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Original Article

Long-Term Clinical Outcome of Tubercular Meningitis Patients after Short Course Chemotherapy: A Prospective Study

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ABSTRACT

Background: Tuberculosis (TB) is a global epidemic affecting humans since ages. Tubercular meningitis (TBM) is the most severe form of TB with high rates of mortality and severe disability. Treatment recommendations range from 6 months to 18 months. The current study was aimed to assess the long-term outcome of TBM patients after short course chemotherapy.

Methods: A prospective study was conducted at a tertiary care hospital and included 72 cases of TBM, diagnosis based on consensus criteria for TBM. Patients were divided into three grades based on disease severity. Grade 1 received 6 months of ATT and Grades 2 and 3, 9 months. Clinical outcome was assessed at 9 months and at 36 months using modified Rankin scale. Various predictors of mortality were assessed by univariate and multivariate analysis.

Results: 20 patients (27.8%) were classified as Grade 1, 33 patients as Grade 2 (45.8%) and 19 patients as Grade 3 (26.4%). At 9 months follow-up, a total of 21 patients (29.1%) died, severe disability occurred in 13 patients (18.0%), 10 patients recovered with minor neurological deficits (13.9%), and 28 patients recovered completely (38.9%). At 36 months of follow-up, a total of 33 patients (45.8%) recovered completely, 7 patients (9.7%) had minor neurological deficits, 7 patients (9.7%) had severe disability, and 25 patients (34.7%) died. On univariate analysis, statistically significant predictors of poor outcome included: Grade of TBM (P = 0.001), Glasgow coma scale (GCS) <11(P = 0.0001), presence of neurological deficit at presentation (P = 0.003), seizures (P = 0.014), presence of papilledema (P = 0.005), imaging evidence of hydrocephalus/infarct/tuberculoma and meningeal enhancement (P = 0.001). However, in multivariate analysis, GCS<11 at presentation (P = 0.004), advanced grade of the disease (P = 0.02), presence of neurological deficit (P = 0.01), and imaging evidence of basal meningeal enhancement/tuberculomas/hydrocephalus/infarct (P = 0.019) were associated with poor outcome.

Conclusion: TBM is a disease with high mortality and severe disability. Short course chemotherapy regimens do not worsen the long-term outcome.

Key words: Anti-tubercular therapy, Grade, Outcome, Mortality, Tuberculosis, Tubercular meningitis

INTRODUCTION

Tuberculosis (TB) is a global epidemic affecting humans since ages. Globally, there are 12 million prevalent cases of TB and 1.1 million cases (13%) co-infected with HIV.[1] One-fourth of globally incident TB cases occur in India with the prevalence of 2.8 million cases. About 22 deaths per 100,000 populations are caused by TB in India. As estimated, 11038 patients are registered for TB treatment in Jammu and Kashmir, state of India of which 24% are extrapulmonary cases and 1% are HIV infected.[2] Tubercular meningitis (TBM) is the most lethal form of TB with mortality ranging from 20% to 40% despite treatment and severe disability

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in one-third of survivors.[3] Various studies have reported the incidence of TBM in India around 7-11% of TB cases in adults.[4] Duration of treatment in adults ranges from 6 to 18 months usually. There is no consensus on the duration of treatment in TBM in adults.[5] Data on long-term outcome of TBM with short course chemotherapy in this part of the world is insufficient. Predictors of outcome in TBM are derived mostly from retrospective studies.

Thus, a prospective study was conducted at a tertiary care hospital involving TBM patients who were treated with short-course chemotherapy regimens, to find out the outcome of TBM patients at 36 months and predictors of poor outcome were analyzed.

METHODS

The current study was carried out at a tertiary care hospital in Srinagar city, Jammu and Kashmir, India. The cases in the study included patients above 14 years of age, diagnosed with TBM between August 2010 and March 2012.

Ethical Statement

The study was approved by the Institutional Human Ethics Committee (IHEC) No. IHEC/SKIMS/2-4-12.

