Journal of Communicable Diseases
Volume 54, Issue 3 - 2022, Pg. No. 6-14
Peer Reviewed & Open Access Journal

Research Article

# An Observational, Cross-sectional Study on Epidemiology and Clinical Spectrum of Tuberculous Meningitis in a Tertiary Care Hospital in Eastern India and Role of CSF CBNAAT for Rapid Diagnosis

Alapan Paul[1], Linkon Biswas[2], Soumyasil Das[3], Souvonik Mandal[4], Nirendra Mohan Biswas[5]

[1]Senior Resident, Department of Neuro Medicine, Calcutta Medical College and Hospital.
[2]Senior Resident, Department of Radiotherapy, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India.
[3]Senior Resident, Department of General Medicine Malda Medical College and Hospital, Malda, West Bengal, India.
[4]Assistant Professor, [5]Professor (Retired), Department of General Medicine, Nilratan Sircar Medical College and Hospital Kolkata, West Bengal, India.
**DOI:** https://doi.org/10.24321/0019.5138.202283

## I N F O

**Corresponding Author:**
Soumyasil Das, Department of General Medicine Malda Medical College and Hospital, Malda, West Bengal, India.
**E-mail Id:**
drsoumyasil@gmail.com
**Orcid Id:**
https://orcid.org/0000-0002-2461-7553
**How to cite this article:**
Paul A, Biswas L, Das S, Mandal S, Biswas NM. An Observational, Cross-sectional Study on Epidemiology and Clinical Spectrum of Tuberculous Meningitis in a Tertiary Care Hospital in Eastern India and Role of CSF CBNAAT for Rapid Diagnosis. J Commun Dis. 2022;54(3):6-14.

Date of Submission: 2022-06-27
Date of Acceptance: 2022-09-05

## A B S T R A C T

*Background:* Tubercular meningitis (TBM) accounts for 70 to 80 percent of all neurological tuberculosis and is a major health issue in a country like India. But we don't have adequate amount of data regarding the epidemiology and clinical pattern of TBM. In this study we aimed at exploring the epidemiological, clinical picture of TBM and compared different diagnostic modalities for early detection.

*Methods and Materials:* 50 patients with history and clinical features compatible with tuberculous meningitis were assessed through a detailed history and clinical examination followed by CSF study and an MRI of the brain.

*Results:* CSF study showed lymphocytic pleocytosis (92% cases) along with raised mean CSF protein 182.2±80.2 mg/dl (Mean ± SD) and reduced mean sugar 35.8 ±12.3mg/dl. CSF for AFB had least sensitivity (4%) but highest specificity (100%). CBNAAT showed both acceptable sensitivity (77%) and specificity (96%). CSF ADA had high sensitivity (85%)but low specificity (18%). Age >40 years, Altered consciousness, GCS<10, TBM stage 3, CSF glucose ≤30mg/dl& Presence of hydrocephalus were significantly associated with mortality from TBM (p-value<0.05).

*Conclusion:* CSF CBNAAT having acceptable sensitivity and specificity for diagnosis of TBM and can be used for early diagnosis as an alternative to CSF culture due to its rapidity and other bio-medical advantages. Factors associated with adverse outcome can be used in future as components of risk prediction models.

**Keywords:** Tuberculous Meningitis, Epidemiology, CBNAAT, Prognostic Factors

## Introduction

Tuberculosis is one of the leading causes of mortality and morbidity in developing countries. In India 2.2 million people are affected every year and approximately 400,000 people die due to TB.[1] Neurological tuberculosis comprises 5-10% of the cases of extra-pulmonary tuberculosis and tuberculous meningitis (TBM) accounts for 70 to 80 percent of cases of neurological tuberculosis.[1,2] It occurs more frequently in children, particularly below four years and HIV-TB co-infection.[3,4]

Diagnosis of tuberculous meningitis is based on history, CSF study and imaging. Lymphocytic pleocytosis with raised protein and low glucose constitute typical CSF picture of TB meningitis. Demonstration of AFB in the CSF by microscopy is the most crucial part of the investigation but the yield of CSF smears by ZN (Ziehl-Neelsen) staining and auramine staining is low (4%-40%) and is found to be a function of the volume and number of samples of CSF.[5]

