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Total Lymphocyte Count Analysis and Nutritional Status of Patients for Tuberculous Meningitis Patient Outcomes

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Abstract

Introduction: Tuberculous Meningitis (TBM) is a manifestation of extra-pulmonary TB that causes inflammation of the meninges. TBM is also known as the deadliest form of TB disease. Malnutrition is one factor that increases the risk of severity and death of TB patients. In this study, we aimed to analyse the Total Lymphocyte Count (TLC) as a nutritional biomarker in TBM patients as a predictor of mortality by logistic regression technique to determine the effect of each variable on the outcome.

Methods: This study is a multivariate analytic study using secondary data. A bivariate correlation test analysed all the independent variables. Afterwards, the significant variable(s) were analysed independently by logistic regression to predict the best model for adverse patient outcomes. This study used 95% confidence intervals (CI), and variables with a significance value of $p < 0.05$ were considered significant.

Results: A total of 209 patients' medical records were analysed in this study. The patients consisted of 105 males and 104 females ranging from 17-74 years old, with an average of 34 years old and median of 32 years old. Out of these, 53 patients (25.4%) died, and 156 patients (74.6%) were alive. In this present study, showed age ($p = 0.002$), hospitality duration ($p < 0.001$), GCS ($p = 0.032$) and TLC ($p < 0.001$) were independent predictors of death patient outcome.

Conclusion: In summary, our study showed that the TLC is a promising biomarker for TBM patients' outcomes and coinciding with patient characteristics, we can improve its predictive value. TLC is also known as a nutritional biomarker; thus, nutritional management is crucial to improve the outcome of TBM patients.

Keywords: Tuberculous meningitis; TBM; Total lymphocyte count; TLC; predictor; mortality

Introduction

Tuberculosis (TB) is an infectious disease that is one of the leading causes of death in the world. Indonesia has a very high TB prevalence, the third largest in the world after China, with 8.4% cases. There were 824,000 TB incidents in Indonesia in 2020, with a ratio of 312 cases per 100,000 population. This disease is caused by *Mycobacterium tuberculosis* (MTB) and is transmitted through inhaled droplets[1]. Mainly, TB is an infection that attacks the lungs (pulmonary TB). However, it can spread to other organs (extra-pulmonary TB). Extra-pulmonary TB has clinical manifestations in accordance with the organs attacked by MTB. In 2020, Indonesia reached 9% of patients with extra-pulmonary TB cases [1].

Tuberculous Meningitis (TBM) is a manifestation of extra-pulmonary TB that infects the meninges, especially the subarachnoid space in the human central nervous system (CNS), causing inflammation of the meninges. TBM is the deadliest form of TB diseases[2]. TBM patients will show symptoms similar to meningitis characterised by fever, headache, decreased consciousness, or impaired central nervous function [3]. TB meningitis is a form of extra-pulmonary TB complication that is a global challenge. With a relatively low incident ratio but a high death rate along with a neurological deficit or a permanent disability [3,4], namely 36.1%-45.1% one-year mortality for HIV-uninfected patients and almost 70% for HIV-infected patients of all cases [2,5].

In this study, we measured the condition of which using TLC. Total lymphocyte count (TLC) is a rapid biomarker value test commonly used as a parameter of nutritional status and a determinant of the outcome of a disease [6,7]. Malnutrition is one factor that increases the risk of severity and death of TB patients six to ten times higher, and a quarter of the world's TB cases are associated with malnutrition [8,9]. In a previous study, Rocha et al. stated that a decrease in TLC value indicates an increase in the frequency and severity of infection; hence TLC can be a handy indicator that can be used as a predictor of morbidity and mortality associated with nutritional status and infection in clinical conditions [7]. TLC depletion is a sign of malnutrition. TLC <1.200 cell/mm^3 can be interpreted as a malnutrition sign, and TLC <800 cell/mm3 is interpreted as severe malnutrition sign [6].