TBM was diagnosed based on clinical characteristics, laboratory data, cerebrospinal fluid (CSF) findings, and radiology. The consensus criteria[6] (Table 1) for diagnosis of TBM was applied for case definition, which includes:

Table 1: Diagnostic criteria for classification of TBM

Clinical criteria (max score=6)	
Symptom	**Score**
Symptom duration >5 days	4
Weight loss, night sweat, cough >2 weeks	2
Recent contact with pulmonary TB within 1 year or positive tuberculin test or IGRA	2
Focal neurological deficit (excluding cranial nerve palsy)	1
Cranial nerve palsy	1
Altered sensorium	1
CSF criteria (max score=4)	
Clear appearance	1
Cells 10-500	1
Lymphocytes >60%	1
Protein >100 mg/dl	1
CSF glucose/plasma glucose conc. <50%	1
Imaging criteria (max. score=6)	
Hydrocephalus	1
Basal meningeal enhancement	2
Tuberculoma	2
Infarct	1
Pre-contrast basal hyper density	2
Evidence of TB elsewhere (max. score=4)	
Chest radiograph suggestive of active TB	2
Miliary TB	4
Imaging evidence of TB outside CNS	2
AFB identified or cultured outside CNS	4

AFB: Acid-fast bacilli, TB: Tuberculosis, SD: Standard deviation, CNS: Central nervous system, TBM: Tubercular meningitis

A. Clinical entry criteria
   Signs and symptoms of meningitis include one or more of the following: Headache, irritability, vomiting, fever, neck stiffness, convulsions, focal neurological deficits, altered sensorium, and lethargy.
B. Consensus criteria score, based on following four parameters
   a. Clinical criteria (maximum score = 6)
   b. CSF criteria (maximum score = 4)
   c. Brain imaging criteria (maximum score = 6)
   d. Evidence of TB elsewhere (maximum score 4)

Cases were then classified as definite, probable, possible, and no TBM based on their total diagnostic score. Definite TBM (cases): Clinical entry criteria plus microbiological identification or evidence from nucleic acid amplification tests of CNS mycobacterial TB infection. Probable TBM: Clinical entry criteria plus a diagnostic score of 12 or above when imaging is available and a diagnostic score of 10 or above when imaging is not available (cases). Possible TBM: Clinical entry criteria plus a score of 6-11 when imaging is available and a score of 6-9 when imaging is not available (cases).

The severity of TBM was assessed based on British Medical Research Council grades.[7] Grade 1 included patients with mild symptoms and no neurological deficit or altered sensorium. Grade 2 included patients with mild alteration in consciousness and minor neurological deficits such as cranial nerve palsy. Grade 3 included patients with major neurological deficits, coma, and seizures.

Laboratory Investigations

All patients were subjected to baseline investigations including a complete hemogram, erythrocyte sedimentation rate, liver function tests, kidney function tests, electrolytes, electrocardiogram, X-ray chest, and urinalysis. CSF specimens were stained and cultured for pyogenic bacteria, fungi, and mycobacterium. CSF samples were sent for polymerase chain reaction (PCR) for *Mycobacterium TB* (MTB) and adenosine deaminase (ADA) analysis. Brain imaging including (computed tomography/magnetic resonance imaging [CT/MRI]) was done in all patients. Relevant investigations were done to look for other possible sites of TB infection. All patients were tested for HIV infection.

Treatment

The cases with Grade 1 TBM were treated with 6 months of ATT: 2 months of daily oral isoniazid (5 mg/kg of body weight), rifampicin (10 mg/kg), pyrazinamide (25 mg/kg; maximum 2 g/day), ethambutol (15 mg/kg), and then 4 months of daily isoniazid and rifampicin. Grades 2 and 3 TBM were treated with 9 months of ATT: 2 months of daily isoniazid, rifampicin, ethambutol, and pyrazinamide, followed by daily isoniazid and rifampicin for 7 months (same dose as above). Steroids were added for initial 8 weeks. ATT was given orally or via nasogastric tube in those who could not swallow. Daily monitoring was done during a hospital stay. Supportive care and management of complications, such as aspiration and sepsis, were provided.

