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Association between Absolute Neutrophil Count and Mortality in Bacterial Pneumonia following Acute Ischemic Stroke

R Retnaningsih

Diponegoro University, Indonesia

Abstract— Background: Bacterial pneumonia following acute ischemic stroke occured as a result of inflammatory reaction, one of body defense mechanism against infection, which lead to neutrophils invasion in lung tissue. Absolute neutrophil count (ANC) is related to mortality in patients with bacterial pneumonia after acute ischemic stroke. Methods: This was a prospective observational study conducted in Dr. Kariadi hospital, Semarang, from November 2013 to April 2014. 34 patients diagnosed with bacterial pneumonia after acute ischemic stroke were recruited. Association between ANC and mortality as well as ANC and NIHSS score at 7th day of diagnosis of bacterial pneumonia were determined using correlation test. The cut-off point of 7.600/μL from previous studies was used to determine the magnitude of the relative risk of ANC in association with mortality. Results: ANC was positively correlated with mortality in patients with bacterial pneumonia after acute ischemic stroke. ANC was also positively correlated with NIHSS scores at 7th day of diagnosis of bacterial pneumonia among surviving patients. Using cut off point of 7.600/μL from previous studies, with sensitivity of 85.7% and specificity of 40.7%, a non-significant p value of 0.203 and rho of 0.224 was obtained. Conclusions: The study showed that ANC was positively correlated with mortality in patients with bacterial pneumonia after acute ischemic stroke; however it was statistically not significant. This was due to excessive response of neutrophils in the inflammatory reaction which can adversely affect mortality and neurological deficits status showed in NIHSS score.

Keywords— absolute neutrophil count (ANC), acute ischemic stroke, pneumonia, mortality.

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I. Introduction

STROKE is the third most common cause of death in industrialized countries. In Europe, the death rate reaches 63.5 to 273.4 per 100,000 cases, with incidence varying between 100 and 200 new cases per 100,000 populations [1]. In the United States, approximately 700,000 people suffer from stroke each year resulting in more than 150,000 deaths [2]-[4]. Ischemic stroke is approximately 75% of all cases of stroke [1],[5]. Infection following acute stroke phase are common. Urinary tract infection and bacterial pneumonia are the most common infection [6].

Corresponding author: R. Retnaningsih (email: retnaku_icu@yahoo.com).
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The incidence of bacterial pneumonia after stroke is between 5% and 22% [6]. Pneumonia often occurs within 48-72 hours after first ischemic stroke and resulted in approximately 15% - 25% stroke-related mortality [3]-[5]. Pneumonia due to aspiration post-stroke is caused by neurological deficits, such as loss of consciousness, impaired protective reflexes or dysphagia. Risk factors for pneumonia after stroke are stroke severity, stroke type, lesion size, mechanical ventilation, age, sex, immune deficiency, and history of diabetes [6],[7].

A wealth of data from both human and animal studies indicates that inflammation mediated by inflammatory cells, cytokines, cell adhesion molecules, and eicosanoids occurs after ischemic injury and may exacerbate ischemic injury. Increased infiltration of peripheral leukocytes into the brain has been observed within hours to days after the ischemic insult in human cases of stroke [3]-[6]. Generally, neutrophils are first among the leukocyte species to accumulate in the brain after stroke, and their number has direct correlation with infarction volume [8],[9]. As demonstrated by Buck et al, higher neutrophil count is associated with larger infarct volume [10]. Neutrophils are recruited to the brain within 30 minutes to a few hours of focal cerebral ischemia, peak earlier (Days 1–3) then disappear or decrease rapidly with time. Neutrophils play roles to brain inflammation and injury by releasing a number of pro-inflammatory mediators, such as inducible nitric oxide synthase (iNOS) and matrix metalloproteinases (MMPs), which are stored in granules and vesicles of neutrophils [10],[11]. Some researches proposed malondialdehyde (MDA) as a predictor for infarct volume in patients with acute ischemic stroke. However, Retnaningsih proved that there was no significant correlation between plasma MDA levels elevation and infarct volume size [12].