The British Medical Research Council (BMRC) staging system for determining the severity of an illness is widely used to predict patient outcomes; however, predicting the patient outcome is still difficult [10-13]. This study aimed to analyse the TLC as a nutritional biomarker in

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TBM patients as a predictor of mortality.

Methods

Participants

This study is a multivariate analytic study with cohort retrospective design using secondary data. Subjects were patients from the Department of Neurology, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, from January 2018 to December 2019 after obtaining ethical approval from the Institutes (886/UN6. KEP/EC/2021). The consecutive patients of adult (≥17 years of age), diagnosed as TBM according to consensus TBM criteria of Marais et al., were included in the study (n = 294) [10,11,14]. The study did not include the patients' records with incomplete or errored data. A total of 85 patients were excluded later because of the reasons mentioned earlier.

Clinical evaluation and diagnosis

All the patients were diagnosed with TBM using Marais case definition score and staged according to disease severity as per BMRC criteria[5]. The data for the duration of hospitality, nutritional status, routine laboratory, and patient's outcomes were all recorded. All the patients underwent a thorough neurological examination, which included assessing level of consciousness by Glasgow Coma Scale (GCS), signs of meningeal irritation, cranial nerve involvement, and any other neurological deficits. Other medical information included a history of previous TB, dissemination of TB, human immunodeficiency virus (HIV) co-infection and any other comorbid.

The patient's nutritional status assessed using body mass index (BMI) Asia-Pacific classification which convsist of four categories such as underweight (<18.5 Kg/m^2), normal (18.5-22.9 Kg/m^2), overweight (23-24.9 Kg/m^2) and obese (≥25 Kg/m^2) [15]. This study also used malnutrition screening tool (MST) as nutritional status assessment tool to detect risk of malnutrition in adult patient in hospital settings comprising 2 factors, weight loss and decreased appetite with score ≥2, showing malnutrition risk [16].

Data Processing and Statistical Analysis

The outcomes of patients were divided into two categories: alive and dead. The study was carried out following the analytics study protocol. The data was analysed by the SPSS software version 26 (SPSS Inc., Chicago, IL, USA). The data was then tested for its normality using the *Kolmogorov-Smirnov test*. Quantitative data were expressed using the median, minimum, and maximum values due to the abnormal distribution. Qualitative data were expressed as a proportion of the total number of patients. A bivariate correlation test analysed all the independent variables. Afterwards, the significant variable(s) were analysed independently by logistic regression to predict the best model for adverse patient outcomes [17]. This study used 95% confidence intervals (CI), and variables with a significance value of p <0.05 were considered significant.

Results

A total of 294 TBM patients' data were collected in this study, of whom 85 data were excluded due to incomplete and error data. As a result, 209 patients' medical records were analysed in this study. The patients consisted of 105 males and 104 females ranging from 17-74 years old, with a median of 32 years old and out of these, 53 patients (25.4%) died in hospitalisation.

The median of patient's hospitalisation duration was 20 (ranged 1-39) days. Most of the patient admitted to hospital in unconscious condition, varies from GCS score 3-15, with a median of 13. Furthermore, 174 patients (83.3%) have a neurological deficit. The nutritional status examination, evaluated using BMI and MST assessment, showed a high number (BMI <18.5 (underweight) = 114 (54.5%); MST ≥2 (malnutrition risk) = 203 (97.1%)) of patients having malnutrition status[15,16,18]. TLC, show that only 24 patients (11.5%) have normal TLC (≥2000 cell/mm^3) and most patients having depletion vary from mild to severe [6,7]. Patients' data also shown some comorbid with distribution as 141 patients (67.5%) having active TB or history with TB pulmonary, 19 patients (9.1%) showed HIV positivity test and 3 patients (1.4%) having diabetes mellitus type 2 management. The details for patients' demographic, clinical features, and laboratory results are shown in Table 1.