Assessment of Outcome

The outcome was assessed using modified Rankin scale,[8] which is a well-validated scale of disability assessment. A score of 0 indicated no symptoms; 1 indicated minor symptoms not interfering with lifestyle; 2 indicated symptoms that might restrict

lifestyle but patients could look after themselves; 3 indicated symptoms that restricted lifestyle and prevented independent living; 4 indicated symptoms that prevented independent living, although constant care and attention were not required; 5 indicated total dependence on others, requiring help day and night; and 6 indicated death. The final outcome was classified as good (score of 0), intermediate (score of 1 or 2), and severe disability (score of 3, 4, or 5).

Follow-Up

Patients were assessed periodically for neurological disability. Follow-up methods included clinic visits, home visits, and telephonic. The outcome was assessed at 9 months and then at 36 months of initial presentation. Deaths which occurred on follow-up were recorded, and a possible cause was searched.

Data Analysis

Data analysis was performed using IBM SPSS version 20. Continuous variables were expressed as mean ± standard deviation. Univariate analysis was performed using either a Chi-square test and Fisher test for discrete variables and Student's *t*-test for continuous variables. Multivariate stepwise logistic regression analysis was performed to detect independent predictors of mortality using factors that had a significant relation in univariate analysis. A $P < 0.005$ was considered statistically significant.

RESULTS

A total of 72 cases were included in the study, of which 54.2% were females (n = 39). Mean age of the patients was 35 ± 17 years (range 14-70 years). The majority of the patients (94.4%) belonged to rural areas (n = 64). Mean duration of symptoms was 23 days (range 6-90 days). Duration of symptoms was <1 week in 8 patients (11.1%), 1-3 weeks in 21 patients (29.1%), and >3 weeks in 43 patients (59.7%). The most frequent symptom at presentation was a headache (91.7%), followed by fever (83.7%), vomiting (66.7%), altered sensorium (54.2%), and seizures (19.4%). The most common signs were meningeal irritation (90.2%), focal neurological deficits (51.3%); Cranial nerve palsy in (19.4%), hemiparesis in 16.7% of patients, and paraparesis in 6.9%. Fundoscopy revealed the presence of papilledema in 47.2% patients. Concurrent other focus of TB infection was found in 29% patients with pulmonary TB being most common site (18.0%), followed by lymph node (9.7%), disseminated TB (4.2%), and bone marrow TB (1.4%).12.5% patients had taken ATT in the past, and 27.8% had a history of significant contact with a patient of active TB within last 1 year. Tuberculin testing was positive (>10 mm) in 19.4% of patients. Four patients tested positive for human immunodeficiency virus (5.5%) (Table 2).

On admission, 20 patients (27.8%) were classified as Grade 1, 33 patients as Grade 2 (45.8%), and 19 patients as Grade 3 (26.4%) (Table 3). Mean CSF Total leukocyte count was 238 cells/mm^3 (range 20-2500), with lymphocytic predominance in 71%. Mean CSF protein was 236 mg/dl (range 37-1200) and mean glucose was 41mg/dl (range 11-55). CSF smear was positive for acid-fast staining in 5.5% patients (n = 4) and culture showed growth of TB bacilli in 5.5% of patients (n = 4). PCR detected specific mycobacterium isolates in 20.8% (n = 15) and ADA level was positive (>12 IU/ml) in 33.3 % (n = 24). Brain imaging (CT/MRI) was normal in 36.1% patients (n = 26), meningeal enhancement in 25.0% (n = 18), tuberculomas 18.0% (n = 13), hydrocephalus 15.2% (n = 11), and infarcts in 5.5% (n = 4). Hyponatremia was found in 13.2%

Table 2: Clinical, laboratory, and imaging findings in TBM patients (n=72)

