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COMPARISON OF INFLAMMATION PARAMETERS IN THE ELDERLY AND ADULTS TO THE OUTCOMES OF CONFIRMED COVID-19 PATIENTS

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Abstract:

The elderly is susceptible to infection due to immunosenescence causing high cases of infection with significant deaths due to Coronavirus Disease 2019 (COVID-19) pandemic. Many studies have examined inflammatory parameters as predictors of the outcome of COVID-19 cases, but there has been no comparison of the values of these parameters between the elderly and adult groups. This study aims to explain the relationship between inflammatory parameter values in the elderly group compared to the adult group with the outcome of confirmed COVID-19 patients treated at Ulin Hospital Banjarmasin. An analytical observational cross-sectional design study with the samples was patients with examined Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), Erythrocyte Sedimentation Rate (ESR), and C-reactive protein (CRP) when admitted to the COVID-19 isolation room at Ulin Banjarmasin Hospital and was divided into elderly and adult groups. A bivariate correlation test was conducted to assess the relationship between each parameter and continued by finding the cut-off value using the Receiver Operating Characteristic (ROC) curve. Odds Ratio (OR) is sought to find out how much the outcome risk prediction is based on the cut-off value. The relative coefficients of NLR, PLR, CRP, and ESR in the elderly group of 1147 subjects were 0.304; 0.119; 0.378; and 0.071. While the cut-off value of NLR, PLR, CRP, and ESR for the elderly group is 6.77; 257.5; 95.65, and 53.4. Outcomes prediction of the confirmed COVID-19 patients in the elderly group from the most significant are CRP, NLR, and PLR. Meanwhile, ESRs are statistically insignificant. The results showed that there are differences in inflammatory parameter values between the elderly and adult groups to predict the outcome of COVID-19 cases.

Keywords: COVID-19 in elderly; CRP; ESR; NLR; PLR

Introduction

The population of people aged 60 years and over which is defined in the Regulation of the Ministry of Health of the Republic of Indonesia (PERMENKES RI) number 79 of 2014 as the elderly group (elderly),[1] has several consequences in various aspects of life, including health, in the form of a decrease in intrinsic capacity and functional abilities of the body with age, including in terms of body defenses known as immunosenescence, namely the decline in normal aging-related immune system functions that affect almost all immune cells from innate and adaptive components, making them susceptible to infection.[2,3,4]

One of the infections that often occur in the elderly is pneumonia with a poor prognosis due to complications and requires a longer treatment. Pneumonia which most often occurs in the elderly is caused by bacteria and viruses. Since the 2019 Coronavirus Disease (COVID-19) pandemic began, this population is most at risk of developing severe disease.[4,5] For the elderly death cases themselves have not been reported globally, but regional data reports that the percentage of elderly deaths in the United States is 81% of all deaths due to COVID-19 until September 2020.[6] It is reported that the percentage of elderly deaths due to COVID-19 in Indonesia, as of February 2022 is 47%, while in South Kalimantan 37.9%.[7] Previous research at the Ulin Regional General Hospital (RSUD) itself recorded cases of elderly deaths (aged 65 years). years) due to COVID-19 between March-August 2020 with a sample population of 108 patients obtained 14.8%.[8]

The high number of cases with significant deaths in COVID-19 is due to a lack of immunity to the virus and the ability of the virus to fight the innate immune response that causes severe inflammation. The pro-inflammatory process is characterized by changes in inflammatory parameters such as peripheral blood components, albumin, C-reactive protein (CRP), ferritin, D-dimer, cytokines, and other inflammatory chemokines. Immunosenescence and comorbid conditions in the elderly cause a greater pro-inflammatory effect due to the accumulation of cytokines and chemokines produced by dysfunctional (inflammatory) cells. So it is estimated that the value of inflammation parameters will also be higher in the elderly group than in the adult group.[9-11]

Several studies have demonstrated the role of inflammatory parameters as prognostic indicators of COVID-19. Chan and Rout's study showed that high values of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) had poor prognosis in patients.[12] Pakos et al reported that patients who died had high leukocytes, neutrophils, and NLR while low platelets compared to patients who survived.[13] Mahat et al also reported that CRP, erythrocyte sedimentation rate (ESR), and NLR were significantly increased in severe cases.[14] A study in Saudi Arabia reported a significant difference between the values of neutrophils, lymphocytes, and ESR in the elderly and young adults.[15] However, there has been no reported comparison of the values of these parameters between the elderly population and adults in Indonesia and the best parameters for predicting the outcome of COVID-19 in the elderly.

