Neurology Asia 2025; 30(4) : 1047 – 1056

A prospective observational study of tuberculous meningitis with hydrocephalus in Sarawak, Borneo

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Abstract

Background: The incidence of hydrocephalus is high in patients with tuberculous meningitis (TBM). Over the past 20 years, studies have shown a tendency to use ventriculoperitoneal shunt (VPS) to treat all patients with TBM and hydrocephalus. *Methods:* A prospective observational study was conducted in Sarawak, Borneo (Sibu Hospital and Sarawak General Hospital) from 2019 to 2022. This study aimed to identify patients who would benefit from VPS by assessing Modified Rankin Scale (MRS) post-treatment, survival rate, and various prognostic factors. *Results:* 30 cases were recruited and classified using Modified Vellore Grading (MVG). There was no significant difference between the first month and final post-treatment outcomes. However, mortality rates among poor-grade patients increased significantly after the first month. This study followed up on all surviving patients until 31/5/2024, with a follow-up period of 26 to 63 months. We only performed VPS if there was at least a one-grade improvement in MVG or GCS. Despite VPS, mortality rates remained high, particularly among patients with poor grades, specifically MVG 3 and 4. The study also found that baseline MVG or GCS, cerebrospinal (CSF) protein levels, and the presence of infarcts had a statistically significant effect on patient outcomes.
Conclusion: Poor-grade patients often have cerebral infarcts in addition to hydrocephalus. We recommend an extended external ventricular drainage trial of 5 to 7 days as a preliminary procedure for VPS selection in poor-grade patients. This approach allows for a more objective identification of patients who are most likely to benefit from permanent CSF diversion.

Keywords: Tuberculous meningitis, hydrocephalus, CSF diversion, external ventricular drainage, ventriculoperitoneal shunt, shunt selection

INTRODUCTION

According to the WHO Global Tuberculosis 2023 data, tuberculosis (TB) was the world's second-leading cause of death from a single infectious agent after coronavirus disease (COVID-19). An estimated 10.6 million people (95% UI: 9.9–11.4 million) fell ill with TB worldwide in 2022. Southeast Asia has the highest TB incidence rate.[1] In 2023, according to the Malaysian Ministry of Health (MOH), TB is endemic in the country. In 2023, Malaysia recorded 26,781 TB cases, representing a 5.5% increase from the 25,391 cases reported in 2022 and a significant rise from the 21,727 cases reported in 2021. The state of Sarawak reported 3,177 TB cases, making it the third highest in the country, following Sabah with 5,814 cases and Selangor with 5,631 cases in 2023.[2]

Central nervous system (CNS) TB accounts for approximately 5 to 10% of all extrapulmonary TB (EPTB) cases, as well as approximately 1% of all TB cases.[3] Hydrocephalus is one of the most common complications of TB meningitis (TBM). It is commonly present in patients who have had the disease for four to six weeks.[4] In the study conducted by Bullock et al. and Schoeman et al., hydrocephalus was found in 26 out of 34 patients (76%) and in 161 out of 193 patients

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Date of Submission: 24 March 2025; Date of Acceptance: 1 September 2025

https://doi.org/10.54029/2025zrk

(83%) with TBM, respectively.[5-6] Hydrocephalus is also highly prevalent in children. Out of the total of 185, 167 of them (90.3%) were diagnosed with hydrocephalus.[7]

The current management of hydrocephalus in patients with TBM is mainly based on Modified Vellore Grading (MVG)/Vellore Grading (VG).[8] Most patients had shunts inserted, according to previous literature reviews. However, recent research revealed that shunting did not yield favorable outcomes for all patients, particularly those with poorer grades, and not all patients who undergo shunt surgery for TBM with hydrocephalus show a significant improvement in their sensorium or symptoms. Poor Glasgow Coma Scale (GCS) recovery and prolonged neurological deficits are primarily attributable to two mechanisms: encephalitis, arising from widespread inflammatory processes involving the brain parenchyma, and ischemia, secondary to arteritis with a predilection for small perforating arteries. Multiple infarcts are often observed in the basal ganglia, thalamus, and brainstem.[9,10]

This study aims to identify the patients who benefit from VPS by assessing Modified Rankin Scale (MRS) post-treatment, survival rate, and various prognostic factors. Current studies clearly indicate poor outcomes in MVG/VG 3 and 4 patients. A trial of extended duration of external ventricular drainage (EVD) of 5 to 7 days can serve as a preliminary procedure for selecting candidates for VPS placement. Additionally, EVD allows for CSF sampling and monitoring of protein and glucose levels, as high protein levels in cerebrospinal fluid (CSF) can lead to shunt failure.[11] Moreover, bacterial meningitis can be excluded through CSF culture, which takes 3 to 5 days. This approach provides more time to monitor the patient's GCS recovery and response to EVD. Finally, we aim to formulate a treatment algorithm that is tailored to our local practice.

