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Clinical profile and mortality predictors in hospitalised patients of tuberculous meningitis

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Abstract

Background& Objective: Tuberculous meningitis (TBM) is a serious public health problem in developing countries like India as it leads to significant mortality and neurological sequelae. Aim of study was to describe clinico-radiological profile of TBM and determine predictors of mortality. *Methods:* This was a prospective study and data collected including demographic details, clinical, laboratory parameters and neuroimaging finding. Diagnosis of TBM was based according to a standard case definition proposed by Marais *et al*.(2010). *Results:* One hundred and forty two TBM patients were recruited with 54.93% males and 45.07% females. Fever was most common symptom followed by headache, vomiting, altered sensorium and seizure. Most common cranial nerve palsy was of 6th cranial nerve followed by 2nd cranial nerve. Cerebrospinal fluid (CSF)study in 77.46% of patients showed protein ≥100 mg/dL, 61.27% patients had CSF sugar ≤40 mg/dL while 87.32% of patients had total cell count ≥10 cells/cumm. Most common Neuroimaging finding was meningeal enhancement followed by hydrocephalus, infarcts, basal exudates and tuberculoma. In-hospital mortality was 17.61%. Higher age, low Glasgow Coma Scale (GCS) score, absence of headache, seizure, altered sensorium, anemia, low CSF glucose, infarct, hydrocephalus, and British medical research council (BMRC) Stage III at presentation were predictors of in-hospital mortality.
Conclusions:. Age, GCS score, absence of headache, seizure, altered sensorium, anemia, low CSF glucose, infarct, hydrocephalus, and BMRC Stage III at presentation were predictors of in-hospital mortality based on this study from Bihar, India.

Keywords: Tuberculosis, tuberculous meningitis, TBM, predictors, mortality

INTRODUCTION

Tuberculosis is a major public health problem with a huge worldwide burden, particularly in developing countries like India. Tuberculous meningitis (TBM) is the most serious extrapulmonary complication of tuberculosis. The estimated mortality due to TBM in India is 1.5 per 100,000 populations.[1] Studies have shown association of various factors with the prognosis of the disease like age, stage of disease, level of consciousness, presence of extraneural TB, biochemical studies, infarcts and hydrocephalus. This was a prospective study from Bihar, India to assess the clinical profile, laboratory values and neuroimaging features of adult TBM patients, and to find out predictors of mortality in these patients.

METHODS

This is a prospective study and TBM patients were recruited between March 2019 and December 2020. Written informed consent for participation in the study was obtained from all patients or their guardians. Patients fulfilling the following inclusion criteria were included: 1) age 12 years and above; 2) diagnosed as TBM; 3) written informed consent.

Case definition

Diagnosis of TBM was based according to a standard case definition proposed by Marais *et al*. in 2010.[2] Patients were classified as definite, probable and possible TBM. Severity of TBM was graded by BMRC staging i.e. stage 1, 2 and 3.

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Data collection

The detailed information including demographic details such as age, sex and clinical presentations including fever, headache, vomiting, altered sensorium, cranial nerve palsy and seizure were taken. GCS was used to assess the level of consciousness. Patients underwent investigations that included routine blood counts, serum biochemistry, erythrocyte sedimentation rate (ESR), human immunodeficiency virus (HIV) serology and chest radiograph. CSF was examined for opening pressure, cells (lymphocyte and neutrophil differential count), glucose, protein, acid-fast bacilli smear, culture and geneXpert nucleic acid amplification test. India ink preparation was done to exclude cryptococcal meningitis. Brain magnetic resonance imaging (MRI) was performed on 1.5 T system incorporating whole brain axial FLAIR, diffusion weighted imaging, apparent diffusion coefficient, in addition to T2 weighted and pre and post gadolinium T1 weighted sequence. The patients were assessed for leptomeningeal enhancement, basal exudates, tuberculoma, cerebral infarction and hydrocephalus.

Statistical analysis

The presentation of the Categorical variables were done in the form of number and percentage (%). Presentation of the continuous variables were done as mean ± SD and median values. The association of the variables which were quantitative in nature was analysed using Mann-Whitney Test and independent t test. The association of the variables which were qualitative in nature was analysed using Chi-Square test/Fisher's exact test. Multivariate logistic regression was used to find out significant risk factors of mortality after adjusting for confounding factors. The analysis was done with the use of Statistical Package for Social Sciences (SPSS) software version 21.0. For statistical significance, p value of less than 0.05 was considered as significant.

