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P-ISSN : 25024825 < > E-ISSN : 25029495 Subject Area : Health

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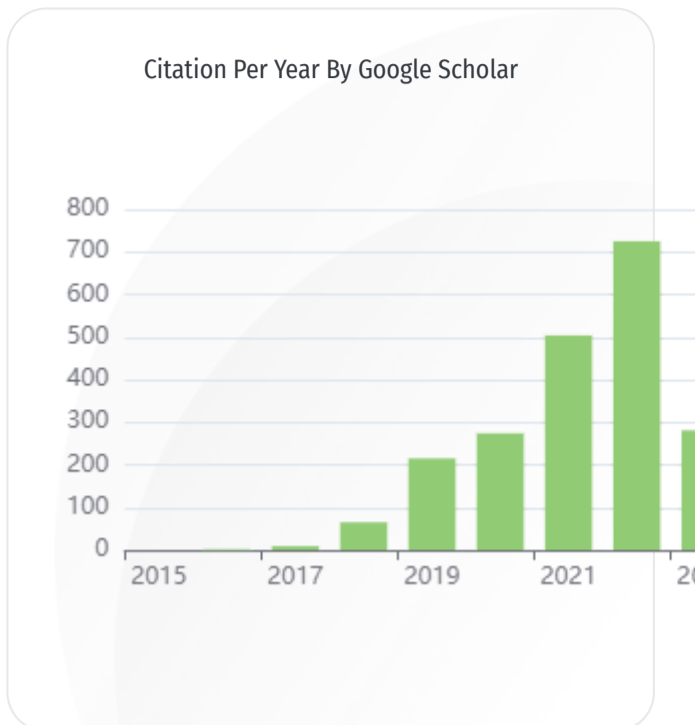
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Online ISSN 2502-9495

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ISSN Online : 2502-9495 (<http://u.lipi.go.id/1454309604>)

ISSN Printed : 2502-4825 (<http://u.lipi.go.id/1454312280>)



Correlation between Blood and Cerebrospinal Fluid (CSF) Neutrophil-Lymphocyte Ratio with Bacterial Meningitis Prognosis Patient

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ARTICLE INFO

Article history:

Received 21 January 2023
Accepted 1 April 2023
Published 10 June 2023

Keyword:

Bacterial Meningitis
Inflammation
Neutrophil-Lymphocyte Ratio
Mortality

ABSTRACT

Bacterial Meningitis is a bacterial infection of the central nervous system's protective membranes called the meninges. Bacterial Meningitis has a high disability and case fatality rate. This inflammatory process not only manifests in CSF but also systemically. The neutrophil-lymphocyte ratio (NLR) can be a predicting factor of severity and prognosis in systemic inflammation. Only a few studies in Indonesia evaluate the neutrophil-lymphocyte ratio as a predictor of mortality in adult bacterial meningitis. This study also aimed to compare neutrophil-lymphocyte ratio in LCS and systemic as a predictor of mortality in patients with adult bacterial meningitis. This is an analytic cross-sectional study in Dr. Soetomo's general hospital—a total sample of 44 bacterial meningitis patients from the inpatient ward of Dr. Soetomo General Hospital Surabaya. The blood Neutrophil- Lymphocyte ratio, Glasgow Coma Scale upon admission, and Absolute lymphocyte count were significant with bacterial meningitis outcome with p -value < 0.05 . Early detection of bacterial meningitis patient prognosis could alert the healthcare provider to give careful monitoring and aggressive treatment.

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Kata kunci:

Meningitis Bakterial
Inflamasi
Rasio neutrophil-limfosit darah
Mortalitas

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DOI: 10.30604/jika.v8i2.1993
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ABSTRAK

Meningitis bakterial adalah inflamasi akibat bakteri di selaput otak dan sumsum tulang belakang bernama meningen. Meningitis merupakan penyakit dengan angka kematian dan angka kecacatan yang cukup tinggi walaupun sudah memberikan pengobatan yang tepat. Proses inflamasi ini terjadi tidak hanya pada system saraf pusat namun juga terjadi di seluruh tubuh. Rasio neutrophil-limfosit pada darah selama ini dapat menjadi tanda derajat keparahan dan prognosis pada kasus inflamasi sistemik. Hanya beberapa penelitian yang mencari tentang hubungan rasio limfosit dan neutrophil pada cairan serebrospinal apakah dapat menunjukkan derajat keparahan pada infeksi meningitis bakteri. Dalam penelitian ini juga ingin mencari rasio limfosit dan neutrophil darah apakah selaras dengan rasio di dalam cairan serebro spinalis. Penelitian ini merupakan studi retrospektif krosesional analitik. Total sampel dari populasi ini adalah 44 yang memenuhi kriteria inklusi dan eksklusi. Secara Statistik didapatkan rasio neutrophil-limfosit darah, tingkat Glassgow Coma Scale saat masuk, dan nilai limfosit absolut signifikan dalam menentukan prognosis pasien dengan meningitis bakteri dewasa ($P < 0.05$).