In this study, significant inflammatory parameters as predictors of outcome for elderly patients will be studied along with a comparison of the values of these parameters between the elderly and adult groups treated at Ulin Hospital Banjarmasin as the main COVID-19 referral in South Kalimantan. It is hoped that the results of this study provide a new perspective on stratifying the risk of elderly COVID-19 patients to accelerate the provision of effective therapy to reduce the mortality rate of elderly patients due to COVID-19 in the future.

Research Method

This study is an observational study with cross-sectional analysis, with total sampling taken from the population of patients with confirmed PCR COVID-19 who were treated in

the COVID-19 isolation room at Ulin Hospital Banjarmasin from March 2020 to December 2021 who met the inclusion criteria in the form of (1) patients who were examined for inflammatory parameters (NLR, PLR, ESR, and CRP) at the time of their initial admission to the COVID-19 isolation room at the Banjarmasin Hospital, and (2) Patients aged 18 years, who were divided into two groups, namely the elderly group (≥60 years) and the adult group (18-59 years) based on the date of birth listed on the Identity Card (KTP) or Family Card (KK). While the exclusion criteria were patients with incomplete medical record data, patients with a diagnosis of malignancy, and patients who were pregnant or had just given birth during treatment.

Data from medical records that have been collected is then analyzed using a statistical program by descriptive analysis to assess the normality and homogeneity of the data, ordinal bivariate categorical correlation analysis using Spearman rho to determine the correlation coefficient of each parameter based on the age group in the survivor or non-survive group, Receiver Operating Characteristics (ROC) curve analysis was used to obtain the optimal cut-off, sensitivity, and specificity values from the parameter variable values, and Odds Ratio (OR) analysis based on the cut-off value of the ROC curve to determine the association to patient outcomes.

The research has passed the ethical review from the Ethics Committee of the Research and Development Agency of ULIN Hospital Banjarmasin (No. 037/PPDS-Paru/Diklit-Med/RSUDU/IV/2022) and the Faculty of Medicine, University of Lambung Mangkurat (No. 81/KEPK-FK ULM/ EC/III/2022).

Results

Characteristics of research subjects

Table 1 shows the characteristics of the study sample and shows that age, gender, degree, and comorbidities have a significant relationship with the outcome of confirmed COVID-19 patients treated at Ulin Hospital Banjarmasin. The non-survive adult group had a median age that was older than the surviving adult group, but the median of the elderly group was the same, only interquartile different. The study sample was also dominated by the male sex, had a critical degree, and had a comorbid disease.

Table 1 Characteristics of the study sample with survivors and non-survive confirmed COVID-19 patients

Variable	Total n=1147	*Survive* n=902 (79%)		*Non-survive* n=245 (21%)		*p-value*
		Elderly n=356 (21%)	Adult n=662 (58%)	Elderly n=116 (10%)	Adult n=129 (11%)	
Age - median (IQR)	53 (18)	65 (8)	48 (16)	65 (9)	50 (12)	<0,001*
Sex						0,002*
Man (%)	627 (55)	134 (15)	338 (37)	79 (32)	76 (31)	
Women (%)	520 (45)	106 (12	324 (36)	37 (15)	53 (22)	
Level						<0,001*
Mild (%)	123 (11)	8 (1)	112 (13)	2 (1)	1 (0,4)	
Moderate (%)	285 (25)	75 (8)	200 (22)	3 (1)	7 (3)	
Severe (%)	187 (16)	55 (6)	113 (13)	7 (3)	12 (5)	
Critical (%)	552 (48)	102 (11)	237 (26)	104 (42)	109 (45)	
Comorbid						<0,001*
0 (%)	237 (21)	36 (4)	176 (19)	13 (5)	12 (5)	
1 (%)	383 (33)	74 (8)	234 (26)	30 (12)	45 (18)	
2 (%)	287 (25)	66 (7)	151 (17)	35 (14)	35 (14)	
3 (%)	164 (14)	41 (4)	73 (8)	24 (10)	26 (11)	
4 (%)	62 (5)	17 (2)	23 (3)	11 (5)	11 (5)	
≥5 (%)	14 (1)	6 (1)	5 (1)	3 (1)	0 (0)	

Correlation of inflammatory parameters to patient outcome

Table 2 shows the results of the correlation regression test for the parameters of NLR, PLR, CRP, and LED with the outcome of confirmed COVID-19 patients being treated at Ulin Hospital Banjarmasin. The four parameters from each age group each had a significant relationship with patient outcomes with a higher median value in the non-survive group compared to the survival group except for PLR and ESR in the elderly group. This shows that the NLR and CRP parameters are the most significant in predicting the outcome of confirmed patients in the elderly group. Based on the correlation coefficient, in order from the most influential to the least influential are CRP, NLR, PLR, and LED.

