Outcome of Hydrocephalus in Tuberculous Meningitis. A Retrospective Study

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Research

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Abstract

Purpose

To study outcome of Hydrocephalus in Tuberculous Meningitis (TBMH) and factors associated with poor clinical outcome.

Methods

Clinical data of 143 adult patients diagnosed with TBM over a 6-year period in 2 tertiary hospitals in Malaysia were retrospectively reviewed. Relevant clinical and radiological data was studied. Patients with Hydrocephalus in TBM (TBMH) were further analysed based on their clinical grade and rendered treatment to identify prognostic factors and outcome of this subgroup of patients. The functional outcome of patients was assessed at 12 months from treatment.

Results

The mean age of patients was 35.6P12.4 year, with a male gender predominance of 67.1%. Forty four percent had TBMH, of which 42.9% had surgical intervention. In the good Modified Vellore Grade, 76.5% was managed medically with concurrent ATT, steroids and osmotic agents. Four patients had surgery early in the disease as they did not respond to medical therapy and reported a good outcome subsequently. Poor outcome (65.2%) was seen in the poor Modified Vellore Grade despite medical and surgical intervention. Multivariate model Multiple Cox Regression showed significant results for seizure (adjusted HR: 15.05, 95%CI: 3.73, 60.78), GCS (adjusted HR: 0.79, 95%CI: 0.70, 0.89) and CSF cell count (adjusted HR: 1.11, 95%CI: 1.05, 1.17).

Conclusion

Hydrocephalus was seen in 44% of patients in this study. GCS score, seizure and high CSF cell count were factors associated with a poor prognosis in TBM. Patients with TBMHM had better survival function compared to those with TBMHS (p value <0.001). This retrospective study emphasizes that TBMH is still a serious illness, as 47.6% of these patients had poor outcome despite adequate treatment.

Background

According to the World Health Organization, in 2018, approximately 10 million cases of tuberculosis (TB) were detected with 1.3 million of them resulting in death. Approximately 10% of these patients were children, and 15% of these patients presented with extra pulmonary tuberculosis. About 1.7 billion people, 23% of the world's population, are estimated to have a latent TB infection, and are thus at risk of developing active TB disease during their lifetime.¹ In Malaysia, TB is an endemic problem and an important public health issue. The incidence of TB in the general population of Malaysia at present is 79–107/100 000.¹

Tuberculous meningitis (TBM) is a non-suppurative inflammatory disease of the dura mater and spinal cord meninges caused by tubercle bacillus. It is the most lethal form of tuberculosis. High mortality and neurological disability among survivors is often encountered. Hydrocephalus is one of the most common complications of TBM and is almost always present in patients having disease for 4–6 weeks.^{2,3} It occurs in approximately 70% patients and is even more common in children.^{3,4,5} The varied pattern of clinical features makes the clinical diagnosis of TBM difficult. It is often diagnosed when brain damaged has already occurred.^{4,5,6,7} The emergence of drug-resistant strains has increased in many parts of the world and this disease presents a therapeutic challenge.^{1,8}

When hydrocephalus is the presenting feature, urgent neurosurgical decompression may be required; the underlying TBM should be promptly diagnosed to minimize any delay in the use of specific anti-tuberculous drugs. The clinical implication of hydrocephalus upon presentation in adult patients with TBM is uncertain. Hydrocephalus in patients with TBM could be either of the communicating or the obstructive type, the former being more common. Lamprecht et al, in their study of 217 cases, had managed BMRC stages II and III TBM with communicating hydrocephalus with medical therapy and reportedly were able to avoid shunt surgery in 70% of these patients. Even in the other 30% who underwent shunt surgery, 41.5% had obstructive hydrocephalus.² Although shunting is recommended particularly in obstructive hydrocephalus, surgical relief of hydrocephalus may not alter the neurological status or long-term outcome.^{9,10} Palur et al, reported that those is grade III and IV of TBM had mortality rates of 51.9% and 100% respectively despite CSF diversion procedures.⁹ The grade of patients at admission usually determines the management strategy. There are various grading systems for patients of TBM with hydrocephalus (TBMH). One of the commonly used systems is the Vellore grading system proposed by Palur et al.¹¹ The internal drainage of CSF, in the form of VP shunt, has been accepted as standard of care in patients presenting in good neurological grade (I and II).⁹ There is still no consensus on the treatment protocol for patients of TBM with hydrocephalus, presenting in poor neurological grade (III and IV). In general, a trial of EVD is an accepted method of treatment, to decide whether a patient will benefit from shunt surgery.¹² However, it has been shown that improvement after CSF diversion may take many days or even weeks.^{11, 13} Prolonged EVD is fraught with the risk of infections.

