Neutrophil-to-Lymphocyte Ratio and Covid-19 Symptom-based Severity at Admission

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Abstract

Background: Increased Neutrophil-to-Lymphocyte Ratio (NLR) is an independent risk factor for mortality in Covid-19 patients and is considered as an early warning sign of Covid-19 severity. This study aimed to observe the differences in NLR at admission between patients with mild, moderate, and severe symptoms of Covid-19 treated in a referral hospital in Banda Aceh, Indonesia.

Methods: A total of 114 patients with Covid-19 admitted to a referral hospital in Banda Aceh, Indonesia, during March–September 2020 were included in this study. Demographic information and baseline laboratory data, including the NLR, were collected. Descriptive and inferential statistics were used to analyze the data.

Results: The median NLR at admission was higher among patients with moderate to severe symptoms than those with mild symptoms [6.54 (2.80–97.00, IQR 4.81–9.44) vs 2.27 (0.79–5.07, IQR 1.43-2.98), p <0.001]. Covid-19 patients who died had a higher NLR than those who survived [10.88 (4.17–47.50, IQR 7.00–15.17) vs 6.15 (2.80–97.00, IQR 4.63–8.50), p 0.02]. Patients with moderate-severe symptoms had an initial NLR of 4.63–8.50 and decreased to 2.75–5.43 at the end of the treatment had a greater chance of survival. There was an increased probability of death in patients with moderate-severe symptoms whose initial NLR was 7.00–15.17, which was then elevated to 14.33–23.25.

Conclusions: Different NLR at admission is seen among Covid-19 patients with mild and moderate-severe symptoms, leading to significantly different outcomes. The NLR can be used as a simple parameter to determine the severity of the disease and predict the outcome of Covid-19 patients.

Keywords: Covid-19, neutrophil-to-lymphocyte ratio, symptoms severity

Introduction

The novel coronavirus, the SARS-CoV-2, was first recognized in the city of Wuhan, China in December 2019. The disease caused by the virus, the Covid-19, since then become a global emerging concern due to its rapid outbreak, fast worldwide spread, and high fatality rate. By the end of December 2020, the World Health Organization (WHO) confirmed more than 80 million positive cases and more than 1.7 million death globally.[1] In Indonesia, more than 700.000 cases and more than 21,000 death have been confirmed.[2] Meanwhile, in the province of Aceh, more than 8,700 cases, 344 death, and more than 7,400 have recovered from the disease by the end of December 2020.[3] Studies related to Covid-19 have been focused on various aspects of the disease, ranging from clinical factors, patients' condition and outcome as well as the community perception, attitude, and behavior toward the disease. Description of clinical factors of the disease is important to help clinicians in treating and predicting the outcome of treatment.

Neutrophil to Lymphocyte Ratio (NLR) is

an independent risk factor of mortality among hospitalized Covid-19 patients.[4] The NLR is a reflection of the balance between the innate immune response (neutrophils) and adaptive immunity (lymphocytes). NLR is calculated by dividing the absolute number of neutrophils by the absolute number of lymphocytes or the percentage of neutrophils divided by the percentage of lymphocytes from the peripheral blood sample.[5] Thus, the NLR value can be obtained immediately by carrying out routine blood tests upon admission to the hospital. The physician can identify the risks in the early stages of Covid-19 patients; thus, the treatment can be adjusted to reduce hospital deaths.

During admission, a high level of NLR defines the severity of the diseases and predicts a poor prognosis.[6-8] Increased NLR in Covid-19 patients, along with age and white blood cells count are also associated with a higher rate of mortality,[9] and it remains as the independent predictor of critical illness of Covid-19.[10] However, there is a study that has found a non-significant contribution of NLR toward the death in Covid-19 cases.[11] Nevertheless, it is generally approved that NLR can be used as an early warning signal for the deterioration of covid-19 patient condition[12] and high NLR can be considered as a prognostic marker of diseases severity in patients with Covid-19.[13,14] Examination the NLR is, therefore, an important step in the treatment of Covid-19 patients.

Furthermore, the vast majority of earlier reports come from developed countries, where the treatment of patients is at the most sophisticated level. The report from developing countries such as Indonesia is limited. Therefore, this study aimed to observe the differences of NCL between mild, and moderate to severe symptoms of Covid-19 admitted to a Covid-19 provincial referral hospital in the province of Aceh, Indonesia.

Methods

This retrospective cross-sectional study was conducted at the Respiratory Intensive Care Unit (RICU) and Special Covid-19 nursing ward of a general - teaching hospital in Banda Aceh, Indonesia. The hospital is the main provincial referral hospital that serves approximately 5 million population in the province.