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INTRODUCTION

Bacterial meningitis is an acute bacterial infection attacking the meninges (Mentis et al., 2016). There were limited data about CNS infection in Indonesia. CNS infection has a high mortality rate but also a disability rate worldwide (Imran et al., 2019). It is rapidly growing due to an increase in the HIV population in developing countries (Imran et al., 2019; Mentis et al., 2016). The global incidence of bacterial meningitis is estimated to be 20 cases per 100,000 population, or 1.2 million people (Brouwer et al., 2010).

World health organization showed that 1 out of 10 people die in bacterial meningitis. The mortality rate could reach 15% with proper treatment and 70% without appropriate treatment within 1-2 days after the onset (Imran et al., 2019; S Saleh et al., 2020). Sequele in developing countries is higher at 50-65%. Following study results conducted in Yogyakarta, 65% of bacterial meningitis had neurological sequelae. (Widjaja et al., 2022) In Indonesia, the barrier to diagnostic and prompt treatment is not only caused by the severity of the disease but also by the facility and society's understanding of the disease.

Neutrophil lymphocyte ratio (NLR) is a biomarker of inflammation derived from leukocytes. The NLR calculation divides the absolute neutrophil count by the absolute lymphocyte count (Widjaja et al., 2022). A simple complete blood count could obtain this data. Having an accessible biomarker to predict the outcome of bacterial meningitis would be helpful in the decision of how bacterial meningitis should be treated (Imran et al., 2019). Studies of NLR as a predictor of mortality in adult bacterial meningitis have not been widely reported. This study is to find the role of NLR in adult bacterial meningitis patients as a predictor of mortality.

METHODS

This study was a retrospective cross-sectional conducted in April 2023. The population was all admitted patients in the neurology ward of Dr. Soetomo General Hospital diagnosed with bacterial meningoencephalitis from January

– December 2022. Using the sample size calculation formula, the minimum sample size was 44 subjects. Inclusion criteria were all adult patients diagnosed with bacterial meningitis according to the Indonesia neurological association guideline, complete blood count, positive bacteria culture from cerebrospinal fluid, age \geq 18 years old, and complete medical record. Data were analyzed using IBM SPSS Statistics for Windows ver. 23.0 (IBM Corp, Armonk, USA). Descriptive data were expressed as mean \pm standard deviation. Depending on the data distribution, each parameter will be calculated and evaluated using Shapiro-Wilk, independent t-test or Mann-Whitney test, and chi-square. Receiver operating characteristic curves were used to determine the NLR cut and analyze specificity and sensitivity. The study was conducted under the declaration of Helsinki. This study received approval from the Health Research Ethics Committee of Dr. Soetomo General Hospital (Ref. Number: 1209/LOE /301.4.2/IV/2023).

RESULTS AND DISCUSSION

A total of 44 subjects in this study, 18(40.9%), died during admission, and 26 (59.1%) were discharged with neurological deficits. The youngest subject was 18 years old, and the oldest was 78 years old, with a mean age of 41 years old. The overall assessment from research consisted of descriptive statistics, and the NLR value test results for predicting the prognosis of bacterial meningitis patients in the inpatient ward of Dr. Soetomo general hospital was described in Table 1. Table 1 presents factors that probably contribute to the biomarker of blood inflammation and CSF, such as total white blood cells count, Absolute lymphocyte ratio (ALR), and absolute neutrophil count (ANC). The overall result showed 3 category correlates significant for predicting mortality in bacterial meningitis GCS entry (P = 0.036), Blood NLR (p= 0.001), and Absolute lymphocyte count (p= 0.003). Pathogen distribution of bacterial meningitis can be shown in Table 2. The most prevalent was 58.6% gram-positive coccus bacteria, and the least was gram-negative cocci with 6.2%.