Thus, a retrospective study at two tertiary teaching hospitals in Malaysia over a 6-year period to study the outcome of Hydrocephalus in Tuberculous Meningitis (TBMH) and factors associated with poor clinical outcome was conducted.

Methods

Study Design

A retrospective cohort study of patients with TBM.

Patients and Methods

Data obtained from patients (aged ≥ 18 years) admitted and treated in 2 tertiary centers, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan and Hospital Umum Sarawak, Kuching, Sarawak between January 2012 and December 2017 with a diagnosis of TBM was analyzed retrospectively. The patients' medical records were reviewed, and the following information was collected: demographic characteristics, underlying diseases, clinical features, laboratory data, bacteriology, image studies, use of steroids, ATT (anti tuberculosis treatment), surgical interventions or drainage, and clinical outcome. Most patients had CSF taken on admission, and the following tests performed: total cell count, glucose, protein, and mycobacterial smears and cultures. Chest radiography and brain computed tomography (CT) scans was performed on all patients upon admission.

Inclusion Criteria

In our study, all patients classified as "Definite" and "Probable" TBM based on the standardized clinical case definition that was mentioned in the 2010 article of Marais was included.¹⁴ The criteria used in classification of Marais are as follows:

- I. Clinical Criteria (maximum category score = 6)
- II. CSF Criteria Score (maximum category score = 4)
- III. Cerebral imaging criteria (maximum category score = 6)
- IV. Evidence of tuberculosis elsewhere (maximum category score = 4)

A diagnosis of definite TBM is made when AFB are seen, *Mycobacterium tuberculosis* is cultured, or is detected by a reliable molecular method from the CSF in someone with symptoms or signs suggestive of the disease. Probable TBM when imaging is available, a diagnostic score of 12 or above is required, and when imaging is not available, a diagnostic score of 10 or above is required. A diagnosis of TBMH is made when there is accompanying radiological evidence of hydrocephalus on the CT brain.

The severity of TBM at the time of admission was assessed using the British Medical Research Council (BMRC) TBM stages.¹⁵ Stage I is defined as a Glasgow coma score (GCS) of 15 without focal neurological signs; Stage II is defined as a GCS of 15 with

neurological deficit, or a GCS of 11–14; and Stage III is defined as a GCS of ≤ 10 . Those with TBMH, were further graded according to the Modified Vellore Grade by Mathew et al.¹³: Grade I, GCS 15 with headache, vomiting, fever $\pm$ neck stiffness, and no neurological deficit; Grade II, GCS 15 but neurological deficit present; Grade III, GCS 9-14 and neurological deficit may or may not be present; Grade IV, GCS 3-8 and neurological deficit may or may not be present.

Exclusion Criteria

Patients who did not fulfill the diagnostic criteria of TBM, age <18 years old or an alternative diagnosis to TBM (i.e. Cryptococcal Meningitis) was excluded from study.

Treatment and Outcome

The cases were treated with the classical four-drug ATT (combination of isoniazid-INH, rifampicin-RIF, pyrazinamide-PRZ, and ethambutol-EMB) for 12–18 months. Some cases with prior TB received a five-drug therapy including streptomycin. Dexamethasone was given as an adjunct and tapered off over 4 to 6 weeks. Hydrocephalus was treated medically with dehydrating agents, or surgical intervention via an external ventricular drain (EVD), ventriculoperitoneal shunt or a combination of both. The functional outcome of patients was assessed at 12 months from treatment. These outcomes were based on the Glasgow outcome scale (GOS) as shown below:¹³

Glasgow Outcome scale:

1. Death – dead
2. Persistent Vegetative State – absent of awareness
3. Severe Disability – ADL - Dependent
4. Moderate Disability – ADL - Independent
5. Good Recovery – Full recovery or mild disabilities not affecting daily life

In our study good recovery and moderate disability were considered a “Good outcome” while severe disability, persistent vegetative state or death was reckoned as “Poor outcome”.

Ethics Approval

The study protocol was approved by the National Medical Research Register (NMRR ID: NMRR-17-174-34329) and the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (USM/JEPeM/17040234) for both hospitals.

