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Predictors Modifying the Outcome of Tuberculous Meningitis (TBM) in Adults: A Hospital Based Study in Bangladesh

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Abstract

Background: Outcome of TBM can be modified by several predictors. **Objective:** This study was undertaken to evaluate the predictors of outcome of tuberculous meningitis (TBM) at 6 and 9 months. **Methodology:** This hospital based prospective cohort study was carried out from October, 2016 to September, 2017 (1 year) in the in-patient Department of Neurology at the National Institute of Neurosciences & Hospital (NINS & H), Dhaka, Bangladesh. All the patients with age 18 years or more of both sexes with features of TBM fulfilling the case definition criteria was included as the study population. The outcome was measured at 6 and 9 months by modified Rankin Scale (mRS) with no disability (score=0-1), mild disability (score = 2), moderate disability (score=3-4), severe disability (score=5) and dead (score=6). For statistical analysis outcome was classified as death and survival group. A number of clinical, laboratory and radiological parameters were evaluated initially by univariate and finally multiple regression analysis. **Results:** A total 54 TBM patients were included in this study. Over 70% of the patients were adolescent or young adult (< 30 years) with mean age of 28.2 ± 12.3 years and 63% were female. Staging of the TBM showed that nearly half (48.1%) were at stage II and 37% cases were in stage III disease. Baseline imaging (CT-scan and MRI) showed basal meningeal enhancement in 40.7% cases, hydrocephalus in 40.7%, infarction 46.3% and tuberculoma in 29.6% cases. Final diagnosis was established as definite TBM in 3(5.6%) cases, probable TBM 30(55.6%) and possible TBM in 21(38.9%) cases. In terms of 6-months outcome, 16(29.6%) cases died and 10(18.5%) had recovered without any neurological sequelae; however, mild, moderate and severe disability were in11.1%, 27.8% and 13% cases respectively. At the 9 months of evaluation 13 (24.0%) had complete recovery without any neurological sequelae, 22 (40.9%) patients survived with various degree of disabilities like visual impairment, hemi or paraplegia, cognitive impairment, rests died giving a total mortality of 19(35.1%). In univariate analysis, age >50 years (p=0.019), duration of illness before initiation of treatment (>45 d) (p = 0.041), convulsion (p = 0.010), altered sensorium (p<0.001), delayed initiation of treatment >1 month (p=0.041) and stage III TBM (p<0.001) were significantly associated with mortality. In multivariate analyses stage III TBM (p=0.004), altered sensorium (p=0.036), delayed initiation of treatment >1 month (p=0.043) emerged as independent predictors of mortality. **Conclusions:** In conclusion stage III TBM, altered sensorium and delayed initiation of treatment more than 1 month are the independent predictors of mortality in TBM patients. *[Journal of National Institute of Neurosciences Bangladesh, January 2021;7(1): 14-19]*

Keywords: Predictors; Outcome; Tuberculous Meningitis; TBM

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Introduction

Tuberculosis (TB) is a global pandemic and is caused by the Mycobacterium tuberculosis complex[1]. It causes ill-health for approximately 10 million people each year and is one of the top ten causes of death worldwide[2] and second leading causes of death from an infectious disease after HIV[3]. Bangladesh is one of the high burden countries (HBCs) among 30 for tuberculosis reported by WHO with the incidence of 221/100000 and mortality 40/100000 annually[2].

TB most commonly affects the lungs (pulmonary TB), although it can also affect other organs and systems (extra pulmonary TB). About 15.0% to 20.0% of TB cases are extra pulmonary[4-5]. The World Health Organization (WHO) reported 0.8 million extra pulmonary TB cases worldwide in 2013. TBM is the severe form of CNS tuberculosis[6]. The relative incidence of this disease is 0.4% to 1.0% of all cases of TB[7-9]. The disease affects all the age groups. However recent data suggests that 15 years or more age group comprises about 88.0% of all patients[10]. The actual incidence and prevalence of TBM is not yet clearly defined in our country. The worldwide mortality rate of this disease is 20.0% to 69.0% and about half of the survivors developed neurological sequelae like visual loss, motor and cognitive deficits[5,7,11-13]. Early diagnosis is an essential component in management of tuberculous meningitis to prevent mortality and morbidity[5]. However prediction of ultimate outcome of this condition is difficult due to its prolonged course, the virulence of the infecting agent, non specific pathological mechanisms, difference in host immunity and CSF penetration for ATT[12,14].

