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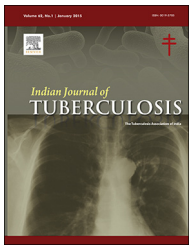

Original Article

# Predictors of adverse outcome in patients of tuberculous meningitis in a multi-centric study from India

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ABSTRACT

*Introduction:* This study aimed to investigate the factors which may predict mortality and neurological disability at one year follow up in patients of tuberculous meningitis (TBM) in India.
*Methodology:* Patients with TBM were prospectively enrolled from July 2012 to September 2014 from four tertiary care hospitals of Delhi. The demographic characteristics, clinical features and laboratory findings were collected and patients were followed up till 1 year. These were analyzed by univariate and multivariate multinomial logistic regression analysis to identify predictors of adverse patient outcome at 1 year follow up.
*Results:* Out of 478 patients enrolled, 391 patients could be followed up to 1 year. Sixty-four patients (16.3%) died and 150 patients (39%) survived with one or more neurological disability. Altered sensorium, motor deficit, cranial nerve palsy, seizures, isolation of *M. tuberculosis* and presence of multi-drug resistance were independently associated with any adverse outcome (death or disability) but by multivariate analysis only motor deficit, altered sensorium and isolation of *M. tuberculosis* on culture produced a statistically significant model for prediction of patient outcome.
*Conclusion:* The three-predictor model with motor deficit, altered sensorium and isolation of *M. tuberculosis* produced a statistically significant model with correct prediction rate of 60.4%. These three variables predicted death with odds ratio of 39.2, 6.7 and 2.1 respectively in comparison to recovery whereas only motor deficit and isolation of *M. tuberculosis* predicted neurological disability at 1 year with odds ratio of 3.9, 2.4 respectively.



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## 1. Introduction

Tuberculous meningitis (TBM) is the most severe clinical manifestation of tuberculosis and leads to significant mortality and morbidity in spite of many advances in diagnosis and treatment modalities.[1] Timely initiation of chemotherapy and active management of complications of TBM has reduced the mortality rate but morbidity is still unacceptably high.[1,2] Though TBM is endemic in India but there is limited data on patient outcome after initiation of anti-tubercular drug treatment (ATT) and there are very few studies which have followed up the patients till treatment completion. British Medical Research Council (BMRC) staging for evaluation of disease severity is extensively used to predict patient outcome but is not built on multivariable approach.[3,10] It is still challenging to predict patient outcome on the basis of different clinical and laboratory parameters exhibited by the patients.[3–11] Some earlier studies have evaluated the association of different combinations of clinical, neuro-imaging and laboratory variables in limited number of patients (19–100) with prediction of disease outcome as either good or poor, death or recovery, neurological sequelae or no sequelae with clubbing of neurological sequelae in recovery or poor patient outcome depending upon scoring systems. The clubbing of neurological sequelae with either the recovery or death may lead to some degree of bias, e.g. patients with focal neurological deficit like optic atrophy cannot be clubbed with either recovery or death.[3,11]

This multicentric study aimed to analyze the demographic, clinical and laboratory variables in patients diagnosed as TBM on prediction of mortality and neurological sequelae separately at 1 year follow up by multinomial logistic regression technique so as to determine the effect of each predictor variable on the outcome with and without controlling for confounding.

## 2. Methodology

### 2.1. Settings

The patients for this study were prospectively recruited (purposive sampling) from Department of Neurology, Institute of Human Behaviour and Allied Sciences and GB Pant Hospital, Dept of Medicine and paediatrics, Guru Tegh Bhadur Hospital and Department of Paediatrics, Chacha Nehru Bal Chikitsalaya, Delhi, India from July 2012 to September 2014 after obtaining ethical approval from all the Institutes (IHBAS/ethics/2011/010, MAMC/(30)/2/2012/197, MAMC/(35)/1/2013/70, UCMS/2012/23/3). Informed written consent was obtained from all patients recruited in the study. All the diagnostic testing was done in Dept. of Microbiology, Institute of Human Behaviour and Allied Sciences, Delhi.