METHODS

This prospective observational study involved neurosurgical centers in Sarawak, i.e., Sibu Hospital and Sarawak General Hospital. The study spanned 36 months, from 2019 to 2022. This study was registered under the National Medical Research Register (NMRR), NMRR-19-933-48010 (approval date on 1/7/2019).

Patient enrollment

We included individuals who received empirical treatment for tuberculosis meningitis with hydrocephalus (either smear positive or negative), had a Thwaites' diagnostic score of 4 or lower for smear-negative tuberculosis, and had imaging [Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)] indicating hydrocephalus associated with tuberculosis meningitis. All these individuals underwent treatment with an EVD or a VPS. We excluded individuals with meningitis and hydrocephalus (proven non-TB cases in the subsequent investigation) and those who were terminally ill, pregnant, or who declined surgery.

Data collection

We subgrouped patients by MVG (Figure 1). We collected baseline data upon admission and conducted follow-up clinic visits every 3–6 months over a period of three years. In our assessments, we included questionnaires and the Modified Rankin Scale (MRS). In the event of missed clinic visits, we conducted telephone interviews. We obtained CSF samples from EVD or VPS, and routine CSF samples were sent for analysis (cell count, biochemistry, culture) and TB investigation. Patients underwent CT and MRI brain scans, primarily to assess ventricle size (hydrocephalus), basal enhancement, infarct, and tuberculoma.

Subject withdrawal

The National TB Control Program (NTP) did not recommend discontinuing treatment, but subjects could withdraw at any time. We provided anti-TB medication for 9–12 months. The reasons for withdrawal included violation of criteria, refusal of further treatments, health risks, or loss of follow-up. To meet the study targets, we replaced the withdrawn subjects.

Consent

Trained neurosurgical doctors obtained written informed consent. If a patient could not provide consent, a personal representative provided assent

Grade	Presentation
1	GCS 15 No neurological deficit present
2	GCS 15 Neurological deficit present
3	GCS 9–14 Neurological deficit may or may not be present
4	GCS 3–8 Neurological deficit may or may not be present

Figure 1. Modified Vellore Grading

consent. All patients received a copy of the consent form and study documents and provided their consent for the preservation of data and publication of the study results.

Statistical analysis

We estimated the total sample size required for this study using EpiCalc 2000. The TB incidence in Malaysia in 2017 was 0.9% of 26,168 TB cases, including 3,925 EPTB cases. We took the average rate of 7.5% (within the range of 5–10%) for CNS TB among 3,925 EPTB cases. We used a proportion of 244/26168 and estimated an average incidence of hydrocephalus in TBM at 83.2% (within the range of 76–90.3%) based on existing literature.[6-8] The initial sample size estimate was 14, with a confidence interval of 95% and a precision level of 5%. We increased the sample size by 20% to account for potential losses from follow-up, resulting in a final sample size of 17.

The primary outcome was based on the prognosis, with patients classified as good (scores 0-3) or poor (scores 4-6) outcomes, determined by the Modified Rankin Scale (MRS) in the first month post-treatment.

Secondary outcomes included analyzing patient demographics, assessing the frequency and percentages of clinical, CSF, and radiologic features of TBM, identifying prognostic factors, evaluating complications from EVD and VPS, assessing survival rates over a 24 to 36-month period, and developing a standard practice guideline for managing hydrocephalus associated with TBM.

The primary analysis involved a simple categorical frequency comparison using the Chi-Square test to assess the prognosis based on good and poor outcomes. We reported the data using descriptive statistics, including frequencies, percentages, means, ranges, and medians.

We employed the Chi-Square test and the Independent Samples T-test to determine significant relationships between various factors and outcomes. The variables of interest include age (years old), HIV status, duration of symptoms (days), preoperative MVG, CSF analysis parameters such as CSF AFB, CSF cell count (cells/mm^3), CSF glucose (mmol/l), and CSF protein (g/l), as well as radiological findings including basal enhancement, infarct, and tuberculoma. We used simple Cox regression (univariate analysis) to explore the prognostic factors, followed by multiple Cox regression (multivariate analysis).