Many prognostic predictors have been studied globally to predict the outcome of these serious disorders. Among them important are the stage of the disease (stage I, II, III), age, sex, seizure, H/O close contact with tuberculous patient, underlying co morbidities, duration of illness, fever, headache, visual impairment, alteration of consciousness, mental status abnormalities, neck stiffness, cranial nerve palsy, changes in fundus, focal neurological deficit, extra meningeal tuberculosis, CSF cell (TC of WBC), protein, glucose, image (hydrocephalus, infarction, basal meningeal enhancement, tuberculoma), timing of initiation of anti-TB drugs, treatment with corticosteroid, drug toxicity, shunt surgery and neurophysiological findings (EEG, motor and somatosensory evoked potentials)[7,13-15]. Outcome of TBM depend on more than one variable, in that circumstances multivariate analysis is a useful method for it's benefit of determining the effect of each variable while controlling the influence of the others[16]. As evidence suggest that neurological status in TBM patient changes at 6 and 9 months[13,16-17]. The purpose of the present study was to identify the prognostic predictors of outcome in adult of TB meningitis in Bangladesh at 6 and 9 months.

Methodology

This present study was designed as hospital-based

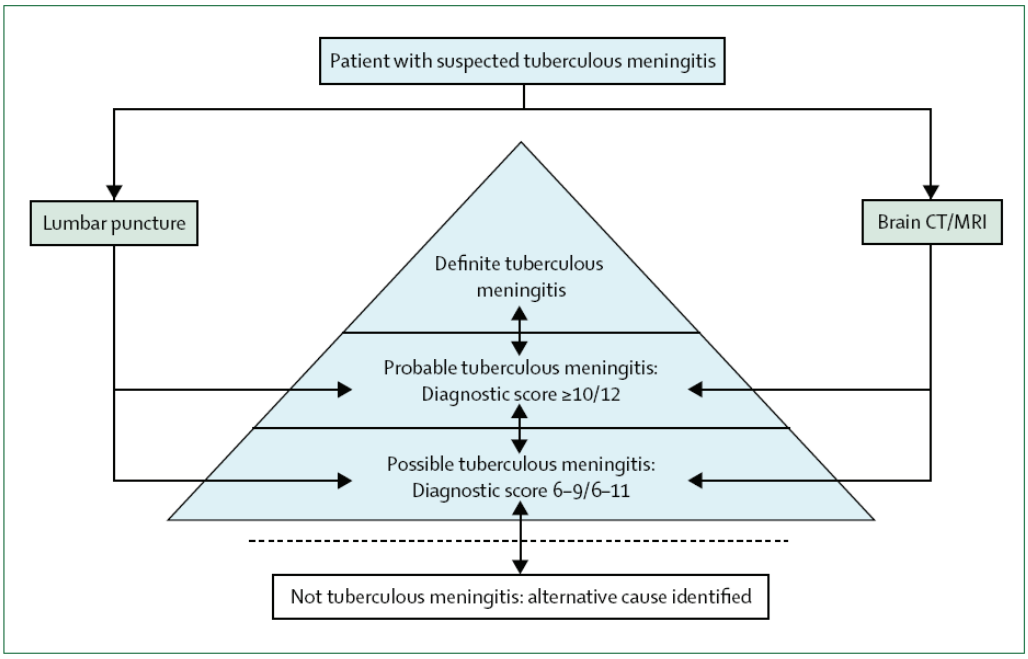

Figure I: Categories for patients with suspected tuberculous meningitis[18]