ROC curve of inflammation parameters NLR, PLR, CRP, and ESR on patient outcome

The analysis of inflammation parameters as outcome predictors was continued by finding the cut-off value using the ROC curve so that the efficacy could be known. The cut-off values were determined as shown in table 3, with the results found to be statistically significant in all parameters except ESR and PLR in the elderly group. This is in accordance with the correlation test that has been done previously. AUC values above 0.7 (considered good) were found in NLR and CRP in the adult group and CRP in the elderly group. The ROC curves for each group and the overall age are shown in Figure 1.

The odds ratio of inflammation parameters NLR, PLR, CRP, and ESR to patient outcome

The Odds Ratio (OR) value for each age group and as a whole is then searched by logistic regression test using the cut-off value that has been obtained. The test results are shown in Table 4 which shows the OR results of the most dominant overall groups, namely the elderly and adults, namely CRP, NLR, PLR, and LED. The CRP parameter became the most dominant parameter in predicting the outcome of confirmed COVID-19 patients, and even had a higher OR in the elderly group than the whole and adult group, with an OR value of 5.291. This value indicates a CRP that is more than the cut-off value, 5,291 times the chance of being in a group of confirmed COVID-19 patients who do not survive compared to a CRP below the cut-off.

Table 2 Comparison of inflammatory parameters (NLR, PLR, CRP, and ESR) between the outcomes of patients with confirmed COVID-19 survival and non-survive

Variable	Normal range	Survive		Non-survive		r	p-value
		Median	IQR	Median	IQR		
NLR		4,36	4,38	7,96	7,46	0,314	<0,001*
Elderly		5,47	5,16	8,85	8,11	0,304	<0,001*
Adult		4,02	4,31	7,09	6,51	0,271	<0,001*
PLR		206	155	258	190,5	0,145	<0,001*
Elderly		233,5	171	285	234,25	0,119	0,025
Adult		195	142,25	252	195,5	0,126	<0,001*
CRP	< 6.00 mg/L	32,95	68,2	99	141,75	0,346	<0,001*
Elderly		50,15	83,35	126,2	134,6	0,378	<0,001*
Adult		28,55	58,03	89	127,45	0,288	<0,001*
LED	0-20 mm/jam	52	51	67	47	0,122	<0,001*
Elderly		60	51	69	47,5	0,071	0,183
Adult		49	51	65	48,3	0,123	0,001*

Table 3 Outcome predictive efficacy of confirmed COVID-19 inflammatory parameters NLR, PLR, CRP and LED

Variable	AUC	*p-value*	95% CI	*Cut of Value*	Sensitivity	Specificity
NLR	0,714**	<0,001*	0,680 – 0,749	5,97	66,5%	66,3%
Elderly	0,687	<0,001*	0,629 – 0,745	6.77	66,4	65,8
Adult	0,712**	<0,001*	0.667 – 0,756	5.36	65,1	65,1
PLR	0,602	<0,001*	0,561 – 0,643	226.50	61,2	56,8
Elderly	0,573	0,025	0,509 – 0,638	257.50	55,2	57,5
Adult	0,599	<0,001*	0,543 – 0,654	227.50	58,1	60,1
CRP	0,744**	<0,001*	0,709 – 0,779	63	67,8	69,3
Elderly	0,733**	<0,001*	0,677 – 0,789	95.65	68,1	71,3
Adult	0,725**	<0,001*	0,677 – 0,773	47.9	69	65
LED	0,568	<0,001*	0,546 – 0,626	58.50	58,4	56,9
Elderly	0,544	0,183	0,480 – 0,607	64.50	53,4	54,2
Adult	0,596	0,001*	0,542 – 0,649	55.50	58,9	57,3