We continued to follow up with patients on a regular basis to assess their outcomes. We generated survival curves using the Kaplan-Meier method.

RESULTS

From 2019 to 2022, a total of 36 patients were enrolled in the 3-year prospective study. Of these, six were subsequently excluded: one patient was found to have leptomeningeal metastatic lung carcinoma, three were diagnosed with bacterial meningitis, and two were lost to follow-up. The final cohort comprised 30 patients who underwent EVD and VPS. Table 1 summarizes the demographic and clinical features. The distribution of patients by MVG grade was as follows: grade 1 (n = 1), grade 2 (n = 3), grade 3 (n = 19), and grade 4 (n = 7). 43% were male and 57% were female. The mean age was 37 years. The mean duration of symptoms was 16 days. The most common clinical features were altered consciousness, headache, fever, and signs/symptoms of meningitis. Out of all the patients, 2 (6.7%) tested positive for HIV, and 20 (67%) had positive TB smears. A few poor-grade patients refused surgical interventions and were excluded from recruitment. In fact, we achieved a targeted sample size of 17 in the second year. However, we decided to continue a comprehensive 3-year study after obtaining permission from the Medical Research and Ethics Committee (MREC) to increase the sample size.

Between the first month and final follow-up post-treatment, there was no significant recovery in patients with poor grade (MRS 4-6). Nevertheless, we observed a substantial rise in mortality rates for poor outcomes following the first month. The mortality rates at one-month post-treatment for preoperative MVG 1, 2, 3, and 4 were 0%, 33%, 53%, and 57%, respectively. Following that, the mortality rates for MVG 3 and 4 rose to 84% and 86%, respectively, as shown in Figure 2. We followed up on all surviving patients until 31/5/2024. The follow-up period ranged from 26 to 63 months, with a mean of 48 months. All patients initially underwent EVD placement. We only performed VPS surgery if there was at least a one-grade improvement in MVG. Among the surviving patients, all underwent EVD placement, followed by VPS surgery.

Despite VPS, mortality rates remained high, particularly among patients with poor grades, specifically MVG 3 and 4 (Table 2). Figure 3

Table 1: Demographic and Clinical features of the patients, n=30

Demographic and Clinical Features	Mean (SD), Range	Frequency (Percentage)
Age (Year-old)	37(17), 16-76	
Duration of sympton (Day)	16(13), 2-68	
Gender		
Male		13 (43%)
Female		17 (57%)
Signs and symptoms of meningitis		21 (70%)
Fever		21 (70%)
Headache		23 (77%)
Altered consciousness		25 (83%)
Vomiting		19 (63%)
Seizure		0
Neurological deficit		19 (63%)
Photophobia		3 (10%)
Neck stiffness		9 (30%)
History of PTB		4 (13%)
History of EPTB		0
Cranial nerve palsies		12 (40%)
Preoperative MVG		
MVG I		1 (3.3%)
MVG II		3 (10%)
MVG III		19 (63%)
MVG IV		7 (23%)
HIV status		2 (6.7%)
Smear positive TB		20 (67%)