Amplification of the Mycobacterium tuberculosis specific DNA sequences by polymerase chain reaction (PCR) has been evaluated as a means of rapid diagnosis of TBM. The Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) is an automated, real-time PCR for detecting MTB (Mycobacterium tuberculosis) complex and rifampicin (RIF) resistance.[6-8] It is an easily operable closed-cartridge based system that not only gives results within 2 hours but also helps in detection of multidrug resistance (MDR). Moreover, it has reduced risk of cross-contamination of study sample and safe in terms of bio-safety parameters. So, for rapid diagnosis of TB meningitis where delay in treatment initiation can cause severe neurological sequelae inupto 25% of cases this testing system is a paradigm shift.[9,10]

In this study we wanted to have a look at the epidemiology and clinical spectrum of tuberculous meningitis in HIV sero-negative adults, to compare the efficacy of CSF microscopy, CSF ADA, CSFCBNAAT and CSF culture in detection of Mycobacterium tuberculosis in patients suspected of having TBM. This study also aimed at determining the sensitivity & specificity of CSF CBNAAT for diagnosis of TB meningitis. We also searched for correlation between mortality among TBM patients and different clinical and laboratory parameters.

## Materials & Methods

It was an observational, cross-sectional, single institutional, prospective study in all adult patients, with history and clinical features compatible with tuberculous meningitis, admitted in the medicine department of our hospital from January 2020 to June 2021.

### Inclusion Criteria

- Patients having clinical features of meningitis with or without signs of irritation
- MRI brain findings suggestive of tubercular meningitis
- CSF showing features of pleocytosis, predominantly lymphocytosis, decreased glucose levels (CSF: plasma glucose ratio less than 0.5), high protein levels and an ADA>9.5IU/L
- Presence of tuberculosis elsewhere (e.g., miliary tuberculosis or abdominal TB) presented with signs and symptoms of tubercular meningitis

### Exclusion Criteria

- Children less than 13 years
- HIV-TB co-infection
- Already on anti-tubercular drugs
- Patients with features suggestive of pyogenic meningitis

## Study Methods

Patients selected based upon the above-mentioned inclusion and exclusion criteria were thoroughly examined clinically (including Fundoscopic examination) and their clinical history was taken in detail.

From this we collected data regarding various study parameters then we did some investigations to identify different factors of clinical spectrum that has an effect on outcome. We did following investigations:

1. Complete hemogram with ESR, serum electrolytes, LFT
2. CSF study (Lumbar Puncture) for:

- Cell count, Cell type
- Protein, Glucose, CSF: Plasma glucose ratio
- Gram stain, pyogenic culture & sensitivity
- ZN stain for AFB & CSF culture (BACTECMGIT 960 method)
- Fungal stain
- CSF ADA (Adenosine De-Aminase)
- CSF CBNAAT (Gene Xpert MTB/RIF)

3. Contrast enhanced MRI brain

The cases were divided into definite TBM, probable TBM and possible TBM according to Diagnostic Criteria in the Uniform Tuberculous Meningitis Research Case Definition as given by Suzaan Marais et al.[11]

Ethical clearance was taken from institutional ethics committee for conducting this study.

No source of financial support was there for doing the study.

### Statistical Analysis

For statistical analysis SPSS 24.0 and Graph Pad Prism version 5 was used. For numerical variables mean and standard deviation were used to represent the data. Categorical variables were represented by count and percentages. For categorical variables, Chi-Square and Fisher Exact tests were used, while for continuous variables, the mean and SD were compared using independent samples t test with 95% confidence interval (CI). All tests were 2-tailed and p value less than 0.05 was taken as significant.

