Journal of Medicine and Health (JMH) **e-ISSN: 2442-5257**
Vol. 8 No. 1 February 2026 **https://doi.org/10.28932/jmh.v8i1.11841**

Research Article

Neutrophil-to-Lymphocyte Ratio Cut-off of > 10,75 as a Predictor of Mortality in Adult Patients with Bacterial Meningitis at Prof. Ngoerah General Hospital

Rasio Neutrofil Limfosit >10,75 sebagai Prediktor Mortalitas pada Pasien Dewasa dengan Meningitis Bakteri di RSUP Prof. Ngoerah

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Received: May 19, 2025
Accepted: January 31, 2026

Abstract

Pathogenic microorganisms of Mycobacterium tuberculosis cause bacterial meningitis. One in six patients with bacterial meningitis dies, according to WHO (2023). Inflammatory marker neutrophil-lymphocyte ratio (NLR) is easy to measure and inexpensive. The objective of this investigation is to validate NLR >10,75 as a prognostic indicator of mortality in adult patients with bacterial meningitis at Prof. Ngoerah General Hospital. This retrospective cohort observational analytic analysis included 156 patients treated from March 2021 to October 2024. Chi-square bivariate testing and logistic regression using SPSS IBM version 30 will be performed on this research data. After statistical analysis, the research subjects were separated into high and low NLR groups based on ROC of 10.75 and AUC of 79.8%. A study found that NLR >10.75 increases mortality risk in adult patients with bacterial meningitis by 2.842, with a 95% Confidence Interval of 1.871-4.317 and a p-value of <0.001. Bivariate and multivariate analyses indicated that sex, cerebrospinal fluid glucose levels, and NLR significantly affect mortality from bacterial meningitis. This study demonstrated that an NLR value exceeding 10.75 is a predictor of mortality in adult patients with bacterial meningitis at Prof. Ngoerah General Hospital.

Keywords*: NLR; meningitis; bacterial meningitis; mortality*

How to Cite:
Margo W, Susilawathi NM, Laksmidewi AAAP, Widyastuti K, Widyantara IW, Sudewi AAR. Neutrophil-to-lymphocyte ratio >10,75 as a predictor of mortality in adult patients with bacterial meningitis at Prof. Ngoerah General Hospital. Journal of Medicine and Health. 2026; 8(1): 37-46. DOI: https://doi.org/10.28932/jmh.v8i1.11841.

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Abstrak

Meningitis bakteri disebabkan oleh bakteri patogen *Mycobacterium tuberculosis*. Data WHO tahun 2023, sekitar satu orang meninggal di antara enam orang dengan meningitis bakteri. Rasio neutrofil limfosit (RNL) merupakan pemeriksaan yang mudah diukur dan murah. Penelitian ini bertujuan mengetahui RNL >10,75 sebagai prediktor mortalitas pada pasien dewasa dengan meningitis bakteri di RSUP Prof. Ngoerah. Penelitian ini merupakan analitik observasional dengan desain kohort retrospektif. Subjek penelitian sebanyak 156 subjek dari Maret 2021 hingga Oktober 2024. Data penelitian dilakukan uji bivariat dengan *Chi-square* dan multivariat dengan analisis logistik menggunakan SPSS IBM versi 30. Hasil analisis statistik, subjek penelitian dibagi menjadi kelompok RNL tinggi dan rendah berdasarkan *Receiver Operating Characteristic* (ROC) yaitu 10,75 dan nilai *Area Under the Curve* (AUC) yaitu 79,8%. Penelitian ini membuktikan RNL >10,75 meningkatkan risiko mortalitas pada pasien dewasa dengan meningitis bakteri: *Relative Risk* sebesar 2,842, nilai Indeks Kepercayaan 95% 1,871– 4,317, dan nilai p= <0,001. Analisis bivariat dan multivariat didapatkan jenis kelamin, kadar glukosa cairan serebrospinal, dan RNL berhubungan secara signifikan terhadap mortalitas pada pasien meningitis bakteri. Hasil penelitian ini didapatkan simpulan bahwa nilai RNL >10,75 sebagai prediktor mortalitas pada pasien dewasa dengan meningitis bakteri di RSUP Prof. Ngoerah.