The Ministry of Health Republic of Indonesia had divided the severity of Covid-19 symptoms into five categories; which were no symptoms, mild symptoms with no complication, moderate symptoms, severe symptoms with pneumonia, and critical.[15] Mild Covid-19 was defined as patients with viral respiratory tract infection with non-specific symptoms (fever, malaise, cough with/without sputum, anorexia, muscle pain, sore throat, shortness of breath, mild pneumonia, nasal congestion, headache, diarrhea, nausea, and vomiting). Moderate Covid-19 was defined as a patient with pneumonia without severe pneumonia, no need for oxygen supplementation. Severe Covid-19 was defined as pneumonia with either respiratory rate more than 30/minutes, respiratory distress, oxygen saturation <93% in room air, PaO2/FiO2 ratio < 300.[15]

All patients with Covid-19, aged 18 above, admitted to the hospital between March to September 2020, were included in the study. Patients with an incomplete blood test, suffering from cancer, or already had blood problems prior to Covid-19 were excluded from the study.

Secondary data on the patient's clinical features were generated from the hospital medical record, including the patient's diagnosis and its severity during admission, blood test examination results such as neutrophil and lymphocyte, duration of hospitalization, and outcome of the treatment.

The characteristics of the patients were described using the frequency and percentage parameters. For numerical data, the normality test was performed first using the Shapiro Wilk test, then descriptively presented in the form of mean and standard deviation if the data were normally distributed or median and ranges (minimum-maximum) if the data were not normally distributed. To observe the difference in the neutrophil lymphocyte ratio in Covid-19 patients with mild and moderate-severe symptoms, the unpaired t-test was used, if the data were normally distributed and the Mann Whitney test if the data were not normally distributed. The result of the statistical test was significant if $p<0.05$. The analysis was performed using the SPSS statistical program.

Results

The characteristics of patients with moderate to severe symptoms of Covid-19 were older, spent the longer duration of hospitalization, a higher proportion of comorbid including hypertension, diabetes, health problem and secondary infection, a higher mean of neutrophil percentage but a lower mean of lymphocyte percentage compared to the

Table 1 Demographic and Clinical Characteristics of the Patients during Hospital Admission

Variable	COVID–19 Symptoms		p-value
	Mild (n=60)	Moderate–Severe (n=54)	
Age (year), mean±SD	41±15	53±11	<0.001[a*]
Gender, n (%)			0.728[c]
Male	37 (61.7)	35 (64.8)	
Female	23 (38,3)	19 (35,2)	
Day of hospitalization–, median (min–max)	4 (2–8)	5 (2–10)	0.001[b*]
Comorbid, n (%)			
Hypertension	6 (10)	14 (25.9)	0.026[c*]
Diabetes mellitus	5 (8.3)	24 (44.4)	<0.001[c*]
Hearth problem	0 (0.0)	9 (16.7)	0.001[d*]
Chronic obstructive pulmonary disease	1 (1.7)	1 (1.9)	1.000[d]
Secondary Infection	0 (0.0)	5 (9.3)	0.022[d*]
Clinical, median (min–max)			
Breathing (x/min)	20 (12–60)	26 (20–32)	<0.001[b*]
Body Temperature (ºC)	36.7 (35.8–38.9)	37 (35.8–39.2)	0.002[b*]
Periphery Oxygen saturation (%)	98 (94–99)	90 (70–98)	<0.001[b*]
Blood test			
Hemoglobin (g/dl), mean ± SD	14±1.7	13.6±1.8	0.265[a]
Hematocrit (%), mean ± SD	41.4±4.9	40.3±4.9	0.238[a]
Leukocyte total (x1000/mm3), median (min–max)	7.1 (3.1–15.9)	9.2 (4.6–25)	0.001[b*]
Thrombocyte (x1000/mm3), median (min–max)	285 (115–636)	231 (85–577)	0.260[b]
Neutrophil (%), mean ± SD	60±10	82±7	<0.001[a*]
Lymphocyte (%), mean ± SD	29±9	13±5	<0.001[a*]
Monocyte (%), median (min–max)	8 (3–14)	5 (1–16)	<0.001[b*]
Duration of hospitalization (day), median (min–max)	8 (4–19)	9 (2–25)	0.015[b*]
Treatment outcome, n (%)			0.001[d*]
Death	0 (0)	9 (16.7)	
Recover	60 (100)	45 (83.3)	

Note: [a]t–test, [b]Mann Whitney U test, [c]Chi Square, [d]Fisher Exact, *significant at <0.05

patients with mild symptoms of Covid-19, as shown in Table 1.

