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Clinical features of adult patients with a definite diagnosis of central nervous system tuberculosis in an endemic country: A 13-year retrospective review

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ABSTRACT

Rationale: Clinical features of central nervous system tuberculosis (CNS-TB) are nonspecific. The decision for treatment of the disease in an endemic area is challenging.
Objectives: We aimed to study predictive factors for a definite diagnosis and outcome of patients with CNS-TB.
Methods: A case-control study was performed in adults with a provisional diagnosis of CNS-TB in Thailand to determine predictive factors for a definite diagnosis of CNS-TB. Predictive factors for a definite diagnosis of CNS-TB were analyzed by multivariable logistic regression analysis. Factors associated with two-year mortality after the diagnosis of definite CNS-TB were determined using a cox regression analysis.
Measurements and main results: A total of 114 patients received a provisional diagnosis of CNS-TB during the study period. A median (interquartile range) age was 40.8 (31.7–55.4) years, and 75 patients (65.8%) were male. Of these, 66 cases (57.9%) had definite CNS-TB, and 43 cases (38.4%) had HIV coinfection. By logistic regression, age, confusion, and nausea/vomiting were associated with definite CNS-TB (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.93–0.99; $p = 0.015$, OR 2.86, 95% CI 1.03–7.94; $p = 0.044$, and OR 0.30, 95% CI 0.11–0.82; $p = 0.019$, respectively). In patients with definite CNS-TB, age and HIV coinfection were associated with two-year mortality (hazard ratio [HR] 1.07, 95% CI 1.01–1.13; $p = 0.022$, and HR 11.81, 95% CI 2.09–66.78; $p = 0.005$, respectively).
Conclusions: Younger age, confusion, and absence of nausea/vomiting are predictive factors of a definite diagnosis of CNS-TB. In patients with definite CNS-TB, older age and HIV coinfection are associated with higher mortality. The results of this study might be helpful for the management of suspected CNS-TB cases as well as predicting the prognosis of CNS-TB cases in an endemic area.

1. Introduction

Central nervous system tuberculosis (CNS-TB), including tuberculous meningitis (TBM), tuberculoma, and spinal tuberculosis, is an uncommon but highly fatal manifestation of tuberculosis (TB). It accounts for approximately 1% of all cases of TB, and carries high morbidity and mortality [1]. CNS-TB is caused by the hematogenous spreading of Mycobacterium tuberculosis (MTB) from primary pulmonary infection and the formation of small subpial and subependymal foci in the brain and spinal cord. Rupture or growth of these small tuberculous lesions leads to various types of CNS-TB [2].

The usual patient with TBM presents with a subacute progressive febrile illness and development of meningeal irritation. The correct diagnosis of CNS-TB is challenging due to nonspecific clinical presentations that mimic other diseases, both infectious and non-infectious ones (e.g., neoplastic meningitis). In addition, a definite diagnosis of CNS-TB is difficult, partly due to the lack of sensitivity of current diagnostic tests [3]. Microbiological tests have limitations from the low sensitivity of cerebrospinal fluid (CSF) microscopy and the slow growth rate of MTB in conventional culture systems. Molecular tests increase the opportunity for diagnosis of CNS-TB, but its sensitivity is still low. A *meta*-analysis of nucleic acid-based amplification tests (NAATs) for TB meningitis showed a pooled sensitivity of 56% [4]. Taken together, negative microbiological or molecular tests cannot exclude the possibility of CNS-TB, and clinical judgment remains important. Clinical features and cerebrospinal fluid parameters can help distinguish TBM

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from other causes of meningitis but are of little help in the specific diagnosis. A confirmed diagnosis is often delayed, and a number of patients do not receive immediate treatment. Delayed treatment of CNS-TB is associated with death and neurological sequelae [1,5]. On the other hand, given the long duration of CNS-TB treatment, patients who do not have CNS-TB would suffer from the untoward effects of empirical treatment. Complications of antituberculosis treatment, e.g. drug reaction and hepatitis, occur frequently especially in elderly patients or patients with liver diseases [6,7]. Balancing between morbidity and mortality from delaying treatment and adverse events from unnecessary treatment is a major concern and presents the greatest challenge in the management of CNS-TB, especially in endemic areas.

World Health Organization (WHO) classified Thailand as one of the 30 countries with the highest TB burden. In 2018, Thailand had an estimated TB incidence of 153 per 100,000 population. Ten percent of TB patients were HIV positive [8]. We studied factors associated with a definite diagnosis of CNS-TB among patients who received a provisional diagnosis of CNS-TB in the high TB prevalence setting, as well as clinical outcomes of patients with a definite diagnosis of CNS-TB.

2. Methods

2.1. Patients

We performed a case-control study by retrospectively reviewed charts of all adult patients (age ≥ 15 years) with a provisional diagnosis of CNS-TB at Ramathibodi Hospital, a 1,300-bed university hospital in Bangkok, Thailand, during 2003–2015. A provisional diagnosis of CNS-TB was made from: (1) clinical symptoms, including chronic headache, fever, nausea/vomiting, anorexia, and weight loss; (2) clinical signs, e.g., stiffness of the neck, confusion, coma, cranial nerves palsy, focal neurological deficit and seizure; and (3) imaging studies consistent with CNS-TB, including lesion at basal cisterns, hydrocephalus, rim/gyral enhancement, tuberculoma, vasculitis, abscess, or infarction [1]. Radiologic findings, either from computed tomography (CT) or magnetic resonance imaging (MRI) scan, of CNS-TB (both tuberculous meningitis and tuberculoma) were defined as previously described [9]. Patients whose medical records could not be retrieved were excluded.

