Original article

SYSTEMATIC META-ANALYSIS OF TUBERCULOSIS MENINGITIS: THE BURDEN AND THE CHALLENGES IN SOUTH ASIA

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ABSTRACT

Tuberculosis meningitis (TBM) is an important global health challenge. It causes significant morbidity and mortality, especially in low and middle income countries. Its early recognition, diagnosis and management, continues to pose complex and challenging issues for healthcare teams and personnel. A better understanding of the global epidemiology of TB meningitis, would help allocate appropriate healthcare resources for its management. Currently, diagnosis relies on a combination of clinical, radiological, and laboratory findings and needs to be made in timely fashion. A multidisciplinary approach is needed for optimal management and for preventing complications. Although progress has been made in recent years, several uncertain questions remain. HIV co-infection and increasing drug resistance, adds further complexity to any management decisions. This review would outline current knowledge, challenges and perspectives regarding the presentation, pathogenesis, complications, diagnosis, treatment and control of TB meningitis, especially in relation to Asian countries.

Key words: Tuberculosis Meningitis, South Asia, Sri Lanka

INTRODUCTION

Tuberculosis (TB) is a highly prevalent global human infection caused by Mycobacterium tuberculosis (MTB)[(1)(2)]. Although the causative organism of tuberculosis was discovered over a hundred years ago, this disease remains a major public health problem worldwide [(3)(4)(5)].

One-third of the world's population is infected with latent tuberculosis and these individuals are not clinically affected but carry a lifetime risk of 10% for developing the active disease [(5)(1)]. Tuberculosis meningitis (TBM) is the most severe form of extra-pulmonary tuberculosis resulting in high morbidity and mortality [(6)(3)]. In the recent past, number of immunocompromised patients has increased due to high prevalence of HIV/AIDS, increasing incidence of diabetes mellitus, growing geriatric population and increased use of immunosuppressive drugs [(7)(8)(9)(10)(11)].

Tuberculosis meningitis (TBM) still poses significant diagnostic and management challenges, especially in the developing world[(12)(13)(13)]. The incidence of TBM is on the rise with the increase in immune-deficient states such as HIV/AIDS and concomitant with an increase in the incidence of TBM. Furthermore, development of multi-drug resistance in AIDS patients is a major obstacle associated with its treatment[(14)(15)(16).] Despite modern anti-tuberculosis chemotherapy, 20% to

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50% of patients still die, and many of the survivors have significant neurological deficits [17][18]. Death from TBM is strongly associated with the delays in the proper diagnosis and management[12][13] [19] [20]. This review discusses the burden and the challenges of TBM in South Asia.

Global Tuberculosis Disease Burden

The global rise in TB cases that began during the COVID-19 pandemic has slowed and stabilized at 10.8 million cases in 2023, with most of the increase due to population growth [21]. The highest burden is in 30 countries, particularly India, Indonesia, China, the Philippines, and Pakistan. TB-related deaths declined to 1.25 million, reinforcing progress since the pandemic, but TB remains the leading cause of death from a single infectious agent [21].

Despite some progress, reductions in TB incidence (8.3%) and mortality (23%) from 2015 to 2023 remain far from WHO's 2025 targets. Post-COVID recovery in TB diagnosis and treatment has helped narrow the gap between estimated and reported cases. In 2023, 8.2 million people were newly diagnosed, reducing the backlog from previous years[21]. However, multidrug-resistant TB remains a challenge, with only 44% of estimated cases receiving treatment. Treatment success rates remain high, at 88% for drug-susceptible TB and 68% for multidrug-resistant TB[21].

Tuberculosis Meningitis burden in South Asia

Tuberculosis meningitis is a serious infection commonly found to occur in the developing countries endemic to tuberculosis[22][23]. In the developing countries with poor resources, the morbidity and mortality is high, due to poor sanitary conditions, delayed diagnosis, non-optimal treatment, and inadequate immunization by BCG [19][24][25][26].