Sample Size and Study Power

The sample size was calculated based on specific objective no. III of this study, to compare and analyze outcome of patients with TBMH treated with or without CSF diversion. Based on a dichotomous endpoint, two independent sample group (TBMHM and TBMHS), the sample size was calculated as below.

PS Power and Sample Size Calculations. Version 3.0, January 2009 William D. Dupont and Walton D. Plummer.

- Alpha: 0.05
- Beta: 0.2
- Power: 0.8
- Incidence in Group 1: 70% (Good outcome in TBMHM)
- Incidence in Group 2: 30% (Good outcome in TBMHS)

Data published by Lamprecht et al. on management of TBMH was used as a reference to calculate the sample size.² A minimum of 23 patients in each arm is required to achieve the above study parameters. Thereby, the calculated sample size is 46 patients. Including a dropout rate of 15% into the sample, a total sample of 54 patients is required.

Statistical Analysis

Statistical analysis was performed using commercially available statistical software (SPSS 22.0; SPSS, Inc.). Data were first explored and screened. Continuous variables were presented in mean and standard deviation or median and interquartile range. Categorical variables were expressed as frequency and percentage. Meanwhile univariate analysis Simple Cox Regression was used to explore the prognostic factors for poor GOS outcome followed by Multiple Cox Regression. Kaplan Meier survival curves was used to compare TBMHM and TBMHS. A *p* value of < 0.05 was regarded as significant.

Results

Clinical descriptive data

A total of 143 patients with mean age of 35.6 ± 12.4 years were included in this study. Majority of them were male (67.1%). Only 10.5% of patients were diagnosed with definite TBM, the rest were probable TBM based on Marais criteria. The most common presenting symptoms in TBM according to order were; fever (86.7%), neck stiffness (63.6%), constitutional symptom (33.6%), altered consciousness (30.1%), raised intracranial pressure symptoms (28.7%), hemiplegia (23.8%), cranial nerve palsies (10.5%), and seizure (9.1%). Mantoux test results was positive in 58.7% of patients. Abnormal chest x-ray findings suggestive of TB were seen in 51% of patients. Positive CT Brain findings were cerebral edema (56.6%), hydrocephalus (44.1%), basal enhancement (32.2%), tuberculoma (14.7%), and infarcts (11.9%). A negative CT finding was seen in 9.1% of patient. All patients received ATT, and 85.3% had steroids as an adjunct. Forty four percent had TBMH, of which 42.9% had surgical intervention for the management of hydrocephalus. Table 1 summarizes the clinical and laboratory findings in our patients.

Table 1
Clinical, surgical and laboratory characteristics in patients with TBM (*n* = 143)

	Mean (SD)	Median (IQR)	Frequency (%)
Clinical Data			16(11.2)
Duration of symptoms*			92(64.3)
Acute (< 2 weeks)			35(24.5)
Subacute (2–8 weeks)			32 (22.4)
Chronic (> 8 weeks)			14 (9.8)
TB History			97 (67.8)
TB contact			
Co-existing TB			
Not available/ unknown			
GCS	12.43 (3.20)	14 (3)	
TBM Grade [†]			46 (32.2)
Stage 1			65 (45.4)
Stage 2			32 (22.4)
Stage 3			
Modified Vellore Grading [‡]			7 (11.1)
Grade 1			10 (15.9)
Grade 2			36 (57.1)
Grade 3			10 (15.9)
Grade 4			
Pupils			118 (82.5)
Normal			13 (9.1)
Unequal			12 (8.4)
Dilated			
Footnotes: *symptoms related to TBM, † based on BMRC TBM grade on admission, ‡ grading for TBMH, ** functional status at 12 months			
TB: tuberculosis, GCS: Glasgow Comatose Scale, TBM: Tuberculosis Meningitis, GOS: Glasgow outcome scale, TBMH: Tuberculosis Meningitis with hydrocephalus, EVD: External ventricular drain, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, HIV: Human Immunodeficiency Virus, CSF: Cerebrospinal fluid, AFB: Acid-Fast bacilli			

