females: 35.0% (36) Age, median (range): TBM: 42.9 years (18-76) BM: 41.0 years (16-99)	TBM: *M. tuberculosis* isolated from CSF or Clinical meningitis with negative Gram and India ink stains, plus sterile bacterial and fungal culture, plus one or more of the following: (1) Cranial CT scan consistent with tuberculous meningitis (hydrocephalus, edema, basal meningeal enhancement) Chest radiograph consistent with active pulmonary tuberculosis (2) Good response to	With cut off score of ≤4: Sensitivity: 95.8% Specificity: 71.6% ROC of AUC: 0.920 Subgroups: Microbiologically proven cases: Sensitivity: 91.7% Specificity:

		antituberculosis chemotherapy	79.7%	
	Subgroups: TBM: n=23 • Confirmed microbiologically: n=12 Bacterial meningitis (BM): n=103 • Confirmed microbiologically: n=59	BM Pathogenic bacteria isolated from CSF or clinical meningitis with all of the following: (1) Lymphocytes and neutrophils in CSF (2) Low concentration of glucose in CSF (<50% of that in blood) (3) Sterile blood and CSF (4) Full recovery (without anti-tb chemotherapy) 3 months after admission		
Erdem et al, 2015	n=484 Location: Turkey Gender (n): TBM: Male: 52.1% (99)	TBM Clinical evidence of meningitis and microbiological confirmation of TBM, including culture, PCR analysis and Ehrlich-Ziehl-Neelsen staining	With cut off score of ≤4: Sensitivity: 95.8% Specificity: 0.680%	Thwaites' score falsely identified more BME patients as TBM

Female: 47.9% (91) BME: Male: 54.1% (159) Female: 45.9% (135) Age, mean (range) TBM: 41 years (21-61) BME: 37 years (21-53) Inclusion criteria: BME: all of the following: • Presence of clinical symptoms consistent with either meningitis or meningoencephalitis • Presence of typical cerebro- spinal fluid (CSF) findings consistent with meningitis	from CSF	patients as compared to Lancet.

		• Presence of positive culture or serological tests for brucellosis in the blood or in the CSF • Absence of an alternative neurological diagnosis		
Checkley et al, 2008	Subgroups: TBM: n=190 Brucellar meningoencephalitis (BME): n=294 n=86 Location: Malawi (2004) Gender (n): TBM: Male: 67.0% (6) Female: 33.0% (3) BM:	TBM Clinical meningitis with negative gram and India ink stains, plus sterile bacterial anti fungal cultures, plus ≥ 1 of the following: (1) Chest radiograph consistent with active pulmonary tuberculosis	With cut off score of ≤4: Sensitivity: 78.0% Specificity: 43.0% PPV: 14.0% NPV: 94.0%	Study location has high HIV prevalence (15% in general population, 70% of adult admissions

Male: 55.0% (36) Female: 45.0% (29) CM: Male: 58.0% (7) Female: 42.0% (5) Age, mean (SD) TBM: 32 years ± 6 BM: 30 years ± 11 CM: 39 years ± 13 Inclusion criteria: Sufficient data to make a firm diagnosis of TBM, BM or CM and apply Thwaites score Exclusion criteria: Insufficient data to make a firm diagnosis of TBM, BM or CM	(2) Good response to antituberculosis chemotherapy BM Pathogenic bacteria isolated from CSF fluid OR clinical meningitis with all of the following: (1) Lymphocytes and neutrophils in CSF (2) Low concentration of glucose in CSF (<50% of that in blood) (3) Sterile blood and CSF cultures (4) Full recovery from signs of active infection without antituberculosis chemotherapy 1 month after admission CM Positive India ink staining of	With cut off score of ≤3.5: Sensitivity: 78.0% Specificity: 63.0%	to study hospital) as compared to lower prevalence in original location of study by Thwaites et al (2002).

and apply Thwaites score	CSF	
Subgroups: TBM: n=9 Bacterial meningitis (BM): n=65 Cryptococcal meningitis (CM): n=12		

Supplementary Table 21 Vibha (2012)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Comments	Limitations
Vibha et al, 2022	n=590 Location (years): India (2004-2008) Gender (n): TBM: Males: 47.6% (100) Females: 52.4% (110) BM: Males: 86.7% (322) Females: 13.3% (58) Age, median (range): TBM: 26 years (13-82) BM: 22 years (13-86) Subgroups:	TBM: *M. tuberculosis* isolated from CSF OR clinical meningitis with negative gram and India ink stains, plus sterile bacterial anti fungal cultures, plus ≥ 1 of the following: (1) Cranial CT scan consistent with tuberculous meningitis (hydrocephalus, oedema, basal meningeal enhancement) (2) Chest radiograph	Sensitivity: 95.7% Specificity: 97.6% AUC of ROC: 0.995 PPV: 95.7% NPV: 97.6%	Several factors were found to be independently associated with TBM: (1) rural area of residence, (2) longer duration of disease, (3) lower percentage of CSF neutrophils, (4) presence of diplopia, (5) hemiparesis)	Low culture positivity in both TBM and BM subgroups. 9.3% (18) of TBM patients were TB-PCR positive. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