A higher mortality rate was also found among patients with moderate to severe symptoms in this study (16.6%). The patients who died had significantly, (p=0.02) higher NLR than surviving patients [10.88 (4.17–47.50, IQR 7.00–15.17)] vs [6.15 (2.80–97.00, IQR 4.63–8.50)]. The median of NLR during admission was 2.27 (IQR 1.43–2.98) among patients with mild symptoms, while among moderate to severe symptoms patients was

6.54 (IQR 4.81–9.44). Before the hospital discharge, the median NLR was 1.92 (IQR 1.39–2.52) among those with mild symptoms and 4.14 (IQR 2.91–8.50) among patients with moderate to severe symptoms, as shown in Table 2.

Discussion

A higher level of NLR among patients with moderate to severe symptoms compared to those with mild symptoms has been found

Table 2 Difference of NLR during Admission and before the Hospital Discharge among COVID–19 Patients

Variable	COVID–19 symptoms		p–value
	Mild n=60	Moderate-severe n=54	
NLR during admission			<0.001*
Median (min–max)	2.27 (0.79–5.07)	6.54 (2.80–97.00)	
IQR	1.43–2.98	4.81–9.44	
NLR before discharge			<0.001*
Median (min–max)	1.92 (0.51–4.00)	4.14 (0.93–95.00)	
IQR	1.39–2.52	2.91–8.50	

Note: p–value using Mann Whitney U test, *significant at < 0.05, IQR= Interquartile Range, NLR= Neutrophil to Lymphocyte Ratio

in the present study, supporting the earlier findings.[6-8] High level of NLR during admission should become an alarming sign of the patients' prognosis, thus the physicians require to treat them differently than lower NLR patients. The patients with a higher level of NLR that usually come with moderate to severe symptoms, such as fever, cough, respiratory tract infection–pneumonia, oxygen saturation lower than 93%, usually require immediate treatment at the respiratory intensive care unit. Immediate treatment in this unit could improve the outcome of the treatment.[16,17]

The changes of NLR value during admission in moderate to severe symptom Covid-19 compared to the NLR value on hospital discharge could predict the outcome. The chance of survival is greater in moderate to severe symptom Covid-19, whose NLR value is decreasing. In contrast, death risk is greater in those who have NLR elevation. The changing of NLR during the course of the disease could be reflected as inflammation process alteration in line with clinical improvement or deterioration. In deteriorated patients, there is an increase in inflammation, reflected by neutrophil elevation and declined of lymphocyte which resulted in NLR elevation. Until now, there is no study addressing the changing of NLR along the course of Covid-19 in Indonesia.

The higher mortality rate among patients with moderate to severe symptoms in this study (16.7%) is consistent with previous reports, which also suggest the importance of prompt treatment of those with moderate to severe symptoms.[18,19] Higher NLR among patients who died in this study confirms that NLR is a single independent risk factor of mortality in Covid-19 patients.[4] Scoring the NLR is therefore considered as a powerful predictive and prognostic nomogram which could guide the clinicians to shorten the course of the disease, fasten the recovery, alleviate the shortage of medical supplies and lower mortality rate in Covid-19 patients.[20]

Meanwhile, none of those mild symptoms died but have recovered following the treatment. The 16.6% mortality rate in this study is significantly higher than reported in an epidemiological study, where only 6.3% of death is found among Covid-19 patients with moderate and severe cases, administered in Brazilian hospitals.[18] The reason for a higher mortality rate in this study population is not well understood, since other possible determinants, such as age and other physical problems, have not been examined in this study.

Our study has several limitations. This study did not evaluate the correlation of comorbidity in NLR such as diabetes and secondary infection, which could also increase neutrophil. Second, this study did not evaluate the changes of NLR and severity of the illness on a day-to-day basis. Moreover, we have retrieved secondary data from the medical records where some laboratory data were missing. Further study on the correlation among other demographic factors toward mortality of Covid-19, which are not specifically investigated in this study, could be conducted.

In conclusion, this study has highlighted several important clinical findings. The NLR could be used as one of the standpoints for the treatment of patients with suspected Covid-19 during admission. A higher level of NLR tends to get severe and poor prognosis, thus special attention and treatment are required. Furthermore, the NLR can be used as a simple parameter to help determine the severity of the disease and predict the outcome of Covid-19.

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