Neutrophil is also pathological marker in the presence of bacterial lung disease. Migration of neutrophils into the lung is critical for lung defense mechanisms, excessive influx of neutrophils will result in diffuse lung parenchymal damage [10],[13]. Deployment of neutrophils involves several stages including activation of transcription factors, production of chemokines, up regulation of cell adhesion molecules, and cell interaction [15]. Leukocyte and neutrophil counts are often used as a blood marker of acute inflammatory status [16]. Clinical trial by Kustiowati, et al (2008) showed that the absolute

neutrophil count was an indicator of acute ischemic stroke on 10-72 hours of onset. Absolute neutrophil count of 4850/µL worsen NIHSS scores on 10-72 hours to 7 days of onset [28]. Al-Gwaiz & Babay (2007) found that the absolute neutrophil count was more sensitive than the overall number of leukocytes in predicting bacteremia [30]. However, Muller et al in their study suggested that a specific cut-off point of ANC which indicate outcome after acute ischemic stroke was difficult to determine [29].

Increased number of neutrophils is associated with destruction of lung parenchyma and patients with bacterial pneumonia after stroke is more likely to have greater mortality rate. Research on association between absolute neutrophil counts with mortality of patients with bacterial pneumonia following acute ischemic stroke has never been done yet. In this study, we determine whether there is an association between peripheral blood absolute neutrophil counts and mortality in patients with bacterial pneumonia after acute ischemic stroke. In addition, this study also determines the association between peripheral blood absolute neutrophil count and neurologic deficit status as patients with significant damage of the lung parenchyma is more likely to have more extensive brain damage.

II. Material and Methods

Thirty-four patients diagnosed with acute ischemic stroke in Dr. Kariadi Hospital, Semarang were treated for bacterial pneumonia as major complication of ischemic stroke. Patients with acute ischemic stroke were included in the study after he/she or their families signed the informed consent. Exclusion criteria in this study were experience of mixed hemorrhagic and non-hemorrhagic stroke, urinary tract infections, as well as forcibly discharge. Until the study was completed, no patients were excluded. Baseline data include patient characteristics, vital signs, hemoglobin, hematocrit, leukocyte differential count, platelet count, blood sugar level, cholesterol, triglycerides, HDL, LDL, Blood Gas Analysis (BGA), and neurological deficit (NIHSS score) were gathered from all patients. Then the patients were subsequently followed up for 7 days, and total patients who died was noted. ANC measurement and NIHSS score analysis was reassessed in patients who were still alive after 7 days of follow-up.

The data gathered was recorded, coded, tabulated and entered in the computer. Nominal/ordinal data were presented infrequency distribution, while ratio/intervals data were presented as mean and standard deviation. Shapiro-Wilk test was conducted to determine the normality of each numerical data distribution. Comparative test (Chi-square, Fisher exact, T-independent, or MannWhitney) was performed on the results of the baseline examination which includes: sample characteristics, vital signs, laboratory test results, and CT-scan results.

Cut-off values of ANC obtained from previous studies were 7.600/µL to predict mortality as well as NIHSS score examined on 7-day of after diagnosis of bacterial pneumonia was established [13]. Relative risk of ANC value on mortality was then calculated. Spearman correlation test was used to determine the relationship between the absolute neutrophil count and mortality, whereas 2×2 table was used to identify the trends neutrophil count had which contribute to increased rate of mortality in patients with bacterial pneumonia after acute ischemic stroke. It was considered significant when $p \leq 0.05$. Analysis of the data was performed using the Statistics Program for Social Science (SPSS).

III. Results

Thirty-four patients with bacterial pneumonia following ischemic stroke admitted to neurological ward, stroke unit, and ICU of Dr. Kariadi Hospital, Semarang were included in this study. The patients were grouped based on their ANC. Those with ANC < 7600 were in the first group while those with ANC ≥ 7600 in the second group. Characteristics of patients are shown in **Table 1**. Mean age of patients with ANC < 7600 and those with ANC ≥ 7600 were not significantly different. Mean age of patients with ANC < 7600 was 66.0 ± 10.8 years while patients with ANC ≥ 7600 had mean age of 59.8 ± 7.95 years. The youngest patient in this study was at the age of 42 years old while the oldest was at 81 years of age. **Table 2** showed there were no significant differences in the patient's vital signs between the two groups.