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**

**Table I .Distribution of General Characteristics of Study Population**

| Characteristics | | Number of Patients (N=50) |
|---|---|---|
| Age of Patients (In years) | | |
| 15-29 | | 22 (44%) |
| 30-44 | | 18(36%) |
| 45-60 | | 07 (14%) |
| >60 | | 03 (6%) |
| Mean Age(In Years) | | 29.8 |
| Gender | Female | 24 (48%) |
| | Male | 26 (52%) |
| Residence | Rural | 32 (64%) |
| | Urban | 18 (36%) |

**Table 2.Distribution of Symptoms among Patients**

| Characteristics | | Number of Patients (N=50) |
|---|---|---|
| **Duration of Symptoms (In Days)** | | |
| <28 | | 10 (20%) |
| 28-60 | | 31 (62%) |
| >60 | | 09 (18%) |
| Fever | Present | 47 (94%) |
| | Absent | 06 (6%) |
| Headache | Yes | 33 (66%) |
| | No | 17 (34%) |
| Vomiting | Yes | 32 (64%) |
| | No | 18 (36%) |
| Convulsion | Yes | 05 (10%) |
| | No | 45 (90%) |
| Dimness of Vision | Yes | 07 (14%) |
| | No | 43 (86%) |

## Results and Analysis

Total 50 patients were analyzed in this study, a majority of the study population was male (52%) and most of them were in the age group of 15-29 years (Mean age 29.8 years) (Table 1).

Most of the (94%) patients presented with fever and headache (66%). Only 10% presented with convulsion and 14% with dimness of vision. Mean duration of symptom was 42.1 days (Table 2).

Half of the patients had no sputum for AFB report. Among the other half 24 (96%) patients had a negative sputum for AFB report and only 1 (4%) patient had a positive report. Among the study population only 13 (26%) patients had military shadow/ chest infiltrates present in their chest x-ray.

On clinical examination, it was found that 58% Patients had an altered state of consciousness,32 patients had a GCS score of <10.Around 20 patients (40%) had cranial nerve (CN) palsy involving 6th cranial nerve most commonly along with 2nd, 3rd and 7th CN.10 patients had features of paresis either in form of hemiparesis/ quadriparesis (Table 3).

**Table 3.Distributionof Clinical Findings Amongpatients**

| Characteristics | Number of Patients (N=50) |
|---|---|
| **Meningeal Signs** | |
| Present | 33 (66%) |
| Absent | 17 (34%) |
| **Level of Consciousness** | |
| Conscious | 21 (42%) |
| Drowsy | 13 (26%) |
| Stuporous | 10 (20%) |
| Comatose | 06 (12%) |
| **Glasgow Coma Scale (Gcs Score)** | |
| ≤10 | 16 (32%) |
| 11-14 | 13 (26%) |
| 15 | 21 (42%) |
| **Cranial Nerve (Cn) Palsy** | |
| No Palsy | 30 (60%) |
| 2nd CN Palsy | 04 (8%) |
| 3rd CN Palsy | 02 (4%) |
| 6th CN Palsy | 13 (26%) |
| 7th CN Palsy | 01 (2%) |
| **Paresis of Limb** | |
| No Paresis | 40 (80%) |
| Hemiparesis | 09 (18%) |
| Quadriparesis | 01 (2%) |
| Pupillary Size and Reaction | |
| Normal Size and Reacting | 34 (68%) |
| Mild Dilated and Sluggishly Reacting | 11 (22%) |
| Fully Dilated and Non-Reacting | 05 (10%) |
| **Papilledema** | |
| Absent | 26 (52%) |
| Present | 24 (48%) |

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**

**Table 4.Stage Wise Distribution of Patients**

| Tbm Stage (British Medical Council Staging) | Frequency (%) |
|---|---|
| Stage 1 | 15 (30%) |
| Stage 2 | 19 (38%) |
| Stage 3 | 16 (32%) |