Characteristics	*n*	%
Demography		
Age (mean±SD)	35±17 (range 14-70 years)	
Male	33	45.8
Female	39	54.2
Rural	68	94.4
Urban	4	5.6
Clinical findings		
Headache	66	91.7
Fever	60	83.3
Vomiting	48	66.7
Altered sensorium	39	54.2
Motor deficit	37	51.4
Cranial nerve palsy	14	19.4
Hemiparesis	12	16.7
Paraparesis	5	6.9
Multiple neurodeficit	6	8.3
Meningeal signs	65	90.2
Papilledema	34	47.2
Ataxia	3	4.1
Seizure	14	19.4
CSF findings		
AFB stain positive	4	5.5
AFB culture positive	4	5.5
PCR MTB positive	15	20.8
ADA positive	24	33.3
Radiological findings		
Normal	26	36.1
Basal meningeal enhancement	18	25.0
Tuberculoma	13	18.0
Hydrocephalus	11	15.2
Infarct	4	5.5
Other foci of TB		
Pulmonary	13	18.0
Lymph node	7	9.7
Disseminated	3	4.2
Bone marrow	1	1.4
Other findings		
HIV positive	4	5.5
Tuberculin positive	14	19.4
History of exposure to active TB patient	20	27.8
Previous ATT intake	9	12.5
Hyponatremia	10	13.9
Hypertension	6	8.3
Diabetes	4	5.5

TBM: Tubercular meningitis, ATT: Anti-tubercular therapy, AFB: Acid-fast bacilli, TB: Tuberculosis, PCR: Polymerase chain reaction, ADA: Adenosine deaminase, MTB: *Mycobacterium tuberculosis*, SD: Standard deviation

of patients (n = 10). 37.5% patients were categorized as definite TBM (n = 27), 25.0% as probable TBM (n = 18), and 37.5% as possible TBM (n = 27) (Table 4).

Patients in Grade 1 category received 6 months of ATT and Grade 2 and Grade 3 received 9 months of ATT, and corticosteroids were added for initial 8 weeks. Five patients developed intolerance to first-line ATT and were transferred to second-line drugs, and treatment duration was extended to more than 9 months, whereas 5 patients underwent neurosurgical interventions (6.9%).

After discharge, patients were followed for 36 months. At 9 months follow-up, a total of 21 patients (29.1%) died, severe disability occurred in 13 patients (18.0%), 10 patients recovered with minor neurological deficits, i.e. intermediate outcome (13.9%) and 28 patients recovered completely, i.e. good outcome (38.9%) (Table 5). Out of 20 Grade 1 patients, only 2 patients died (10.0%), 16 patients recovered completely (80.0%), and 2 patients (10.0%) recovered with minor residual symptoms. In Grade 2 (n = 33), 10 patients died with a mortality of 30.3%, 7 (21.2%) persisted with severe disability, 8 patients (24.2%) recovered with minor residual symptoms, and 8 patients (24.2%) recovered completely. Of Grade 3 (n = 19), 9 patients died with a mortality of 47.4%, 6 patients (31.6%) had severe disability, and 4 patients (21.0%) recovered completely.

At 36 months of follow-up (Table 6), a total of 33 patients (45.8%) recovered completely, 7 patients (9.7%) had minor neurological deficits, 7 patients (9.7%) had a severe disability, and 25 patients (34.7%) died. One of the Grade 1 patients who made recovery at 9 months died during follow-up. In Grade 2, 12 patients recovered completely, only 7 patients had minor deficits, and 4 patients had a severe disability. Similarly, 3 patients in Grade 3 with severe disability died on follow-up taking total mortality in Grade 3 up to 12 (63.2%), whereas 4 (21.1%) patients recovered completely and 3 patients (15.8%) were left with severe disability (Table 7).

On univariate analysis, statistically significant predictors of poor outcome included: Grade of TBM, Glasgow coma scale (GCS) <11, the presence of neurological deficit at presentation, seizures, presence of papilledema, imaging evidence of hydrocephalus/infarct/tuberculoma, and meningeal enhancement (Table 8). However, on multivariate analysis, GCS<11 at presentation (P = 0.004), advanced grade of the disease (P = 0.02), presence of neurological deficit (P = 0.01), and imaging evidence of basal meningeal enhancement/tuberculomas/hydrocephalus/infarct (P = 0.019) were associated with poor outcome.