Table 1 Characteristics of sample

Variable		ANC ≥ 7600	ANC < 7600	p
Age		59.8 ± 7.95	66.0 ± 10.8	0.064‡
Sex	Male	10 (55.6%)	8 (44.4%)	0.236*
	Female	12 (75.0%)	4 (25.0%)	
Marital status	Married	19 (63.3%)	11 (36.7%)	1.000*
	Divorced/widow	3 (75.0%)	1 (25.0%)	
Education	Elementary	11 (57.9%)	8 (42.1%)	0.728*
	Junior High	6 (75.0%)	2 (25.0%)	
	High	1 (50.0%)	1 (50.0%)	
	Bachelor	2 (100.0%)	0	
	Unschooled	2 (5.88%)	1 (2.94%)	
Occupation	Civil servant	4 (100.0%)	0	0.355*
	Private employe	4 (66.7%)	2 (33.3%)	
	Seller	2 (40.0%)	3 (60.0%)	
	Labor/farmer	6 (54.5%)	5 (45.5%)	
	Unemployment	6 (75.0%)	2 (25.0%)	

‡Independen t-test; *Chi Square test, p ≤0,05 showed significant difference

Table 2 Distribution of sample based on their vital sign

Vital sign	ANC ≥7600	ANC <7600	p
Sistolic	165.0 ± 27.7	158.3 ± 24.8	0.557©
Diastolic	99.5 ± 18.9	89.1 ± 9.96	0.168©
HR	87.9 ± 8.74	88.0 ± 12.9	0.901©
RR	28.6 ± 4.51	26.3 ± 2.90	0.168©
Temperature	38.2 ± 0.66	38.1 ± 0.59	0.929*

©Mann Whitney test; *Chi Square test;
p ≤ 0.05 showed significant difference

Table 3 showed no significant difference in the results of some variables in laboratory examination between the two groups, whereas **Table 4** showed no significant difference in the infarct location of CT-scan result. **Table 5** showed no significant difference in the results of BGA, which includes PaO2, FiO2, SaO2, and ratio PaO2/FiO2.

TABLE 3 LABORATORY TESTS RESULT

Variable	ANC ≥ 7600	ANC < 7600	p
Hb	13.4 ± 1.60	12.8 ± 2.20	0.309‡
Ht	40.9 ± 5.18	38.4 ± 6.60	0.237‡
Leukocytes	12726.4 ± 3679.9	12118.3 ± 4800.8	0.423©
Thrombocytes	272590.9 ± 88927.3	300666.7 ± 108967.3	0.157©
Random Blood Sugar (RBS)	138.4 ± 44.0	167.1 ± 99.1	1.000 ©
Cholesterol	202.4 ± 54.2	181.9 ± 42.4	0.102©
Triglycerides	132.0 ± 57.8	181.5 ± 207.4	0.683©
HDL	44.4 ± 10.0	39.8 ± 11.6	0.238‡
LDL	128.0 ± 49.9	105.8 ± 25.0	0.159‡

‡Independen t-test; ©Mann-whitneytest,
p ≤ 0.05 showed significant difference

TABLE 4 DISTRIBUTION OF SAMPLE BASED ON THEIR CT SCAN, CHEST X-RAY AND HOSPITAL LENGTH OF STAY (LOS)

Variable	ANC ≥ 7600	ANC < 7600	p
Infarct location (*CT Scan*)			0.202*
• Cortical	3 (75.0%)	1 (25.0%)	
• Subcortical	14 (77.8%)	4 (22.2%)	
• Brain stem	1 (100.0%)	0	
• Mixed	3 (37.5%)	5 (62.5%)	
• Normal	1 (33.3%)	2 (66.7%)	