	Mean (SD)	Median (IQR)	Frequency (%)
Fundus			40 (28.0)
Normal			20 (14.0)
Papilledema			83 (58.0)
Not available			
Functional status (GOS) ^{**}			17 (11.9)
Death			17 (11.9)
Persistent vegetative state			28 (19.5)
Severe Disability			34 (23.8)
Moderate Disability			47 (32.9)
Good recovery			
Surgical intervention for TBMH			8 (29.6)
EVD			3 (11.2)
Shunt			16 (59.2)
Both			
Laboratory Data	8.98 (3.70)		
Peripheral WBC (x10 ³ /μL)			
Serum Na ⁺ (mmol/L)	128.79 (6.51)		
ESR – mm/hr	46.97 (25.74)		
HIV			21 (14.7)
Positive			97 (67.8)
Negative			25 (17.5)
Not available			

Footnotes: *symptoms related to TBM, † based on BMRC TBM grade on admission, ‡ grading for TBMH, ** functional status at 12 months

TB: tuberculosis, GCS: Glasgow Comatose Scale, TBM: Tuberculosis Meningitis, GOS: Glasgow outcome scale, TBMH: Tuberculosis Meningitis with hydrocephalus, EVD: External ventricular drain, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, HIV: Human Immunodeficiency Virus, CSF: Cerebrospinal fluid, AFB: Acid-Fast bacilli

	Mean (SD)	Median (IQR)	Frequency (%)
CSF for AFB			15 (10.5)
Positive			121 (84.6)
Negative			7 (4.9)
Not available			
CSF cell count (cells/ μ L)	15.27 (8.61)		
CSF Protein (> 0.5 g/L)	1.66 (1.06)		
CSF Glucose (mmol/L)	2.69 (0.84)		
Random serum glucose (mmol/L)		5.70 (1.10)	
Footnotes: *symptoms related to TBM, † based on BMRC TBM grade on admission, ‡ grading for TBMH, ** functional status at 12 months			
TB: tuberculosis, GCS: Glasgow Comatose Scale, TBM: Tuberculosis Meningitis, GOS: Glasgow outcome scale, TBMH: Tuberculosis Meningitis with hydrocephalus, EVD: External ventricular drain, WBC: White blood cell, ESR: Erythrocyte sedimentation rate, HIV: Human Immunodeficiency Virus, CSF: Cerebrospinal fluid, AFB: Acid-Fast bacilli			

Descriptive analysis was used to study the treatment rendered in the good and poor Modified Vellore Grade, as the numbers were small in this subgroup of patients. All patient in the good grade had a good outcome, of which only 4 had CSF diversion procedures, the remaining was managed medically (Table 2). In the poor grade, only 2 patients benefitted from surgery, the other 21 patients despite CSF diversion procedures had poor outcome (Table 3).

Table 2

Descriptive data of TBMH treatment in the good Modified Vellore Grade (I and II) and outcome ($n = 17$)

GOOD MODIFIED VELLORE GRADE (I and II)					
	EVD	Shunt [†]	EVD + Shunt [†]	Medical [*]	TOTAL
Good outcome	0	2	2	13	17
Poor outcome	0	0	0	0	0
TOTAL	0	2	2	13	17
Footnotes: †: Ventriculoperitoneal shunt, *: osmotic agents, TBMH: Tuberculosis Meningitis with hydrocephalus, EVD: External ventricular drain					

Table 3

Descriptive data of TBMH treatment in the poor Modified Vellore Grade (Grade III & IV) and outcome ($n = 46$)

POOR MODIFIED VELLORE GRADE (III and IV)					
	EVD	Shunt [†]	EVD + Shunt [†]	Medical [*]	TOTAL
Good outcome	0	0	2	14	16
Poor outcome	8	1	12	9	30
TOTAL	8	1	14	23	46
Footnotes: †: Ventriculoperitoneal shunt. *: osmotic agents, TBMH: Tuberculosis Meningitis with hydrocephalus, EVD: External ventricular drain					

Risk factors for poor outcome in TBM

A total of 17(11.9%) patients died, 17(11.9%) persistent vegetative state, 28(19.6%) severe disability, 34 (23.8%) moderate disability, and 47 (32.9%) with good recovery. These functional outcomes were further grouped into good outcome (moderate disability and good recovery) and poor outcome (death, persistent vegetative state and severe disability). Event was defined as poor outcome and censored for good outcome. Figure 1 shows the median survival time for patients with TBMH was 432 days. The median survival time for TBM without hydrocephalus was not calculated as the smallest survival function did not reach 0.5 or below. Figure 2 shows the Kaplan-Meier survival curve for patients with TBMH treated medically (TBMHM) and surgically (TBMHS). Patients with TBMHM had better survival compared to those with TBMHS (p value < 0.001). Simple Cox regression was used to explore the significant variables to be included in multivariate model. Multivariate model Multiple Cox Regression only showed significant results for seizure (adjusted HR: 15.05, 95%CI: 3.73, 60.78), GCS (adjusted HR: 0.79, 95%CI: 0.70, 0.89) and CSF cell count (adjusted HR: 1.11, 95%CI: 1.05, 1.17). Table 4 summarizes the results for Simple and Multiple Cox Regression.