RESULTS

Demographic data and clinical feature

One hundred and forty two admitted patients were included in the study with 78(54.93%) males and 64 (45.07%) females. Mean age was 31.27 ± 14.9 years (range=13-70 years), 30.99% (n= 44) belonged to age group 12-20 years. 6.34% (n= 9) in 51-60 age groups. On presentation, 42.25% (n=60) patients were in BMRC stage 2 and 26.76%(n=38) in BMRC stage 3. For diagnosis, 44.37%(n=63) were categorized as probable and 27.46%(n=39) were categorized as definite TBM. Fever was the most common symptom (95.77%) followed by headache (91.55%) and vomiting (59.86%). Median duration of hospital stay was 11 days (range=2-50 days). HIV was detected in 2 patients. (Table.1)

Laboratory and MRI features

CSF was clear in all subjects. Mean CSF protein was 319.75 ± 560.21 mg/dL, ≥100 mg/dL in 77.46% of patients. Mean CSF sugar was 37.4 ± 20.92 mg/dL, ≤40mg/dL in 61.27% of patients. Mean CSF WBC total count was 132.51 ± 160.83 cells/cumm, ≥10 cells/cumm in 87.32% of patients. Mean CSF ADA was 28.66 ± 19.92 U/L. In 90.85% of patients, Adenosine deaminase (ADA) was ≥10 U/L. Acid fast bacilli (AFB) smear was positive in 4 patients. Mycobacterium tuberculosis (MTB) was detected on gene Xpert in 27.46% (n=39) patients. Rifampicin (RIF) resistance was detected in 4 patients. In blood study, 62.68% (n=89) of patients were anemic with mean hemoglobin of 11.7 ± 1.84 mg/dL, leukocytosis was present in 23.24% (n=33), hyponatremia in 59.15% (n=84) with mean serum sodium of 133.13 ± 7.47 mmol/L. Hypoalbuminemia was present in 25.35% (n= 36) of patients. Majority of patients (95.07%, n=135) had abnormal MRI Brain, most common being meningeal enhancement (74.65%) and hydrocephalus (39.44%) followed by infarcts, basal exudate and tuberculoma in 36.62% (n=52) patients. (Table 2)

Outcome

The overall mortality was 17.61% (n=25). Median age of patients who died was 35 years, which was significantly higher as compared to discharged patients which was 25 years (p value=0.023). Median duration of stay in discharged group was 11 days which was significantly higher as compared to patients who died which was 7 days (p value=0.004). There was significantly higher mortality in patients without headache (p value = 0.0001), patients with altered sensorium and seizure (p value ≤0.0001 and 0.032 respectively). There was significantly higher mortality in patients with CSF sugar ≤40 mg/dL (p value = 0.034) and anemic patients (p value=0.048). After quantitative analysis, it was found that mean serum sodium in discharged patients was 134.13 ± 6.9 mmol/L which was significantly higher as compared to patients who died i.e.

Table 1: Demographic and clinical profile of TBM patients (n =142)

Variables	Frequency	Percentage
Male	78	54.93%
Female	64	45.07%
Contact with TB	34	23.94%
BCG vaccination	94	66.20%
Fever	136	95.77%
Headache	130	91.55%
Neck rigidity	127	89.44%
Vomiting	85	59.86%
Altered sensorium	71	50.00%
Seizure	38	26.76%
Weight loss	31	21.83%
Hemiparesis	20	14.08%
Bowel/bladder	20	14.08%
Abnormal movements	11	7.75%
Paraparesis	11	7.75%
6th CN	26	18.31%
2nd CN	13	9.15%
3rd CN	7	4.93%
7th CN	2	1.41%
GCS score		
<11	39	27.46%
11-14	32	22.54%
15	71	50.00%
BMRC stage		
Stage 1	44	30.99%
Stage 2	60	42.25%
Stage 3	38	26.76%
Category of TBM		
Probable	63	44.37%
Possible	40	28.17%
Definite	39	27.46%

128.48 ± 8.42 mmol/L (p value=0.0005). There was significantly higher mortality in patients with infarct and hydrocephalus (p value = 0.027 and 0.02 respectively). There was significantly higher mortality in patients with BMRC stage 3 as compared to BMRC stage 1 and stage 2 (p value <0.0001). (Table. 3) On performing multivariate regression, patients with higher age at presentation were found to be associated with mortality in TBM. (Table. 4)