Kata kunci: RNL; meningitis; meningitis bakteri; mortalitas

Introduction

Meningitis is one of the infectious diseases of the central nervous system with high mortality and morbidity rates worldwide, especially in developing countries, including Indonesia. Based on information from the World Health Organization (WHO) in 2023, meningitis is an important global health issue with a high mortality rate, and bacterial meningitis is the most dangerous type of meningitis that can be fatal within 24 hours.[1] Bacterial meningitis can be caused by pathogenic microorganisms and *Mycobacterium tuberculosis*. The cause of mortality in meningitis is not only based on the severity of the disease, but the difficulty in diagnosis also contributes to the high mortality rate.

Globally, there were approximately 236,000 fatalities and 2.51 million cases of meningitis in 2019, as per the Global Burden of Disease Study report. *Streptococcus pneumoniae* (18.1%), *Neisseria meningitidis* (72.3%), and *Klebsiella pneumoniae* (12.2%) were responsible for the highest percentage of meningitis-related fatalities.[2] From July 2013 to July 2014, Setiawan et al. conducted a study at Prof Ngoerah General Hospital. The team discovered that the percentage of patients with meningitis who survived was 42.6%, while the percentage of patients who perished was 57.4%.[3] In addition, *Streptococcus suis* (*S.suis*) is commonly found in Asia. The epidemiology of *S. suis* infections differs between Western and Asian countries, and there is a high risk associated with the consumption of raw or undercooked pork, such as pig blood, organs, and meat, which is common in Asian countries. Several factors that influence the

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prognosis of bacterial meningitis include gender, age, level of consciousness, seizures, cerebrospinal fluid (CSF) glucose levels, and the causative bacteria.

One of the inflammatory markers is the neutrophil-lymphocyte ratio (NLR), which is easily measurable and inexpensive compared to other microbiological examinations. The NLR is a biomarker that integrates the innate immune response (neutrophils) and the adaptive immune response (lymphocytes) of the body. It is defined as the ratio of the number of neutrophils to lymphocytes. Several conditions, including acute stroke, atherosclerosis, severe trauma, cancer, postoperative complications, and bacterial infections, can be characterized by an elevated NLR.[4] In the study by Widjaja et al, in 2022, it was shown that high NLR affects the outcomes of pediatric patients with bacterial meningitis.[5]

This research aims to demonstrate that a high NLR value is a mortality factor in adult patients with bacterial meningitis as an early detection effort. This will enable doctors to increase their vigilance towards patients with bacterial meningitis and to make the necessary clinical decisions for the required intervention and management.

Methods

This study is observational analytic research using a retrospective cohort design on adult patients with bacterial meningitis based on secondary data (medical records).[5] It was conducted at Prof. Ngoerah General Hospital, Denpasar, Indonesia. Data were taken from the medical records of adult patients with bacterial meningitis who were treated from March 2021 to October 2024. The inclusion criteria for research subjects include adult patients diagnosed with bacterial meningitis at Prof. Ngoerah General Hospital with available NLR laboratory results upon hospital admission and complete medical records. Exclusion criteria include patients with heart, lung, liver, kidney diseases, malignancies, immunocompromised conditions, stroke, and COVID-19. The calculation of the minimum sample size in this study amounts to 156 subjects.[6] The sampling technique was through consecutive sampling. The variables studied include NLR (>10,75 and ≤10,75), gender (male and female), age (>60 years old and ≤60 years old), consciousness status (GCS 15 point and GCS < 15 point), seizures (presence and absence), LCS glucose levels (<40 mg/dL and ≥40 mg/dL, and causative bacteria (*S. suis*, *M. tuberculosis*, and probable bacterial meningitis [such as *S. pneumoniae*, *N. meningiditis*, *Group B streptococcus*, etc]). Probable bacterial meningitis is a case with clinical symptoms and cerebrospinal fluid examination results indicating bacterial meningitis, but no pathogenic bacteria causing meningitis are found or there is no bacterial growth.[7]