* Chi Square test;p ≤ 0.05 showed significant difference

TABLE 5 DISTRIBUTION OF SAMPLE BASED ON THEIR BGA (PAO2/FIO2 RATIO)

Variable	ANC < 7600	ANC ≥ 7600	p
BGA Result			
PaO_2	111.3 ± 42.4	111.4 ± 50.9	0.817©
FiO_2	0.43 ± 0.13	0.40 ± 0.12	0.557©
PaO_2/FiO_2 ratio	275.6 ± 107.5	290.7 ± 135.5	0.743‡
SaO_2	96.8 ± 2.14	96.3 ± 4,03	0.817©

©Mann Whitney test; ‡Independen t-test
p ≤ 0.05 showed significant difference

TABLE 6 CROSS TABULATION OF ANC AND MORTALITY

		Mortality	Survive	p	RR
ANC	≥ 7600.0	6 (27.3%)	16 (72.7%)	0.378	3.27 (0.44-24.10)
	< 7600.0	1 (8.30%)	11 (91.7%)		

Spearman test to determine association between ANC and mortality of patients after 7 days follow-up with ANC cut-off values 7.600/µL derived from previous research [13] produced rho value of 0.224. These results indicated a positive correlation between absolute neutrophil counts with mortality in patients with bacterial pneumonia after acute ischemic stroke. However, p value of 0.203 showed no significant correlation. Furthermore, comparative test between the two variables also produced p-value of 0.378 which was not significant with a relative risk value of 3.27 (0.44 to 24.10). The relative risk showed a weak causal relationship, while the p values and 95% confidence intervals confirmed the results of the Spearman correlation test. Pearson correlation test was performed on both variables ANC and NIHSS score considering both of them were interval ratio. Pearson correlation test results demonstrated a correlation between the variables of the ANC and the NIHSS score with rho value of 0.074; although the correlation is not significantly larger with a p-value of 0.714. Scatter plot between the ANC and NIHSS scores can be seen in **Figure 1**.

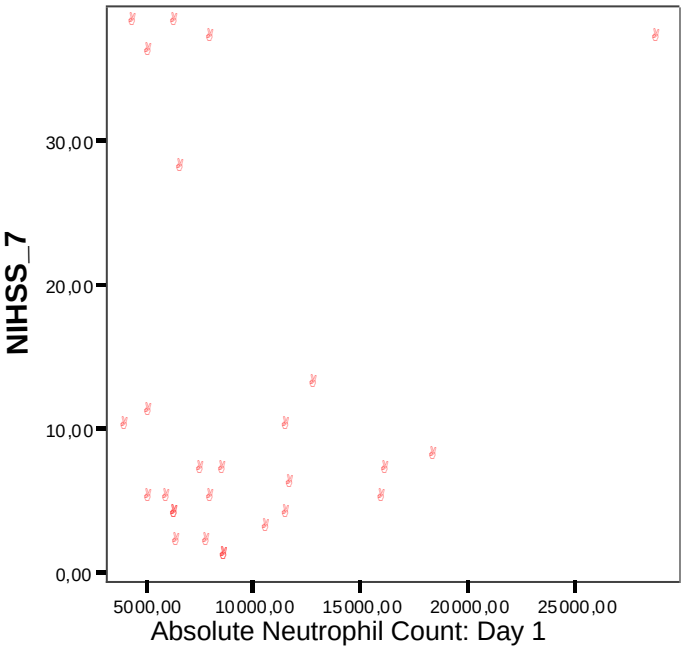

Figure 1 *Scatter* plot of ANC and NIHSS score

IV. DISCUSSION

Study was conducted on 34 patients with bacterial pneumonia following acute ischemic stroke admitted at inpatient neurological ward, stroke unit, and ICU, Dr. Kariadi Hospital, Semarang. As showed in some researches, the most common serious complication of acute ischemic stroke was bacterial pneumonia which contribute to increased mortality rate as well as worse clinical outcome [16]-[18]. Out of 34 respondents in this study, 7 (20.59%) died before 7-days of diagnosis of pneumonia, including 3 men and 4 women. Fifteen men and 12 women survived.