Definite CNS-TB was defined by: (1) positive microbiological or molecular evidence of MTB from CSF or consistent histopathological reports of brain tissue; or (2) positive microbiological or molecular evidence of MTB from any organs, or chest radiography compatible with active pulmonary TB together with clinical suspicion of CNS-TB [1,10]. Possible CNS-TB was defined as patients with a provisional diagnosis of CNS-TB in the absence of criteria for definite CNS-TB, and no identified alternative cause(s).

2.2. Microbiological study of MTB

Appropriate clinical specimens were prepared for microscopic examination by the Ziehl-Neelsen method to detect acid-fast bacilli. Each specimen was inoculated in Lowenstein–Jensen (LJ) solid medium and Mycobacteria Growth Indicator Tube (MGIT) liquid medium (Becton Dickinson Diagnostic Systems, Sparks, MD, USA). Molecular assays were performed with either Anyplex™ plus MTB/NTM/MDR-TB assay (Seegene, Seoul, South Korea) or FastSure TB DNA Rapid Test (MP Biomedicals, Santa Ana, CA, USA).

2.3. Data collection

Medical records of patients who met the criteria were reviewed. We collected the following data: demographic characteristics, clinical presentations, underlying diseases, HIV status, radiological findings, evidence of pulmonary and extrapulmonary TB, microbiological evidence of TB and sensitivity patterns, CSF parameters, treatment, and clinical outcomes. Hepatitis was defined as an asymptomatic elevation of alanine aminotransferase (ALT) above five times the upper reference limit or elevation of ALT more than three times the upper reference limit with associated symptoms such as anorexia or pruritus.

2.4. Statistical analysis

Median, interquartile range (IQR), and frequency were used to describe patients' characteristics. Chi-square test or Fisher's exact test and Mann–Whitney *U* test were used to compare categorical variables and continuous variables, respectively. A p-value of < 0.05 was considered statistically significant. Logistic regression was used to determine the

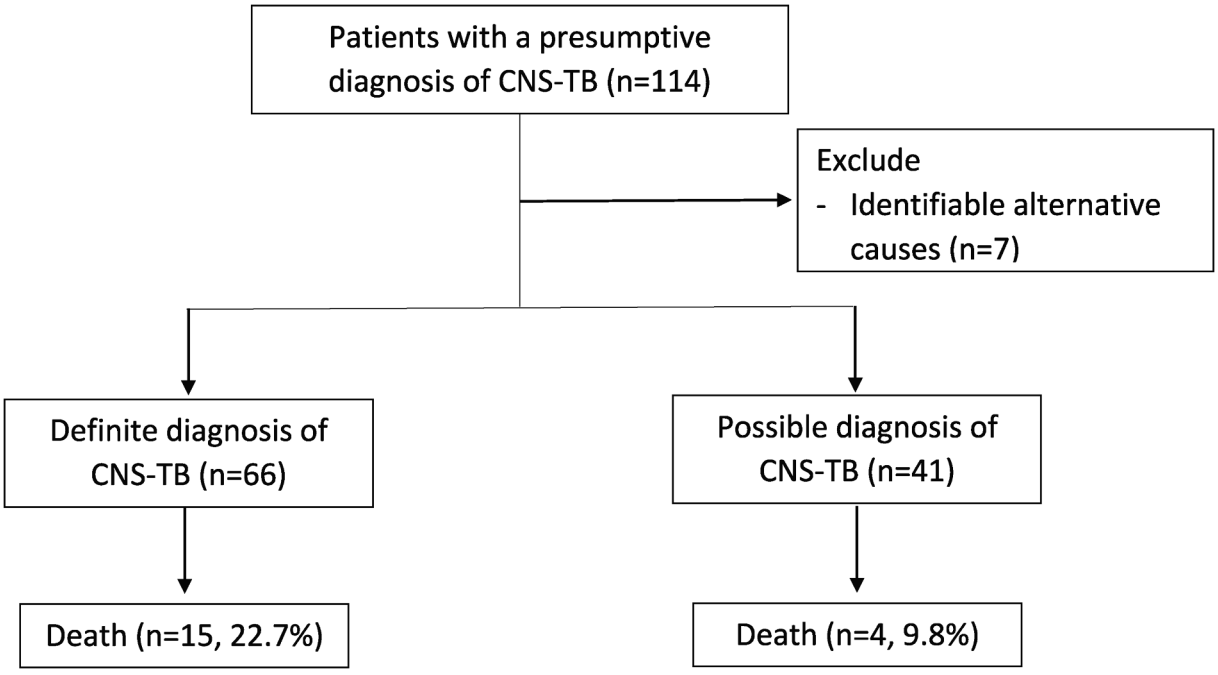


Fig. 1. Flow diagram of study patients.

Table 1
Demographic data and clinical features of patients with a provisional diagnosis of CNS-TB.