DISCUSSION

The present study was conducted at Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, India, and the

Table 3: Grades of TBM

TBM grades	*n* (%)
Grade 1	20 (27.8)
Grade 2	33 (45.8)
Grade 3	19 (26.4)
Total	72 (100)

TBM: Tubercular meningitis

Table 4: Classification of TBM

Variables	*N* (%)
Definite	27 (37.5)
Probable	18 (25.0)
Possible	27 (37.5)
Total	72 (100)

TBM: Tubercular meningitis

Table 5: Outcome of TBM patients at 9 months (n=72)

Outcome	*n* (%)			
	Grade 1	Grade 2	Grade 3	Total
Good	16 (80)	8 (24.2)	4 (21.0)	28 (38.9)
Intermediate	2 (10)	8 (24.2)	0 (0.0)	10 (13.9)
Severe disability	0 (0.0)	7 21.2)	6 (31.6)	13 (18.0)
Death	2 (10)	10 (30.3)	9 (47.4)	21 (29.1)
Total	20 (27.8)	33 (45.8)	19 (26.4)	72 (100.0)

Outcome determined as per modified Rankin scale: Good (0), intermediate (1 or 2), severe disability (3-5), death (6). The grade was assessed as per British Medical Research council Grading system, TBM: Tubercular meningitis

Table 6: Outcome of TBM patients at 36 months (n=72)

Outcome	*n* (%)			
	Grade 1	Grade 2	Grade 3	Total
Good	17 (85.0)	12 (36.4)	4 (21.1)	33 (45.8)
Intermediate	0 (0.0)	7 (21.2)	0 (0.0)	7 (9.7)
Severe disability	0 (0.0)	4 (12.1)	3 (15.8)	7 (9.7)
Death	3 (15.0)	10 (30.3)	12 (63.2)	25 (34.7
Total	20 (27.8)	33 (45.8)	19 (26.4)	72 (100)

Outcome determined as per modified Rankin scale: Good (0), intermediate (1 or 2), severe disability (3-5), death (6). The grade was assessed as per British Medical Research council Grading system, TBM: Tubercular meningitis

Table 7: Outcome at 9 months and 36 months

Outcome	*n* (%)				
	Good	Intermediate	Severe disability	Death	Total patients
9 months	28 (38.9)	10 (13.9)	13 (18.0)	21 (29.1)	72
36 months	33 (45.8)	7 (9.7)	7 (9.7)	25 (34.7)	72

Table 8: Univariate analysis of risk factors associated with poor outcome of TBM

Variable	Odds ratio	Lower limit	Upper limit	*P* value
Symptom duration >3 weeks	2.185	0.8264	5.774	0.1151
Neurodeficit	7.031	2.467	20.03	0.003
GCS <11	59.769	7.295	489.6	0.0001
Grade of TBM	7.291	2.108	25.21	0.001
Seizures	5.579	1.402	22.19	0.014
Abnormal brainimaging[#]	12.946	3.771	44.43	<0.001
Papilledema	3.972	1.489	10.595	0.005

[#]Abnormal imaging: Basal meningeal enhancement, Tuberculomas, Hydrocephalus, Infarct, TBM: Tubercular meningitis, GCS: Glasgow coma scale

only tertiary care institute in the valley of Kashmir, catering to a population of around 60 lakh. The study included 72 consecutive patients aged 14 and above, admitted in the institute with a diagnosis of TBM. Mean age of patients was 35.72 ± 17 which is comparable to the study done by Salakeen *et al.,*[9] and Qureshi *et al.*[10] Female patients out-numbered males (1.18:1), which is in consonance with previous studies.[9,10] The headache (91.7%) was found as the most common clinical presentation, followed by fever 83.3% and vomiting 66.7%, which is in accordance with other studies.[11,12] Most of the patients (*n* = 64) reported meningeal signs, which is consistent with the other studies.[11,13] Motor weakness was present in 51.4% (*n* = 39) which included cranial nerve palsy in 14 patients (19.4%), hemiparesis in 12 patients (116.7%), paraparesis in 5 patients (6.9%), which is consistent with the study done by Rroca *et al.*[14] Seizure at presentation was present in 19.4% (*n* = 14) patients which is consistent with the studies done by Christensen *et al.,*[15] and Filiz *et al.,*[16] but is slightly higher than that reported by Hosoglu *et al.*[11] Altered sensorium was present in 54.2% (*n* = 39) of the patients which is consistent with Hosoglu *et al.,*[11] and Christensen *et al.*,[15] but is lower than the percentage reported by other studies.[13,15,17,18] Papilledema was seen in 47.