As mentioned previously, neutrophil count increased within minutes to days after ischemic injury in brain [19]-[21]. In this study, twelve patients (35.3%) had absolute neutrophil count (ANC) less than 7.600/µL, while 22 patients (64.7%) had ANC equal or more than 7.600/µL.

There were no significant differences in vital signs between the two groups. Vital signs include blood pressure (systolic and diastolic), pulse, respiration, and temperature. Previous studies report that hyperthermia brought significant negative effect on prognosis after acute ischemic stroke [22]-[26] and that fever on the first 7 days of stroke was an independent predictor of poor outcomes [28]-[32].

There is a relationship between infarct location and functional outcome after acute ischemic stroke [33]-[36]. This

study showed no significant difference on infarct location from CT-Scan result of the two groups. This was in contrast with Ovbiagele et al study, which suggested that location of stroke also affect post stroke complications [37]-[40]. Blood gas analysis patients with bacterial pneumonia after acute ischemic stroke should be monitor as it also contributes to patient's prognosis [41]-[45]. Preview of PaO2/FiO2 ratio on 7 days of treatment between the two groups showed no significant difference.

This study used 7.600/μL as cut-off value for absolute neutrophil count (ANC) as derived from previous study. This study tried to determine whether ANC was significantly associated with mortality in patients with bacterial pneumonia after acute ischemic stroke. Sensitivity of 90% was better but 55% specificity was low. The results of this study with these cut-off point also produced relatively low 3.27 (0.44 to 24.10) relative risk (RR) value and the p value was not significant ($p < 0.05$). Spearman correlation test showed a positive correlation with the value of R 0.224 but it was not significant with p-value 0.203. According to researchers, this is most likely due to the small number of samples who died in this study. This small amount caused the gap in total patients in both groups. Some confounding variables on mortality that were not analyzed still might be the cause of these results is not significant.

Pearson correlation test results demonstrated a correlation between variables of ANC and NIHSS scores with a value of R 0.074. The correlation was not significant with p-value of 0.714. The more absolute neutrophil count, the greater the mean NIHSS score which implied in worsening deficits neurological status of the patient. Neutrophil counts are increased in response to infection. Increased number of neutrophils may lead to an excessive inflammatory reaction and aggravates patient's medical condition. This is consistent with previous study by Gwaiz et al which showed that the absolute neutrophil count (ANC) and toxic granulation appeared to be more sensitive than the band counting predicting bacterial infection. Correspond well with other studies that most of pneumonia in stroke was caused by bacterial infection. The severity of pneumonia can be assessed using Pneumonia Severity Index [46]-[49].

This study used 7-day observations based on the Saposnik et al. study that examined factors affecting mortality in acute ischemic stroke patients was severity of stroke particularly on day 7, day 30 and one year post-ichemic stroke [50]-[52]. Saposnik et al. study also showed that several factors associated with mortality 7-days after stroke was also related to a 1 year post-stroke mortality. This indicates that observation of 7-days mortality became an indicator that was more easily done for output stroke observation [53]-[58]. This study has limitations that may affect the results, which include fewer samples which were died, despite meeting the criteria of minimal number of samples. Further research associated with this topic should be conducted with a larger sample size, in which total samples that died in the study group was just 7 patients. The addition of more diverse predictor variables is also needed in further studies to identify the variables that are significant predictors of mortality, such as extensive infarction.

V. Conclusion

Absolute neutrophil count has positive correlation with rho value of 0.224, however it is not statistically significant ($p = 0.203$). Patients with absolute neutrophil count more than equal to 7.600/μL have a risk of 3.27-fold more likely to die before7-day of treatment. However, this trend was not significant with p value of 0.378. This study also found a positive correlation between the absolute neutrophil count and NIHSS scores with rho value of 0.074. However, the correlation is not significant ($p=0.714$). The more absolute neutrophil count, the greater the mean NIHSS score that implied worsening deficits neurological status of the patient.

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