	Definite diagnosis of CNS-TB (n = 66)	Possible diagnosis of CNS-TB (n = 41)	p-value
Median (IQR) age, years	39.5 (30.7–49.2)	44.4 (35.7–59.6)	0.090
Male, n (%)	48 (72.7)	24 (58.5)	0.128
Presumptive diagnosis			
TB meningitis, n (%)	54 (81.8)	35 (85.4)	0.633
Tuberculoma/abscess, n (%)	29 (43.9)	16 (39.0)	0.617
Spinal TB, n (%)	3 (4.8)	1 (2.4)	> 0.999
Symptoms			
Headache, n (%)	42 (64.6)	35 (85.4)	0.020
Fever, n (%)	52 (80.0)	32 (78.1)	0.809
Photophobia, n (%)	1 (1.5)	1 (2.4)	> 0.999
Nausea/vomiting, n (%)	14 (21.9)	18 (43.9)	0.017
Weight loss, n (%)	8 (12.3)	2 (4.9)	0.310
Seizure, n (%)	4 (6.1)	3 (7.3)	> 0.999
Signs			
Stiff neck, n (%)	44 (67.7)	30 (73.2)	0.550
Confusion, n (%)	47 (72.3)	19 (46.3)	0.007
Coma, n (%)	6 (9.2)	0 (0.0)	0.080
Cranial nerve palsy, n (%)	7 (10.8)	4 (9.8)	> 0.999
Focal neurological deficit, n (%)	12 (18.5)	4 (9.8)	0.223
Co-morbidities			
HIV coinfection, n (%)	28 (43.1)	12 (30.0)	0.180
Solid cancer, n (%)	2 (3.0)	2 (4.9)	0.636
Hematologic malignancy, n (%)	2 (3.0)	2 (4.9)	0.636
Diabetes mellitus, n (%)	3 (4.6)	3 (7.3)	0.673
Autoimmune disease, n (%)	5 (7.6)	3 (7.3)	> 0.999
Organ transplant, n (%)	2 (3.0)	0 (0.0)	0.523
Risk factors			
Alcoholism, n (%)	5 (7.6)	2 (4.9)	0.583
Steroids, n (%)	5 (7.6)	3 (7.3)	> 0.999
Previous TB history, n (%)	8 (12.3)	1 (2.5)	0.148

CNS, central nervous system; HIV, human immunodeficiency virus; IQR, interquartile range; TB, tuberculosis.

factors associated with a definite diagnosis of CNS-TB. Variables that presented a p-value of < 0.2 from univariable logistic regression were considered in a multivariable logistic regression model. Odds ratio (OR) and its 95% confidence interval (CI) were estimated. Factors associated with two-year overall mortality after the diagnosis of definite CNS-TB were analyzed by multivariate Cox regression analysis. The survival of patients was illustrated by the Kaplan-Meier curve stratified by groups of patients, groups of significant factors, and time of treatment initiation. All statistical analyses were performed using Stata statistical software version 15.1 (Stata, College Station, TX).

3. Results

This study included 114 patients with a presumptive diagnosis of CNS-TB. The flow of the study is demonstrated in Fig. 1. Presumptive diagnoses included 95 cases (83.3%) of TB meningitis, 19 cases (16.7%) of tuberculoma/abscess, and 4 (3.5%) of spinal TB. Some patients had more than one diagnosis. A median (interquartile range) age was 40.8 (31.7–55.4) years, and 75 patients (65.8%) were male. Forty-three cases (38.4%) had HIV coinfection with a median (IQR) CD4 count of 72 (41–140 cells/mm^3). Alternative causes were later identified in seven patients (6.1%) who received empirical antituberculosis treatment. Such causes included CNS vasculitis, leptomeningeal metastasis of solid cancer, cytomegalovirus encephalitis, herpes zoster meningoencephalitis, and ruptured Rathke's cleft cyst. Sixty-six cases (61.7%) had definite CNS-TB. Demographic data and clinical features are shown in Table 1. Baseline characteristics were not different between patients with definite CNS-TB and those with possible CNS-TB. CSF parameters and findings from brain imaging were not different between the two groups (Table 2).

Evidence of TB was as follows. CSF acid-fast bacilli were positive in only 1 of 101 specimens (1.0%). For CSF specimens, molecular assays and isolation of MTB were positive in 19 of 101 cases (18.8%) and 12 of 101 specimens (11.9%), respectively. Both molecular assays and isolation of MTB were positive in five patients. Twenty-two of 105 cases (21.0%) had positive blood culture for MTB. Chest radiography and chest CT were consistent with active pulmonary TB in 45 of 104 patients (43.3%) and 11 of 19 patients (57.9%), respectively. Sputum AFB and isolation of MTB were positive in 16 of 90 specimens (17.8%) and 8 of 87 specimens (9.2%), respectively. Pulmonary TB was diagnosed in 56 cases (52.3%). Other foci of infection by MTB included pleura (2 cases; 1.9%), lymph node (11 cases; 10.3%), peritoneum and/or

Table 2
Investigative features of patients with a provisional diagnosis of CNS-TB.