prospective cohort study conducted in the inpatient Department of Neurology at the National Institute of Neurosciences & Hospital (NINS & H), Dhaka, Bangladesh. The patients with features of TBM fulfilling the 'consensus case definition criteria for TBM'[18] were included as the study population. According to the consensus case definition the cases were categorized as definite, probable, possible and not TBM group. Not TBM patients were excluded from the study. After the enrollment, necessary investigation including CSF study and neuroimaging like MRI of brain with contrast were performed. Inclusion criteria were patients of 18 years or more of both sex categorized as definite, probable and possible Tuberculous Meningitis. Exclusion criteria were positive CSF for Gram or India Ink stain, ICSOL, serum bilirubin > 2.5 x ULN, ALT >5 x ULN, S. Creatinine >3 x ULN, pregnancy. All the patients were treated initially (intensive phase) for 2 months and then a maintenance phase for 10 months with standard anti TB four drugs regimen according to weight based NTP schedule under DOTS along with corticosteroid coverage[3,17,19]. CSF diversion surgery was considered in selective cases of hydrocephalus. Pyridoxine was given with isoniazid therapy throughout the treatment. Paradoxical response was managed with short course of corticosteroid in standard dose and duration[20-21]. Second line antituberculous therapy was used in resistance cases of first line drug according to the standard protoco[l3,17]. Follow-up was done at OPD of NINS&H at 6 and 9 months. The outcome was measured at 6 and 9 months by modified Rankin Scale (mRS) with no disability (score=0-1), mild disability (score=2), moderate disability (score=3-4), severe disability (score=5) and dead (score=6)[11]. For statistical analysis outcome was classified as death and survival group. A number of clinical, laboratory and radiological parameters were evaluated initially by univariate and finally by multiple regression analysis.

Statistical Analysis: Statistical analysis of the study was done by SPSS version 25.0. Confidence interval was considered at 95.0% level. Less than 0.05 was taken as statistically significant. Univariate analysis was conducted first using Chi-square test and Fisher's Exact Test to determine association of different variables on outcome. Then independent predictor was determined on mortality using logistic regression analysis. To eliminate confounding factors in predicting the risk for mortality, variables with p value ≤0.05 by univariate analysis were entered into a multivariate logistic regression model for further assessment.

Results

A total 54 TBM patients were included in this study. Over 70.0% patients were adolescent or young adult (more than 30 years) with mean age of 28.2 ± 12.3 years with a female preponderance (63%) (Table 1).

Table 1: Distribution of Patients by their Demographic Characteristics (n=54)

Demography	Frequency	Percent
Age (Years)		
< 30	38	70.4
30 – 40	5	9.3
40 – 50	7	13.0
≥ 50	4	7.3
Sex		
Male	20	37.0
Female	34	63.0

At admission nearly half (48.1%) were at stage II and 37% cases were in stage III disease [Table:2].

Table 2: Categorization of Patients according to the Stages (n=54)

Stages of TBM	Frequency	Percent
I	8	14.8
II	26	48.1
III	20	37.0
Total	**54**	**100**

Baseline imaging (CT-scan and MRI) showed basal meningeal enhancement and hydrocephalus in equal number of patients (40.7%), infarction in 46.3% and tuberculoma in 29.6% cases [Figure I].

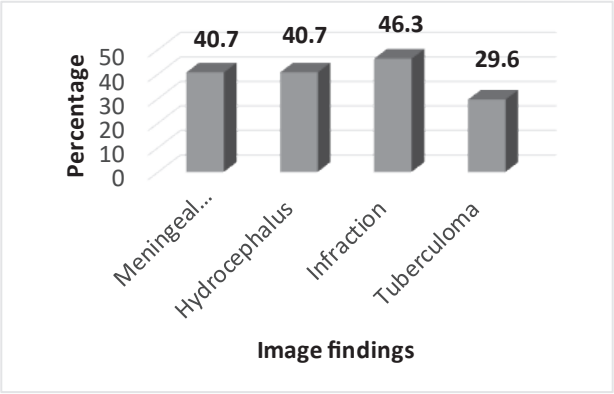

Figure I: Categories for patients with suspected tuberculous meningitis[18]

Table 3 shows in terms of 6-months outcome, 10(18.5%) came round without any sequalae. over one-quarter (38.8%) had mild to moderate disability. 13% had severe disability. In this period 16(29.6%) patients died due to disease process.

Final diagnosis was established as definite TBM in 3(5.6%) cases, probable TBM 30(55.6%) and possible TBM in 21(38.9%) cases. In terms of 6-months outcome, 16(29.6%) cases died while 10(18.5%) had recovered without any neurological sequelae; however, mild, moderate and severe disability were observed in 11.1%, 27.8% and 13% cases respectively (Table 3).

