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Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Absolute Lymphocyte Count as Mortality Predictor of Patients with Coronavirus Disease-2019

Abstract

Coronavirus Disease 2019 (COVID-19) has a various spectrum of symptoms, asymptomatic to severe. At previous research, hematological examination could predict the severity of the infection. This study aims to evaluate Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Absolute Lymphocyte Count (ALC) as a predictor of COVID-19 mortality.

The study was cross sectional research with retrospective design by collecting data from medical records of the COVID-19 patients at a General Hospital Anwar Medika of East Java, for the period June 2020 to January 2021. A comparative test was performed using the Mann-Whitney test. The predictive ability was assessed using the ROC curve.

A total of 70 subjects were involved in this study with 16 (22.9%) mortal patients. And the average NLR and PLR were 4.11 and 174.39. The Mann-Whitney test showed significant results ($p < 0.05$) on leukocytes, NLR, PLR, and ALC of the patients. The ROC curve showed that under the curve of leukocytes, NLR, PLR, and ALC were 0.749, 0.731, 0.719, and 0.306, respectively. With higher sensitivity and specificity by leukocytes 75% and 70.4%. Leukocytes, NLR, and PLR showed good ability to predict patient mortality from COVID-19.

Keyword: *Coronavirus, mortality, predictive tools*

Introduction:

Coronavirus is a family of viruses found in humans and animals, the emergence of a new virus outbreak belonging to the coronavirus group was first discovered in the city of Wuhan, China. Within a few weeks, this virus spread to various parts of the continent. On February 20, 2020, the World Health Organization (WHO) announced that the outbreak caused by this new type of Coronavirus, namely Coronavirus Disease 2019 (COVID-19), became global. It is recorded that at this time, around 184 million people have been affected, and almost 4 million death by the Coronavirus, which has infected 222 countries around the world¹.

In Indonesia alone, there are 2.3 million confirmed cases with nearly 60,000 deaths². In SARS-CoV-2 infection, there are changes in several laboratory indicators which are also found in several other viral infections, because the hematopoietic

system is a system that feels the impact of a viral infection^{3,4}. Several previous studies have shown that there is lymphocytopenia, neutrophilia, eosinopenia, thrombocytopenia, or thrombocytosis, as well as the presence of reactive lymphocytes which indicate an acute infection⁴. Apart from the changes in the results of the hematological examination, the results can also be used to predict the severity of COVID-19. A meta-analysis stated that leukocytosis, lymphopenia, and thrombocytopenia are predictors of the severity of COVID-19 and increase the incidence of mortality with these results⁵.

Several other studies have also shown that NLR, PLR, and ALC can predict mortality from COVID-19 infection^{6,7}. In this study, we evaluate the COVID-19 mortality hematologic predictors at Anwar Medika General Hospital as one of the COVID-19 referral hospitals in Indonesia

Materials and Methods:

The study used an observational analytic cross sectional research with retrospective design. The profile description is carried out retrospectively by collecting data from medical records of the COVID-19 patients' data consisting of age, gender, leukocytes and the differential count, platelets, length of stay, and mortality status. The hematological result then calculated to produce NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio), and ALC (absolute lymphocyte count).

These were the following equation:

$$NLR = \frac{A \times 10^9 / L \times 10^9}{\mu L} \quad \mu L$$

$$PLR = \frac{\text{Thrombocyte count (Cells}/\mu L)}{\text{Absolute lymphocyte count (Cells}/\mu L)}$$

The sample used in this study were patients infected with COVID-19 at the Anwar Medika General Hospital during the period of June 2020 to January 2021. With the inclusion criteria of patients who have been confirmed positive for COVID-19 through PCR examination results, while patients with a history of blood transfusions were excluded from this study.

Furthermore, comparative tests were conducted between the hematological profile to the length of stay (LoS) and patient mortality. Comparative tests were conducted using a two-sample independent t2 test on data with a normal distribution and using the Mann-Whitney test on data with an abnormal

distribution. Variables that have significant values were then tested for predictive ability using the ROC curve then interpreted as sensitivity and specificity. The highest sensitivity and specificity are obtained by the curve reading that produced by IBM® SPSS®

Results:

Research subject's information

A total of 70 subjects were involved in this study. From the subjects, 10 subjects (14.3%) were male and the rest were female (85.7%). The average age of the research subjects was 51.03 years with the youngest being 30 years old and the oldest 82 years old

Table 1. Characteristic of the subject

Variable	Mortality status	
	Survive	Mortal
Gender		
Male	7 (70%)	3 (30%)
Female	47 (78.3%)	13 (21.7%)

