CLINICAL FACTORS PREDICTIVE OF FUNCTIONAL OUTCOMES IN TUBERCULOUS MENINGITIS

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Abstract. Reasons for poor outcomes in tuberculous meningitis (TBM), which accounts for 2.3% of all tuberculosis cases in Thailand, are still being debated. Here, we studied factors associated with functional outcomes of TBM patients in Thailand where tuberculosis is endemic. We retrospectively reviewed all patients diagnosed with TBM at Srinagarind Hospital, Khon Kaen University, Thailand, between January 2002 and December 2008. Twenty-five patients met the study criteria; 11 of these (44.0%) had good or distinctly improved status at discharge. Duration of TBM symptoms for more than 14 days was significantly negatively associated with good discharge status (aOR 0.068; 95% CI: 0.005-0.945). Long-term functional status, assessed using the modified Rankin scale, was also significantly higher in those who had good discharge status compared with those who had poor discharge status (p=0.005). In conclusion, shorter duration of TBM symptoms was correlated with good outcomes with respect to both short- and long-term functional status.

Keywords: tuberculous meningitis, predictors, short-term, long-term, outcomes, modified Rankin scale, functional status

INTRODUCTION

Tuberculosis, caused by *Mycobacterium tuberculosis*, is a common infectious disease and may affect many organs. The global prevalence of tuberculosis is 136/100,000 population (WHO, 2014). Prevalence is highest in Africa (343/100,000), with Southeast Asia in second place (181/100,000). In Thailand, the prevalence is 49/100,000 (WHO, 2014).

In Thailand, pulmonary tuberculosis is the most common form (83.3%), while tuberculous meningitis (TBM) accounts for 2.3% (WHO, 2014). Even though TBM constitutes a low proportion of all tuberculosis, it may cause high mortality and morbidity such as leaving patients in a dependant state. Previous studies showed that having hydrocephalus, and also disease severity, are predictors for long-term outcomes (Tan *et al*, 1999; Lu *et al*, 2001). There are limited data on predictors of both short- and long-term treatment outcomes in Thailand where tuberculosis is endemic.

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MATERIALS AND METHODS

We retrospectively reviewed all patients who were diagnosed with TBM at Srinagarind Hospital, Khon Kaen University, Thailand, between January 2002 and December 2008. The diagnosis of TBM was made based on one of the following criteria: 1) acid-fast stain or culture positive for *M. tuberculosis* in cerebrospinal fluid (CSF); 2) evidence of lymphocytic meningitis, CSF culture negative for bacteria or fungus, and positive response to anti-tuberculosis treatment; 3) presence of subacute meningitis, CSF culture negative for bacteria or fungus, and positive response to anti-tuberculosis treatment; or 4) presence of subacute meningitis and evidence of tuberculosis in other organs (Thwaites *et al*, 2002).

Clinical features were collected from medical charts of all eligible patients. All patients were classified by TBM severity at initial presentation into stages 1-3 (Byrd and Zinser, 2001), as follows: stage 1, signs of meningitis with no neurological deficit and Glasgow Coma Scale (GCS) score of 15; stage 2, evidence of focal neurological deficit and GCS score of 11-14; and stage 3, stupor or coma or GCS less than 10. The duration of follow-up was recorded as the last day of follow-up. Each patient's modified Rankin scale (MRS) score was also evaluated on the last day of follow-up. The MRS was classified into grades 1-4: 1, no symptoms or slight disability; 2, moderate disability; 3, severe disability; and 4, death (Bonita and Beaglehole, 1988).

Patients were divided into two groups, by discharge status: good or poor. Good discharge status was defined as having complete recovery. Patients with some or no improvement, or who had died, were classified as having poor discharge status. Initial clinical characteristics of patients in both groups were compared using descriptive statistics. Wilcoxon rank-sum and Fisher's exact tests were applied to compare the differences in numbers and proportions between the two groups, respectively.

Univariate logistic regression analyses were applied to calculate the crude odds ratios of individual variables for good discharge status. All clinically significant variables or $p<0.20$ by univariate analyses were included in subsequent multivariate logistic regression analyses. Analytical results were presented as crude odds ratios (OR), adjusted OR, and 95% confidence intervals (CI). All data analyses were performed with STATA software (College Station, TX).

RESULTS

There were 25 eligible TBM patients during the study period: 6 patients met diagnostic criterion 1; 11 patients, criterion 2; 7 patients, criterion 3; and 1 patient, criterion 4. Of those, 11 patients (44.0%) had good status at discharge. All clinical features were similar between good and poor status at discharge (Tables 1 and 2). The good status group had a lower percentage of patients with duration of TBM symptoms more than 14 days (27.3% *vs* 57.1%), higher CSF protein level (175 mg/dl *vs* 156 mg/dl), and higher CSF glucose/plasma glucose ratio (37% *vs* 28.5%) compared with those with poor discharge status; however, the differences were not statistically significant (Tables 1 and 2).

All patients received the standard regimen of tuberculous treatment: 2IRZE/4IR. Prednisolone treatment was administered to 6 patients (24.0%), but this was not correlated with discharge status ($p=0.350$). Those who had good discharge status had significantly longer follow-up time

Table 1
Clinical factors of tuberculous meningitis patients, categorized by discharge status.