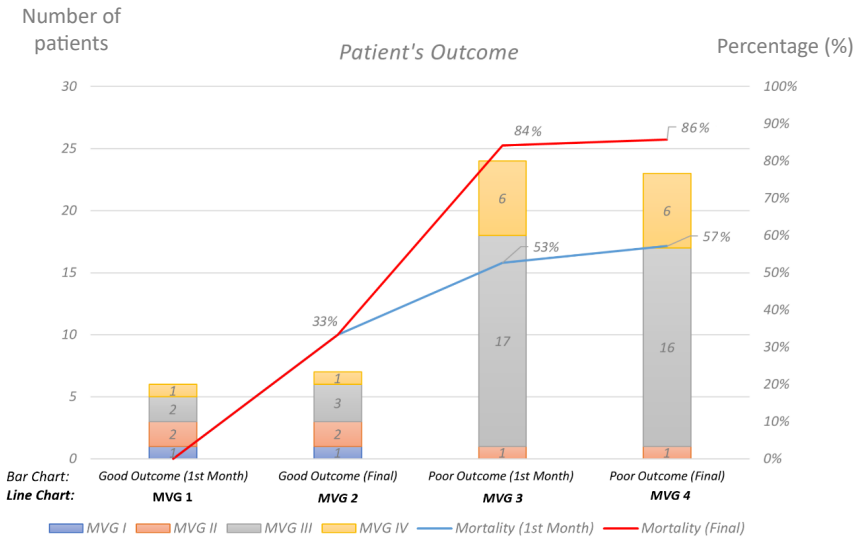
shows the Kaplan-Meier survival curve for preoperative MVGs 1, 2, 3, and 4. Furthermore, the study also discovered that baseline MVG or GCS, CSF protein levels, and the presence of infarcts had a statistically significant effect on the patient's outcome, with p-values of 0.031, 0.004, and 0.003, respectively (Table 3). We used a univariate model (simple Cox regression) to explore the significant variables for inclusion in the multivariate model. The multivariate model yielded significant results for only two variables: HIV status (HR: 0.005, 95% CI: 0.001-0.136) and infarct (HR: 0.121, 95% CI: 0.019-0.783) (Figure 4). We performed a subgroup analysis regarding the influence of the infarct on MVG grade and mortality. We discovered a significant association between infarcts and mortality, particularly for cortical/subcortical and brainstem infarcts (Table 4). MVG 3 and 4 tend to associate with the infarct compared to good grades (MVG 1 and 2); however, the location of the infarct was not statistically significant.

In terms of complications arising from VPS placement, the mean duration from EVD placement to shunt conversion was 5.3 ± 2.4 days, with a range of 2 to 10 days. There were no reported incidences of intraventricular hemorrhage, malposition, or implant failure, such as dislodgment or fracture.

DISCUSSION

Overview and current challenges

The primary options for managing hydrocephalus in TBM are EVD and VPS. However, there is no universal consensus regarding the optimal treatment protocol. There has been a tendency to shunt all patients with TBM and hydrocephalus, including those in poor grades. Current studies and literature reviews clearly state that poor outcomes are observed in patients with poor or severe grades despite shunting. A systematic review by Yiek SH[12], which included 23 studies from 1991 to 2023, reported that poor-grade patients had approximately double the morbidity



Remark:

1. Good outcome: MRS 1-3; Poor outcome: MRS 4-6
2. The stacked column bar chart showed a comparison between the number of patients in the first month and the final follow-up post-treatment. The colored column represented different MVG.
3. The line chart showed the overall mortality rate (in percentage) for each MVG.

Figure 2. Patient's outcome based on MRS

and mortality rates (63%) compared to good-grade patients (30%), with only 37% of poor-grade patients achieving a favorable outcome.

Pathophysiology and implications for treatment

The poor outcomes in these patients are not solely due to hydrocephalus but are strongly associated with vasculitic infarcts in the deep gray nuclei and brainstem, caused by inflammatory exudates from TB infection. This exudate leads to vasculitis, vasospasm, and even necrotizing arteritis, compromising cerebral perfusion and resulting in ischemic injury. Therefore, relieving hydrocephalus with a VPS may not lead to meaningful clinical improvement if irreversible ischemic injury is already present.

Rationale for extended EVD trial

It is generally agreed that relieving hydrocephalus through VP shunt placement is beneficial for patients with good grades. In 1991, Palur *et al*. published their management guidelines, which advocated for EVD placement for 24 to 48 hours for shunt selection, in response to observations of a high morbidity and mortality rate in previous case series.[13] Subsequently, many authors, such as Mathew *et al*. and Agrawal *et al*., have adopted this protocol in their studies.[14,15]

In our centers, we have implemented an extended duration of EVD placement. The duration from EVD placement to shunt conversion ranged from 2 to 10 days (mean 5.3 ± 2.4 days). This prolonged duration allows for more comprehensive monitoring of the patient's GCS recovery and response to EVD therapy. Additionally, the local laboratory requires 3 to 5 days for culturing and sensitivity testing, which fits within the 7 days necessary to exclude superimposed bacterial meningitis. Notably, none of our cases had superimposed bacterial infections. VPS was performed only when there was at least a one-grade improvement in MVG (Table 2).