Tuberculosis meningitis (TBM) is the most frequent form of central nervous system (CNS) tuberculosis and peak incidence is in children under 4 years of age. However, the number of adults presenting with TBM has increased as a result of the HIV epidemic [27][11][28]. The incidence of CNS tuberculosis generally reflects the incidence and prevalence of tuberculosis in the community [29]. Tuberculosis meningitis is seen in 5 to 10% of extra pulmonary tuberculosis, and accounts for approximately 1% of all TB cases. The case fatality rate of untreated TBM is almost 100% and a delay in treatment may lead to permanent neurological damage[30][31][32]. HIV infection predisposes to the development of extra-pulmonary tuberculosis, particularly tuberculosis meningitis[33][34][35]. HIV co-infection is associated with higher complication and case fatality rates [36] [37][38]. In comparison to other regions, the number of HIV-negative TBM cases remains the majority in Asia [39].

METHODOLOGY

A literature survey was conducted using Google and PubMed search engines with the keywords "tuberculosis meningitis," "South Asia," and "case reports." All case reports published in English from 2001 to 2024 and originating from South Asia were reviewed **(figure 1)**. These are summarized in **Table 1**, which provides access to the detailed case reports. No relevant case reports were identified after 2021 using the specified search criteria; therefore, the review includes case reports up to the year 2020.

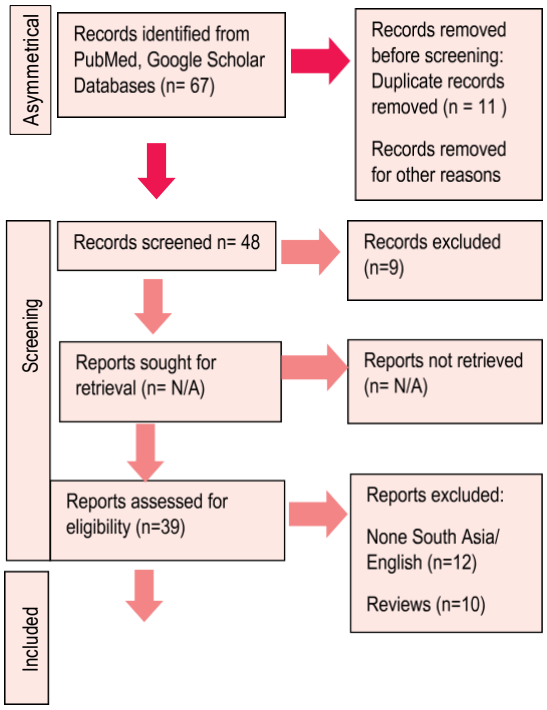

Figure 1. PRISMA flow diagram for systematic reviews

RESULTS

A total of 17 case reports on tuberculosis meningitis (TBM) published between 2001 and 2020 were identified; 4 from PubMed and 13 from Google search engine and included in the review. These reports highlight the ongoing clinical significance of TBM in South Asian countries, particularly in India, which accounted for the majority of cases. Other reports originated from Pakistan, Bangladesh, Nepal, and Sri Lanka, reflecting TBM as a regional public health Concern

Table 1:

Year	Country and the Hospital	Study population	Number and the percentage of EPTB patients	Number and the percentage of TBM patients	Gender and the affected age group of TBM patients	Reference
2005-11	**India -** University Hospital Karnataka	1267 patients registered for treatment (DOTS) of all forms of tuberculosis	528 (41.67%)	66 (12.50%)	Females 15-44 years	40
2013	**India -** University Hospital Himachal Pradesh	EPTB cases from two medical colleges and four additional randomly selected Tuberculosis Units (TUs) of Himachal Pradesh	463	24 (5.20%)	Males 20-35 years	41
2012-14	**India -** Tertiary Care Hospital in Central India	491 patients registered for treatment of all forms of tuberculosis	130 (26.40%)	3 (2.30%)	Males 0-19 years	42
2007-09	**India -** Tertiary Care Hospital in Karnataka	326 meningitis patients admitted to the paediatric department		187 (57.37%)		43
2009-11	**India -** tertiary referral center in North India	Diagnosis of intracranial tubercular infection who were admitted (from emergency, neurology outpatient department)		244	age >12 years , both male and female	44
2005-07	**Pakistan-** Tertiary Care Hospital in Karachchi	Retrospective audit of 194 patients under treatment for extra-pulmonary TB	2194	18 (9.30%)		45
2019-20	**Nepal-** Tertiary care centre in Nepal	descriptive cross-sectional study	60	39 (65.00%)	25 (64.10%)-males 14 (35.90%)-females	46
2010	**Pakistan-** Ayub Teaching Hospital, Abbottabad	500 patients admitted to medical wards from Out Patient Department with confirmed tuberculosis	120 (24.00%)	45 (9.10%)		47