	Definite diagnosis of CNS-TB	Possible diagnosis of CNS-TB	p-value
Lumbar puncture	(n = 63)	(n = 39)	
Median (IQR) opening pressure, cmH_2O	20 (14–28)	19 (15–30)	0.965
Median (IQR) white blood cells, /mm^3	139 (44–300)	150 (67–400)	0.513
Median (IQR) total protein, mg/dL	175.0 (117.9–295.0)	168.0 (121.0–264.9)	0.839
Median (IQR) CSF glucose, mg/dL	36.0 (23.0–50.0)	32.0 (23.0–53.0)	0.529
Median (IQR) CSF/serum glucose	0.32 (0.22–0.42)	0.36 (0.21–0.40)	0.671
CT findings	(n = 38)	(n = 27)	
Meningeal enhancement, n (%)	32 (84.2)	22 (81.5)	> 0.999
Infarction, n (%)	6 (15.8)	5 (18.5)	> 0.999
Tuberculoma, n (%)	1 (2.6)	1 (3.7)	> 0.999
Hydrocephalus, n (%)	16 (42.1)	8 (29.6)	0.304
Rim-enhancing lesion, n (%)	7 (18.4)	1 (3.7)	0.126
Perilesional edema, n (%)	5 (13.2)	1 (3.7)	0.388
MRI findings	(n = 18)	(n = 13)	
Meningeal enhancement, n (%)	15 (83.3)	12 (92.3)	0.621
Infarction, n (%)	5 (27.8)	2 (15.4)	0.667
Tuberculoma, n (%)	3 (16.7)	0 (0.0)	0.245
Hydrocephalus, n (%)	8 (44.4)	3 (23.1)	0.275
Rim-enhancing lesion, n (%)	6 (33.3)	0 (0.0)	0.028
Perilesional edema, n (%)	4 (22.2)	1 (7.7)	0.368

cmH_2O, centimeters of water; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; IQR, interquartile range; MRI, magnetic resonance imaging; TB, tuberculosis.

Table 3
Univariable and multivariable logistic regression analysis of factors associated with a definite diagnosis of CNS-TB.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age	0.98	0.96–1.00	0.101	0.96	0.93–0.99	0.015
Male	1.89	0.83–4.31	0.130	1.13	0.42–3.06	0.813
Headache	0.31	0.11–0.85	0.023	0.31	0.08–1.16	0.081
Fever	1.13	0.43–2.93	0.809			
Photophobia	0.63	0.04–10.3	0.742			
Nausea/vomiting	0.36	0.15–0.84	0.019	0.30	0.11–0.82	0.019
Weight loss	2.74	0.55–13.58	0.218			
Seizure	0.82	0.17–3.85	0.799			
Stiff neck	0.77	0.32–1.82	0.550			
Confusion	3.02	1.33–6.86	0.008	2.86	1.03–7.94	0.044
Cranial nerve palsy	1.12	0.31–4.08	0.868			
Focal neurological deficit	2.09	0.626–7.00	0.230			
HIV coinfection	1.77	0.77–4.07	0.182	0.95	0.35–2.64	0.928
Solid cancer	0.61	0.08–4.50	0.627			
Hematologic malignancy	0.61	0.08–4.50	0.627			
Diabetes mellitus	0.60	0.12–3.14	0.548			
Autoimmune disease	1.04	0.23–4.60	0.961			
Alcoholism	1.60	0.30–8.65	0.586			
Steroids	1.04	0.23–4.60	0.961			
Previous TB history	5.47	0.66–45.53	0.116	4.01	0.44–36.55	0.218

CI, confidence interval; OR, odds ratio; TB, tuberculosis.

gastrointestinal tract (2 cases; 1.9%), bone marrow (2 cases; 1.9%), bone (3 cases; 2.8%), and pericardium (1 case; 0.9%). Six of the definite CNS-TB cases (9.1%) had isoniazid-resistant TB. Of these, only one definite CNS-TB patient had multidrug-resistant TB.

By univariable logistic regression analysis (Table 3), factors associated with definite CNS-TB included age (OR 0.98, 95% CI 0.96–1.00; $p = 0.101$), male gender (OR 1.89, 95% CI 0.83–4.31; $p = 0.130$), headache (OR 0.31, 95% CI 0.11–0.85; $p = 0.023$), nausea/vomiting (OR 0.36, 95% CI 0.15–0.84; $p = 0.019$), confusion (OR 3.02, 95% CI 1.33–6.86; $p = 0.008$), HIV coinfection (OR 1.77, 95% CI 0.77-4.07; $p = 0.182$), and previous TB history (OR 5.47, 95% CI 0.66–45.53; $p = 0.116$). By multivariable logistic regression, age, confusion, and nausea/vomiting were associated with definite CNS-TB (OR 0.96, 95% CI 0.93–0.99; $p = 0.015$, OR 2.86, 95% CI 1.03–7.94; $p = 0.044$, and OR 0.30, 95% CI 0.11–0.82; $p = 0.019$, respectively).

The median time of antituberculosis initiation after a provisional diagnosis of CNS-TB was 1 (0–3) days in both definite and possible diagnosis of CNS-TB ($p = 0.353$). Complications of antituberculosis treatment occurred in 30 cases. The most common complications were hepatitis (20 cases, 18.7%) and rash (7 cases, 6.5%). Fifteen patients (22.7%) with a definite CNS-TB died, whereas four patients (9.8%) with a possible diagnosis of CNS-TB died (Table 4). There was no statistical difference in mortality among these groups ($p = 0.088$). Multivariate

Table 5
Multivariate Cox regression analysis of factors associated with two-year mortality in patients with a definite diagnosis of CNS-TB.