In this present study, the patient's outcome was found to be significantly correlated with age (p = 0.005), hospitality duration (p <0.001), GCS (p <0.001) and TLC (p <0.001). The result also found that hospitality duration, GCS, and TLC have a moderate correlation coefficient. However, there was no significance between patient's outcome with gender, neurologic deficit, BMI, MST or any comorbid. These results are also can be seen in Table 1. (Table 1)

Further analysis was performed using logistic regression to predict the best model for the adverse patient outcome between age, hospitality duration, GCS, and TLC independently. The analysis result in Table 2 showed age (p = 0.002), hospitality duration (p <0.001), GCS (p = 0.032) and TLC (p <0.001) were independently predicting the patient mortality. The statistical detail and analysis were correct prediction rate of 92.8% and -2 log-likelihood ratio of 62.2. (Table 2)

Discussion

This study aims for variables as predictors of TBM patient outcome, particularly death, by binary logistic regression analysis in 209 patients. The mortality rate in this study was 23.9%; moreover, the prior published studies have reported that TBM has high mortality rates varying from 16.3% to 67.2%. Previous studies were conducted in different settings, yet they concluded that further studies are required to improve the management and outcome of TBM[5,10,12,19-23].

This study shows that the TLC is a helpful tool for monitoring TBM in-hospital patients, especially in resource-limited settings. The TLC was a strong predictor (p <0.001) of mortality and corresponded reasonably well with hospitality duration and GCS in this setting. However, our finding that TLC is a strong predictor of mortality in TBM patients is not in concurrence with previous study yet might be due to different settings from our study[23]. Nevertheless, the study that includes TLC as a predictor of other diseases has been designed before, predicting HIV-related mortality, cancer prognosis, and COVID-19 severity[24-26].

Hospitalisation duration is also shown to have a significant result (p <0.001) predicting the mortality of TBM patients in-hospital, with a shorter duration which 7 days or less is highly accompanied (n = 55, 80% death) by the outcome of patient death. The same result was shown in Gupta et al., a study conducted in 2017, which concluded that shorter hospitalisation duration correlated to patients' outcomes but was not found to be significant predictors for death in its study [23].

This study also showed that age was significantly (p = 0.002) predict the mortality of TBM patients; in particular, a higher mortality rate was in the age group 45 years old and older. Similar characteristics

Table (1): Analysis of demographic, clinical and laboratory with patient outcome.

Variable	Patients Outcome		P-Value	'Spearman's Coefficient
	Dead	Alive		
	N=53	N=156		
Gender				
Males (n=105) Females (n=104)	29 (27.6%) 24 (23.1%)	76 (72.4%) 80 (76.9%)	0.453	0.52
Age (Median: 32 (17-74 years))				
17-24 (n=51) 25-34 (n=73) 35-44 (n=50) 45-54 (n=17) 55-64 (n=15) ≥65 (n=3)	7 (13.7%) 17 (23.3%) 15 (30.0%) 8 (47.1%) 5 (33.3%) 1 (33.3%)	44 (86.3%) 56 (76.7%) 35 (70.0%) 9 (52.9%) 10 (66.7%) 2 (66.7%)	**0.005**	**0.193**
Hospitalisation Duration (Median: 20 (1-39 days))				
0-7 (n=55) 8-28 (n=144) ≥29 (n=10)	44 (80.0%) 9 (6.3%) 0 (0%)	11 (20.0%) 135 (93.0%) 10 (100%)	**<0.001**	**-0.679**
GCS (Median: 13 (3-15))				
≤10 (n=55) 11-14 (n=73) 15 (n=81)	24 (43.6%) 22 (30.1%) 7 (8.6%)	31 (56.4%) 51 (69.9%) 74 (91.4%)	**<0.001**	**-0.324**
Neurologic Deficit (n=174)	46 (26.4%)	128 (73.6%)	0.427	0.055
BMI (Median: 18.17 (7.21-30.22) Kg/m^2))				
<18.5 (n=114) 18.5 – 22.9 (n=67) 23.0 – 24.9 (n=16) ≥25 (n=12)	26 (22.8%) 18 (26.9%) 6 (37.5%) 3 (25.0%)	88 (77.2%) 49 (73.1%) 10 (62.5%) 9 (75.0%)	0.702	0.027
MST (Median: 4 (0-7)				
<2 (n=6) ≥2 (n=203)	1 (16.7%) 52 (25.6%)	5 (83.3%) 151 (74.4%)	0.053	0.134
TLC (Median: 863.1 (116.7-3810.8 cell/mm^2))				
0-399 (n=35) 400-799 (n=59) 800-1199 (n=46) 1200-1999 (n=45) ≥2000 (n=24)	24 (68.6%) 14 (23.7%) 10 (21.7%) 5 (11.1%) 0 (0%)	11 (31.4%) 45 (76.3%) 36 (78.3%) 40 (88.9%) 24 (100%)	**<0.001**	**-0.402**
TB active or history (n=141)	38 (27.0%)	103 (73.0%)	0.449	0.053
HIV positive (n=19)	6 (31.6%)	13 (68.4%)	0.516	0.045
DM (n=3)	1 (33.3%)	2 (66.7%)	0.751	0.22