**Table 5.CSF Picture among Patient Population**

| Characteristics | Number of Patients(N=50) |
|---|---|
| **CSF Cell-Count** | |
| ≤100 | 14 (28%) |
| 101-200 | 18 (36%) |
| 201-300 | 06 (12%) |
| 301-400 | 06 (12%) |
| 401-500 | 03 (6%) |
| >500 | 03 (6%) |
| **CSF Differential Cell Count** | |
| Lymphocytic | 46 (92%) |
| Neutrophilic | 04 (8%) |
| **CSF Protein (Mg/Dl)** | |
| <40 | --- |
| 41-100 | 04 (8%) |
| 101-200 | 32 (64%) |
| 201-300 | 09 (18%) |
| 30-400 | 03 (6%) |
| >400 | 02 (4%) |
| **CSF: Plasma Glucose** | |
| <0.5 | 44 (88%) |
| >0.5 | 06 (12%) |
| AFB In CSF (Zn Stain) | |
| Present | 49 (98%) |
| Absent | 01 (2%) |
| **CSF Culture (Bactec Method)** | |
| Positive | 26 (52%) |
| Negative | 24 (48%) |
| **CSF CBNAAT** | |
| MTB Detected | 21 (42%) |
| MTB Not Detected | 29 (58%) |

According to the British Medical Council Staging System most of the Patients (38%) were of Stage II tubercular meningitis followed by stage III (32%) and Stage I (30%) (Table 4).

The CSF study showed a picture of lymphocytic pleocytosis in a large number (92%) of patients.

The mean value of CSF protein was 182.20 mg/dl, the mean value of CSF glucose was35.8 mg/dl (Range 12mg/dl-66mg/dl).88% patient had CSF: Plasma glucose value of <0.5.

80% of study population had high CSF ADA (>9.5). The mean value of CSF ADAwas10.69 with minimum value was1.7 and the maximum value was 20.9.

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**

**Table 6.Comparison of Different Diagnostic Test Methods**

| Characteristics (According To Csf Culture Positivity) | CSF CBNAAT (95%Ci) | CSF ADA (95%Ci ) | CSF AFB (ZN Stain) (95%Ci) |
|---|---|---|---|
| Sensitivity | 0.77 (0.50-1.06) | 0.85 (0.57-1.13) | 0.04 (-0.24-0.32) |
| Specificity | 0.96 (0.68-1.24) | 0.18 (-0.03-0.530) | 1.0 (0.72-1.28) |
| PPV | 95.23% | 55% | 100% |
| NPV | 79.31% | 60% | 82.8% |
| Likelihood Ratio | 18.52 | 1.13 | Undefined |

**Table 7.Distribution of MRI Brain Findings among Study Population**

| Mribrain Findings | Frequency (%) |
|---|---|
| **Meningeal Enhancement** | |
| Absent | 31 (62%) |
| Present | 19 (38%) |
| Infarction | |
| Present | 17 (34%) |
| Absent | 33 (66%) |
| **Hydrocephalus** | |
| Present | 26 (52%) |
| Absent | 24 (48%) |
| **Tuberculoma** | |
| Present | 08 (16%) |
| Absent | 42 (84%) |

**Table 8.Predictors of Mortality among TB Patients**

| Variables | Outcome | | P-Value | Significance |
|---|---|---|---|---|
| | Death | Discharge | | |
| **Age** | | | | |
| ≥40Yrs | 9 | 5 | 0.001 | Significant |
| <40Yrs | 6 | 30 | | |
| **Duration of Illness (Days)** | | | | |
| >28Days | 14 | 25 | 0.087 | Not Significant |
| ≤28 Days | 1 | 10 | | |
| Fever | 2 | 1 | 0.153 | Not Significant |
| Noyes | 13 | 34 | | |
| Headache | 9 | 8 | 0.011 | Significant |
| Noyes | 6 | 27 | | |
| **Level of Consciousness** | | | | |
| Conscious | 0 | 21 | 0.003 | Significant |
| Altered Consciousness (Drowsy, Stuporous, Comatose) | 15 | 14 | | |
| Cranial Nerve Palsy Absent | | | | |
| Absent | 9 | 21 | 1.000 | Not Significant |
| Present | 6 | 14 | | |