From the results of the hematological examination, the average leukocytes, platelets, neutrophils, and lymphocytes were 9,730/ μ L, 265,671/ μ L, 5,960/ μ L, and 1,830/ μ L. And from the calculation, the average NLR and PLR were 4.11 and 174.39. With an average length of stay (LoS) of 10.91 days

Table 2. Comparison variable between mortality status

Variable	Mean \pm SD			p
	Total subject	Survived subject	Dead subject	
Age (Years old)	51.03 \pm 11.77	50.58 \pm 12.814	53.19 \pm 7.332	Dup. NS
Leucocyte (μ L)	9,730 \pm 4,720	8,672 \pm 3,687	13,200 \pm 6,219	0.003
Thrombocyte (μ L)	265,671 \pm 101,263	259,113 \pm 106,998	286,812.5 \pm 82,743.1	NS
Neutrophil (μ L)	5,960 \pm 3,310	5,183.8 \pm 2,287.4	8,505.3 \pm 4,820.2	NS
NLR	4.11 \pm 3.40	3.23 \pm 2.10	11 \pm 5.02	0.005
PLR	174.40 \pm 97.80	160.76 \pm 94.797	223.55 \pm 96.64	0.008
ALC (μ L)	1,830 \pm 981.5	1,895.4 \pm 967.3	1,572.4 \pm 1,035.8	0.019
Length of Stay (days)	10.91 \pm 4.52	11.91 \pm 4.42	75 \pm 3.45	0.001

NS, Not significant

From the mortality data, 16 patients (22.9%) died and the rest survived. The average age of the subjects who died was 53.19 years, higher than the group who survived 50.58 years. From the calculation of leukocytes, platelets, neutrophils, NLR, and PLR, it was found that the average death group was higher than the survival group. Meanwhile, ALC and LoS were lower in the mortal group than in the surviving group. The comparative test showed significant results ($p < 0.05$) on leukocytes, NLR, PLR, ALC, and length of stay (LoS) of the patients.

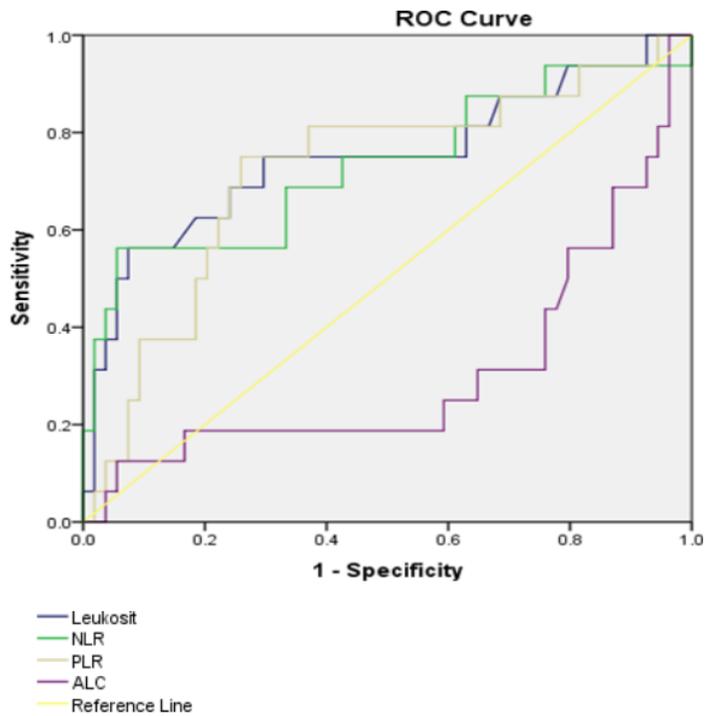


Figure 1. ROC Curve of the predicting variable

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The results of the receiver operating characteristic (ROC) curve the largest area under the curve (AUC) was produced by leukocytes, 0.749, followed by NLR and PLR. Meanwhile, ALC has the lowest AUC of 0.306. From the results of the highest sensitivity obtained PLR of 81.3% and the highest specificity is 70.4% leukocytes.