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Descriptive analysis is used to see the basic characteristic overview of the research subjects. Determining the cut-off point of NLR with mortality using the receiver operator curve (ROC) and then establishing the optimal cut-off point with the best specificity (95% confidence interval). The stages of analytical statistics are carried out in two phases, namely hypothesis testing for bivariate analysis with independent and dependent variables on a dichotomous nominal scale using the Chi-Square method with continuity correction. If the Chi-Square test conditions are not met, the method used is the Fisher test. The level of significance is expressed with p and relative risk (RR) with a 95% confidence interval (CI). To determine the influence of other factors as predictors of the outcomes of bacterial meningitis treatment, a multivariate analysis using logistic regression method was conducted.

Results

This study included 156 adult patients with bacterial meningitis, treated between March 2021 and October 2024 at Prof. Ngoerah General Hospital. In this study, the cutoff point value of NLR as a predictor of mortality in adult patients with bacterial meningitis using the ROC curve was found to be an optimal cutoff value of 10.75, with a sensitivity of 72.6% and a specificity of 71.1%. The research data, the NLR value was then grouped into two categories: high NLR value greater than 10.75 and NLR value ≤ 10.75, with an AUC value of 79.8% (Figure 1).

Characteristics of the research subjects can be seen in Table 1. This study involved 156 patients with bacterial meningitis, grouped into patients with NLR > 10.75 and NLR ≤ 10.75, with each group consisting of 78 individuals. Based on the results, most of the study subjects were male, totaling 103 individuals, while 53 were female.

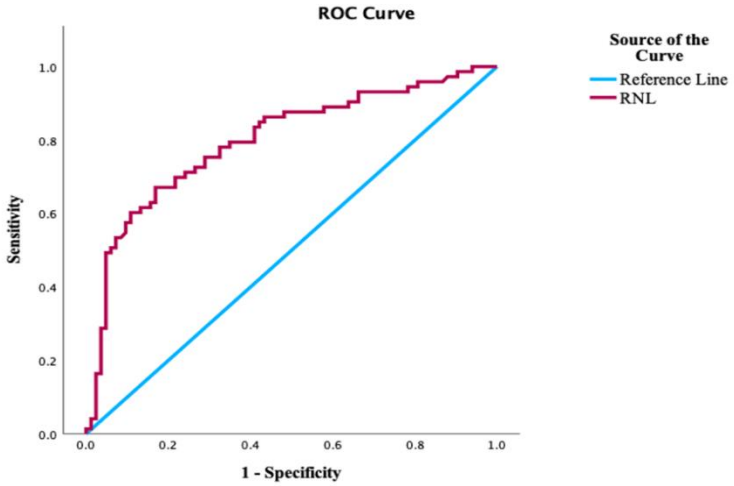

Figure 1 The ROC curve NLR as a Predictor of Mortality

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The NLR > 10.75 group was higher in men at 55.3%. Research subjects in the elderly age group (over 60 years) had a high percentage in the NLR > 10.75 group, which was 57.1% compared to the ≤ 60 years age group, which was 47.9%.