Table 3: Distribution of patients by their Outcome at 6 months (n=54)

Outcome at 6 months	Frequency	Percent
No disability (good outcomes)	10	18.5
Mild / Moderate Disability (intermediate outcomes)	21	38.8
Severe disability (Poor outcome)	7	13.0
Death	16	29.6
Total	**54**	**100**

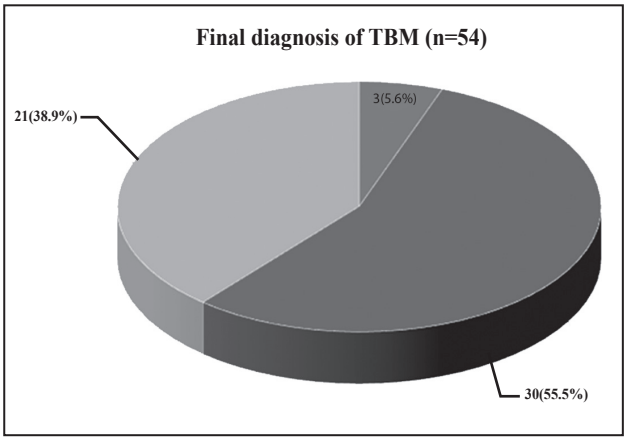

Figure II: Pie diagram showing final diagnosis in 54 cases

At the 9 months of evaluation 13 (24.0%) had complete recovery without any neurological sequelae, 22 (40.9%) patients survived with various degree of disabilities like visual impairment, hemi or paraplegia, cognitive impairment and rest of the patients died 19(35.1%) (Table 4; Figure III).

Table 4: Distribution of patients by their outcome at 9 months (n=38)

Outcome at 9 months	Frequency	Percent
No disability (good outcomes)	13	34.2
Mild / Moderate Disability (intermediate outcomes)	19	50
Severe disability (Poor outcome)	3	7.9
Death	3	7.9
Total	**38**	**100**

16 patient were died at 6 month follow up were excluded from the analysis.

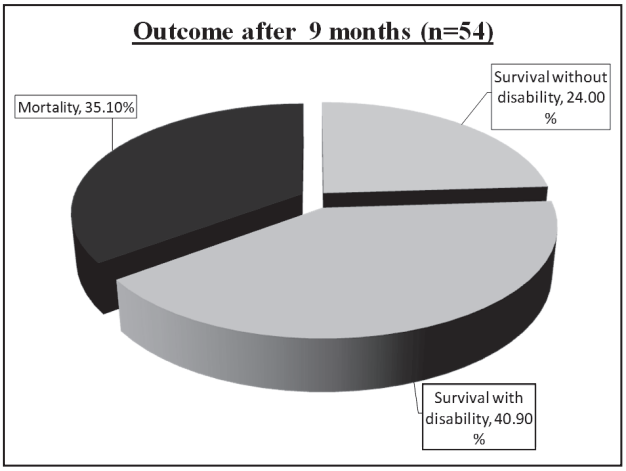

Figure III: Pie diagram showing net outcome after 9 months of follow up (n=54)

Table 5: Univariate analysis of predictors of mortality related to clinical, CSF and diagnostic findings

Risk Factors	Group		P value	Relative Risk (95% CI of RR)
	Dead (n = 19)	Survived (n = 35)		
Age >50 years	3(15.8)	1(2.9)	0.019	2.3(1.1 – 4.7)
Sex (Male)	8(42.1)	12(34.3)	0.570	Not computed
Duration of illness (> 45 d)	12(63.2)	12(34.3)	0.041	2.1(1.0 – 4.6)
Convulsion	11(57.9)	8(22.9)	0.010	2.5(1.2 – 5.2)
Altered sensorium	13(68.4)	7(20.0)	<0.001	3.6(1.6 – 8.1)
Focal neurological deficit	8(42.1)	24(68.6)	0.059	Not computed
Hemiplegia/paraplegia	4(21.1)	4(11.4)	0.583	Not computed
Cranial nerve palsy	7(36.8)	19(54.3)	0.221	Not computed
Optic neuritis	2(10.5)	7(20.0)	0.610	Not computed
Papilloedema	1(5.3)	4(11.4)	0.417	Not computed
Extra-meningeal TB	1(5.3)	9(25.7)	0.064	Not computed
Comorbidities	4(21.1)	9(25.7)	0.951	Not computed
Raised CSF protein	10(52.6)	17(48.6)	0.776	Not computed
Low glucose	13(68.4)	22(62.9)	0.683	Not computed
Delayed initiation of Rx > 1 month	12(63.2)	14(40.0)	0.041	1.8(0.8 – 3.9)
WBC > 11000 (cu-mm)	11(57.9)	16(45.7)	0.393	Not computed
Definite & probable TBM	10(52.6)	23(65.7)	0.346	Not computed
Stage III TBM	14(73.7)	6(17.1)	< 0.001	4.7(2.0 – 11.2)
CSF diversion (VP shunt)	2(10.5)	3(8.6)	0.583	Not computed
Paradoxical response	0(0.0)	5(14.3)	0.103	Not computed

In univariate analysis, age >50 years (p=0.019), duration of illness before initiation of treatment (>45 d) (p = 0.041), convulsion (p = 0.010), altered sensorium (p<0.001), delayed initiation of treatment >1 month (p=0.041) and stage III TBM (p<0.001) were significantly associated with mortality (Table 5).