DISCUSSION

TBM is one of the common and serious CNS infection. The 142 TBM patients in our study were categorized as probable (n=63), possible (n=40) and definite (n=39) TBM. Age distribution showed preponderance (30.99%) of younger age (≤ 20 years) group with median age of study population 26 years (range=30-70 years). Age distribution is comparable to previous studies with median age of presentation ranging from 22 years to 36 years.[2-9] In present study, TBM was found to be slightly more common in males similar to another study from north India.[6] Median duration of hospital stay was 11 days which is comparable to another study from Pakistan.[10] Around half of patients in our study presented with BMRC stage 2 followed by stage 1 and stage 3. Earlier studies with similar staging system showed comparable data.[6,7,11,12]

Table 2: MRI brain and laboratory profile of TBM patients

Variables	Frequency	Percentage
MRI findings		
Abnormal MRI brain	135	95.07%
Meningeal enhancement	106	74.65%
Hydrocephalus	56	39.44%
Infarct	52	36.62%
Basal exudate	52	36.62%
Tuberculoma	52	36.62%
CSF parameters		
CSF Protein (mg/dL)		
>=100	110	77.46%
CSF Sugar (mg/dL)		
<=40	87	61.27%
CSF Total count (cells/cumm)		
>=10	124	87.32%
CSF ADA(U/L)		
>=10	129	90.85%
Gene Xpert		
Detected	39	27.46%
Biochemical parameters		
Anemia	89	62.68%
Leucocytosis	33	23.24%
Hyponatremia	84	59.15%

We found that around quarter of TBM patients had history of contact with tuberculosis and around two third of patients had BCG vaccination. Previous study from Madagascar has reported lower proportion (4%) of close contact with person with active tuberculosis and fewer (16%) recipient of BCG vaccination compared to our study.[11] A study in pediatric population showed higher recipient of BCG vaccination.[13] The protective role of BCG vaccination against TBM in children is well known[14], but its effect in adults remains uncertain. HIV was detected in only 2 patients. Prevalence of HIV is relatively low in Bihar, which is 0.22% (men 0.26%, women 0.19%) compared to the national average of 0.31% (men 0.36%, women 0.25%).[15]

Fever was most common symptom in our study followed by headache, vomiting, altered sensorium, seizure and hemiparesis. Occurrences of these symptoms are similar as compared to earlier studies.[6,7,11,12,16-19] Neck rigidity was found in 89.44% patients, which is comparable with the earlier studies, where it ranged from 18% to 91%.[4,8] In present study we found that 6th CN involvement was most common, followed by 2nd CN and 3rd CN. 7th CN palsy was found in only 2 patients. It is consistent with the findings of earlier studies where 6th nerve has been reported to be most commonly involved in TBM[6,7], as it has long intracranial course and formation of adhesion leading to entrapment of the nerve in the subarachnoid space. We found that median duration of symptoms prior to admission was 4 weeks. Duration of symptom prior to admission reported in previous studies was longer than one week which is consistent with sub-acute meningitis.[7,9,19,20] However, duration of symptoms in our study and study by Jaipuriar *et al*. was comparatively higher than reported in other studies.[7] It may be due to referral to our institute after initial visit to local health care center or hospital. Lack of awareness towards health and low education may be other reasons for delayed presentation. The CSF biochemical findings were consistent with the known CSF findings of TBM i.e. raised protein, low sugar and pleocytosis seen in previous studies[8,11,21], with minority of patients showing normal CSF biochemical parameters.