However, the incidence of bacterial meningitis was higher in the age group ≤ 60 years, with 121 patients. Most of the research subjects experienced decreased consciousness, with 127 individuals, the highest percentage being in the group with NLR > 10.75, which was 53.5%. In the seizure variable, it was found that the group of subjects without seizure symptoms was larger, totaling 129 people, with the highest percentage in the NLR > 10.75 group, which was 51.2%. In addition, in the group of patients with LCS glucose levels < 40 mg/dL, 82 individuals were found, with the highest percentage in the NLR > 10.75 group, which was 61%. The variable of bacteria that cause meningitis is divided into three groups: *S. suis*, *M. tuberculosis*, and the probable bacterial meningitis group. The group with *S. suis* had 25 people (61%) with NLR > 10.75, while in the group with *M. tuberculosis* etiology, patients with NLR > 10.75 and NLR ≤ 10.75 were found to be equal in number, with 15 people (50%) in each subgroup. The last group, the probable bacterial meningitis group, was found to have 38 people (44.7%) with NLR > 10.75 and 47 people (55.3%) with NLR ≤ 10.75. In the probable bacterial meningitis group, several research subjects were found to have no microbial growth in the culture results, and other bacteria that are not meningitis pathogens were also found.

Table 1 Characteristics of The Research Subjects

Variable		Total (N = 156)			
		NLR >10.75 N (%)	NLR ≤10.75 N (%)	Total (n=)	P
Gender	Male	57 (55.3%)	46 (44.7%)	103	0.063
	Female	21 (39.6%)	32 (60.8%)	53	
Age	> 60 years old	20 (57.1%)	15 (42.9%)	35	0.337
	≤ 60 years old	58 (47.9%)	63 (52.1%)	121	
Consciousness status (GCS)	GCS < 15	68 (53.5%)	59 (46.5%)	127	0.064
	GCS = 15	10 (34.5%)	19 (65.5%)	29	
Seizure	Presence	12 (44.4%)	15 (55.6%)	27	0.525
	Absence	66 (51.2%)	63 (48.8%)	129	
LCS glucose	< 40 mg/dL	50 (61%)	32 (39%)	82	0.004
	≥ 40 mg/dL	28 (37.8%)	46 (62.2%)	74	
Bacteria causes meningitis	*Streptococcus suis*	25 (61%)	16 (39%)	41	0.231
	Mycobacterium tuberculosis	15 (50%)	15 (50%)	30	
	Probable bacterial meningitis	38 (44.7%)	47 (55.3%)	85	

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The results in Table 2 show that the mortality status of patients with bacterial meningitis in the NLR > 10.75 group as 69.2%, whereas in the NLR ≤ 10.75 group, 24.4%. The difference in mortality status was obtained with an RR value of 2.842 and a 95% CI value between 1.871 – 4.317, as well as a p-value < 0.001, meaning that the group with NLR > 10.75 has a 2.842 times higher risk of death compared to the group with NLR ≤ 10.75 and has a statistically significant relationship. The results of the bivariate analysis with the Chi-square test showed that other statistically significant factors (p < 0.05) as predictors of mortality in adult patients with bacterial meningitis are male gender (p = 0.008) and LCS glucose levels < 40 mg/dL (p < 0.001), while age, consciousness status, seizures, and the bacteria causing meningitis did not show statistically significant results. In the bivariate analysis, variables with a p-value < 0.25 were subjected to multivariate analysis, including the NLR variable, gender, level of consciousness, LCS glucose levels, and the bacteria causing meningitis. Based on the results of the multivariate logistic regression analysis, NLR and LCS glucose levels (p < 0.001), as well as gender (p = 0.024), showed a significant relationship with the mortality of adult bacterial meningitis patients.

Table 2 Bivariate Analysis of Variables with Mortality Status in Adult Patients with Bacterial Meningitis