	Unadjusted HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Age	1.02 (0.99–1.05)	0.174	1.07 (1.01–1.13)	0.022
Male	1.70 (0.48–6.05)	0.411		
Headache	1.32 (0.42–4.18)	0.634		
Fever	0.82 (0.26–2.58)	0.734		
Confusion	1.15 (0.36–3.62)	0.814		
HIV coinfection	3.54 (1.20–10.46)	0.022	11.81 (2.09–66.78)	0.005
Solid cancer	5.34 (1.19–24.22)	0.029	1.98 (0.23–16.71)	0.531
Hydrocephalus	2.02 (0.72–5.70)	0.183	2.30 (0.70–7.60)	0.173
Perilesional edema	2.48 (0.70–8.86)	0.161	2.29 (0.57–9.16)	0.241
Positive CSF MTB culture	0.42 (0.09–1.88)	0.256		
Anti-TB initiation > 48 h	1.29 (0.44–3.78)	0.642		

CI; confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; HR, hazard ratio; MTB, *Mycobacterium tuberculosis*; TB, tuberculosis.

Cox regression analysis of factors associated with two-year mortality of patients (Table 5) showed that age and HIV coinfection was associated with overall mortality (adjusted HR 1.07, 95% CI 1.01–1.13; $p = 0.022$, and adjusted HR 11.81, 95% CI 2.09–66.78; $p = 0.005$, respectively). Kaplan-Meier survival curves stratified by factors that showed significant association in the unadjusted analysis are shown in Fig. 2. We also showed the Kaplan-Meier survival curves of possible vs. definite CNS-TB patients and treatment initiation within vs. after 48 h after diagnosis.

4. Discussion

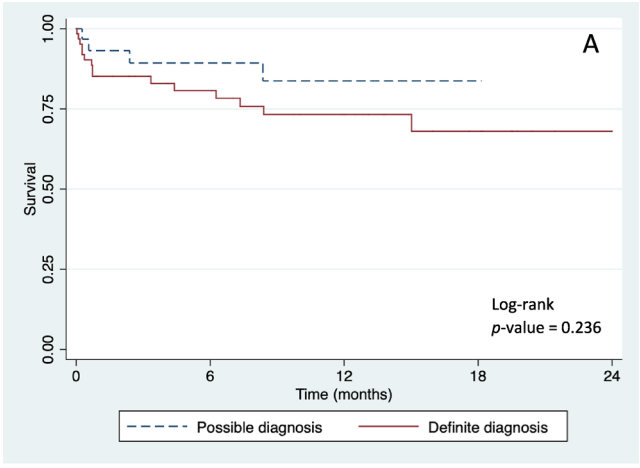
Diagnosis of CNS-TB can be difficult because of nonspecific clinical presentation, laboratory and neuroimaging findings. Our study compared a definite with a possible CNS-TB in an endemic area of TB. We demonstrated that younger age, confusion, and absence of nausea/vomiting at clinical presentation in patients with suspected CNS-TB had significant associations with a definite diagnosis of CNS-TB. In this setting, neither specific CSF parameters nor findings from brain imaging could predict a definite CNS-TB.

Previous studies have compared the predictive factors of CNS-TB with other central nervous system diseases. Hristea and coworkers compared TBM with viral meningitis and demonstrated that duration of symptoms of at least five days, presence of neurological impairment, CSF/blood glucose ratio < 0.5, and CSF protein level > 100 mg/dL were predictive factors for diagnosis of TBM [11]. Mihailescu et al. showed that duration of symptoms more than seven days before admission, altered clinical-stage, CSF/blood glucose ratio < 0.5, and CSF

Table 4
Outcomes of treatment of patients with a provisional diagnosis of CNS-TB.

	Definite diagnosis of CNS-TB	Possible diagnosis of CNS-TB	*p*-value
Death, n (%)	15 (22.7)	4 (9.8)	0.088
Complications from the disease, n (%)	13 (19.7)	4 (9.8)	0.171
Hydrocephalus, n (%)	9 (33.3)	3 (23.1)	0.716
New infarction, n (%)	4 (14.8)	1 (7.7)	> 0.999
Expanded tuberculoma, n (%)	5 (18.5)	0 (0.0)	0.154
Complications from the treatment, n (%)	20 (30.3)	10 (24.4)	0.508
Hepatitis, n (%)	11 (40.7)	9 (69.2)	0.091
Rash, n (%)	6 (22.2)	1 (7.7)	0.393
Optic neuritis, n (%)	2 (8.3)	0 (0.0)	> 0.999
Neuropathy, n (%)	1 (3.7)	1 (7.7)	> 0.999

CNS, central nervous system; IQR, interquartile range; LFT, liver function test; TB, tuberculosis.