Table 2: Mortality in patients with shunt

Preoperative MVG	I	II	III	IV
Dead	0	0	9 (75%)	1 (50%)

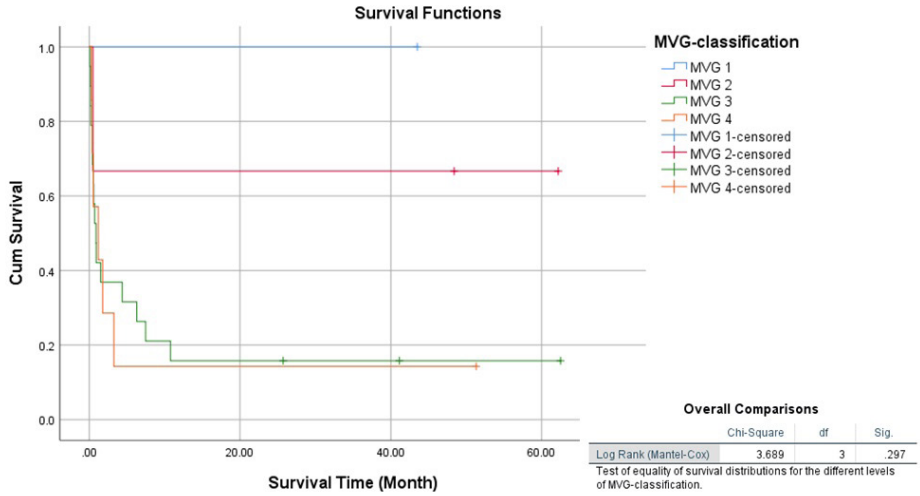


Figure 3: Kaplan-Meier survival analysis

Table 3: Different variables and their effect on outcome in patients with TBM and hydrocephalus Chi-square test (for categorical variable) and Independent samples T-test (for numerical variable)

	Variables	Good outcome MRS 0-3	Poor outcome MRS 4-6	P-Value[2]
Preoperative MVG	Grade I and II	3	4	**0.031**
	Grade III and IV	1	22	
Age	Mean (SD)	30 (9.8)	39(19)	0.24
HIV status	Present	0	2	1.0
	Absent	7	21	
Duration of symptoms	Mean (SD)	24 (22)	14 (8.5)	0.07
CSF AFB detection[1]	Present	1	14	1.0
	Absent	3	12	
CSF-Cell Count(c.m.m)	Mean (SD)	5.6 (5.1)	38 (64)	0.20
CSF-Glucose (mmol/l)	Mean (SD)	3.4 (0.9)	2.7(1.3)	0.26
CSF-Protein (g/l)	Mean (SD)	0.7 (0.4)	1.9 (1.7)	**0.004**
Imaging-Basal Enhancement	Present	2	18	0.18
	Absent	2	8	
Imaging-Infarct	Present	1	22	**0.003**
	Absent	3	4	
Imaging-Tuberculoma	Present	2	5	0.23
	Absent	4	26	

Remark:
Smear-negative patient was recruited based on Thwaite's diagnostic scoring and overall clinical features.
P-Value *(2-sided)*

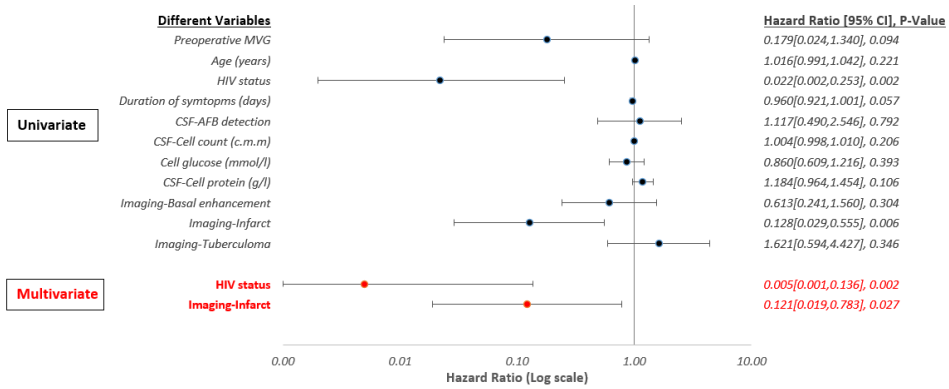


Figure 4. Univariate and Multivariate Cox Regression

Remark: The event was defined as a death.

We recommend maintaining an EVD for no more than 7 days, as this is considered a low-risk and acceptable practice. Once a CSF culture is available, early shunting should be considered to avoid infection, particularly for MVG 1 and 2.