The consecutive patients diagnosed as TBM according to consensus TBM criteria of Marais et al. and decided for initiation of ATT were included in the study ($n = 520$).[12] The patients with absolute contraindications to lumbar puncture, with significant pre-existing neurological deficit, seizure disorder, mental retardation, cerebral palsy were not included in the study. A total of 42 patients were excluded later because of the reasons mentioned in Fig. 1.

### 2.2. Clinical evaluation and diagnosis

#### 2.2.1. Clinical history

The history for duration of illness, fever, signs of meningeal irritation (headache vomiting, neck stiffness), altered sensorium and seizures was taken. All the patients were subjected to detailed neurological examination which included assessment of level of consciousness by Glassgow Coma Scale, signs of meningeal irritation, cranial nerve involvement, fundus examination, motor, sensory deficits and any other neurological signs. Screening was done to rule out the dissemination of tuberculosis to other parts of the body. All the clinical details were recorded in pre-designed performa.

All the patients were staged according to disease severity as per BMRC guidelines: Stage 1 included patients in prodromal phase with no definite neurological symptoms, Stage 2 included patients with signs of meningeal irritation with slight or no clouding of sensorium and minor (cranial nerve palsies) or no neurological deficit, Stage 3 included patients with severe clouding of sensorium, convulsions, focal neurological deficit and/or involuntary movements.[3]

Other medical details included history of past tuberculosis, contact with TB patients, human immuno deficiency virus (HIV) co infection and any other chronic illness.

#### 2.2.2. Laboratory investigations

Besides routine laboratory investigations, lumbar puncture was done in all the clinically suspected patients and 2 ml of cerebro spinal fluid (CSF) was collected and subjected to cytology, biochemistry, smear microscopy, bacterial cultures ((BACTEC MGIT 960, Becton Dickinson, Sparks, MD, USA)) and conventional polymerase chain reaction (PCR) (IS6110 gene, PalmCycler, Genetix Biotech Asia Pvt. Ltd).[13]

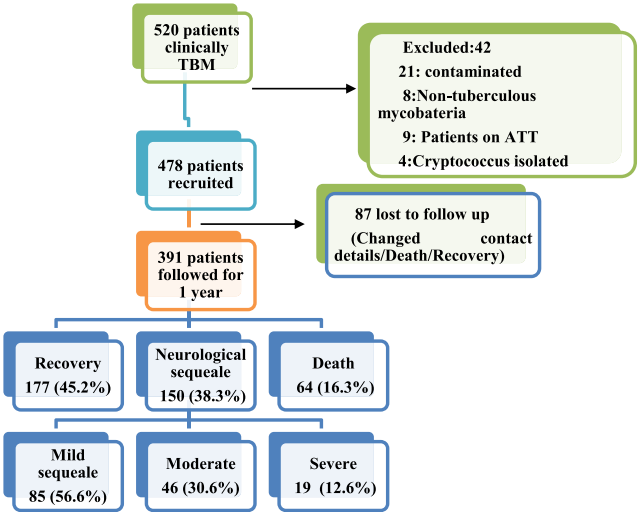


**Fig. 1 – Flow chart of patients recruited in the study with clinical outcome.**

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#### 2.2.3. *Neuroimaging*

Magnetic resonance imaging (MRI) brain/contrast enhanced computerized tomography (CT) head was done in all patients. CT chest and abdomen was done in selected patients with clinical suspicion of dissemination of tuberculosis.

#### 2.2.4. *Management*

All the included patients were admitted, managed for complications and treated by daily treatment regimen of anti-tubercular drugs as per standard treatment guidelines.[14,15]

#### 2.2.5. *Monitoring and follow up*

All the patients were followed up once a month for 1 year. During follow up, patients were clinically evaluated and liver function test of all the patients were done to see any side effects due to ATT. MRI/CT scan was done only if it was essential for clinical management. Response to treatment was judged by improvement in sensorium, neurological disability and constitutional symptoms like fever, headache, appetite, weight. Patient outcome was recorded as complete recovery, with neurological sequelae (if presence of altered sensorium, cranial nerve palsy, extrapyramidal movements, focal neurological deficit, mental retardation, optic atrophy, and/or tone abnormalities) or death.

