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Implications of VP-Shunt, Sodium Level, Glucose Level Ratio and Neurologic Deficit as Clinical Outcome Prognostic Factor in Adult Meningitis Tuberculosis with Acute Hydrocephalus in Dr. Hasan Sadikin General Hospital

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ABSTRACT

Introduction: Meningitis is the most severe and dangerous complication of tuberculosis, and can be fatal if not treated adequately. Acute hydrocephalus is often accompanied by tuberculous meningitis. This study aims to assess the prognostic factors in adult patients with tuberculous meningitis accompanied by hydrocephalus.
Methods: The study was conducted retrospectively by collecting data from the medical records of patients with TB meningitis. Patient data were collected and analyzed using multiple logistic regression to obtain significant prognostic factors.
Result: Fifty-four patients had Grade II TB meningitis and 42 patients had Grade III TB meningitis. In this study, it was found that patients with Grade III had higher mortality than patients with Grade II, especially within 30 days of treatment (HR = 3.73 (2.02-6.89), p<0.0001). In patients with Grade II, low sodium levels increased the risk of mortality compared to near-normal sodium levels (HR = 4.22 (1.44-12.43), p = 0.0088). In patients with Grade III, VP-shunt action reduced the risk of mortality (HR = 0.23 (0.09-0.55), p = 0.0011). Meanwhile, the ratio of glucose levels and neurological deficits was not significant as a prognostic factor (p>0.05).
Conclusions: Patients with grade III TB meningitis generally have a high risk of mortality and require VP-Shunt intervention to increase life expectancy. In patients with grade II tuberculous meningitis, sodium level plays a role in determining the prognosis.

Keywords: Meningitis TB, Hydrocephalus, VP-Shunt, Hyponatremia, Prognosis.
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INTRODUCTION

Tuberculosis (TB) is still a global health problem today. According to a report by the World Health Organization (WHO), it is estimated that there are 9.9 million people with TB worldwide. Indonesia accounted for 8.4% of the total incidence with a prevalence of 487,218 cases in 2020.[1] The high incidence of TB in Indonesia correlates with the high incidence of extrapulmonary TB infection in Indonesia. TB meningitis is the second most common manifestation of extrapulmonary TB (3.2% due to complications of primary TB cases in non-HIV patients, and increasing to 83% in patients with HIV), after lymphadenitis.[2,3] TB meningitis is the most severe and dangerous complication of extrapulmonary tuberculosis and can be fatal if not treated adequately, with a mortality rate that can reach 60%, which far exceeds the mortality rate in non-TB meningitis cases which are around 15%.[4]

The diagnosis of TB meningitis is difficult to confirm, so the disease may go unreported. However, the polarizing picture suggests that the global incidence of TB meningitis could be at least 100,000 cases per year.[4]

Several factors have been associated with a poor prognosis in TB meningitis, including age less than 3 years at onset, low Glasgow Coma Scale (GCS), seizures, hyponatremia, basal exudate, infarction, and hydrocephalus on computed tomography (CT) scan.[5,6] The TB meningitis staging that is commonly used in adult patients globally is the British Medical Research Council (BMRC). The neurology department at the Hasan Sadikin General Hospital, which is in charge of treating and managing patients with TB meningitis, uses Staging from the British Medical Research Council (BMRC) in diagnosing these TB meningitis patients.

Hydrocephalus is the most common complication of TB meningitis, almost always found in patients who have had TB meningitis for 4-6 weeks. Inflammation and the presence of exudate in the subarachnoid space due to tuberculous meningitis result in impaired cerebrospinal fluid (CSF) circulation leading to

intraventricular CSF accumulation, which results in progressive ventricular dilatation. The accumulation of CSF will increase intracranial pressure that can causes impaired brain perfusion, further damage to nerve tissue, and even death. So that the presence of hydrocephalus is a complication that has a significant influence on poor clinical outcomes.[5,7,8]

Hyponatremia (a condition in which the plasma sodium level is <135 mmol/L) occurs in approximately 40-50% of patients with tuberculous meningitis. Previous studies revealed that the presence of hyponatremia is associated with the presence of exudate in the basal cistern, which indicates hyponatremia that occurs due to an inflammatory process in the central nervous system.[4] Further studies found that the majority cause of hyponatremia is cerebral salt wasting (CSW), which results in natriuresis and hypovolemia.[4-6] Hyponatremic conditions are common in patients with severe TB meningitis, which indicates the severity of the disease. In addition, the state of hyponatremia itself can result in increased intracranial pressure due to brain edema. Therefore, the recognition and management of hyponatremia are important in the management of TB meningitis.