Variable		Total (N = 156)			RR (CI 95%)	P
		Died (%)	Survived (%)	Total (n=)		
NLR	> 10,75	54 (69.2%)	24 (30.8%)	78	2.842	<
	≤10,75	19 (24.4%)	59 (75.6%)	78	(1.871-4.317)	0.001
Gender	Male	56 (54.4%)	47 (45.6%)	103	1.695	0.008
	Female	17 (32,1%)	36 (67.9%)	53	(1.103-2.605)	
Age	> 60 years old	20 (57.1%)	15 (42.9%)	35	1.305	0.164
	≤ 60 years old	53 (43.8%)	68 (56.2%)	121	(0.919-1.853)	
Consciousness status (GCS)	GCS < 15	63 (49.6%)	64 (50.4%)	127	1.439	0.141
	GCS = 15	10 (34.5%)	19 (65.5%)	29	(0.846-2.448)	
Seizure	Presence	12 (44.4%)	15 (55.6%)	27	0.94	0.788
	Absence	61 (47.3%)	68 (52.7%)	129	(0.594-1.488)	
LCS glucose	< 40 mg/dL	54 (65.9%)	28 (34.1%)	82	2.565	<
	≥ 40 mg/dL	19 (25.7%)	55 (74.3%)	74	(1.689-3.895)	0.001
Bacteria causes meningitis	*S. suis*	23 (56.1%)	18 (43.9%)	41		
	M. tuberculosis	16 (53.3%)	14 (46.7%)	30		
	Probable bacterial meningitis	34 (40%)	51 (60%)	85		0.172

Discussion

This study shows that patients with an NLR value greater than 10.75 had a higher mortality rate (69.2%) compared to those with an NLR of 10.75 or below (30.8%). A high neutrophil-to-lymphocyte ratio (NLR) indicates an uncontrolled systemic inflammatory response,

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which worsens in patients with severe illnesses, including bacterial meningitis.[8] The immune system activates, releasing inflammatory mediators including IL-1 and TNF-α, which drive neutrophil production in the bone marrow.[9] Neutrophils migrate to the subarachnoid space and emit pro-inflammatory cytokines, lysozyme enzymes, and reactive oxygen species (ROS), which kill pathogens but exacerbate inflammation.[10] Brain tissue injury and increased intracranial pressure can result from excessive neutrophil buildup in CSF.[11] In addition, excessive secretion of pro-inflammatory cytokines (IL-1 and TNF-α) can cause lymphocyte death.[12] Low lymphocyte counts under high NLR conditions indicate a failure of the adaptive immune response and inflammatory regulation, which causes uncontrolled inflammation and brain tissue damage.[10] This syndrome increases blood-brain barrier (BBB) permeability, producing endothelial damage, circulatory failure, blood coagulation problems, and multiorgan dysfunction, which can increase mortality.[9]

Males exhibited a higher incidence of bacterial meningitis and mortality rates in this investigation. This is also in accordance with the research conducted by Hsieh et al. (2021) on bacterial meningitis patients, which found 119 male and 70 female deaths.[13] Tarini et al hypothesized that men's high occurrence rate is linked to their work, domicile, and behavioral factors, such as eating raw or undercooked pork-based foods and handling pigs or their processed products, especially in Bali. Males with severe infections, such as bacterial meningitis, activate neutrophils.[14] Men have fewer lymphocytes during acute infection, supporting pro-inflammatory factors.[15] Estrogen protects tissue from systemic inflammation in women by suppressing neutrophil activation and increasing T lymphocyte activity. Women have a lower NLR and better balanced immune system than men.[16] Although the largest age group in this study was ≤ 60 years, mortality rates were higher in the age group > 60 years (57.1% vs. 43.8%). According to earlier studies, bacterial meningitis fatality rates increase with age, with a median age of death between 65 and 77 years.[17,18]

Table 3 Multivariate Analysis of Variables with Mortality Status in Adult Patients with Bacterial Meningitis

Variable	Multivariate analysis	
	p	CI 95%
Gender	0.024	1.133 – 6.075
LCS glucose	< 0.001	2.449 – 11.756
NLR	< 0.001	2.748 – 12.794

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Immuno-senescence is the decline in immunological function with age, which is linked to aging. Deficiencies in naive T cells and uncontrolled neutrophil dominance raise the risk of systemic inflammation and death in this situation. Comorbidities common in the elderly worsen clinical circumstances and raise the NLR. These findings suggest that older age and immuno-senescence impair bacterial meningitis outcomes.[11]