2011	**Bangladesh**	A total of 152 EPTB patients from villages in Narsingdi district of Bangladesh	152	7 (4.60%)		48
2003-06	**Nepal-** Manipal college of Medical sciences	526 TB patients registered in the DOTS clinic in western Nepal	230 (48.50%)	17 (7.20%)		49
2001-10	**Bhutan**	all TB cases registered as EPTB over a period of 10 years	Varied from 30% to 40%	7 (1.00%)		50
2010-11	**Sri Lanka-** National hospital of Sri Lanka (NHSL)	all the adult cases of TB Meningitis		22 definitive cases, 46 probable cases and 21 possible cases		51
2023	**Nepal**	Case report		GeneXpert negative		52
2009-19	**Pakistan**	All TB meningitis cases reported in 10 years	25 (559)			53
2015-18	**Pakistan**	hospital	110	11 deaths		54
2018	**India**	hospital	50%			55
2017	**India**	Tertiary care hospital	209 (542)			56

Diagnosis of TBM

Early diagnosis and effective treatment are the key factors to better outcome in TBM [57][39]. In a significant number of patients, the diagnosis of TBM is empirical and is based on the clinical, laboratory and neuroimaging data[58].

Clinical diagnosis

Tuberculosis meningitis (TBM) remains a diagnostic challenge due to nonspecific symptoms and varied clinical presentations, often leading to delayed diagnosis when brain damage has already occurred [58]. TBM can present acutely but is typically a slowly progressive disease with symptoms such as fever, headache, meningeal signs, altered mental status, and cranial nerve deficits [59-63].

In adults, classic symptoms include fever, headache, neck stiffness, and focal neurological deficits [64, 65]. In children, presentation varies with age: older children commonly have fever, headache, anorexia, and vomiting, while younger children often show failure to thrive, poor appetite, vomiting, and sleep disturbances [66, 67]. In HIV-infected patients, TBM symptoms are influenced by immunosuppression, with a higher likelihood of extra-meningeal tuberculosis and systemic HIV features [38].

Several studies highlight common clinical presentations:

Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India. Among 38 adult TBM patients, fever, headache, and meningeal irritation were present in 78-84%; vomiting (63%) and cranial nerve palsy (36%) were also common [68].

Department of Medical Microbiology and Neurology of tertiary care referral centre in North India: Among 55 cases, fever (90.9%), headache (72.7%), neck rigidity (67.3%), altered sensorium (65.5%), and vomiting (54.5%) were frequent (69).

Aga Khan University, Pakistan: Among 46 children with TBM, fever (97%), vomiting (43%), headache

(39%), drowsiness (32%), and seizures (45%) were common findings [67].

Jinnah Postgraduate Medical Centre, Pakistan: Among 93 adults, neck stiffness was universal, while cranial nerve palsies increased with disease severity (24% in Stage I, 75% in Stage III) [73].

Civil Hospital Karachi: In 52 confirmed cases, fever (98.1%), neck stiffness (84.6%), altered consciousness (76.9%), headache (59.6%), and vomiting (36.5%) were observed. Mortality was 21.1%, with older age, advanced TBM stage, hydrocephalus, and mechanical ventilation being major risk factors [74].

Dhaka, Bangladesh: Among 30 TBM patients, fever (91.7%), headache (70%), altered consciousness (45%), vomiting (43.3%), and neck stiffness (28.9%) were predominant [75].