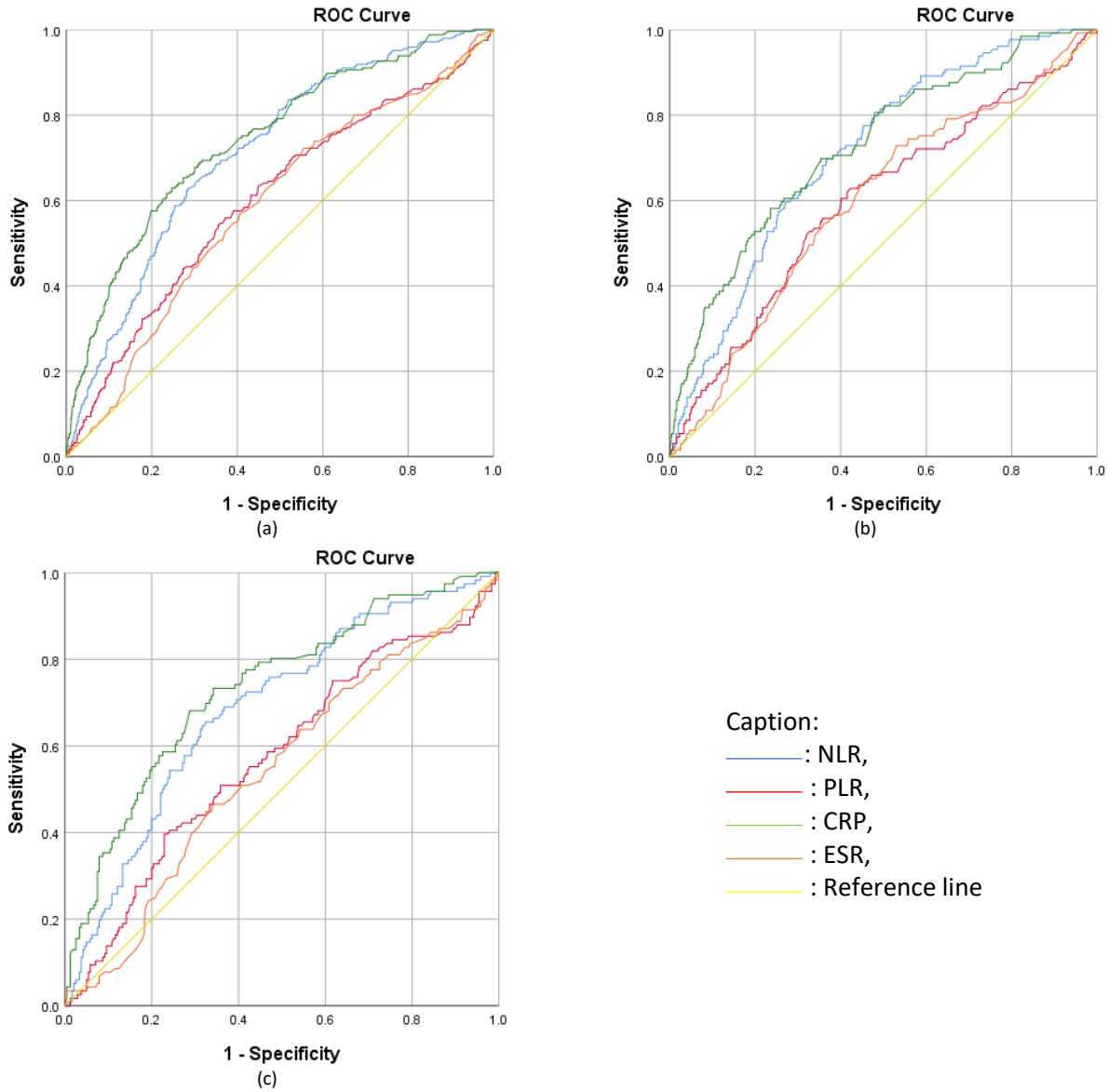

Figure 1 ROC curves of NLR, PLR, CRP and LED parameters to the outcome of confirmed COVID-19 patients; (a) the whole group; (b) the adult group; and (c) the elderly group

Table 4. Comparison of the Odds Ratio of each inflammatory parameter to the outcome of patients with confirmed COVID-19 based on the overall group and age

Variable	OR	95% CI	p-value
NLR	3,910	2,899-5,274	<0,001*
Elderly	3,804	2,381-6,078	<0,001*
Adult	3,506	2,369-5,209	<0,001*
PLR	2,073	1,553-2,767	<0,001*
Elderly	1,665	1,065-2,602	0,025
Adult	2,094	1,428-3,070	<0,001*
CRP	4,741	3,502-6,419	<0,001*
Elderly	5,291	3,274-8,553	<0,001*
Adult	4,124	2,748-6,188	<0,001*
LED	1,849	1,389-2,461	<0,001*
Elderly	1,357	0,870-2,116	0,178
Adult	1,920	1,309-2,817	0,001*