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**

| | | | | |
|---|---|---|---|---|
| Gcs | | | | |
| ≥10 | 3 | 34 | 0.00 | Significant |
| <10 | 12 | 1 | | |
| **TBM Stage** | | | | |
| Stage 3 | 13 | 3 | 0.000 | Significant |
| Others (Stage1 &2) | 2 | 32 | | |
| **CSF Cell Count** | | | | |
| ≥200 | 06 | 15 | 0.851 | Not Significant |
| <200 | 09 | 20 | | |
| **CSF Protein** | | | | |
| ≥100 | 15 | 31 | 0.172 | Not Significant |
| <100 | 00 | 04 | | |
| **CSF Glucose** | | | | |
| ≤30 | 10 | 09 | 0.002 | Significant |
| >30 | 05 | 26 | | |
| **CSF Cbnaat** | | | | |
| Positive | 05 | 16 | 0.416 | Not Significant |
| Negative | 10 | 19 | | |
| **Basal Meningeal Enhancement** | | | | |
| Absent | 11 | 20 | 0.280 | Not Significant |
| Present | 04 | 15 | | |
| **Hydrocephalus** | | | | |
| Absent | 01 | 25 | 0.001 | Significant |
| Present | 14 | 10 | | |

CSF based ZN staining was positive in around 98% of patients. CSF culture (BACTEC Method) among TBM patients showed positive culture in 26 (52%) of patients. CSF CBNAAT detected MTB in 21(42%) patients. Amongst the 21 patients in whom CSF CBNAAT was positive for MTB, only 1 patient had Rifampicin resistant MTB (Table 5).

CSF ZN staining had the highest specificity (ability to detect true negative) followed by CBNAAT (100% vs 96%), but ZN staining had lowest sensitivity (ability to detect true positive). CSF ADA had highest sensitivity (85%) but lowest specificity (18%) among all (Table 6).

On imaging studies (CEMRI Brain) 52% patients had hydrocephalus and 38% cases showed meningeal enhancement. Tuberculoma was seen in only 8 patients (Table 7).

15 (30%) patients died of tubercular meningitis while the rest of the 35 (70%) patients were discharged.

There was statistically significant association between mortality and different clinical, investigational variables, (p-value less than 0.05). Age, headache, level of consciousness, GCS score, TBM stage, CSF glucose content & hydrocephalus showed statistically significant association with death rate among tubercular meningitis patients (Table 8).

## Discussion

The present study was a hospital based observational study which included 50 suspected TB meningitis patients (definite, probable and possible). In the present study out of the 50 patients 44% of them were within the range of15-29 years of age and median age was 28 years. (Table 1) It was comparable to the study conducted by Christensen et al where 55.26% were in the age group of 20-39 years.[12] In our study there 52% of the patients were male which was in concordance with the sex distribution in the study done by Sarkar D.N. Hossain MI et al.[13]

Almost all (94%) TBM patients had fever and most (66%) of them had headache and vomiting, which are very pathognomonic features of meningeal irritation/infection (Table 2). Findings are comparable to the study conducted by Sharma et al and Archana Aher et al.[14,15] 10% of the study population had convulsion, which was consistent with the study results conducted by Sirajus Salekeen et al.[16]

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**

In the present study it was shown that 66% patients had meningeal sign which was to some extent corroborative to the study done by Sarkar D.N. Hossain M.I. et al.[13] 58% of patients had altered sensorium at the time of admission in our study which was comparable to the study conducted by Sharma et al, where altered sensorium was present among 65.5 % of the patients.[14]

Distribution of Glasgow Coma Scale (GCS) among TBM patients in the present study revealed that 32% had GCS ≤10 (Table 3). Besides that, 62% patients were in TBM stage 2 and 3 as per Medical Research Council grading system for tuberculous meningitis. In our study distribution of stage 2 & 3 disease and GCS ≤10 on admission was among higher side due to late presentation, misdiagnosis from primary & secondary health care level and late initiation of anti-tubercular therapy.