Table 4
Risk factors for poor outcome in TBMH (*n* = 63)

	Simple Cox Regression			Multiple Cox Regression		
	b	Crude HR (95%CI)	p	b	Adjusted HR (95%CI)	p
Fever	0.00	1.00	-			
No	-3.01	0.05 (0.01, 0.48)	0.009			
Yes						
Neck Stiffness	0.00	1.00	-			
No	1.52	4.59 (1.39, 15.17)	0.013			
Yes						
Altered consciousness	0.00	1.00	-			
No	1.78	5.90 (2.83, 12.31)	< 0.001			
Yes						
Seizure	0.00	1.00	-	0.00	1.00	-
No	3.08	21.64 (6.35, 73.72)	< 0.001	2.71	15.05 (3.73, 60.78)	< 0.001
Yes						
Raised ICP symptoms	0.00	1.00	-			
No	1.14	3.12 (1.33, 7.30)	0.009			
Yes						
TB history	0.00	1.00	-			
TB contact	2.30	10.00 (2.00, 49.95)	0.005			
Co-existing TB	1.24	3.47 (0.81, 14.76)	0.093			
Not available						
GCS	0.339	0.71 (0.65, 0.78)	< 0.001	-0.24	0.79 (0.70, 0.89)	< 0.001

Forward LR Cox proportional hazards regression model applied.

Log-minus = log plot, hazard function plot and partial residuals were applied to check the model assumption and found fulfilled

Footnotes: ICP: Intracranial pressure, TB: Tuberculosis, GCS: Glasgow Comatose Scale, HIV: Human Immunodeficiency Virus, CT: Computed tomography, CSF: Cerebrospinal fluid, AFB: Acid-Fast Bacilli, *: Modified Vellore Grade I and II, **: Modified Vellore Grade III and IV

	Simple Cox Regression			Multiple Cox Regression		
	b	Crude HR (95%CI)	p	b	Adjusted HR (95%CI)	p
Mod. Vellore Grade	0.00	1.00	0.023			
Good Grade*	3.68	39.58 (1.66,944.77)				
Poor Grade**						
Pupils	0.00	1.00	-			
Normal	2.15	8.59 (3.36, 21.96)	< 0.001			
Unequal	2.03	7.60 (3.16, 18.26)	< 0.001			
Dilated						
Serum Na ⁺ (mmol/L)	-1.95	0.82 (0.77, 0.88)	< 0.001			
HIV status	0.00	1.00	-			
Positive	-1.34	0.26 (0.12, 0.58)	0.001			
Negative	-2.22	0.11 (0.02, 0.50)	0.004			
Not available						
CT Brain - Infarcts	0.00	1.00	-			
No	2.28	9.78 (4.31, 22.20)	< 0.001			
Yes						
CSF for AFB	0.00	1.00	-			
Negative	2.07	7.96 (3.29, 19.27)	< 0.001			
Positive						
CSF cell count (cells/ μL)	0.12	1.13 (1.09, 1.18)	< 0.001	0.10	1.11 (1.05, 1.17)	< 0.001
CSF Protein (> 0.5 g/L)	0.92	2.51 (1.85, 3.40)	< 0.001			

Forward LR Cox proportional hazards regression model applied.