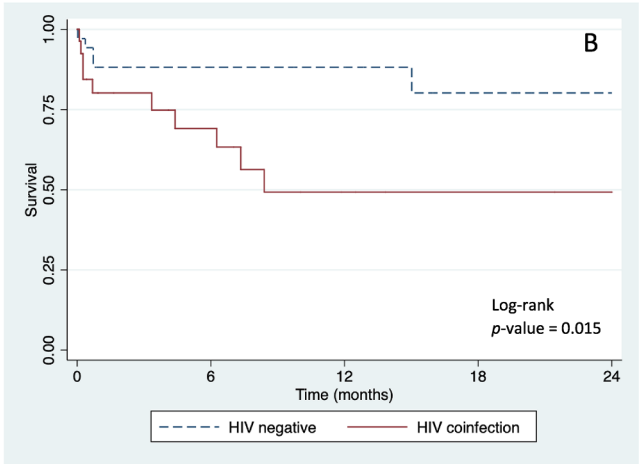


Fig. 2. Kaplan-Meier survival curve of (A) definite or possible CNS-TB cases, (B) HIV co-infection or not, (C) solid organ cancer or not, (D) presence of hydrocephalus or not, (E) presence of perilesional edema or not, and (F) treatment initiation within and > 48 h. Y-axis denotes the survival probability of CNS-TB patients, x-axis denotes time after diagnosis (months). *p*-values of log-rank tests are shown.

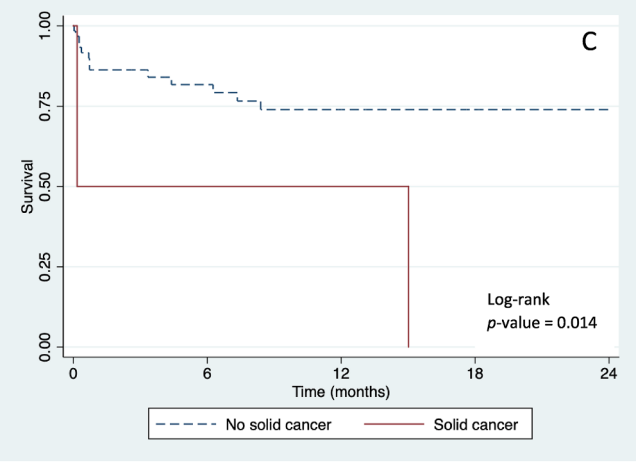
protein concentration > 200 mg/dL were predictive factors of TB in patients with acute aseptic meningitis syndrome [12]. Taken together, altered mental status was predominantly present in patients with CNS-TB. Although nausea/vomiting was considered as one of the clinical features of CNS-TB [13], we found that this presentation was less common in patients with definite CNS-TB. Thwaites et al. compared TBM with bacterial meningitis and demonstrated that younger age was one of the predictive factors of TBM [14]. Our study agreed with the finding that CNS-TB was more common in young adults.

In this study, only 18.8% of CSF specimens were positive for the molecular detection of MTB. A *meta*-analysis performed by Pai et al. showed that commercial NAATs had 56% sensitivity (95% CI 46–66%) and 98% specificity (95% CI 97–99%) [4]. The majority of commercial NAATs included in the study were Amplicor *M. tuberculosis* tests (Roche Molecular Systems, Branchburg, NJ, USA), and Amplified *M. tuberculosis* Direct Test (Gen-Probe Inc, San Diego, CA, USA). However, Anyplex™ plus MTB/NTM/MDR-TB assay and FastSure TB DNA Rapid Test were used in our study. Only one study showed that Anyplex™ plus MTB/NTM/MDR-TB assay had sensitivity and specificity of 83% and 100%, respectively [15]. The use of either test for diagnosing CNS-TB awaits more clinical studies. This may explain the lower rate of MTB detection from CSF specimens in our study.

Currently, some novel NAATs have been developed and might help to improve the diagnosis of CNS-TB. Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) has been endorsed by WHO for the diagnosis of extrapulmonary TB since 2013 [16]. Comparing to CSF culture-based method, Xpert® MTB/RIF helps in the diagnosis of TBM with shorter turnaround time. The diagnostic sensitivity in definite TB meningitis was 88% for Xpert® MTB/RIF compared with 75% for MGIT culture or LJ culture [17]. Xpert®MTB/RIF Ultra is a recently developed test, which detects multicopy amplification targets (*IS6110* and *IS1081*), resulting in increased sensitivity for the diagnosis of TBM. In definite TBM, the diagnostic sensitivity were 59.5% for Xpert®MTB/RIF Ultra compared with 55.3% for Xpert®MTB/RIF [18]. However, both tests were not available in our hospital at the time of the study.

Hepatotoxicity was the most common adverse effect of anti-tuberculosis treatment in our study. It was demonstrated to associate with advanced age, malnutrition, alcoholism, HIV coinfection, and chronic hepatitis B or hepatitis C infections [19,20]. Hepatotoxicity may resolve spontaneously, but some experts recommend stopping antituberculosis drugs immediately if the serum transaminases rise above five times the upper limit of normal, or if the total bilirubin rises above three times the upper limit of normal [21]. A large proportion of patients in our study had HIV coinfection (37.4%), which may contribute to the risk of hepatotoxicity. Hepatotoxicity occurred approximately 20% in the possible CNS-TB group. Our finding emphasized the challenge in the diagnosis of CNS-TB.