Table 3: Outcome predictors in TBM patients on univariate analysis

Variables	Survived (n =117)	Died (n =25)	P value
Age (years)			
Mean ± SD	30.03 ± 14.5	37.04 ± 15.9	0.023
Median	25 (18-39)	35 (25-50)	-
Gender			
Male	60 (76.92%)	18 (23.08%)	0.059
Duration of stay (days)	13.77 ± 7.81	10.8 ± 10	0.004
Contact with TB	25 (73.53%)	9 (26.47%)	0.12
BCG vaccination	80 (85.11%)	14 (14.89%)	0.235
HIV positive	2 (100%)	0 (0%)	1
Fever	111 (81.62%)	25 (18.38%)	0.591
Headache	112 (86.15%)	18 (13.85%)	0.0001
Vomiting	71 (83.53%)	14 (16.47%)	0.665
Altered sensorium	48 (67.61%)	23 (32.39%)	<0.0001
Seizure	27 (71.05%)	11 (28.95%)	0.032
Hemiparesis	14 (70%)	6 (30%)	0.116
Duration of illness (days)			
Mean±SD	52.84 ± 45.84	44.16 ± 44.53	0.201
Median	30 (20-60)	30 (15-60)	
GCS			
Mean	13.41 ± 2.21	8.4 ± 3.04	<0.0001
6th CN palsy	24 (92.31%)	2 (7.69%)	0.167
CSF protein			
≥100 mg/dl	88 (80%)	22 (20%)	0.197
Mean	238.08 ± 331.12	701.98 ± 1062.6	<0.0001
CSF sugar			
≤40 mg/dl	67 (77.01%)	20 (22.99%)	0.034
Mean	40.07 ± 20.9	24.92 ± 16.23	0.0002
CSF total cell count			
≥10 cells/cumm	100 (80.65%)	24 (19.35%)	0.198
Mean	96.13 ± 111.75	302.76 ± 234.43	<.0001
Infarct	38 (73.08%)	14 (26.92%)	0.027
Basal exudates	39 (75%)	13 (25%)	0.079
Hydrocephalus	41 (73.21%)	15 (26.79%)	0.02
Tuberculoma	46 (88.46%)	6 (11.54%)	0.149
Hyponatremia	66 (78.57%)	18 (21.43%)	0.355
Stage III TBM	19 (50%)	19 (50%)	<0.0001
Definite TBM	28 (71.79%)	11 (28.21%)	0.054

CSF study in more than three-fourth of patients showed protein ≥ 100 mg/dL. CSF sugar was ≤40 mg/dL in 61.27% patients and 87.32% patients showed CSF total count >=10 cells/cumm.

Meningeal enhancement and hydrocephalus were the most common abnormal findings on MRI brain. Similar findings were seen in previous reviews with hydrocephalus been most common finding on neuroimaging.[6,7,22] However, the study conducted in Turkey and Pakistan, most common neuroimaging feature was tuberculoma.[10,12]

We found that more than half of patients had anemia and hyponatremia. The prevalence of hyponatremia ranges from 35% to 71%, which was comparable to our study.[23]

Table 4: Multivariate logistic regression for predictors of mortality after adjusting for confounding factors

Variable	P value	Odds ratio	95% Confidence interval
Age	0.043	1.047	1.001-1.095
Duration of stay (days)	0.355	0.959	0.877-1.048
Headache	0.101	0.153	0.016-1.440
Altered sensorium	0.1872	9.160	0.341-246.227
Seizure	0.719	1.300	0.311-5.444
Infarct	0.746	1.271	0.298-5.418
Hydrocephalus	0.395	1.767	0.476-6.555
Anemia	0.531	0.627	0.146-2.703
Stage 3	0.4826	0.088	0.000-77.502

A total of 17.61% TBM patients succumbed during hospital stay in our study and was comparable with study done in other Asian countries like Pakistan and Taiwan. In-hospital mortality was 30.4% in a study from Peru[3], 18% in a study from Pakistan[10], 28% in a study from Madagascar[11], 7% in a study from Turkey[24] and 13% in a study from Taiwan.[25] Higher age, low Glasgow Coma Scale (GCS) score, absence of headache, seizure, altered sensorium, anemia, CSF glucose ≤40 mg/dL, infarct, hydrocephalus, and BMRC Stage III at presentation were observed as predictors of mortality in our study. Study from Taiwan and Kerala (India) had shown that increasing age is a predictor of in-hospital mortality.[26,27] Similar to our study median duration of hospital stay between two groups was significant in a study from Kerala with shorter duration of stay was associated with mortality in TBM patients.[26] None of the TBM patient with HIV died as in our study only 2 cases were HIV positive. HIV infection is significantly associated with TB-associated morbidity and mortality.[28] But, it has been shown in few studies that HIV seropositivity do not affect the mortality in patients of TBM in short term study.[26,29] Absence of headache at presentation was found to be associated with higher mortality. Similar findings were observed in previous studies.[26,27] It was speculated that absence of headache could result in delay of the diagnosis, leading to higher mortality. Altered sensorium and seizure were also found to be a predictor of mortality. Severity of TBM at presentation serves as a prognostic marker. This observation correlates with the previous studies which had identified the most important determinant for survival being the stage of the disease at presentation.[30,31] Proportion of mortality was significantly higher in patients with low GCS score<11 in our study. In the earlier studies, GCS score at admission was found to be independent predictor of in-hospital mortality.[8,19,32]

We found that low CSF sugar (<=40 mg/dL) was associated with high mortality. Low CSF glucose levels and high CSF protein concentration are the factors which have been observed in previous studies to predict mortality in TBM.[19,27]

Anemia is also found to be predictor of mortality in our study. Anemia is a marker of poor health in developing countries like India. Low hematocrit is found to be predictor of mortality in TBM patients.[33] Mean value of serum sodium was significantly lower in TBM patients who died compared to patients who were discharged. Previous studies were also found that hyponatremia is a significant predictor of mortality[6,31] but we did not find significant association of mortality with mild hyponatremia.