Log-minus = log plot, hazard function plot and partial residuals were applied to check the model assumption and found fulfilled

Footnotes: ICP: Intracranial pressure, TB: Tuberculosis, GCS: Glasgow Comatose Scale, HIV: Human Immunodeficiency Virus, CT: Computed tomography, CSF: Cerebrospinal fluid, AFB: Acid-Fast Bacilli, *: Modified Vellore Grade I and II, **: Modified Vellore Grade III and IV

	Simple Cox Regression			Multiple Cox Regression		
	b	Crude HR (95%CI)	p	b	Adjusted HR (95%CI)	p
Glucose CSF	-3.19	0.04 (0.01, 0.13)	< 0.001			
Forward LR Cox proportional hazards regression model applied.						
Log-minus = log plot, hazard function plot and partial residuals were applied to check the model assumption and found fulfilled						
Footnotes: ICP: Intracranial pressure, TB: Tuberculosis, GCS: Glasgow Comatose Scale, HIV: Human Immunodeficiency Virus, CT: Computed tomography, CSF: Cerebrospinal fluid, AFB: Acid-Fast Bacilli, *: Modified Vellore Grade I and II, **: Modified Vellore Grade III and IV						

Discussion

Before *Mycobacterium tuberculosis* was identified by Robert Koch in 1882, TBM was clinically described by Robert Whytt in 1762 for the first time in children with acute hydrocephalus.⁷ Until the discovery of anti-TB drugs in the second half of the 20th century, TBM was a fatal disease for everyone. However, its mortality can still reach 60% today particularly in developing countries. Sequelae can be seen in 25% of survivors despite five major and numerous minor drug options available.^{16,17} As advanced disease stage and delay in therapy are considered poor prognostic factors, early diagnosis and treatment is important.

The definitive bacteriological diagnosis of TBM depends on demonstration of *Mycobacterium tuberculosis* by smear or culture in CSF, meninges or brain tissue. Confirmatory CSF culture isolation and PCR for TBM are known to have low yield and sensitivity, this by itself presents another challenge to an already constrained setting.^{18,19} Positive culture has been found in 12–74% of patients.^{8,20,21,22} In our study, the rate of bacteriological diagnosis was lower than most other large studies, 10.5%. This was via direct smear for AFB, as cost was a limiting factor for TB-polymerase chain reaction (PCR) or GeneXpert then. Mantoux test results were positive in 58.7% of patients, however this result alone is not specific for the diagnosis of TBM, as it has been reported in various literatures ranging from 39–85% in TBM confirmed patients.^{19,21} Abnormal CXR findings were seen in 51% of our patients, which was within the reported incidence of its occurrence (44–71%).^{19,21} Our results showed TBM had a higher incidence in the middle-young age (mean age: 35.62 ± 12.44 years) and in males (67.1%).

During hospital admission, 45.4% of the cases were TBM stage II, and 22.4% were TBM stage III. In our study, we had similar results for patients in stage III (22.4%) upon admission, compared to series from Turkey (22.4%) and Northern Taiwan (25.9%).^{7,8} This reduction in number compared to previously reported studies could be largely due to the advancement in rural and district health particularly in our country. The BMRC staging of TBM depends on the neurological signs and state of consciousness on

admission. Previous studies indicate a correlation between the severity of TBM and poor outcome,^{19, 21, 23} and this was also seen in our study.

There have been many studies on poor prognostic factors in TBM, some of which were advanced age, low GCS on admission, hydrocephalus, concomitant TB at other sites, and BMRC stage III on admission.^{8, 28, 31, 32} Table 4 summarizes all the risk factors for poor prognosis in TBM following Simple and Multiple Cox regression. Seizure, admission GCS and CSF cell counts were significant results following Multiple Cox regression. Those who presented with seizures has 15 times higher risk of developing poor outcome compared to those without seizure ($p < 0.001$, 95%CI: 3.73, 60.78). A unit increase in GCS score in patient will decrease the risk of developing poor outcome by 21% ($p < 0.001$, 95%CI: 0.70, 0.89), whereas a unit increase in the CSF cell count will increase the risk of developing poor outcome by 11% ($p < 0.001$, 95%CI: 1.05, 1.17).