P <0.05 significant; GCS: Glasgow Coma Scale, BMI: Body Mass Index, MST: Malnutrition Screening Test, TLC: Total Lymphocyte Count.

Table (2): Binary logistic regression for significant predictors.

Variable	p-value	Exp(B) (95% CI)	95% CI Interval
Age (years)	0.002	1.135	1.047-1.231
Hospitality duration (days)	<0.001	0.681	0.595-0.779
Glasgow Coma Scale	0.032	0.765	0.599-0.977
Total Lymphocyte Count	<0.001	0.997	0.995-0.999
P <0.05 significant; Exp(B): odds ratio; R^2 = 0.835 (Nagelkerke); Percentage of correct = 92.8%			

were shown in a study conducted by Soria et al., in 2019, with subjects median age of 35 years old, concluding that the in-hospital TBM mortality rate is higher among patients over 40 years old [10]. The same results were also shown in Thao et al., a study with subjects median age of 34 years old; older age was an additional predictor of mortality risk [27]. Compared with the WHO Global TB Reports data, which states that most TB patients in Indonesia are patients of productive age, it can be concluded that older patients have a high mortality ratio even though the incidence ratio is relatively low [1].

In this study, most patients in stage 2 disease show a GCS score of 11–14 or 15 with neurological signs. With a median of 13, a higher mortality rate (n = 55, 43% death) was found in patients with GCS score lower than equal to 10. The previous study also had similar results, showing associations between lower GCS score and mortality in TBM patients [5]. Furthermore, different studies showed GCS as a predictor of mortality and neurologic deficit, specifically classified into BMRC grade [27].

Our study showed that the TLC is a promising biomarker for TBM patients' outcomes and coinciding with patient characteristics, we can improve its predictive value. Moreover, patients characteristics are unmodifiable factor whilst TLC is also known as a nutritional biomarker, so nutritional management is crucial to improve the outcome of TBM patients [6].

Our findings in this study relied solely on secondary data analysis by the author; therefore, some researcher bias might have occurred. This study did not perform more profound and more thorough patient management. Moreover, this study only observes TLC at the patients' first-time examination. Thus, external factors can improve or worsen patient condition during hospitalisation, which could be brought upon in future research.

Furthermore, we hope that future studies dive deeper into tuberculous meningitis to understand the disease better and give more tailored assessment and management to its patient.

Conclusion

This study suggests that lower TLC value, shorter duration of hospitalisation duration, older age, and lower score of GCS assessment are independent predictors for death in TBM patients. Also, TLC examination should be done as a routine assessment in clinical settings to provide reliable biomarkers. The involvement of health professionals to provide nutritional management is also crucial to preserve the normal value of TLC and decrease mortality risk in TBM patients.

Geolocation Information

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Disclosure Statement

No potential conflict of interest to declare by the author(s).

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