In our study it was shown that; there was cranial nerve palsy among 40 %of patients and papilledema among 48% patients which was comparable to the study conducted by Paithankar et al.[15] It revealed 6$^{th}$ cranial nerve involvement was the commonest one and 3 patients had B/L6$^{th}$ CN involvement. 18% of patients had hemiparesis and 2% had quadriparesis. That was in concordance with the distribution of long tract signs in the study done by Hossain M. I. et al.[13]

In the present study 36% patients had CSF cell-count of 101-200/cu.mm and a mean value of the CSF cell-count was 202.82 (Table 5). The finding was similar to a previous study conducted by Garg et al.[17] In 92% patients the CSF picture was lymphocytic similar to the study done by Sirajus Salekeen et al, where lymphocytic CSF seen among 96.15%of TBM patients.[16]

In our study, 64% patients had CSF protein in the range of 101-200 mg/dl and 18% had a range of 201-300.The mean value of CSF glucose is 35.8 mg/dl. These results are consistent with the study findings of Sharma et al and Garg et al.[14,17]

In the present study 2% of TBM patients had CSF AFB positive by ZN stain and the sensitivity is only about 4%. The finding was similar to the study done by Guo-Dong Feng, Ming Shi et al.,[18] where sensitivity for TBM rarely exceeds 20%.

80% of TBM patients have high ADA (cut-off 9.5) and the mean value was10.69. Sensitivity and specificity of CSF ADA was 85% and 18% respectively. A study conducted by Bharat et al, where CSF ADA level 10 U/L as a cut off value exhibited 94.73% sensitivity and 90.47% specificity in differentiating tuberculous from non-tuberculous meningitis; it also has 90% positive predictive value and 95.00% negative predictive value.[19] The present study was not concordance to the previous studies.

In the present study 52% of patients have positive culture by BACTEC MGIT960.In a study by Heemskerk et al.,[20] sensitivity of CSF culture was slightly better at around 66.5%.

In our study MTB detected among 42% of patients by CSF CBNAAT i.e. Among 21 patients out of 50 patients and rifampicin resistance detected among 1 TBM patient which was subsequently confirmed by drug sensitivity testing [TABLE6]. The sensitivity & specificity of CSF CBNAAT was 77% and 96% respectively. Study by Patel et al., showed 67% sensitivity with Gene Xpert and Nhu et al in their study showed that Gene Xpert had 59% sensitivity and 99% specificity.[21,22] But, sensitivity of Gene Xpert is dependent on bacterial concentration in CSF (minimum 100CFU/mL organisms). Thus, centrifugation of CSF sample can further increase the diagnostic yield. In our study 12% cases that was positive by culture were not detected by CBNAAT which might be due to inadequate bacterial concentration in study sample. Gene Xpert has been recognized by WHO as the preferred initial diagnostic test for TBM.[9]

In our study MRI Brain showed basal meningeal enhancement among 38%, infarction in 34% and Hydrocephalus among 52% of patients. 16% of TBM patients had hydrocephalus. (Table 7). A study conducted by Archana Aher et al showed meningeal enhancement among 62%, hydrocephalus in 8 %, infarcts among 32 % and tuberculomas among16 % of TBM patients.[15] Another study by Sharma et al where distribution of imaging findings included hydrocephalus (24%), presence of basal exudates (22%), meningeal enhancement (20%), presence of tuberculomas (7%) and presence of infarcts (3.6%).[14]

Multivariate analysis shows there is statistically significant association that (p-value<0.05) exist between death and different variables including Age ≥40years, no headache (may be related to delayed presentation), altered consciousness, GCS<10, TBM stage 3, CSF glucose≤30mg/dl and Presence of hydrocephalus (Table 8).

With the age of more than 40 years, an absence of headache at presentation was found to be associated with higher mortality, which was also observed in a study by Elizabeth Litta George, Thomas et al.[23] In a study by Yasar KK et al., showed age, stage of TBM, altered sensorium, underlying comorbidities, pulmonary tuberculosis, leukocytosis and CSF/ blood glucose ratio< 0.30 were associated with an increased risk of death, which was consistent to our study.[24]

But there are certain limitations present in this study- First, the sample size was small, involving only 50 patients. Secondly, this was a single centered study, had it been multicentric, the results would have been more corroborative to the results found in study involving a larger population. Third, the duration of the study was short. Lastly, the study population was not randomized so there might be some confounding and biasing factors behind our

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**

results and it did not include HIV sero-positive patients, so results can't be extrapolated to general population.