India (HIV-TBM Study): Among 100 HIV-positive patients with presumptive TBM, fever was the only symptom in 20%, 89% had elevated CSF protein, and 50% experienced TB immune reconstitution inflammatory syndrome (TB IRIS). The study suggested that current diagnostic criteria may not be reliable in early-stage TBM [76].

Across all studies (table 2) , fever emerged as the most common symptom, ranging from 78% to 98.1%, followed by headache (39%-84%) and neck stiffness/meningeal irritation, which was universally present in some studies (100% at Jinnah Postgraduate Medical Centre, Pakistan) but lower in others (28.9% in Dhaka, Bangladesh). Vomiting was also frequently reported, though its prevalence varied from 36.5% to 63%. Altered sensorium/consciousness was noted in 32%-76.9%, particularly in more severe cases. Cranial nerve palsies were observed primarily in adult studies, with prevalence increasing with disease severity (24% in Stage I to 75% in Stage III at Jinnah Postgraduate Medical Centre, Pakistan). The Civil Hospital Karachi study reported a mortality rate of 21.1%, with risk factors including older age, advanced TBM stage, hydrocephalus, and mechanical ventilation. The HIV-TBM study in India found that 20% of patients had fever as their only symptom, while 50% developed TB immune reconstitution inflammatory syndrome (TB-IRIS), indicating unique challenges in diagnosing TBM in immunocompromised individuals. Despite regional and demographic variations, fever, headache, neck stiffness, vomiting, and altered sensorium were the most consistent symptoms across studies, with prognosis worsening in severe TBM stages, paediatric cases, and HIV-positive individuals.

TBM Severity Classification

TBM is classified into three British Medical Research Council (BMRC) grades based on Glasgow Coma Score (GCS) [70].

Stage I: GCS 15, no focal neurological deficits.

Stage II: GCS 11-14, or GCS 15 with focal deficits.

Stage III: GCS ≤10, severe neurological impairment.

Table 2: Summary of Symptoms Reported in Case Reports Published from Asian Countries

Study	Symptoms	Reference
Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India.	fever, headache, and meningeal irritation, vomiting	68
Department of Medical Microbiology and Neurology of tertiary care referral centre in North India	fever, headache, neck rigidity, altered sensorium, and vomiting	69
Aga Khan University, Pakistan	fever, vomiting, headache, drowsiness, and seizures	67
Jinnah Postgraduate Medical Centre, Pakistan	neck stiffness	73
Civil Hospital Karachi	fever, neck stiffness, headache, and vomiting	74
Dhaka, Bangladesh	fever, headache, altered consciousness, vomiting and neck stiffness	75
India (HIV-TBM Study)	fever	76

TBM presents with diverse and nonspecific symptoms, making early clinical suspicion essential. Severity at presentation strongly impacts prognosis, with Stage III disease, cranial nerve involvement, and immunosuppression being significant predictors of poor outcomes. Timely empirical treatment is critical to reduce morbidity and mortality [58-76].

Laboratory diagnosis

Laboratory services are very important in the diagnosis, management and epidemiological investigation of mycobacterial diseases.

Direct smear and culture

The Ziehl-Neelsen (ZN) staining technique is the most widely used method for detecting acid-fast bacilli (AFB) in patient samples for tuberculosis (TB) diagnosis, especially in resource-limited regions [77]. However, AFB microscopy has low sensitivity (10-20%) in detecting extrapulmonary TB, particularly tuberculosis meningitis (TBM) [78]. The gold standard for TBM diagnosis is the culture of cerebrospinal fluid (CSF) to detect Mycobacterium tuberculosis [79], with a 60-70% sensitivity in adults, making it essential for drug susceptibility testing [80]. However, culture-based methods take 3 to 5 weeks [80].

Recent advances have led to faster diagnostic techniques. Broth-based cultures have reduced turnaround times compared to solid media [81]. The Microscopic Observation Drug Susceptibility (MODS) assay is an emerging cost-effective and rapid technique that is more sensitive than CSF smear microscopy and faster than conventional culture [80].