2% of the patients (*n* = 34), which is higher than that reported by Salakeen *et al.,*[11] probably because the majority of our study patients presented in advanced stages of the disease. The majority of the patients presented in stages 2 or 3 of TBM, which matches other studies.[17-19] The delayed presentation of TBM appears to be multifactorial and probably reflects overall flaws in our health care system which includes poor primary health care, reduced awareness among both primary care physicians as well as poor population. Many of the patients also present from remote rural areas having false myths and believe in spiritual healing as well as traditional medicine. Further studies are needed on this subject to highlight the causes. Most of the patients presented in Stage 2 which is in accordance with most of the other studies.[10,11,19,20] CSF pleocytosis with predominant lymphocytes, increased proteins, and reduced sugar was found in 70 patients. These findings are consistent with other studies.[11,12] AFB smear was found positive in 4 patients only (5.5%) which is comparable to the yield found by Mishra *et al.,*[21] and other studies.[10,11,19,20] However, the AFB positivity of CSF is lower than the international data.[11,44] The reason for low yield may be the small quantity of CSF, which is usually taken. CSF culture revealed the growth of mycobacterium TB in 4 patients (5.5%), which is comparable to Desai *et al.*[22] Which is lower than what is reported in the international studies.[11,16] Low yield can be mainly attributed to the small quantity of CSF collected for the culture studies and also the failure to repeat the lumbar puncture for collection of CSF.

CSF PCR MTB was positive 20.8% of the patients (*n* = 15) which is lower than a study done by Wang *et al*.,[23] where PCR MTB was positive in 31% of patients and Desai *et al*., (31.42%).[22] CSF ADA was positive in 33.3% of patients when 12 IU was taken as cut-off which is lower than Satya *et al.*[13] The findings of neuroimaging studies of patients revealed the most common finding to be meningeal enhancement (25.0%), usually basal, followed by tuberculoma (18.0%) and hydrocephalus (15.2%). These findings are comparable to Salakeen*et al.*,[9] and Bhargava *et al*.,[24] wherein hydrocephalus was present in 12% of adult TBM patients. Most of other studies, however, have described hydrocephalus as the most frequent finding.[12,26-28] These studies included mainly children, which explain the high incidence of hydrocephalus.

In our study, at the end of 9 months, good outcome was reported in 38.9% patients (*n* = 28), intermediate outcome in 13.9% (*n* = 10), severe disability in 18.0% (*n* = 13), and death was final outcome in 29.1% (*n* = 21). The mortality at 9 months is lesser than as reported by Hsu *et al.*[17] (mortality of 38.9% at 9 months). In their study, mortality was 16.4% in Grade 1, 40.5 % in Grade 2, and 43% in Grade 3. Whereas, our study reported mortality of 10%, 30.3%, and 47.7% in Grade 1, Grade 2, and Grade 3, respectively. The mortality rate in our study is less than Hsu *et al*.,[17] probably because of more elderly patients in their study and duration of ATT was 6 months in Grades 2 and 3. Ramachandran *et al*.,[25] has reported in their study a mortality rate of 10% in Grade 1, 36% in Grade 2, and 43% in Grade 3 at the completion of 9 months of chemotherapy which is comparable to the present study. The mortality for Grade 1 TBM in our study patients is comparable despite only 6 months of treatment. Thwaites *et al.,*[26] reported a mortality rate of 16.7% in Grade 1 (dexamethasone group) after 9 months of treatment, which is higher than that of the present study, despite only 6 months of chemotherapy. The mortality rate for Grades 2 and 3 patients was, respectively, 31% and 54.8% in their study. Our study has shown a comparable rate of mortality in Grade 2 patients with the above study, but the mortality rate in Grade 3 patients is lower in our study patients. The high mortality in this study is because of more HIV-infected patients who are associated with increased chances of death.