The incidence of TBMH has been reported up to 70% in recent literatures.^{3,4,5,24,25,26} In our study, 44.1% of patients had hydrocephalus on neuroimaging. TBMH could be either the communicating or the obstructive type, with the former being more common.⁴ In either stage of the disease, the thick gelatinous exudates block the subarachnoid spaces in the base of the brain (notably the interpeduncular and ambient cisterns), leading to communicating hydrocephalus.²⁷ TBMH has been reported in various literatures to have an unfavorable impact on the prognosis.^{24, 28} In our study, 65.2% of patients in the poor Modified Vellore grade had poor outcome, whereas all patients in the good Modified Vellore Grade had a good outcome. Further analysis of patients in the poor Modified Vellore grade showed that only 2 patients had good outcome following surgery, and the remaining 30 patients despite CSF diversion and ATT reported a poor outcome (Table 3). In the good Modified Vellore Grade, 76.5% ($n = 13$) was managed medically with a combination of ATT, steroids and osmotic agents. Four patients had surgery early in the disease as they did not respond to medical therapy and reported a good outcome subsequently (Table 2). Figure 2 showed that patients with TBMHM (medical management) had better survival compared to TBMHS (surgical management). This was partly due to the poor pre-operative grades of the patients undergoing CSF diversion procedures, which was 85.2% ($n = 23$) (Table 4). Rajashekar et al in his review article, reported a high mortality in excess of 80% in those with poor grade.²⁹

Conclusion

In conclusion, patients receiving medical therapy had better survival than those requiring CSF diversion procedures for TBMH. In our study cohort, majority of the patients were males. Fever and neck stiffness were the most common presenting symptom. Hydrocephalus was seen in 44% in this study. GCS score, seizure and high CSF cell count were factors associated with a poor prognosis in TBMH. In the subgroup descriptive analysis (Table 2), the good Modified Vellore Grade had good outcomes regardless of the method of treatment. However, further study to determine its significance needs to be conducted prospectively. Patients with TBMHM had better survival function compared to those with TBMHS. Finally,

this retrospective study emphasizes that TBMH is still a serious illness, as 47.6% of these patients had poor outcome despite adequate treatment.

Study Limitations

There were a few noticeable limitations in this study, firstly being the management and timeliness of the referral to the neurosurgical unit for the management of hydrocephalus. Not all patients with TBMH was referred to the neurosurgical unit upon diagnosis. Majority of them were referred in the later stages of the disease or following neurological deterioration due to hydrocephalus. This could be the reason why the patients in TBMHS had a worse off outcome compared to TBMHM. Secondly, not all patients had an MRI done during hospitalization as cost was a limiting factor. This is an important modality to rule out other causes of reduced consciousness such as brainstem infarcts in a patient with confounding TBMH. Due to the retrospective nature of this study, the interrater variability was not calculated. The diagnosis of TBM was based on the clinico-radiological diagnosis by the treating physician and radiologist. As the treating physician/radiologist are not constant, the author does agree that there would be a certain degree of interrater variability in the diagnosis and management of TBM or TBMH in this study. Lastly, being a retrospective study, the advantages of a prospective randomized study for direct comparison was not possible. Hence, a future prospective study comparing this management dilemma will be of great significance.

Abbreviations

1. AFB: Acid-Fast bacilli
2. ATT: Anti Tuberculosis Treatment
3. BMRC: British Medical Research Council
4. CSF: Cerebrospinal fluid
5. CT: Computed tomography
6. ESR: Erythrocyte sedimentation rate
7. EVD: External ventricular drain
8. GCS: Glasgow Coma Scale
9. GOS: Glasgow outcome scale
10. HIV: Human Immunodeficiency Virus
11. ICP: Intracranial pressure
12. PCR: Polymerase Chain Reaction
13. TB: Tuberculosis
14. TBM: Tuberculosis Meningitis
15. TBMH: Tuberculosis Meningitis with hydrocephalus
16. TBMHM: Tuberculosis Meningitis with hydrocephalus treated Medically

- 17. TBMHS: Tuberculosis Meningitis with hydrocephalus treated Surgically
- 18. VP: Ventriculoperitoneal
- 19. WBC: White blood cell

Declarations

Ethics approval and consent to participate

The study protocol was approved by the National Medical Research Register (NMRR ID: NMRR-17-174-34329) and the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (USM/JEPeM/17040234) for both hospitals.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interest

The authors declare that they have no competing interests.

Funding

Not applicable

Authors Contributions

DK conceptualise, designed and was the principal investigator for the study. RK was involved in study design, data interpretation and manuscript drafting. AWSH was involved in study design and data interpretations. JT conceptualise and designed the study along with principal investigator. LCJ performed the statistical analysis and data interpretations. JMA was a major contributor in data interpretation, manuscript drafting and review. All authors read and approved the final manuscript.

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Figures

Survival Functions

Figure 1

Kaplan-Meier survival curves showing the median survival time for patients with TBM and TBMH

Figure 2

Kaplan-Meier survival curves showing the median survival time for patient with TBMHM and TBMHS