### 2.3. *Statistical analysis*

Patient outcome were grouped into three categories as complete recovery, neurological sequelae, death and was analyzed for significance at 1 year follow up. Loss to follow up was adjusted by increasing the study period for enrolment of patients for further three months. The study was as per protocol analysis and all those patients who were lost to follow up were not included in analysis. The data was analyzed by the SPSS software version 21 (SPSS Inc., Chicago, IL, USA) Quantitative data was analyzed using mean and ranges and 95% confidence intervals (CI). Qualitative data was expressed as proportion of total number of patients. All the independent variables were analyzed by both chi square and trend chi square test (Pearson's' linear by linear in SPSS). $p < 0.05$ was considered statistically significant. All the significant variables were analyzed independently as well as in blocks by multinomial logistic regression (forward step wise) to predict the best model for adverse patient outcome.[16]

## 3. Results

A total of 520 patients were recruited in this study for management of TBM, 42 patients were excluded for the reasons given in Fig. 1 leaving 478 patients. Out of these only 391 patients could be followed up till 1 year and out of these 64 patients (16.4%) died, 150 had any neurological sequelae (38.3%) and 177 (45.2%) patients had complete recovery (Fig. 1).

The details for demographic, clinical features and laboratory results in relation to patient outcome along with significance of association are shown in Table 1 in numbers and percentages.

The independent multinomial logistic regression analysis of all the significant variables with patient's recovery, any neurological deficit and death showed altered sensorium, motor deficit, seizures and isolation of multi-drug resistant (MDR) *M. tuberculosis* were independent predictors of death as compared to recovery whereas motor deficit, cranial nerve palsy, seizures and isolation of *M. tuberculosis* on culture were independent predictors of neurological disability at 1 year compared to recovery (Table 2).

The multinomial logistic regression of all significant predictors together, revealed that the three-predictor model with altered sensorium, motor deficit and isolation of *M. tuberculosis* produced a statistically significant improvement over the constant only model, $\chi^2(6, N = 391) = 141.65, p = <0.001$ with −2 log likelihood ratio of 62.7 and correct prediction rate of 60.4%. The parameter estimate table shows the logistic coefficient for each predictor variable for death and neurological squeal in reference to recovery (Table 3). Motor deficit, altered sensorium and culture isolation of *M. tuberculosis* played a statistically significant role in predicting death with respect to recovery. A TBM patient with presence of motor deficit was 40 times more likely to die than complete recovery keeping other factors constant and patient with altered sensorium was 6.7 times more likely to die than completely recovery. Isolation of *M. tuberculosis* increased the likelihood of death to twice as compared to recovery. For prediction of neurological deficit vs. recovery both presence of motor deficits and positive culture increased the likelihood of neurological disability to 4, 2 times as compared to recovery keeping other factors constant.

## 4. Discussion

This study is unique as prediction of patient outcome was assessed as death in reference to recovery and neurological sequelae in reference to recovery by multinomial logistic regression analysis in a cohort of 391 patients who could complete follow up till 1 year without clubbing mild neurological sequelae in recovery group and severe sequelae with death. The mortality rate in our study was 16.3% and one or more neurological disability was present in 39% of patients at one year follow up. The earlier published studies have reported mortality rates varying from 15% to 60% and neurological disability of 27–50% but all these studies have treated patients with directly observed thrice a week regimen treatment regimen and have given mortality and morbidity rates at different point of times either at discharge, 6 weeks post treatment, at 6 months or 1 year follow up making it difficult to directly compare these studies with the present study.[3–11] The relative lower mortality in this study could be due to efficient early diagnosis, initiation of treatment in the right time frame, daily treatment regimen, availability of dedicated Intensive care units and neurosurgical expertise at one centre and regular follow up.[3,4,9,10]