The mortality rate of CNS-TB is high. In our study, 17.8% of patients died, which is comparable to other studies [22–24]. Previous studies showed that poor outcome of CNS-TB was correlated with old age, neurological impairment at presentation, the presence of headache, fever or hydrocephalus, the presence of MTB in CSF, and delayed treatment [22,25,26]. In our study, older age and HIV coinfection were



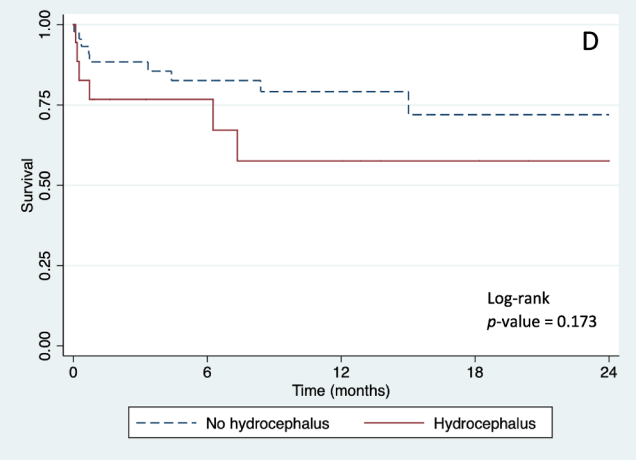


Fig. 2. (*continued*)

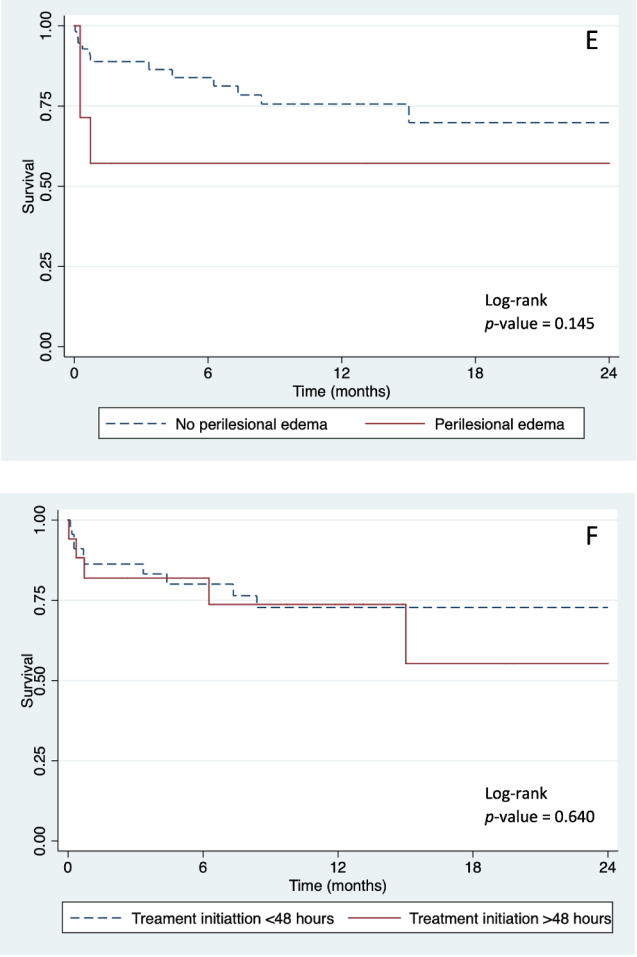


Fig. 2. (*continued*)

identified as the factors associated with two-year overall mortality. Previous studies showed that HIV-infected patients with TBM had a decreased survival rate compared with TBM patients who were HIV negative [27,28]. We could not demonstrate the benefit of early empiric antituberculosis treatment. This might be owing to the fact that most of the patients who received empiric antituberculosis treatment in 48 h of the provisional diagnosis in our study were HIV-coinfected (92.9% in HIV coinfected group vs. 59.5% in non-HIV infected group, $p = 0.002$).

The strength of this study was that we collected data for an extended period in an endemic area of TB. We accepted a limitation of the study. The study design was retrospective. Therefore, some data were incomplete.

In conclusion, younger age and clinical presentation with confusion and absence of nausea/vomiting are predictive factors of a definite diagnosis of CNS-TB. Patients who have definite CNS-TB with older age and HIV coinfection are associated with a higher two-year mortality rate.

Ethical statement

This study was approved by the ethical committee for human research of the Faculty of Medicine, Ramathibodi Hospital.

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CRediT authorship contribution statement