Complications and technical considerations

Shunt surgery complications are reportedly higher in TBM patients than in those with other conditions. Based on the available studies, the overall complication rate is 22%. This includes a rate of 14.9% for shunt revision, 5.4% for shunt infection, 9% for shunt blockage or malfunction, and 1.9% for intracranial bleeding.[12] The high protein and cellular content in the CSF often lead to more frequent shunt obstructions. In our study, three cases required shunt revisions due to suboptimal drainage with CSF protein measuring 1.6, 2.7, and 5.1 g/l, respectively. We used a standard shunt tube in our centers (without an antibiotic coating), and there was no incidence of concurrent shunt infection. A prolonged EVD trial helped reduce CSF protein levels to <1 g/l following anti-TB therapy. Our mean duration from EVD placement to shunt conversion was 5.3 ± 2.4 days. Notably, Singh D *et al*. suggested that shunt functionality is optimal when CSF protein levels are less than 2 g/l.[16] We recommend shunting the patient when the CSF protein level is less than 1 g/l to minimize shunt failure.

Alternative modalities: Role of ETV

The ventriculo-atrial (VA) shunt was the first surgical treatment introduced in 1971. The VPS, which was first introduced in the early 1980s, has since become a standard treatment. Endoscopic third ventriculostomy (ETV), a newer modality introduced in the mid-1990s, avoids inserting a foreign body, potentially reducing

Table 4: Subgroup analysis of the location of the infarct

Variables	Mortality p-value[1]	MVG grade Good /Poor Grade[2] p-value	MVG 1 n (%)	MVG 2 n (%)	MVG 3 n (%)	MVG 4 n (%)	P-value
Infarct	0.003	0.031					
Location of infarct							
Cortical/subcortical	0.031	0.32	0	1 /3 (33%)	11/19 (58%)	4/7 (57%)	0.61
Basal ganglia /Thalamus	0.08	0.10	0	0	9/19 (47%)	6/7 (86%)	0.05
Brain stem	0.024	0.13	0	0	9/19 (47%)	3/7 (43%)	0.37
Cerebellum	1.0	1.0	0	0	1/19 (5%)	1/7 (14%)	0.80

Remark:

1. P-value (2-sided)
2. Good grade: MVG 1 and; Poor grade: MVG 3 and 4
3. Patients might have more than 1 infarct in different locations.

complications such as infections and blockages. However, its success rates vary, especially in post-infectious cases.[17-19] ETV is generally not suitable during the acute phase of TBM due to the thickened ventricular floor and high bleeding risk. In chronic cases, anatomical distortions and a thickened ventricular floor make ETV technically challenging, leading to varied success rates. Overall, the shunt complication rate remains within an acceptable range and comparable to ETV, from 3.8% to 22.5%, as summarized by Chalasani R's systematic review.[20] To date, there is only one randomized trial comparing the outcomes of ETV and VPS in TBM and hydrocephalus.[19] We may need to conduct additional studies with a larger sample size to address this issue. Shunting is still comparable with an acceptable result. ETV has its risks and requires a surgeon with adequate expertise and experience in the endoscopic field. A detailed study of the anatomical landmarks of the third ventricle floor before surgery is the key to success, rather than using a scoring system to select the patients.

Clinical outcomes and prognostic factors

Our findings demonstrated that patients with good preoperative grades (MVG 1 and 2) had better survival. Poor-grade patients, especially those with MVG 3 and 4, showed high mortality (84–85%) despite VPS. Infarcts were significantly associated with poor outcomes ($p = 0.003$), particularly those in the brainstem and cortical/subcortical regions (Table 4). These findings were similar to the recent studies.[21–23] Our multivariate analysis also highlighted HIV status and the presence of infarcts as independent predictors of mortality. Other studies have also proven 100% poor outcomes in HIV-positive patients.[24,25]

Neuroimaging and predictive tools

Early or new infarct identification has a significant prognostic value. MRI is superior to CT in detecting infarcts, with diffusion-weighted imaging (DWI), T2-weighted imaging, and fluid-attenuated inversion recovery (FLAIR) sequences enabling reliable identification and delineation of ischemic lesions. Besides, MRI is a better modality to reveal tuberculomas, meningeal enhancement, and brainstem lesions. As a result, we recommend that all patients undergo a brain MRI for diagnosis and prognostication, as well as to decide on shunt placement. If there are any brainstem infarcts, we recommend palliative care without VPS placement.