Variables	Poor $n = 14$	Good $n = 11$	p-value
Age, years	51.5 (38-59)	44 (37-60)	0.848
Male gender, *n* (%)	10 (71.4)	6 (54.6)	0.434
Diabetes, *n* (%)	1 (7.1)	0	0.999
Hypertension, *n* (%)	2 (14.3)	0	0.487
HIV infection, *n* (%)	2 (14.3)	2 (18.2)	0.999
Duration of symptoms >14 days, *n* (%)	8 (57.1)	3 (27.3)	0.227
Seizure, *n* (%)	2 (14.3)	1 (9.1)	0.999
Body temperature, ºC	38 (37.8-38.8)	38.5 (38.1-38.7)	0.270
Cranial nerve abnormalities, *n* (%)	1 (10.0)	1 (11.1)	0.999
Neck stiffness, *n* (%)	10 (76.9)	9 (81.8)	0.999
Papilledema, *n* (%)	3 (33.3)	2 (25.0)	0.999
Severity grading			0.310
Stage 1, *n* (%)	4 (28.6)	6 (54.6)	
Stage 2, *n* (%)	5 (35.7)	1 (9.1)	
Stage 3, *n* (%)	5 (35.7)	4 (36.4)	

Data presented as median values (interquartile range), unless indicated otherwise.

Table 2
Laboratory results of tuberculous meningitis patients, categorized by discharge status.

Variables	Poor $n = 15$	Good $n = 13$	p-value
CSF white blood cells, cells/mm^3	242.5 (56-660)	160 (120-510)	0.784
Lymphocytes, %	88 (23.9-91.9)	70 (14-90)	0.267
CSF protein, mg/dl	156 (117-250)	175 (131-307)	0.273
CSF glucose/plasma glucose ratio, %	28.5 (15-45)	37 (21-47)	0.476
Culture positive	2 (28.6)	4 (50.0)	0.608
Baseline hydrocephalus, *n*	5 (41.7)	1 (11.1)	0.178

Data presented as median (interquartile range) or numbers (percentage).
CSF, cerebrospinal fluid.

and better MRS at the last day of follow-up than those who had poor discharge status (Table 3).

From multiple logistic regression analysis, only duration of TBM symptoms more than 14 days was negatively associated with good discharge status (aOR 0.068; 95% CI: 0.005-0.945), as shown in Table 4.

DISCUSSION

This study showed that longer duration of TBM symptoms was an independent factor negatively associated with

Table 3
Treatment and outcomes of tuberculous meningitis patients categorized by discharge status.

Variables	Poor $n = 15$	Good $n = 13$	p-value
Prednisolone treatment, n (%)	2 (14.3)	4 (36.4)	0.350
Follow-up time, days	123.5 (22-455)	1,238 (122-1,521)	0.008
MRS	3 (2-4)	1 (1-2)	0.005

Data presented as median (interquartile range), unless indicated otherwise; MRS, modified Rankin score, measured on the last day of follow-up.

Table 4
Factors associated with complete recovery status at discharge in patients diagnosed with tuberculous meningitis, by multiple logistic regression analysis.

Variables	OR (95% CI)	aOR (95% CI)
Duration of symptoms >14 days	0.281 (0.052-1.536)	0.068 (0.005-0.945)
Body temperature, ºC	1.869 (0.409-8.540)	1.891 (0.170-21.033)
Severity grading	0.713 (0.284-1.793)	0.875 (0.213-3.485)
CSF lymphocytes, %	0.990 (0.967-1.013)	0.149 (0.007-3.098)

CSF, cerebrospinal fluid.

good discharge status in TBM; the 95% CI of the duration of symptoms was less than 1 (95% CI: 0.005-0.945). This indicated that TBM patients who had prolonged symptoms tended to have poor discharge status and also poor long-term outcomes. TBM patients with symptoms more than 14 days had reduced chances of complete recovery (by 92.2%) compared with those who had symptoms for less than 14 days. Prolongation of symptoms may increase the risk of having complications from TBM, such as brain infarction, hydrocephalus (Tan *et al*, 1999), or tuberculoma.

Several factors have been considered in relation to prognosis and outcomes in TBM. A study from Taiwan on 36 TBM patients found that presence of hydrocephalus and severity of TBM at admission were associated with treatment failure (Lu *et al*, 2001). A study from Turkey of 160 TBM patients found that tuberculoma and cranial nerve palsy on admission were associated with neurological sequelae (Pehlivanoglu *et al*, 2010). In the same study population from Turkey, factors associated with mortality were age, comorbidities, leukocytosis, and mental status on admission (Yasar *et al*, 2010). However, a study from India on 110 TBM patients did not find an association between tuberculoma and death (Anuradha *et al*, 2011). Our study added that duration of TBM may be another factor associated with both short- and long-term treatment outcomes.

A good outcome or complete improvement at discharge in this study

was 44.0%, which was lower than in a previous study (56%) by Yasar *et al* (2010). Discharge status was correlated with long-term outcomes. The MRS at the last day of follow-up was also significantly better in those with good discharge status compared with those with poor discharge status (Table 3).

In conclusion, shorter duration of TBM resulted in good outcome in both short- and long-term functional status.

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