Table 3. The highest sensitivity and specificity of the variable

Predictive variable	AUC	Sensitivity	Specificity
Leucocyte	0.749	75%	70.4%
NLR	0.731	75%	57.4%
PLR	0.719	81.3%	63%
ALC	0.306	56.3%	20.4%
NLR	0.731	75%	57.4%
PLR	0.719	81.3%	63%
ALC	0.306	56.3%	20.4%

Discussion

The number of deaths due to COVID-19 is increasing every day in Indonesia, with the number of deaths reaching a thousand on 07/08/2021². In addition, there are also more than 300,000 active cases of confirmed patients infected with COVID-19, which further reduces the hospital's ability to handle patients². However, clinical manifestations of the confirmed patients vary from asymptomatic to severe symptoms^{8,9}. Because of this, it is necessary to stratify individuals with confirmed COVID-19 to optimize the capacity of the available hospitals.

From our research, it was found that from 70 subjects consisted of 16 subjects (22.9%) who died during the observation and the rest were able to recover. The mortality rate of 22.9% is higher if you look at the death rate throughout Indonesia, which is 2.6%². This finding could be related to community stigma regarding COVID-19 which causes patients to be late in seeking help to health centers which is associated with increased patient mortality^{10,11}.

From the findings in our study, it was found that the average age of the covid patients we treated was 51.03 years, which is the age group at risk of severe infection in COVID-19¹²⁻¹⁴. This result is also supported by the finding of an older age in mortality cases compared to the survivors. However, in our current study, there were no significant results between age and mortality status which was not in line with previous studies which stated that age was associated with patient mortality¹⁴.

The comparison test result from mortality status and hematological results were found that there was a relationship between mortality status with leukocytes, NLR, PLR, and ALC. There was also a significant relationship between mortality status and length of stay (LoS) of the patients. In the previous study, evaluation of the hematological component compared to the severity of COVID-19 infection showed that there was a relationship between either NLR, PLR, or ALC and infection severity with various degrees of association¹⁵⁻¹⁷. Our findings showed that leukocytes, NLR, and PLR were higher in subjects with mortality compared to surviving subjects. While the ALC showed the opposite results which decreased in subjects who experienced mortality. This finding is in line with research¹⁸. So that leukocytes, NLR, PLR, and ALC could be used as predictors of severity and mortality from COVID-19 patients.

From the ROC curve, it was found that leukocytes, NLR, and PLR had AUC more than 0.50, but not with ALC. From the results of the best sensitivity and specificity, leukocytes were obtained with a sensitivity of 75% and a specificity of 70.4%, followed by PLR with a sensitivity of 81.3% and a specificity of 63%. Although ALC has a relationship with the patient's mortality status, the predictive ability of ALC on mortality status is quite low, seeing the AUC of only 0.306. In the

previous predictive value testing in the research conducted by Yan *et al.* the sensitivity from NLR and PLR were 88% and 77%, respectively⁶. These results indicate that this modality can be used as a basis for predicting mortality in COVID-19 patients.

The association of leukocytes and NLR in infection cases in previous studies has been associated with the occurrence of cytokine storms that often occur in severe COVID-19 patients¹⁹. Although in this study no further investigation was carried out regarding the cause of death suffered by the patient, the increase in the number of leukocytes, which were dominated by polymorphonuclear cells, indicated that this finding was a predictor of increased immune activity in the patient's body which could be a sign of a cytokine storm. In line with the investigation Xiong *et al.* stated that the increase in neutrophils was a result of the release of CXCL-2 and CXCL-8 which increased neutrophil recruitment and indicated high cytokine activity in the patient's body²⁰.

From our findings, it was found that there was a higher PLR in the mortal group compared to the survive group. This finding is in line with previous research²¹. However, the increase in PLR was not in line with increase in platelets, there was no significant difference between the survivors and the mortals group from the platelet count. The increase in PLR is due to a decrease in the denominator component which is ALC. Several hypotheses that the decrease in ALC in COVID-19 patients is due to the P53 signaling process and FAS signaling which causes lymphocytes to undergo apoptosis^{20,22}.

The findings in this study can be used to detect the possible severity and mortality of COVID-19 patients. So that it can be used as consideration for determining the room and therapy to be given to the patient. However, this study has limitations mainly because the focus of this study is to evaluate the predictive ability of NLR, PLR, and ALC on COVID-19 mortality in one of the COVID-19 referral sites in Indonesia. Therefore, the subjects involved in this study are limited and cannot represent subjects in Indonesia in general. However, this study can be the basis that NLR, PLR, and leukocytes can be used as predictors of COVID-19 mortality that are easy and inexpensive.

Conclusion:

Hematological components (Leukocytes, NLR, PLR, and ALC) have a relationship with mortality status in COVID-19 patients. However, only leukocytes, NLR, and PLR showed good ability to predict patient mortality so it could be used as a triage consideration for COVID-19 patients.

the conclusions with the goals of the

study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

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