Previous studies have found that the prognosis of patients with TB meningitis in Indonesia is influenced by several factors, including the level of consciousness, fever, focal neurological deficits, and HIV status.[9] In patients who are not infected with HIV, the mortality rate is associated with a number of supporting medical parameters such as higher CSF neutrophils, lower ratio of CSF and blood glucose levels, positive CSF culture, and blood neutrophilia.[9] Radiological findings do not predict well the prognosis of patients with TB meningitis.[10,11] However, radiological abnormalities including meningeal enhancement, tuberculoma, cerebral infarction, and hydrocephalus are often found in patients with TB meningitis in Indonesia, which indicates delays in access to medical services.[11] Among various radiological abnormalities, the presence of hydrocephalus is associated with mortality rates in patients with TB meningitis.[7,8,10,11]

Ventriculoperitoneal shunt and extraventricular drainage are actions that often performed in patients with TB meningitis who experience acute hydrocephalus.[6,12] There is a high incidence of TB meningitis treated at Hasan Sadikin General Hospital. However, there is currently no study that analyzes prognostic factors in patients with TB meningitis accompanied by acute hydrocephalus at Hasan Sadikin General Hospital. Therefore, the authors are interested in analyzing the prognostic factors in adult patients with TB meningitis accompanied by acute hydrocephalus at Dr. Hasan Sadikin.

METHODS

Study Design

This study is a retrospective cohort by collecting data on adult patients diagnosed with TB meningitis accompanied by hydrocephalus who were treated by the Neurosurgery Department of Hasan Sadikin Bandung General Hospital in 2017-2020.

Data Collection

Data were collected based on purposive sampling, namely all research subjects who met the research criteria. The inclusion criteria of this study were adult patients (aged 18-65 years), patients diagnosed with TB meningitis with hydrocephalus and established based on patients' history, physical examination, laboratory, and head CT scan or MRI examination, as well as patients with a diagnosis of TB meningitis who were treated in 2017-2020. Exclusion criteria in this study were patients with incomplete medical records, patients with grade I TB meningitis, patients who had previous surgery, such as External Ventricular Drainage (EVD) and Ventriculoperitoneal Shunt (VP-Shunt), and patients with the severe comorbid disease. among others; HIV, cancer, stroke, and heart failure. Data were taken from medical records, taken from the time when TB meningitis was first diagnosed with acute hydrocephalus until the last monitoring situation at Department of Neurosurgery Hasan Sadikin General Hospital/Faculty of Medicine Padjajaran University. The research subjects were taken from January 2017 to December 2020.

The sample is part or representative of the population under study, so determining this sample is very important to represent the research population. Based on the existing references43 above, the number of samples in this study is a minimum of 70 patients with the consideration that the number above is the minimum sample size for multivariate analysis where the number of samples should be 10 x the variables studied (10 x 7 = 70) so that the number of samples in In this study, a minimum number of 70 patients was determined.

Statistical analysis

The data obtained were recorded in a form and it will be processed using Graph Pad 8.0 and R studio ver. 3.6.4. Furthermore, survival analysis was performed using Kaplan Meier followed by log-rank Mantle Cox and Cox proportional hazard ratio statistical tests both bivariate and multivariate analysis based on the results of a 2-year follow-up. In this study, the p-value <0.05 was considered to provide significant results.

RESULTS

Subject Characteristics

This study aims to obtain prognostic factors that play a role in predicting clinical outcomes in patients with TB meningitis accompanied by acute hydrocephalus. The total subjects in the study were 96 patients consisting of 54 patients with Grade II TB meningitis and 42 patients with Grade III TB meningitis. In this study, it was found that patients with Grade III tended to be older (median = 32 years) than patients with Grade II (median = 26 years, p = 0.0255). According to the m-BMRC classification, the patient's conscious status at admission as measured by the GCS differed between patients with Grade II (median = 13) and patients with Grade III (median = 9, p < 0.0001). On neurological examination, it was found that paresis of the VII nerve was more common in patients with Grade III (29/42) than in patients with Grade II (22/54, p=0.0058). Another parameter that differed between these two groups was the ratio of glucose levels. Patients with Grade III had a lower glucose level ratio (21.45 ± 12.70%) compared to Grade II patients (33.92 ± 17.16). %, p=0.0002).

Other clinical characteristics did not have a significant difference between patients with Grade II and patients with Grade III. A more detailed description of the patient characteristics is presented in Table 1.