On neuroimaging, infarct and hydrocephalus were found to be a predictor of mortality similar to previous studies.[6,10,34,35] Hydrocephalus is one of the most common complications of TBM causing increased morbidity and mortality. Patients with infarct have worse clinical outcomes with significant mortality, about 3 times more compared to non-infarct patients.[34]

We found that with increasing stage i.e. from I to III, mortality also increased(Stage III-50%, stage II-6.67% and stage I- 4.55%). Similar to observation in earlier studies had shown that stage of the disease independently predict in-hospital mortality.[19,33,35] As the stage of TBM advances, the severity of disease increases which leads to adverse outcome.

Table 5 shows predictors of mortality in TBM patients from various studies.[3,6,8,10,19,26,27,31,33,35-40] Similar to our study, most studies have shown higher age at presentation, advanced stage of

Table 5: Studies showing mortality predictors in TBM

Study	Type of study	Sample size	Predictors of mortality
Soria *et al*.[3] (2019)	Retrospective	263	HIV infection Age older than 40 years BMRC grade II or III GCS < 14
Kaur *et al*.[6] (2015)	Prospective	55	Age ≥ 40 year Loss of appetite Loss of weight Past history of TB Extraneural TB Basal exudates Hydrocephalus
Hosoglu *et al*.[8] (2002)	Retrospective	434	Convulsion Comatose mental status Delayed or interrupted treatment
Wasay *et al*.[10] (2014)	Retrospective	404	Old age High TBM grading Infarction Hydrocephalus
Hosoglu *et al*.[19] (1998)	Retrospective	101	Stage III at presentation Low glucose levels Low CSF/blood glucose ratio High CSF protein levels CT scanning abnormality
George *et al*.[26] (2012)	Retrospective	98	Age >40 years GCS <8 Absence of headache CSF protein ≤60 mg/dL Duration of hospital stay BMRC Stage III
Sheu *et al*.[27](2009)	Retrospective	105	Prolonged physician delay Progression of stage
Sutlas *et al*.[31] (2003)	Retrospective	61	Stage of disease
Thwaites *et al*.[33] (2004)	Prospective	545	GCS 10 or less Hemiparesis Previous treatment for TB Extraneural TB HIV infection Low hematocrit Low CSF TLC Low ratio of CSF glucose to plasma glucose Adverse event requiring alteration to the ATT dose or regimen
Girgis *et al*.[35] (1998)	Retrospective	857	Stage of disease Duration of symptoms
Verdon *et al*.[36] (1996)	Retrospective	48	Clinical stage at admission Delay in starting treatment
Thwaites *et al*.[37] (2002)	Prospective	143	Coma
Modi *et al*.[38] (2017)	Prospective	209	Longer duration of illness Altered sensorium Stage III TBM Hydrocephalus and exudates

Study	Type of study	Sample size	Predictors of mortality
Gupta *et al*.[39] (2017)	Prospective	478	Altered sensorium Motor deficit Cranial nerve palsy Seizures Isolation of MTB MDR
Rizvi *et al*.[40] (2020)	Retrospective	721	Baseline MBI ≤ 12 Higher age Stage III disease Hydrocephalus Papilledema
Our study (2020)	Prospective	142	Higher age Low GCS score Absence of headache Seizure Altered sensorium Anemia Low CSF sugar Infarct Hydrocephalus Duration of stay in hospital BMRC stage III

TBM, seizure, altered sensorium, presence of infarct and hydrocephalus as predictors of mortality in TBM patients. On performing multivariate regression, higher age at presentation was found to be predictor of mortality in TBM patients from our study.

In conclusion, this study provides the epidemiological profile of TBM patients including clinical, laboratory and neuroimaging data. Factors predicting mortality in our study are simple and easy to reproduce. Mortality and morbidity can be reduced by early diagnosis and recognition of complications and providing appropriate treatment. Age, Glasgow Coma Scale (GCS) score, absence of headache, seizure, altered sensorium, anemia, low CSF glucose, infarct, hydrocephalus, and MRC Stage III at presentation were predictors of in-hospital mortality. On performing multivariate regression, patients with higher age at presentation had significantly poor outcome.

DISCLOSURE

Conflict of interest: None

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