In this study majority of patients presented in stage 3 disease which may be due to delayed access to tertiary care hospitals and poor health seeking behaviour in developing countries which is similar to studies from other developing countries.[4,9–11] Presence of motor deficit, seizures, altered

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**Table 1 – Analysis of socio-demographic, clinical and laboratory parameters with patient outcome.**

| Parameter (no. positive) | Death N (%) | Neurological sequelae N (%) | Recovery N (%) | Pearson's p value | Linear by linear association (trend $\chi^2$) |
|---|---|---|---|---|---|
| | N = 64 | N = 150 | N = 177 | | |
| *Age (Mean: 27.8 ± 17.27 years)* | | | | | |
| <18 year (n = 138) | 29 (45.3) | 42 (28) | 68 (38.4) | 0.369 | 0.993 |
| >18 year (n = 253) | 35 (54.7) | 108 (72) | 109 (61.6) | 0.300 | 0.866 |
| Males | 28 (43.7) | 62 (41.3) | 93 (52.5) | 0.112 | 0.093 |
| Females | 36 (56.2) | 88 (58.5) | 84 (47.4) | | |
| *Clinical features* | | | | | |
| HIV positivity (n = 12) | 3 (4.6) | 2 (1.3) | 7 (3.9) | 0.280 | 0.831 |
| Contact with TB person (n = 105) | 16 (25) | 43 (28.6) | 46 (25.9) | 0.270 | 0.190 |
| Past history of TB (n = 58) | 8 (12.5) | 26 (17.3) | 24 (13.5) | 0.380 | 0.327 |
| *Duration of illness (Mean 42.7 ± 62.3 days)* | | | | | |
| 0–7 days (n = 100) | 24 (37.5) | 30 (20) | 47 (26.5) | 0.047 | 0.328 |
| 8-30days (n = 167) | 23 (35.9) | 67 (44.6) | 77 (43.5) | 0.417 | 0.422 |
| 30 and above (n = 123) | 17 (26.5) | 53 (36) | 53 (29.9) | 0.378 | 0.946 |
| Disease stage (3 vs. 2 + 1) (n = 306) | 63 (98.4) | 125 (83.3) | 118 (66.6) | <0.001 | <0.001 |
| Fever (n = 304) | 46 (71.8) | 114 (76) | 144 (81.3) | 0.238 | 0.092 |
| Meningeal irritation (n = 249) | 36 (56.2) | 95 (63.3) | 118 (66.6) | 0.330 | 0.149 |
| Extra meningeal tuberculosis (n = 65) | 14 (21.9) | 25 (16.6) | 26 (14.6) | 0.417 | 0.523 |
| Altered sensorium (n = 197) | 49 (76.5) | 68 (45.3) | 80 (45.1) | <0.001 | <0.001 |
| New onset seizure (n = 147) | 34 (53.1) | 77 (51.3) | 36 (20.33) | <0.001 | <0.001 |
| Neurological deficit (n = 150) | 60 (93.7) | 59 (39.3) | 31 (17.5) | <0.001 | <0.001 |
| Motor deficit (n = 120) | 50 (78.1) | 49 (32.6) | 21 (11.8) | <0.001 | <0.001 |
| Cranial nerve palsy (n = 92) | 10 (6.4) | 48 (32) | 34 (19.2) | 0.007 | 0.673 |
| *CSF findings* | | | | | |
| TLC: 100–500 (n = 144) | 20 (31.2) | 60 (40) | 64 (36.1) | 0.463 | 0.732 |
| 500 and above (n = 65) | 12 (18.7) | 24 (16) | 29 (16.3) | 0.879 | 0.740 |
| Lymphocyte > 50% (n = 324) | 52 (81.2) | 126 (84) | 146 (82.4) | 0.873 | 0.947 |
| Protein > 100 mg/dl (n = 251) | 39 (60.1) | 97 (64.6) | 115 (64.9) | 0.735 | 0.831 |
| Sugar < 50 mg/dl (n = 218) | 38 (59.3) | 83 (55.3) | 97 (54.8) | 0.812 | 0.577 |
| *Microbiological findings* | | | | | |
| Smear positivity (n = 23) | 4 (6.3) | 10 (6.7) | 9 (5.1) | 0.825 | 0.628 |
| Culture positive (n = 170) | 29 (45.3) | 81 (54) | 60 (33.8) | <0.001 | 0.011 |
| PCR positive (n = 283) | 46 (71.8) | 118 (78.6) | 119 (67.2) | 0.070 | 0.174 |
| Confirmed diagnosis (287) | 46 (71.8) | 120 (80) | 121 (68.3) | 0.057 | 0.214 |
| MDR (n = 9) | 6 (9.3) | 1 (0.6) | 2 (1.1) | <0.001 | 0.006 |
| Only INH resistant (n = 24) | 3 (4.6) | 14 (9.3) | 7 (3.9) | 0.520 | 0.906 |