Further studies found differences in survival between Grade II and Grade III patients with a median follow-up duration of 210 days. Patients with Grade II had a survival rate of 64.81% at a follow-up duration of up to 2 years (730 days), while patients with Grade III had a 21.43% survival rate at a follow-up duration of up to 2 years (730 days). this difference in survival was statistically significant (p<0.0001, HR = 3.73 (2.02-6.89), Figure 1).

Table 1. Subject Characteristics

Karakteristik	Grade II	Grade III	*P*
Age	29,65 ± 11,79	35,12 ± 13,66	**0,0255***
Sex			
Male	26	23	0,5202[a]
Female	28	19	
Treatment Status			
Have not received treatment	26	25	0,6089[a]
Have received treatment	22	17	
GCS	13,04 ± 1,45	8,43 ± 1,47	**<0,0001****
Paresis			
N III	0,43 (23/54)	0,48 (20/42)	0,6232[a]
N VI	0,53 (29/54)	0,67 (28/42)	0,1995[a]
N VII	0,41 (22/54)	0,69 (29/42)	**0,0058[b]**
Hemiparesis	0,50 (27/54)	0,55 (23/42)	0,6431[a]
Natrium level (mEq/L)	126,09 ± 9,45	128,39 ± 8,85	0,6686^
Glucose Level Ratio (%)	33,92 ± 17,16	21,45 ± 12,70	**0,0002*****
Intervention			
Conservative	24	22	0,4400[a]
VP-Shunt	30	20	

[a]The differences were analyzed using *chi-square*, with *p-value*>0,05
[b]The differences were analyzed using *chi-square*, with *p-value*<0,05
^The differences were analyzed using *Mann-Whitney U test*, with *p-value*>0,05
*The differences were analyzed using *Mann-Whitney U test*, with *p-value* <0,05
**The differences were analyzed using *Mann-Whitney U test*, with *p-value*<0,0001
***The differences were analyzed using *t-test*, with *p-value* <0,001

Subgroup analysis of grade II patients

In general, the grading of tuberculous meningitis is a significant prognostic factor because different grading has a different life expectancy. To optimizing clinical outcomes after surgical intervention, a review of the available data was followed by a subgroup analysis for each grading of patients with tuberculous meningitis. In a bivariate analysis of each parameter in patients with grade II TB meningitis, it was found that low sodium levels (≤125 mEq/L) at admission had a higher risk of mortality (HR = 3.05 (1.10 - 8.41)), p=0.075). This was confirmed by a multivariate analysis performed, which found that patients with low sodium levels (≤125 mEq/L) at admission had a higher risk of mortality (HR = 4.22 (1.44-12.43), p = 0.0088). Based on the available data, other parameters did not differ in the mortality risk of patients with Grade II TB meningitis (Table 2).

Subgroup analysis of grade III patients

In a bivariate analysis of each parameter in patients with grade III TB meningitis, it was found that patients who underwent surgical intervention in the form of a VP-shunt had a lower risk of mortality compared to patients who did not undergo surgical intervention (HR = 0.31 (0.15). -0.65), p<0.0001). This was confirmed by multivariate analysis, which found that patients who underwent surgical intervention in the form of a VP-shunt had lower mortality (HR = 0.23 (0.09-0.55), p = 0.0011). Based on the available data, the