## Conclusion

CSF CBNAAT has shown an acceptable level of sensitivity and specificity along with rapidity of diagnosis for TBM and so it can be used as an alternative to CSF culture. The present study also provides information regarding certain Clinico-investigational parameters that can predict the mortality and thus the prognosis. But further studies are required to reach a conclusive decision.

## Acknowledgement

We acknowledge the help and support of the Head of the Department of Department of General Medicine, all Faculty members and staff. We also want to thank all the patients who took part in our study and their relatives.

**Conflict of Interest:** None

## References

1. Wang JT,Hung CC,Sheng WH,Wang JY,Chang SC,Luh KT.Prognosis of Tuberculosis meningitis in adults in the era of modern anti-Tuberculosis chemotherapy.J Microbiol Immunol Infect.2002;35:215–22. [PubMed] [Google Scholar]
2. Lu CH, Chang WN, Chang HW. The prognostic factors of adult Tuberculosis meningitis. Infection. 2001 Dec;29(6):299-304.[PubMed] [Google Scholar]
3. George EL, Iype T, Cherian A, Chandy S, Kumar A, Balakrishnan A, Vijayakumar K.Predictors of mortality in patients with meningeal tuberculosis. Neurol India. 2012 Jan-Feb;60(1):18-22. [PubMed] [Google Scholar]
4. Thwaites GE, Duc Bang N, Huy Dung N, ThiQuy H, ThiTuongOanh D, Thi Cam Thoa N, Quang Hien N, Tri Thuc N, Ngoc Hai N, Thi Ngoc Lan N, Ngoc Lan N, Hong Duc N, Ngoc Tuan V, HuuHiep C, Thi Hong Chau T, Phuong Mai P, Thi Dung N, Stepniewska K, Simmons CP, White NJ, Tinh Hien T, Farrar JJ.The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with Tuberculosis meningitis. J Infect Dis. 2005 Dec;192(12):2134-41. [PubMed] [Google Scholar]
5. Ahuja GK, Mohan KK, Prasad K, Behari M. Diagnostic criteria for tuberculous meningitis and their validation. Tuber Lung Dis. 1994 Apr;75(2):149-52.[PubMed] [Google Scholar]
6. Boyles TH, Thwaites GE. Appropriate use of the Xpert(R) MTB/RIF assay in suspected tuberculous meningitis. Int J Tuberc Lung Dis. 2015 Mar;19(3):276-7.[PubMed] [Google Scholar]
7. Seth P, Ahuja GK, Bhanu NV, Behari M, Bhowmik S, Broor S, Dar L, Chakraborty M.Evaluation of polymerase chain reaction for rapid diagnosis of clinically suspected Tuberculosis meningitis.Tuber Lung Dis. 1996 Aug;77(4):353-7.[PubMed] [Google Scholar]
8. Mir AW, Kirmani A, Eachkoti R, Siddiqi MA. Improved diagnosis of central nervous system tuberculosis by MPB64-target PCR. Braz J Microbiol. 2008;39:209-13. [PubMed] [Google Scholar]
9. World Health Organization. Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extra pulmonary TB in adults and children. Available from:www.who.int/tb/laboratory/xpert. Launch update Accessed 7 June 2015.
10. Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, White NJ, Parry CM, Farrar JJ. Diagnosis of adult Tuberculosis meningitis by use of clinical and laboratory features.Lancet. 2002 Oct;360(9342):1287-92.[PubMed] [Google Scholar]
11. Marais S, Thwaites G, Schoeman JF, Török ME, Misra UK, Prasad K, Donald PR, Wilkinson RJ, Marais BJ. Tuberculous meningitis: a uniform case definition for use in clinical research. Lancet Infect Dis. 2010 Nov;10(11):803-12.[PubMed] [Google Scholar]
12. Christensen AS, Andersen AB, Thomsen VO, Andersen PH, JohansenIS. Tuberculosis meningitis in Denmark: a review of 50 cases. BMCInfect Dis.2011;11:47.[PubMed] [Google Scholar]
13. Sarkar DN, Hossain MI, Shoab AK, Quraishi FA. Presentation of tuberculous meningitis patients: Study of 30 cases. Medicine Today. 2013 Aug;25(1):32-5. [Google Scholar]
14. Sharma HK,Gupta SK. Tuberculous meningitis- A clinico-radiological study. JK Science. 2013;15:198-201.[Google Scholar]
15. Aher A, Paithankar M, Bhurke B. Study of central nervous system tuberculosis. J Assoc Physicians India. 2018;66(1):41-4.[PubMed] [Google Scholar]
16. Salekeen S, Mahmood K, Naqvi IH, and Baig MY, Akhter ST, Abbasi A. Clinical course, complications and predictors of mortality in patients with tuberculous meningitis--an experience of fifty two cases at Civil Hospital Karachi, Pakistan. J Pak Med Assoc. 2013;63(5):563-7. [PubMed] [Google Scholar]
17. GargRK.Tuberculosis of the central nervous system. PostgradMedJ.1999;75:133-40.[Google Scholar]
18. Feng GD, Shi M, Ma L, Chen P, Wang BJ, Zhang M, Chang XL, Su XC, Yang YN, Fan XH, Dai W, Liu TT, He Y, Bian T, Duan LX, Li JG, Hao XK, Liu JY, Xue X, Song YZ, Wu HQ, Niu GQ, Zhang L, Han CJ, Lin H, Lin ZH, Liu JJ, Jian Q, Zhang JS, Tian Y, Zhou BY, Wang J, Xue CH, Han XF, Wang JF, Wang SL, Thwaites GE, Zhao G.Diagnostic accuracy of intracellular mycobacterium tuberculosis detection for tuberculous meningitis. Am J Respir Crit Care Med. 2014 Feb;189(4):475-81.[PubMed] [Google Scholar]
19. Gupta BK, Bharat A, Debapriya B, Baruah H. Adenosine deaminase levels in CSF of tuberculosis meningitis