**Table 2 – Univariate multinomial logistic regression for significant predictors.**

| Parameter | Death vs. recovery | | Neurological sequelae vs. recovery | |
|---|---|---|---|---|
| | p value | Exp(B) (95% CI) | p value | Exp(B) |
| Altered sensorium | <0.001 | 3.96 (2.0–7.5) | 0.980 | 1.005 (0.650–1.5) |
| Motor deficit | <0.001 | 26.53 (12.6–56.0) | <0.001 | 3.604 (2–6.3) |
| Cranial nerve palsy | 0.525 | 0.78 (0.36–1.6) | 0.008 | 1.979 (1.2–3.2) |
| Seizures | <0.001 | 4.43 (2.4–8.1) | <0.001 | 4.1 (2.5–6.7) |
| Culture positive | 0.106 | 1.616 (0.90–2.80) | <0.001 | 2.289 (1.5–3.5) |
| MDR | 0.018 | 7.6 (1.4–40.2) | 0.412 | 0.362 (0.032–4.0) |

$p < 0.05$ significant; Exp(B): odds ratio.

sensorium and isolation of MDR *M. tuberculosis* were found to be independent risk factors for death whereas motor deficit, seizures, cranial nerve palsy and positive *M. tuberculosis* culture were independently associated with neurological disability. Motor deficit increased likelihood of death to 26 times and for neurological disability to 3.6 times as compared to recovery. New onset Seizures were associated with fourfold risk of death as well as neurological disability. Previous studies have also reported that motor deficit and seizures are markers of severe intra cerebral damage and are much more frequently associated with death or disability.[3,10,11,17–19] Altered sensorium was found as a significant independent risk factor for death (odds ratio (OR): 3.9) but not for neurological disability. Earlier studies have also reported impairment of sensorium as an important determinant of death.[3,10–12] Cranial nerve palsies were significantly associated with twofold risk of persistent

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**Table 3 – The parameter estimates for death and neurological sequelae in reference to recovery by multivariate multinomial logistic regression.**

| Parameter | | *B* | Std. Error | Wald | Sig. | Exp(*B*) | 95% confidence interval for Exp(*B*) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower bound | Upper bound |
| Death | Intercept | −4.074 | 0.481 | 71.760 | <0.001 | | | |
| | Culture positive | 0.765 | 0.366 | 4.365 | 0.037 | 2.14 | 1.048 | 4.401 |
| | Motor deficit | 3.671 | 0.418 | 77.085 | <0.001 | 39.28 | 17.313 | 89.157 |
| | Altered sensorium | 1.903 | 0.397 | 23.005 | <0.001 | 6.70 | 3.081 | 14.589 |
| Neurological sequelae | Intercept | −0.896 | 0.206 | 18.970 | <0.001 | | | |
| | Culture positive | 0.887 | 0.236 | 14.085 | <0.001 | 2.42 | 1.528 | 3.858 |
| | Motor deficit | 1.367 | 0.300 | 20.773 | <0.001 | 3.92 | 2.179 | 7.062 |
| | Altered sensorium | 0.118 | 0.237 | 0.247 | 0.619 | 1.12 | 0.707 | 1.791 |

The reference category is recovery; Exp(*B*): odds ratio.
$R^2 = 0.35$ (Nagelkerke). Model $\chi^2(6) = 141.65$, $p < 0.001$.

neurological impairment rather than death which was quite similar to findings of Hosoglu et al. and Misra et al. who also showed cranial nerve palsy is associated with threefold risk of neurological deficit.[11,12] Confirmed diagnosis of TBM has been shown to be a predictor of adverse patient outcome in earlier studies but in the present study confirmed diagnosis by microscopy and/or culture and/or PCR did not emerge as a significant contributor to death or neurological sequelae.[18] However, patients who were positive for *M. tuberculosis* culture had twofold higher chances of residual neurological disability than recovery.