Table 1
Descriptive Statistics For Age, Sex, blood test distribution

Variables	Survive	Death	P value*
Age	26 (40.5 \pm 14.4)	18(41.72 \pm 17.49)	-.09
% Female	7(26.92%)	9(50%)	0.118
Blood WBC**	26 (12019 \pm 5134)	18(14440 \pm 6901)	0.210
GCS entry**	26 (11.57 \pm 2.4)	18(9.67 \pm 3.2)	0.036
NLR**	26(9.67 \pm 12.01)	18(17.9 \pm 12.75)	0.001
ALC**	26(1446 \pm 712)	18(859 \pm 596)	0.003
ANC**	26(9676 \pm 4989)	18(12542 \pm 6654)	0.145
CSF WBC**	26(302.93 \pm 788)	18(157.39 \pm 262.5)	0.574
CSF NLR**	26(0.72 \pm 0.99)	18(1.4 \pm 2.58)	0.632

**Notes: WBC : White blood cell; GCS : Glasgow Coma Scale; NLR:Neutrophil-lymphocyte ratio; ALC: absolute Lymphocyte count; ANC: absolute neutrophil count; CSF: Cerebrospinal Fluid.
 * p < .05

This study used the receiver operating characteristic (ROC) curve to calculate the optimal cut-off for NLR as a predictor of mortality in patients with adult bacterial meningitis. The optimal cut-off result is 10.5, with a

sensitivity of 72.2% and a specificity of 80.8%. NLR was statistically significant as a predictor of mortality in bacterial meningitis patients with p < 0.001 and RR 4.84 (Fig. 1).

Table 2
Pathogen distribution by the culture

Pathogen	Survive	Death
Gram Positive Cocci	25(53.8%)	56.8(61.1%)
Pseudomonas	2(7.7%)	3(16.7%)
Gram-negative Cocci	1(3.8%)	0(0%)
Atypical pathogen	2(7.7%)	1(5.6%)
Other	7(26.9%)	3(16.7%)

This study used the receiver operating characteristic (ROC) curve to calculate the optimal cut-off for NLR as a predictor of mortality in patients with adult bacterial meningitis. The optimal cut-off result is 10.5, with a sensitivity of 72.2% and a specificity of 80.8%. NLR was statistically significant as a predictor of mortality in bacterial meningitis patients with $p < 0.001$ and RR 4.84 (Fig. 1).

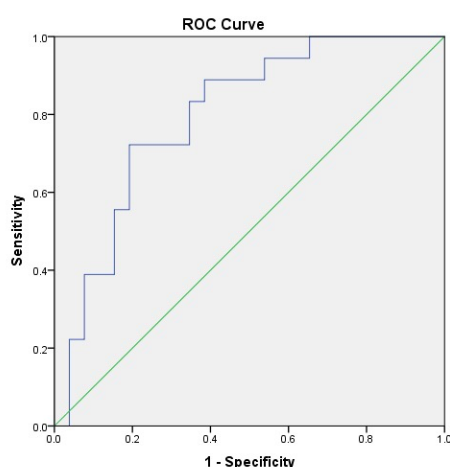


Figure 1. Receiver operating characteristic (ROC) curve for Neutrophil-Lymphocyte ratio

DISCUSSION

The result data showed male to female ratio was 1.75, with age distribution mostly around 41 years old. This ratio was similar to previous data in 2019 at Dr Sotemo general hospital, with value of 1.66

The following study in Dr. Soetomo general hospital showed male to the female ratio was 1.66, mostly occurring in the age of 40 (47.06%) (Andarsari et al., 2019). A more extensive bacterial meningitis Study in Taiwan also gives a similar ratio with age within the productive period. All studies showed males slightly at risk for bacterial meningitis compared to females (Tigabu et al., 2021).

Meningitis in the early era affected age groups of patients who had immature immune system, such as infants, elderly, and HIV patients (Marcus & Walter, 2022). After the introduction of the vaccination and early primary prevention for bacterial meningitis, there was a shifting of distribution age group and pathogens (K.S. et al., 2015). The incidence nowadays is shifting with the most prevalent in infants younger than 90 days, adults around 40 years old, and elderly above 65 years old (Koelman et al., 2021; Tigabu et al., 2021). The current study reported 56.8% gram-positive coccus and 11.4% positive Pseudomonas as adult bacterial meningitis causative agents (Hsieh et al., 2021). The most common germs obtained from CSF cultures were

Staphylococcus epidermidis, Staphylococcus haemolyticus, and Pseudomonas aeruginosa found in patients. Pseudomonas meningitis gram-negative bacillus is a rare cause of meningitis compared to coccus gram bacillus and mainly develops after having a history of neurosurgical procedures (Gallaher et al., 2017). The causative bacteria in our study were consistent with the general population of causative agents in adult bacterial meningitis (Andarsari et al., 2019; Hsieh et al., 2021). Streptococcus pneumoniae mainly affects patients 45 years old, while the younger age group 93% got Neisseria meningitidis (Sigurdardóttir, 1997).