The variable of consciousness status was obtained from the group with decreased consciousness (GCS < 15), with a mortality rate of 49.6%, and in the group of conscious patients (GCS 15), the mortality rate was 34.5%. The research conducted by Okparasta shows that around 92% of patients experience decreased consciousness, and the mortality rate in this group is high at 53%.[19] Decreased consciousness in patients with bacterial meningitis is often a manifestation of increased intracranial pressure and decreased cerebral perfusion, both of which are indicators of poor prognosis.[11] The seizure variable did not exhibit a significant correlation with death (RR = 0.94; 95% CI = 0.594–1.488; p = 0.788). While seizures indicate significant brain impairment, not all individuals with seizures exhibit elevated mortality rates; conversely, those without seizures demonstrate increased rates of NLR and higher mortality. This indicates the potential for undetected non-convulsive seizures, particularly in patients with significant awareness impairment. Seizures can induce cerebral edema and excitotoxicity via blood-brain barrier impairment, excessive glutamate release, and ionic imbalances, thereby exacerbating cerebral damage.[20]

In the LCS, glucose levels < 40mg/dL, there were 65.9% of patients died in this study. This is similar to the study by Arismunandar, where the percentage of the group with a fatal outcome and an LCS glucose level < 40 mg/dL was 53.3%.[22] Hypoglycorrhachia or low LCS glucose levels from normal values in cases of bacterial meningitis result from several pathological mechanisms, namely glucose consumption by bacteria and immune cells, increased glycolytic activity leading to a decrease in LCS glucose levels, increased blood-brain barrier permeability disrupting the glucose transport mechanism to LCS, and increased metabolic activity of cerebral tissue.[21]

In this study, pathogenic bacteria causing meningitis were found, namely *Streptococcus suis* and *Mycobacterium tuberculosis*. The *S. suis* bacteria are associated with the basic characteristics of the research subjects, such as their place of residence, dietary habits of consuming raw or undercooked pork products, and pork production, especially in Bali. In the study by Susilawathi et al., the incidence of *S. suis* bacteria in Bali from 2014 to 2017 involved 44 patients, with 5 of them deceased.[23] Infection by *M. tuberculosis* is commonly found in developing countries, especially Indonesia. Mortality from tuberculous meningitis remains high

despite the availability of effective antituberculosis therapy. Several risk factors closely associated with increased mortality include delayed diagnosis and therapy, where the initial symptoms are nonspecific, thereby increasing the risk of complications, and patients with immune disorders such as those with HIV.[24] Meanwhile, most cases of probable bacterial meningitis show negative culture results or the presence of contaminating commensal bacteria.

The strength of this research lies in the use of the simple and easily accessible laboratory parameter of the NLR across various healthcare facilities, and the lack of studies on high NLR as a predictor of mortality in adult patients with bacterial meningitis, especially in Indonesia. In this study, it can be objectively observed that a high NLR value (>10.75) serves as a mortality factor in adult patients with bacterial meningitis, thereby potentially increasing citations for future research. The weakness of this study is that it has not yet considered several other variables, such as fever symptoms, blood leukocyte levels, LCS protein levels, examination of other inflammatory markers (CRP and Procalcitonin), nutritional status, and antibiotic and anti-inflammatory therapy. These variables have the potential to affect the clinical outcomes of patients.

The results of this study are consistent with the hypothesis where NLR >10.75 is a predictor of mortality in adult patients with bacterial meningitis.

Conclusion

Based on the results of this study, it was concluded that a neutrophil-lymphocyte ratio (NLR) > 10.75 increases the risk of death by 2.842 times and is a predictor of mortality in adult patients with bacterial meningitis at Prof. Ngoerah General Hospital and is statistically significant. These parameters can be used as simple and easily accessible mortality predictors in clinical practice. In this study, it is recommended that medical personnel conduct simple laboratory tests regularly and adopt a more focused management approach to prevent risk factors for bacterial meningitis, which can worsen symptoms and prognosis.

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