A prospective study conducted in a tertiary care hospital in New Delhi, India over two years analyzed 164 CSF samples from suspected TBM cases. ZN staining detected AFB in only 7.9% of samples. The Bactec MGIT 960 system detected M. tuberculosis in 27.4%, while LJ medium detected 10.9%. A combined approach using both increased the culture positivity rate to 29.8%. The average detection time was 18 days with MGIT 960 and 38 days with LJ medium. The study concluded that using a combination of smear microscopy, conventional culture, and automated methods (like Bactec MGIT 960) improves TBM diagnostic sensitivity compared to any single technique [81].

Nucleic acid amplification techniques (NAATs)

Nucleic acid amplification tests (NAATs) can detect fewer than 10 organisms and are useful for identifying Mycobacterium tuberculosis in clinical specimens or cultures. Polymerase chain reaction (PCR) is the most widely used NAAT method, with numerous in-house assays developed [82]. While NAATs have high specificity, their sensitivity varies. A key advantage over microscopy and culture is that DNA remains detectable for up to a month after starting anti-tuberculosis treatment. However, limitations include high cost, laboratory infrastructure requirements, trained staff, and the need for quality control to prevent contamination and assay inhibition [82, 83].

A study at a University Hospital in Varanasi, India (2009-2011) compared BacT/ALERT 3D culture medium with nested PCR for early TBM diagnosis in 50 suspected TBM patients and 20 controls. Culture positivity was 76% (38/50) in TBM patients, but 15% (3/20) of controls showed false positives with BacT/ALERT-MP. Nested PCR detected TBM in 92% (46/50) cases, with a false-positive rate of 5% (1/20) in controls. Sensitivity and specificity for BacT/ALERT-MP were 76% and 85%, while for nested PCR, they were 92% and 95%, indicating poor sensitivity of BacT/ALERT 3D culture [83].

Another study at the Central India Institute of Medical Sciences, Nagpur (2009) compared the Loop-Mediated Isothermal Amplification (LAMP) assay with nested PCR for TBM diagnosis in 27 CSF specimens. LAMP showed a sensitivity of 88.23% and specificity of 80%, whereas nested PCR had 52.9% sensitivity and 90% specificity. The study concluded that LAMP is a rapid, sensitive, and specific method superior to nested PCR, with the added benefit of being simple and suitable for rural laboratories [84].

Adenosine deaminase activity

Adenosine deaminase (ADA), an enzyme involved in purine metabolism, is elevated in the cerebrospinal fluid (CSF) of TBM patients and normalizes within 2-6 weeks of treatment. ADA estimation is a simple, rapid, and cost-effective

diagnostic test that can be conducted in basic laboratories [85].

A study in Kathmandu, Nepal (2009-2010) analyzed 28 TBM and 22 non-TBM (viral) cases. Mean ADA levels in TBM patients were 16.46 ± 6.24 U/L, significantly higher than 5.±132.96 U/L in non-TBM cases (P < 0.001). Using a CSF ADA cut-off of >10 IU/L, the test achieved 82% sensitivity and 90% specificity, making it an effective early diagnostic tool in resource-limited settings [86].

Another study in Vellore, India, assessed 40 HIV-positive meningitis patients (16 TBM, 24 non-TBM). Mean ADA levels in TBM patients were 18.1 ± 19.176 U/L, significantly higher than 2.2 ± 1.8 U/L in non-TBM cases (P < 0.001). A CSF ADA cut-off of 6 IU/L yielded 75% sensitivity and 95.8% specificity for TBM diagnosis. The study concluded that CSF ADA testing at a 6 IU/L threshold is a highly specific and moderately sensitive tool for diagnosing TBM in HIV-positive patients [87].

Interferon-gamma release assays

The Interferon-gamma (IFN-ɣ) release assay (IGRA) is an in vitro test that measures the production of IFN-ɣ release in response to stimulation with specific mycobacterial antigens and this has been used to diagnose TB infections[88] [89]. The sensitivity and specificity of this method on CSF specimens is estimated to be 89-100% and 50-82% respectively[90].