Conclusions and recommendations

In conclusion, CSF diversion remains the only treatment for hydrocephalus. Poor-grade patients often have cerebral infarcts in addition to hydrocephalus. We advocate a trial with an extended EVD duration of 5 to 7 days as a preliminary procedure for VPS selection in poor-grade patients. This approach allows for a more objective identification of patients who are most likely to benefit from permanent CSF diversion by assessing GCS recovery and monitoring serial CSF samples. Finally, we should employ MVG for preoperative classification, given its greater reliability and reproducibility across diverse clinical expertise levels and healthcare disciplines. Based on available data and our local clinical experience, we have formulated a treatment algorithm (Figure 5) to improve the outcomes of patients with TBM and hydrocephalus. Corticosteroids should be started as an adjunct, according to local hospital guidelines.[26]

This study has certain limitations, including a relatively small sample size and a short duration of three years. This study included only 30 cases, as the incidence in our country is far lower than in other endemic nations, which reported an anticipated 2.77 million cases in 2022, according to WHO worldwide TB data, substantially surpassing Malaysia's figures.[1] A comprehensive review by Rizvi *et al*. indicated that the number of cases in various global research ranged from 15 to 114 throughout several years.[27]

The low TBM incidence in Malaysia constrained our statistical power and generalizability, especially when compared to other endemic regions with millions of cases annually. Larger multicenter or retrospective studies are needed to further validate prognostic factors and treatment strategies.

The method of CSF diversion for TBM with hydrocephalus is debatable, and no standard guideline or protocol is being followed. For example, Rajshekhar suggested a treatment algorithm in 2009.[8] We believe this algorithm is not widely adopted internationally, likely due to variability in resources, clinical practices, and disease burden. In addition, most authors from prior research typically shunt the patients or place an EVD for a brief period (48 hours).

We believe our recommendations will continue to serve as a valuable reference or guide rather than a clinical protocol. This represents a suggested treatment algorithm (Figure 5) used in our local practice. We would also like to

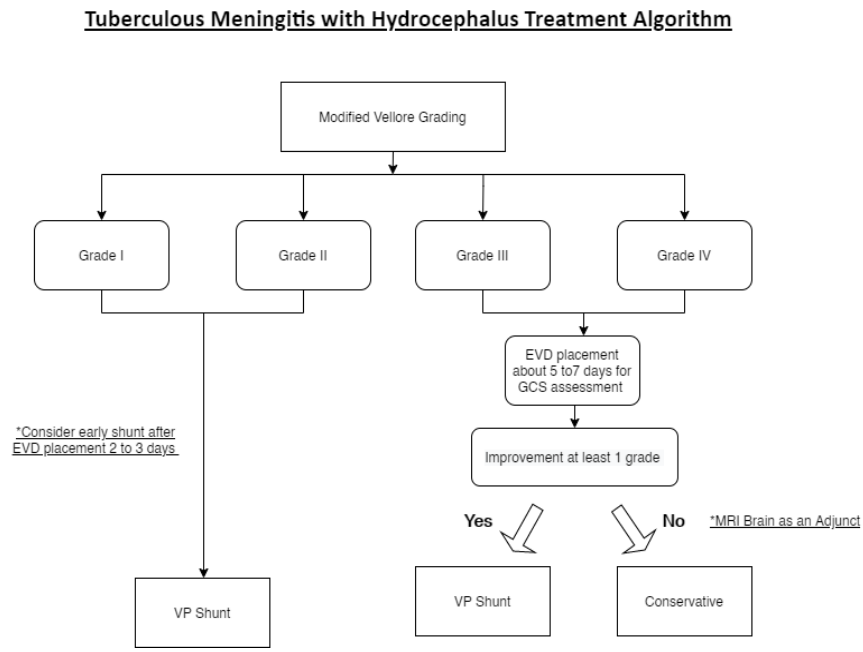


Figure 5: TBM with hydrocephalus treatment algorithm

share our experience treating TBM patients with hydrocephalus.

ACKNOWLEDGEMENT

We extend our appreciation to Dr Adrian Wei-Chih Ng for his support in facilitating the application to the National Medical Research Register (NMRR). His guidance and support were invaluable throughout the research process.

DISCLOSURE

Financial support: None

Conflict of interest: None

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