BM: n=380 TBM: n=210 <u>Inclusion criteria:</u> Patients with clinical and CSF features suggestive of community acquired meningitis of age ≥12 years were included (patients of lesser age are admitted in paediatrics department as a hospital policy). <u>Exclusion criteria:</u> Any of the following: • Meningitis in post operative neurosurgical condition or post traumatic meningitis or parameningeal infections or brain abscess. • Chronic meningitis other than tuberculous meningitis.	consistent with active pulmonary tuberculosis (3) Good response to antituberculosis chemotherapy <u>BM</u> Pathogenic bacteria isolated from CSF fluid OR clinical meningitis with all of the following: (1) Lymphocytes and neutrophils in CSF (2) Low concentration of glucose in CSF (<50% of that in blood) (3) Sterile blood and CSF cultures (4) Full recovery without	and (6) clear CSF).

	• Patients with a positive HIV result.	antituberculosis chemotherapy 3 months after admission

Supplementary Table 22 Wen (2022)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Wen et al, 2022	n=161 Location (years): China (2004-2019) <u>Gender (n):</u> TBM: Males: 60.5% (69) Females: 39.5% (45) BM: Males: 68.1% (32) Females: 31.9% (15) <u>Age, mean ± SD:</u> TBM: 44.5 years ± 29.3 BM: 42.0 years ± 28.0 <u>Exclusion criteria:</u>	<u>TBM:</u> Smear microscopy for AFB in CSF or MTB, which were cultured in CSF or a commercial positive MTB nucleic acid amplification test. <u>BM:</u> Pathogenic bacteria isolated from the CSF; or clinical meningitis with all of the following: lymphocytes and neutrophils in CSF; low glucose concentration in the CSF (< 50% of that in blood); sterile blood and CSF cultures; and full	Sensitivity: 96.0% Specificity: 86.0% AUC of ROC: 0.954 PPV: 0.900 NPV: 0.950	Low culture positivity in both TBM (10.5% [12]) and BM (27.7% [13]) subgroups. Studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

	Insufficient data for a definitive diagnosis. <u>Subgroups:</u> TBM: n=114 Bacterial meningitis (BM): n=47	recovery (without anti-TB chemotherapy) 3 months after admission (these criteria were modified to full recovery at the time of discharge).	

Supplementary Table 23 Yang (2020)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations	Comments
Yang et al, 2020	n=103 Location (years): China (2012-2016) Gender (n): TBM: Males: 62.0% (36) Females: 38.0% (22) BM: Males: 73.0% (33) Females: 27.0% (12) Age, median (range): TBM: 52 years (19-75) BM: 42 years (16-70) Inclusion criteria:	TBM: M. *tuberculosis* isolated from CSF or clinical TBM features BM: Bacteria isolated from CSF	Sensitivity: 98.0% Specificity: 82.0% AUC of ROC: 0.979 PPV: 88.0% NPV: 97.0% Additional 70 pts: Sensitivity: 97.0% Specificity: 81.0%	Study population included a large group of pre-treated patients. In distinguishing pre-treated BM from TBM patients in this cohort, Yang et al (2020) has better outcomes than Thwaites et	Does not include non-bacterial meningitis (viral, fungal and autoimmune causes).

Patients with clinical and CSF features of community-acquired meningitis who were ≥ 12 years Exclusion criteria: • Meningitis in post-operative neurosurgical conditions, post-traumatic meningitis, parameningeal infections, brain abscess • Chronic non-tb meningitis • HIV positive patients Subgroups: TBM: n=58 Bacterial meningitis (BM): n=45		PPV: 86.0% NPV: 96.0%	al (2002).

Supplementary Table 24 Fong (2023)

Study	Patient Population	Control (ref gold standard)	Outcome Data	Limitations
Fong et al, 2023	n=113 Location (years): China (2009-2019) Gender (n): Anti-TBM: Male: 76.0% (41) Female: 24.0% (13) Anti-TBM: Male: 63.0% (37) Female: 37.0% (22) Age, median (range): Clinical resolution by anti-TBM treatment: 39 years (32-51) Clinical resolution by non-anti-TBM treatment: 43 years (27-58) Inclusion criteria:	TBM Positive CSF culture (Ziehl-Neelsen staining) and nucleic acid amplification tests.	**With 3 parameters** Sensitivity: 93.0% Specificity: 77.0% **With 5 parameters** Sensitivity: 97.0% Specificity: 66.0%	TBSA as a CSF biomarker may not be commonly evaluated; tests may not be readily available. Some studies were carried out retrospectively using patients' medical records resulting in potential misclassification bias.

Clinical entry criteria by Lancet: (headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered consciousness, or lethargy)

Exclusion criteria: Patients with missing records, basic information, diagnostic details, TBSA results, or a large amount of laboratory examination data (more than four parameters for each patient)

Subgroups:

Clinical resolution by anti-TBM treatment: n=54

Clinical resolution by non-anti-TBM treatment: n=59