Novel Biomarkers

Novel biomarkers for TB screening, diagnosis and treatment monitoring has come to the forefront of attention in recent years [91][92][93][94][95]. These include MTB-specific antigen and antibody, with sensitivity of 84-94% and specificity of 92-94% [93]. The detection of lipoarabinomannan (LAM), a MTB cell wall lipopolysaccharide antigen, in urine, which has been proposed to be used for TBM diagnosis in immune suppressed HIV-infected patients, have been shown to have a sensitivity of 64% and a specificity of 69%[96].

Neuroimaging

Modern neuroimaging plays a crucial role in the early diagnosis of CNS tuberculosis, potentially reducing morbidity and mortality associated with delayed treatment[97,98]. Both contrast-enhanced CT and MRI are used to visualize TBM-related pathology, including tuberculomas, basal meningitis, meningeal enhancement, hydrocephalus, brain abscesses, cerebral edema, calcifications, and infarcts [99].

A prospective study in Islamabad, Pakistan (2013-2014) examined 100 TBM patients. CT abnormalities were detected in 67% of cases, with hydrocephalus (58%), edema (24%), and infarcts (5%) being the most frequent findings. MRI, performed in 62% of cases, was abnormal in 87%, revealing hydrocephalus (60%), tuberculomas (53%), leptomeningeal involvement (45%), and infarcts (13%). In 10% of patients with normal CT scans, MRI identified abnormalities, highlighting its superior sensitivity for detecting TBM complications [32].

Another study in Bangalore, India (2001-2003) examined 53 TBM patients over 50 years old, focusing on clinical, imaging, and laboratory features. Findings indicated an absence of typical TBM features such as basal meningeal enhancement, hydrocephalus, infarcts, or granulomas in most elderly patients. The study concluded that CT features in older patients are often atypical and non-contributory to diagnosis, likely due to age-related immune senescence. Therefore, strong clinical suspicion and correlation with laboratory tests are essential for early detection in elderly patients [100].

Management

The WHO and UK Guidelines recommend an initial intensive phase treatment for 2-3 months using rifampicin, isoniazid, pyrazinamide, and streptomycin (or ethambutol), followed by a continuation phase of at least 6 months with rifampicin and isoniazid [101]. Fluoroquinolones are particularly beneficial in treating multidrug-resistant tuberculosis meningitis (TBM) [102], and adjunctive corticosteroids are also recommended [103].

A study conducted at a Tertiary Care Hospital in Kerala, India (2010-2011) followed 47 TBM patients under the Revised National Tuberculosis Control Programme (RNTCP). The study found

that most patients adhered to directly observed treatment (DOTS), demonstrating good compliance with comparable mortality and morbidity rates [104].

Another study in India (2008-2011) analyzed 42 TBM patients treated under RNTCP guidelines. Of these, 83% completed the treatment, with 78% receiving actual DOTS. The study concluded that intermittent short-course chemotherapy (9-month regimen) was effective, though 16% of patients died during treatment [105].

CONCLUSION

Tuberculosis is an important public health problem in South Asia. Although the incidence of tuberculosis in South Asian countries is known, the actual incidence of TBM is uncertain. Our review outlines and discusses the findings of studies on TBM in South Asia. Despite advances in our understanding of TBM in the past few years, it continues to be the most lethal form of tuberculosis. The best way to improve survival is by rapid and accurate diagnosis and the prompt initiation of therapy. This analysis is limited by its reliance on published case reports, which may not accurately reflect the true incidence or full clinical spectrum of TBM in South Asia due to under-reporting and publication bias. The exclusion of non-English literature and potential inconsistencies in diagnostic criteria across reports further restrict generalizability. Moving forward, region-specific prospective studies, improved surveillance systems, and standardized reporting are essential to better understand the epidemiology of TBM and to guide effective diagnosis and treatment strategies.

CONFLICT OF INTEREST

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