patients. J Clin Med Res. 2010 Oct;2(5):220-4.[PubMed] [Google Scholar]
20. Heemskerk D, Caws M, Marais B, Farrar J.Tuberculosis in Adults and Children. London: Springer; 2015. Wellcome Trust–Funded Monographs and Book Chapters. [PubMed] [Google Scholar]
21. Patel VB, Theron G, Lenders L, Matinyena B, Connolly C, Singh R, Coovadia Y, Ndung'u T, Dheda K.Diagnostic accuracy of quantitative PCR (XpertMTB/RIF) for tuberculous meningitis in a high burden setting:a prospective study. PLoS Med. 2013 Oct;10(10):e1001536. [PubMed] [Google Scholar]
22. Nhu NT, Heemskerk D, Thu do DA, Chau TT, Mai NT, Nghia HD, Loc PP, Ha DT, Merson L, Thinh TT, Day J, Chau Nv, Wolbers M, Farrar J, Caws M. Evaluation of GeneXpertMTB/RIF for diagnosis of tuberculous meningitis.J Clin Microbiol. 2014 Jan;52(1):226-33. [PubMed] [Google Scholar]
23. Sheu JJ, Yuan RY, Yang CC. Predictors for outcome and treatment delay in patients with Tuberculosis meningitis.Am J Med Sci. 2009 Aug;338(2):134-9. [PubMed] [Google Scholar]
24. Yasar KK, Pehlivanoglu F, Sengoz G. Predictors of mortality in tuberculous meningitis: a multivariate analysis of 160 cases. Int J Tuberc Lung Dis. 2010 Oct;14(10):1330-5. [PubMed] [Google Scholar]

**ISSN: 0019-5138**
**DOI: https://doi.org/10.24321/0019.5138.202283**