Infection with MDR *M. tuberculosis* has been shown to be a strong predictor of death due to slow or non-clearance of MDR organisms from CSF.[20] In this study isolation of MDR *M. tuberculosis* was independently associated with risk of death as 6 out of 9 patients with MDR died within 2 months of initiation of first line ATT. Out of these 5 patients died before the availability of drug susceptibility test results implying the urgent need of early detection of drug resistant strains. One patient died after 1 months of initiating second line drug treatment. Mono resistance to Isoniazid (INH) did not increase the risk of adverse patient outcome in the present study and earlier published studies have also shown conflicting association of mono resistance to INH with poor patient outcome.[20,21]

Age, duration of illness, previous history of tuberculosis, contact with TB patients and presence of extra meningeal tuberculosis, HIV positive serology, hydrocephalus, protein >100 mg%, absence of headache at presentation, presence of brain infarcts were not found to be significant predictors for either death or neurological sequelae in this study in contrast to some earlier published studies.[8,11,21–24]

In multiple multinomial logistic regression, altered sensorium, motor deficit and isolation of *M. tuberculosis* produced a significant model for prediction of patient outcome. Presence of motor deficit (OR: 39.2), altered sensorium (OR: 6.7) and culture isolation (OR: 2.1) had a statistically significant relationship to distinguish death from recovery and presence of motor deficit and isolation of *M. tuberculosis* in culture increased the likelihood of neurological disability to 4, 2 times as compared to recovery. Presence of seizures and isolation of MDR *M. tuberculosis* were not included in final model as seizures displayed co linearity with altered sensorium and inclusion of MDR *M. tuberculosis* and cranial nerve palsy did not contribute to any improvement in significance.

There were two main limitations of this study: (1) The loss to follow up was 18% (statistically acceptable range, 5–20%) and could not be avoided due to inherent nature of the disease which requires long, frequent follow up and partly because of lower socio economic strata of patients who present to public health facilities for treatment finding it difficult to afford repeated visits due to long distance travel/loss of wages or some other reasons. We could not contact these patients due to change of contact details furnished during admission. We tried to adjust for this loss by doing as per protocol analysis rather than intention to treat analysis and increasing the duration of study for 3 months (initially study was planned for 2 years) to recruit more number of patients. (2) Out of 520 CSF samples collected from 4 different Institutes, 21 samples grew non-significant pathogens like, Yeast cells, diphtheroids, Gram negative bacteria in pure or mixed growth suggestive of some extraneous contamination. Ideally, this should not have happened but it reality it is impossible to avoid this problem of contamination due to some pre-analytical problems involving sample collection, transport or processing. A repeat lumber puncture could not be obtained for analysis so these patients were excluded from the study.

## 5. Conclusion

Our findings suggest that presence of motor deficit, seizures, altered sensorium and isolation of MDR *M. tuberculosis* are independent risk factors for death whereas motor deficit, seizures, cranial nerve palsy and positive *M. tuberculosis* culture are independently associated with neurological disability at 1 year. By controlling the effect of variable which can act as confounders we found that the three-predictor model with altered sensorium, motor deficit, and culture isolation of *M. tuberculosis* produced a statistically significant model with correct prediction rate of 60.4%. Presence of motor deficit, altered sensorium and culture positivity emerged as significant predictors of death in comparison to recovery whereas presence of motor deficit and culture positivity predicted neurological disability at 1 year.

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## Conflicts of interest

The authors have none to declare.

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