Suppachok Kirdlarp: Data curation, Methodology, Project administration, Writing - original draft. **Sirawat Srichatrapimuk:** Writing - review & editing. **Sasisopin Kiertiburanakul:** Writing - review & editing. **Angsana Phuphuakrat:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Thwaites G, Fisher M, Hemingway C, et al. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect 2009;59(3):167–87. https://doi.org/10.1016/j.jinf.2009.06.011.
[2] Garg RK. Tuberculosis of the central nervous system. Postgrad Med J 1999;75(881):133–40. https://doi.org/10.1136/pgmj.75.881.133.
[3] Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess 2007;11(3):1–196. https://doi.org/10.3310/hta11030.
[4] Pai M, Flores LL, Pai N, et al. Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis 2003;3(10):633–43. https://doi.org/10.1016/S1473-3099(03)00772-2.
[5] Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. Lancet Neurol 2013;12(10):999–1010. https://doi.org/10.1016/S1474-4422(13)70168-6.
[6] Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. N Engl J Med 2016;374(2):124–34. https://doi.org/10.1056/NEJMoa1507062.
[7] Saha A, Shanthi FXM, Winston AB, et al. Prevalence of hepatotoxicity from antituberculosis therapy: a five-year experience from South India. J Prim Care Community Health 2016;7(3):171–4. https://doi.org/10.1177/2150131916642431.
[8] World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization; 2019. Available from: https://www.who.int/tb/publications/global_report/en.
[9] Bernaerts A, Vanhoenacker FM, Parizel PM, et al. Tuberculosis of the central nervous system: overview of neuroradiological findings. Eur Radiol. 2003;13(8):1876–90. https://doi.org/10.1007/s00330-002-1608-7.
[10] Chin JH, Mateen FJ. Central nervous system tuberculosis: challenges and advances in diagnosis and treatment. Curr Infect Dis Rep. 2013;15:631–5. https://doi.org/10.1007/s11908-013-0385-6.
[11] Hristea A, Olaru ID, Baicus C, et al. Clinical prediction rule for differentiating tuberculous from viral meningitis. Int J Tuberc Lung Dis. 2012;16(6):793–8. https://doi.org/10.5588/ijtld.11.0687.
[12] Mihailescu R, Hristea A, Baicus C, et al. Predictors of tuberculosis in acute aseptic meningitis syndrome. Rom J Intern Med. 2007;45(4):379–85.
[13] Foppiano Palacios C, Saleeb PG. Challenges in the diagnosis of tuberculous meningitis. J Clin Tuberc Other Mycobact Dis. 2020;20:100164https://doi.org/10.1016/j.jctube.2020.100164.
[14] Thwaites GE, Chau TT, Stepniewska K, et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. Lancet 2002;360(9342):1287–92. https://doi.org/10.1016/S0140-6736(02)11318-3.
[15] Sali M, De Maio F, Caccuri F, et al. Multicenter evaluation of Anyplex Plus MTB/NTM MDR-TB assay for rapid detection of Mycobacterium tuberculosis complex and multidrug-resistant isolates in pulmonary and extrapulmonary specimens. J Clin Microbiol. 2016;54(1):59–63. https://doi.org/10.1128/jcm.01904-15.
[16] World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children: policy update. Geneva: World Health Organization; 2013. Available from: https://apps.who.int/iris/handle/10665/112472.
[17] Metcalf T, Soria J, Montano SM, et al. Evaluation of the GeneXpert MTB/RIF in patients with presumptive tuberculous meningitis. PLoS ONE 2018;13(6):e0198695https://doi.org/10.1371/journal.pone.0198695.
[18] Donovan J, Thu DDA, Phu NH, et al. Xpert MTB/RIF Ultra versus Xpert MTB/RIF for the diagnosis of tuberculous meningitis: a prospective, randomised, diagnostic accuracy study. Lancet Infect Dis. 2020;20(3):299–307. https://doi.org/10.1016/S1473-3099(19)30649-8.
[19] Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. J Gastroenterol Hepatol. 2008;23(2):192–202. https://doi.org/10.1111/j.1440-1746.2007.05207.x.
[20] Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology 2006;11(6):699–707. https://doi.org/10.1111/j.1440-1843.2006.00941.x.
[21] World Health Organization. Guidelines for treatment of tuberculosis 4th edition.

Geneva: World Health Organization; 2010. Available from: https://www.who.int/tb/publications/2010/9789241547833/en/.
[22] Lu CH, Chang WN, Chang HW. The prognostic factors of adult tuberculous meningitis. Infection 2001;29(6):299–304. https://doi.org/10.1007/s15010-001-1100-3.
[23] Moreira J, Alarcon F, Bisoffi Z, et al. Tuberculous meningitis: does lowering the treatment threshold result in many more treated patients? Trop Med Int Health 2008;13(1):68–75. https://doi.org/10.1111/j.1365-3156.2007.01975.x.
[24] Pehlivanoglu F, Yasar KK, Sengoz G. Tuberculous meningitis in adults: a review of 160 cases. Sci World J 2012;2012:169028https://doi.org/10.1100/2012/169028.
[25] Hsu PC, Yang CC, Ye JJ, et al. Prognostic factors of tuberculous meningitis in adults: a 6-year retrospective study at a tertiary hospital in northern Taiwan. J Microbiol Immunol Infect 2010;43(2):111–8. https://doi.org/10.1016/S1684-1182(10)60018-7.
[26] Kent SJ, Crowe SM, Yung A, et al. Tuberculous meningitis: a 30-year review. Clin Infect Dis. 1993;17(6):987–94. https://doi.org/10.1093/clinids/17.6.987.
[27] Katrak SM, Shembalkar PK, Bijwe SR, et al. The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. J Neurol Sci 2000;181(1–2):118–26. https://doi.org/10.1016/S0022-510X(00)00440-8.
[28] Thwaites GE, Duc Bang N, Huy Dung N, et al. The influence of HIV infection on clinical presentation, response to treatment, and outcome in adults with tuberculous meningitis. J Infect Dis 2005;192(12):2134–41. https://doi.org/10.1086/498220.