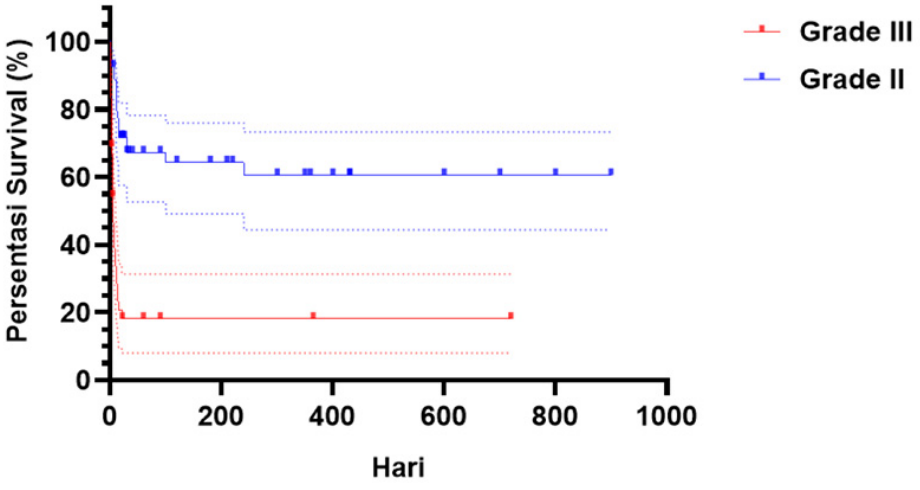

Figure 1. Graph of life expectancy of patients with TB meningitis. The Kaplan-Meier curve chart shows that patients with Grade II have a 64.81% survival rate while patients with Grade III have a 21.43% survival rate at a follow-up duration of up to 2 years (730 days), this difference in survival rates is statistically significant (Log-rank Mantle Cox p<0.0001, HR = 3.73 (2.02-6.89).

Table 2. Prognostic Factor Analysis of TB Meningitis Grade II Patients

	Live	Died	Univariate			Multivariate		
			HR	95% CI	*p*	HR	95% CI	p
Age (median)								
< 26 years	21	10	1,35	0,41 - 4,42	0,6010	1.56	0,45 - 5,57	0,4967
≥ 26 years	14	9						
Sex								
Male	16	10	0,76	0,31 - 1,87	0,5386	0,92	0,25 3,35	0,8633
Female	19	9						
Intervention								
Conservative	15	8	1,17	0,47 - 2,88	0,7317	1,52	0,45 - 5,53	0,5240
VP Shunt	20	11						
Natrium Level								
> 125	27	9	**3,05**	**1,10 - 8,41**	**0,0075***	**4,72**	**1,29 - 19,79**	**0,0262***
≤ 125	8	10						
Glucose Level Ratio								
> 40%	19	9	1,08	0,44 - 2,64	0,8722	0,73	0,20 - 2,54	0,6580
≤ 40%	16	10						
Treatment Status								
Have not received treatment	17	7	0,86	0,35 - 2,13	0,7392	1,32	0,38 - 4,88	0,7076
Have received treatment	18	12						
Paresis N VII								
Yes	14	8	1,24	0,49 - 3,14	0,6386	1,04	0,30 - 3,54	0,9815
No	21	11						

*Statistical analysis using Cox-proportional hazard

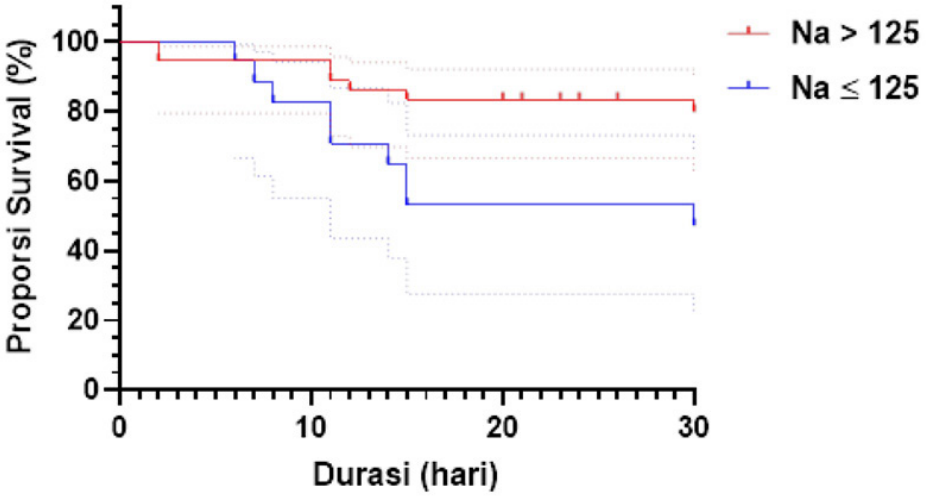

Figure 2. Graph of life expectancy of patients with grade II. The Kaplan-Meier curve shows that patients with low sodium levels (≤125mEq/L) have a 44.44% survival rate, while patients with near-normal sodium levels have a 30-day survival rate of 80.56% (Log-rank Mantle Cox). p=0.0117, HR = 2.95 (1.08-8.07).

other parameters have no difference in mortality risk of patients with Grade III TB meningitis (Table 3).

Further results found that surgical intervention in the form of VP-Shunt was associated with mortality, especially within 30 days of treatment, where the mortality rate reached 100.00% in patients who did not undergo VP-shunt surgery, while in patients who underwent VP-shunt it was close to the mortality was 65.00% (p<0.0001, Figure 3).