At 36 months follow-up, our study reported a mortality rate of 34.7%, which is lower than 39% as reported by Torok *et al*. In current study, mortality at 3 years is 15% Grade 1 (*n* = 3), 30.3% Grade 2 (*n* = 10), and 63.2 % Grade 3 (*n* = 12). 4 patients died on follow-up. In Grade 1, 1 patient who made recovery at 9 months died during follow-up. The patient died because of coronary heart disease. In Grade 3, 3 patients with severe disability died on follow-up taking total death rate to 63.2% (*n* = 12). All 3 patients died of poor supportive care and sepsis which explains the lack of supportive care facilities in our population. Limited comparative data is available on the long-term outcome of TBM with short course chemotherapy. In a study of Torok *et al.*,[27] estimated mortality at 3 years in dexamethasone group in Grade 1 is 23%, Grade 2, 40% and Grade 3 61%. However, current study reports less mortality in Grade 1 TBM, despite receiving 6 months of ATT. Although small number of patients in our study is an important drawback. However, there is an opportunity to conduct further studies in Grade 1 TBM using only 6 months of ATT.

In current study, prolonged duration of symptoms was associated with a poor outcome (*P* = 0.0029) as reported by Hsoglu *et al*.,[11] and Verdon *et al.*[29] Grade of TBM was found to be a significant predictor of outcome in our study with mortality of 63.2% in Grade 3 patients as compared to 15% mortality in Grade 1 which is in agreement with other studies by Kalita *et al.,*[28] Hsu *et al.,*[17] Salakeen *et al.,*[9] Yasar *et al.,*[30] Wang *et al.,*[23] and Lu *et al.*[31] (*P* = 0.008). GCS<11 at presentation was associated with a poor outcome (*P* = 0.001), as evidenced in many studies such as Hsoglu *et al.,*[11] Alarcon *et al.,*[32] Roca *et al.,*[14] Yasar*etal.,*[30] Misra *et al.,*[21] and Ramzan *et al.*[20] Similarly, the presence of neurological deficit at presentation was associated with poor outcome (*P* = 0.001) as reported by Hsoglu*etal*.,[11] Alarcon *et el.,*[32] Misra *et al.,*[21] and Filiz *et al.*[16] In this study, seizures at presentation was associated with a poor outcome (*P* = 0.002) as earlier reported by Hsoglu *et al.,*[11] Gijis*et al.,*[29] Ramzan*et al.*[21] Imaging evidence

of hydrocephalus, meningeal enhancement, and infarct were also associated with a poor outcome in our study ($P = 0.001$) as reported in studies by Alarcon *et at.,*[32] Kalita *et al.,*[28] Hsu *et al.,*[17] Lu *et al.,*[31] and Salakeen *et al.*[9] The presence of papilledema was associated with poor outcome ($P = 0.009$) as reported by Alarcon *et al.*[36] The presence of papilledema signifies raised intra cranial pressure and thus the worst outcome. No association was found between CSF protein/thin layer chromatography and outcome as is reported by other studies.[33] Old age has been reported as a poor predictor in various studies[11,15,33,34] in contrast to our study. The reason could be because the majority of our study population consisted of young patients without any underlying co-morbidity. The presence of extra neural TB had no statistical significance with outcome in our study, as is reported by Tan *et al.,*[35] which is in contrast to other studies.[10,34] Similarly, HIV infection/other comorbidities did not influence the outcome, probably because of the presence of small number of patients with HIV or other comorbidity. The results of other studies have shown that HIV/co-morbidity increases the risk of death.[36,37]

CONCLUSION

TBM is a disease with high rates of mortality and severe disability in survivors. Early diagnosis and treatment before neurological deficits appear, decreases the mortality and severe disability. Short course chemotherapy regimens do not worsen the long-term outcome. 6 months ATT regimen in Grade 1 TBM appears adequate but needs further studies for validation.

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