In multivariate analyses stage III TBM (p=0.004), altered sensorium (p=0.036), delayed initiation of treatment >1 month (p=0.043) emerged as independent predictors of mortality (Table 6).

Table 6: Multivariate Logistic Regression Analysis Showing Predictors of Outcome in TBM

Variables of interest	Univariate analysis (p-value)	Multivariate analysis	
		Relative Risk (95% CI of RR)	P value
Age >50 years	0.019	0.9(0.09 – 2.5)	0.488
Duration of illness (> 45 d)	0.041	0.3(0.05 – 3.8)	0.244
Convulsion	0.010	2.2(1.0 – 5.4)	0.051
Altered sensorium	< 0.001	2.3(1.4 – 6.7)	0.036
Delayed initiation of Rx > 1 month	0.041	1.3(0.7 – 4.4)	0.043
Stage III TBM	< 0.001	3.6(1.5 – 8.5)	0.004

Discussion

Among the 54 TBM patients most (70.0%) were adolescent and young adults (<30 years) with a female preponderance (63.0%). An Indian study also found a female predominance[20]. Most of the patients presented at stage II (48.1%) and stage III (37.0%) on admission. Yasar et al[12] in their study also found maximum patients at stage II on presentation.

In this series only 3 cases (5.6%) were GeneXpert positive and classified as definite TBM. AFB was not found in any of the cases. Sensitivity of AFB stain and GeneXpert in TBM is 37.0% and 59.0% respectively, depending on the procedure, volume of CSF submitted, repetition of LPs and the capacity of laboratories and technician's experience[18,22]. Kalita and Misra[16] also found a very low sensitivity of AFB in CSF during evaluation of 58 TBM cases.

Baseline imaging (CT scan and MRI) findings in the present series revealed that infarction was the commonest (46.3%) finding followed by basal meningeal enhancement and hydrocephalus in equal number of patients (40.7%). Tuberculoma was present in 29.6% cases. However the imaging in 11(20.37%) patients revealed no abnormality. Almost similar findings were observed by Hsu et al[13] during evaluation of 95 TBM patients except a lower frequency of tuberculoma in their study. On the other hand tuberculoma was found to be present in more than half of patients of TBM in study by Tai et al[4].

In the present study definite diagnosis of TBM (Definite TBM) was established only in 3(5.6%) cases which is near (5.2%) to the study by Kalita and Misra[16]. The rest were probable [30(55.6%)] and possible [21(38.9%)]. The rate of definite TBM was more in the series by Lau et al[8] involving 166 patients. In the present series the possible explanation for less number of definite TBM may be submission of conventional volume of CSF (where higher CSF volume could have yielded better), non-repetition of LPs and finally limitation of the laboratories and technician's experience.

The 6- and 9-month mortality rate in this study was 29.6% (16/54) and 35.2% (19/54) respectively which is almost similar to the mortality rate reported by Hsu et al[13]. Other literature also revealed similar findings[11]. In univariate analysis six variables [age more than 50 years, duration of illness before initiation of treatment (more than 45 d), convulsion, altered sensorium, delayed initiation of treatment more than 1 month and stage III TBM] were found to be significantly associated with mortality. Among them stage III TBM, altered sensorium, delayed initiation of treatment more than 1 month emerged as independent predictors of mortality in multivariate analyses. Stage III TBM and altered sensorium (GCS) were reported as independent predictor of mortality in TBM in several studies[8,12,14-16,23]. Delay in initiation of anti-TB therapy turned out to be a poor predictor of outcome in the study by Hsu et al[13].

There are some limitation of the study. It was a single center study with a limited number definite TBM cases. The sample size was also relatively small for performing logistic regression analysis.

Conclusion

In conclusion, stage III TBM, altered sensorium and delay (more than 1 month) in initiation of treatment are independent predictors of mortality in TBM patient.

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