DISCUSSION

Tuberculous meningitis is the most lethal manifestation of extra-pulmonary tuberculosis which is fatal if left untreated. Even with standard anti-TB therapy, short-term mortality remains high; ranging from 20–69%.[2,4,13,17] Countries with limited resources, such as Indonesia still face many problems in accurate diagnosis and early detection of TB and TB meningitis. As a result, the condition is directly linked

Table 3. Prognostic Factor Analysis of Grade III TB Meningitis Patients

	Live	Died	Univariat			Multivariat		
			HR	95% CI	*p*	HR	95% CI	*p*
Age (median)								
< 32 years	4	16	1.58	0.37 – 6.95	0.6909	1.63	0.63 - 4,22	0.3145
≥ 32 years	3	19						
Sex								
Male	3	20	0.56	0,13 – 2.39	0.6819	0.84	0.34 – 2.08	0.7011
Female	4	15						
Intervention								
Conservative	0	22	**0.00**	**0.00 – 0.43**	**0.0029**	**0.23**	**0.09 – 0.55**	**0.0011***
VP Shunt	7	13						
Natrium Levels								
> 125	2	18	0.38	0.07 – 2.30	0.4143	1.34	0.60 – 3.00	0.4781
≤ 125	5	17						
Glucose Level Ratio								
> 40%	1	8	0.56	0.04 – 5.14	>0.9999	1.26	0.45 – 3.52	0.6656
≤ 40%	6	27						
Treatment Status								
Have not received treatment	4	22	0.79	0.19 – 3.54	>0.9999	0.68	0.30 – 1.52	0.3481
Have received treatment	3	13						
Paresis N VII								
Yes	5	23	1.30	0.21 – 7.28	>0.9999	0.86	0.40 – 1.86	0.7013
No	2	12						

*Statistical analysis using Cox-proportional hazard

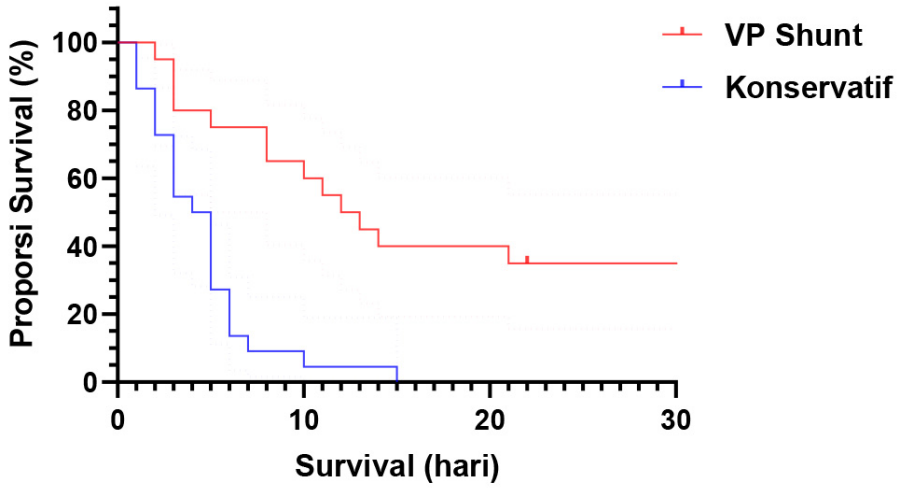

Figure 3. Graph of life expectancy of patients with grade III. The Kaplan-Meier curve chart shows that patients who underwent VP-shunt surgery had a higher survival rate of about 35%, while none of the patients who did not undergo VP-shunt surgery survived within 30 days of hospitalization (Log-rank Mantle Cox p <0.0001, HR = 0.31(0.19-0.65)).

to delayed diagnosis and poor treatment adherence.[18]

In this study, the results were consistent with previous basic studies regarding the survival rate of patients with TB meningitis with different grades having different mortality rates, where patients with grade III TB meningitis had the highest mortality rate (± 78%) compared to patients with grade II TB meningitis (35%). Patients with grade III, generally have more severe conditions such as more prominent neurologic deficits, acute hydrocephalus, or requiring mechanical ventilation.[4,5,10] Patients with grade III are also associated with more prominent exudate in the basal cisterns and complications of vasculitis, problems pulmonary disease, sepsis, and severe hyponatremia.[4,6,11-13] This results in the brain tissue being severely impaired or damaged, so it requires more aggressive therapy to try to save its function.[1,3,8,14,15]