In the following study, fewer patients died from bacterial meningitis (40.9%) than survived (59.1%). The majority pathogen with S. pneumoniae has a mortality rate 34% but the highest with pseudomonas infection due to multiple drug resistance (Rohmah et al., 2023). Other factors that increased the death rate in meningitis were immunocompromise, streptococcus pneumonia, treatment delay, and unclear vaccination status (Zainel et al., 2021). This study found that patients with NLR values above 10.5 died on average more (9.6) than patients with below cut-off. The NLR cut-off value for each disease is different. The normal range of NLR values in healthy subjects is 0.78-3.581 (Novariani, Herini, & Patria, 2016). Another Study with sepsis patients gives an NLR value of 5.68 locally and 11.78-13.16 systemically (Gurol et al., 2015).

The neutrophil-Lymphocyte ratio is a subclinical biomarker of inflammation status in the human biological system. It has recently been used as a marker of infection severity (Rathod et al., 2022). The previous study shows a strong correlation of NLR with sepsis. Further increase in NLR is associated with decreased apoptosis capability, inhibit neutrophils' cell-killing ability, and their anti-inflammatory role, resulting in SIRS and MOD (Zahorec, 2001). The NLR ratio will also increase significantly in bacterial infection, including bacterial meningitis and low viral infection. A higher NLR value indicates septicemia, leading to poorer bacterial infection outcomes (Naess et al., 2017). In Bacterial meningitis, almost 39% of mortality is contributed by septicemia (Sharew et al., 2020).

In addition to neutrophils and lymphocytes, the level of consciousness on admission to the hospital predicts poor outcomes in patients with bacterial meningitis. The most prominent early clinical features were fever, headache, and decreased consciousness (Teixeira et al., 2022). Previous data in Indonesia showed approximately a patient with CNS infection presented with decreased consciousness and headache in the hospital (Imran et al., 2018). In bacterial meningitis, a decrease of consciousness presents 15-20%. The level of consciousness when first undergoing treatment for bacterial meningitis can be related to the outcome that will be obtained. This is supported by other studies, which state that only 1 in 5 patients (20%) survive (Lucas et al., 2014). In this study, the level of GCS entry was statistically significant with the patient's outcome ($p = 0.001$). Poor GCS on admission is also caused by late admission to the hospital. In most cases in Indonesia, patients with bacterial meningitis will be admitted after the onset of more than 3 days of the first symptoms. Post-bacterial meningitis neurological complications could be present in almost 50% (Zainel et al., 2021). This includes seizure, cognitive impairment, hydrocephalus, and hearing loss. Neurological sequelae were not included in this study. However, other recent studies showed a significant correlation between NLR value and higher neurological sequelae (Gong et al., 2022).

The presence of the following NLR biomarkers can predict mortality prognosis so that it can be a preventive

measure for mortality due to bacterial meningitis. In addition, the average bacterial meningitis patient in the following health facilities is enrolled in health insurance or national health insurance, which has a middle to lower economy. Patients can easily reach NLR because the price is low but effective. There was no statistical correlation between CSF NLR and mortality in this study. However, there was less known about CSF NLR with prognosis in bacterial meningitis patients. A previous cohort study showed that CSF NLR can differentiate viral meningitis from bacterial meningitis in the pediatric population. We know that more sample size is needed with all the comorbidities data to improve our research, which can affect NLR value. This would be considered as our study limitations. Further studies with larger sample sizes and details need to confirm this finding.

CONCLUSIONS AND SUGGESTIONS

The blood Neutrophil lymphocyte ratio is a statistically significant predictor of mortality in adult bacterial meningitis patients. This also can be used as a parameter to predict outcomes in patients with bacterial meningitis with cut-off value 5.22. As the healthcare provider high NLR value, patients need intensive monitoring and aggressive management to improve patient outcomes.

Acknowledgement

The Author, thank you to dr. Soetomo general hospital to permit data collection. We thank Cindy C., Jovian Philip S., and Kholifatul M. for assisting with this research.

ETHICAL CONSIDERATIONS

Funding Statement.

The authors did not receive support from any organization for the submitted work.

Conflict of Interest Statement

The Author declare no conflict of interest.

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