In a further study, it was found that sodium level at admission is an important prognostic factor in patients with meningitis grade II accompanied

by acute hydrocephalus regardless of whether the patient underwent VP-Shunt insertion surgery or not. The incidence of hyponatremia ranges from 40-50% in patients with TB meningitis. CSW and SIADH are important causes of hyponatremia in tuberculous meningitis. The presence of hyponatremia is associated with the presence of exudate in the basal cisterns, which indicates hyponatremia that occurs due to an inflammatory process in the central nervous system.[6] Hyponatremia is common in patients with severe TB meningitis, which indicates the severity of the disease. In addition, the state of hyponatremia itself can result in increased intracranial pressure due to brain edema. Identification of the cause of hyponatremia as CSW or SIADH is important because treatment of one may be detrimental to the other. CSW is more common in causing hyponatremia in tuberculous meningitis than in SIADH. Volume contractions in CSW may be more protracted than hyponatremia and may contribute to border zone infarction in tuberculous meningitis. Untreated hyponatremia contributes to poor clinical outcomes and is a major cause of the failure of surgical intervention.[4,5,16]

In this study, it was found that neurosurgical intervention is an important prognostic factor in patients with grade III meningitis accompanied by acute hydrocephalus. Neurosurgical intervention increases life expectancy in TB meningitis patients. Inflammatory infiltrates within the subarachnoid space or ventricular pathways can lead to impaired CSF flow resulting in hydrocephalus. Hydrocephalus can be communicating (caused by abnormal flow through the cistern basalis) or non-communicating (usually a complication due to obstruction of the fourth ventricle). Communicating hydrocephalus is more common and can be managed medically but may require intervention if it develops. Therefore, in some cases, grade II non-operative efforts can still give good results.[19,20] It should be noted that acute non-communicating hydrocephalus requires rapid intervention. When examining the data, it can be assumed that in patients with grade II, the increase in ICP is more dominantly caused by cerebral edema secondary to hyponatremia, which can still be managed through medication. While in patients with Grade III, the massive exudation process, which is generally accompanied by vasculitis, hypoxia, hypercapnia, and electrolyte imbalance, puts the brain tissue in a vulnerable position to increase ICP and requires immediate surgical intervention to reduce ICP.[1,4,8,9]

In this study, the ratio of glucose levels was not significant as a prognostic factor, it was due to the inclusion criteria of this study being patients with acute hydrocephalus. Previous studies involved a range of patients with a wider range of severity, from mild to severe, and not always accompanied by hydrocephalus.[9] A low ratio of glucose levels is associated with exudation in the basal cistern, resulting in hydrocephalus.[9-11] In addition, the glucose levels ratio in this study has a wide variability but tends to have a lower ratio in patients with Grade III. These things may explain the difference in findings from previous studies.

It should be noted that the conservative treatment in this study was generally caused by the refusal of action from the patient's family, as well as technical problems such as the unavailability of a VP-shunt kit, and a postoperative room with a ventilator. These things lead to delays in patient treatment and contribute to the worsening of the condition of TB meningitis patients.

This study only examined TB meningitis patients with acute hydrocephalus, so it cannot be generalized as a prognostic factor for all patients with TB meningitis. TB infection often occurs in immunocompromised patients, such as HIV/AIDS. Previous studies showed that TB meningitis in patients with HIV has a worse prognosis than non-HIV patients. Therefore, further studies are needed to assess the usefulness of prognostic factors in research for a more comprehensive context widely used in the treatment of TB meningitis. In this study, the operative time interval was not taken into account on the survival rate in patients with tuberculous meningitis, which may have a role in the clinical outcome of patients with acute hydrocephalus. In addition, this study did not assess sequelae or disability in patients with tuberculous meningitis, which may be parameters in assessing the success of a surgical intervention.

CONCLUSION

In this study, patients with grade III TB meningitis had a higher mortality rate than patients with grade II TB meningitis. In addition, in patients with grade II tuberculous meningitis with hydrocephalus, low sodium levels (≤125 mEq/L) on admission carry a higher risk of mortality than patients with near-normal sodium levels. The surgical intervention aimed at CSF diversion with VP-shunt reduces mortality risk in patients with grade III tuberculous meningitis with hydrocephalus.

DISCLOSURES

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The authors are responsible for all of the study funding without a grant or any external funding source.

Conflict of Interest

There is no conflict of interest for this manuscript.

Author Contribution

This research was approved by the Health Research *Ethics* Committee of the Faculty of Medicine, Padjadjaran University. Letter of Exemption Ref. No. 20.65/HPPD.35/LL/2020

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