Discussion

COVID-19, which has become a pandemic in the world today, has caused a high death rate worldwide. Death is one of the outcomes that can occur in COVID-19 patients in addition to recovering from the infection. Death in this disease itself is influenced by various factors, such as age, gender, comorbidities, severity, complications, therapy, and vaccination. From previous studies, it is known that the probability of death will be higher in cases with characteristics of elderly, male, having one or more comorbidities, critically ill, having one or more complications, limited therapy, and not being vaccinated.[8,16,17]

Prediction of COVID-19 outcomes can be determined using the above epidemiological data accompanied by the help of laboratory parameters that have been widely studied as predictors of COVID-19 outcomes in various education centers or health services. Laboratory parameters used as predictors in this study were acute inflammatory parameters such as NLR, PLR, CRP, and ESR.

Characteristics of the study sample of confirmed COVID-19 patients

The outcome profile of patients confirmed to be admitted was dominated by survivors (79% versus 21%), adults (69% versus 31%), men (55% versus 45%), had a critical illness rate (48%) and had one type of comorbidity (33%). The results of this study are similar to previous studies conducted at RSUD Ulin regarding the clinical and laboratory features of confirmed COVID-19 patients treated at RSUD Ulin by Haryati., et al, in the form of significant differences between age and gender in patient outcomes.[18] However, in this study, it was found that comorbidities also had a significant difference between the outcomes of patients who survived versus those who did not. This could be due to the heterogeneity of the wider sample due to the larger number of samples compared to previous studies.

When compared with a meta-analysis by Shi., et al on potential predictors of mortality in COVID-19 patients and Booth et al on risk factors for severe illness and death in the population with COVID-19, an association between old age and an increased risk of death from COVID-19 was reported.[19.20] This is consistent with this study in the form of an older median age in the non survive adult group compared to the survivor group because the immunological mechanism in the elderly is different from that in adults. Immunosenescence reduces the immunological response to SARS-CoV-2 infection. In addition, T cell immunity caused by the previous infection does not appear in the circulation system of the elderly so the elderly do not have immunity and are at higher risk of developing severe COVID-19 disease that can cause death.[21,22]

The two meta-analyses reported by Shi., et al. and Booth., et al. also showed that men had a higher likelihood of experiencing an adverse outcome. This is thought to be due to a combination of behavioral health effects,

sex hormone-mediated immune responses, and different ACE2 expressions between the sexes. Health behavior is related to gender differences in the form of smoking prevalence which is more dominant in men. Smokers have upregulation of ACE2 expression in the airways thereby explaining the increased risk of death in smokers from COVID-19 infection. Women are thought to be more capable of fighting viruses because of the protection of the X chromosome and sex hormones (estrogens) which play an important role in innate and adaptive immunity.[18-20]

COVID-19 infection is also more likely to have an adverse outcome in patients with pre-existing comorbidities than those without co-morbidities. Shi., et al reported that the risk of death in COVID-19 patients with any comorbidities was 2.85 times higher than in the group without comorbidities.[19] Patients with chronic kidney disease, cerebrovascular disease, respiratory disease, cardiovascular disease, diabetes mellitus, or hypertension have an approximately 8-fold, 8-fold, 4-fold, 3-fold, 2-fold, and 2-fold risk, respectively, were higher for the occurrence of death than those without comorbidities. Certain comorbidities are associated with strong ACE2 receptor expression and higher proprotein convertase release thereby increasing viral entry into host cells.[14]

The relationship of inflammatory parameters NLR, PLR, CRP, and ESR to the outcome of confirmed patients treated at Ulin Hospital Banjarmasin

Infection with the SARS-CoV-2 virus causes inflammation in the human body that produces a variety of inflammatory mediators and can cause systemic immune damage and even multi-organ failure. In this study, the inflammatory parameters studied were acute inflammatory parameters such as NLR, PLR, CRP, and ESR. This parameter is elevated under cytokine storm conditions which contribute to the fatal outcome of the disease.[8,19]

From the statistical correlation regression test, it was shown that there was a significant relationship between the four parameters and the outcomes of confirmed COVID-19 patients being treated. Based on the correlative coefficients, it was found that the order of parameters with the most significant relationship was CRP, NLR, PLR, and LED. However, when classified by age group, the LED showed no significance in the elderly group, while the PLR in the elderly group was lower than in the adult group. This is in contrast to the CRP and NLR parameters which are more strongly associated with patient outcomes in the elderly group. So it can be concluded that the CRP and NLR parameters are good predictors of COVID-19 outcomes in the elderly.

A meta-analysis by Qin., et al on parameters related to immune dysfunction in severe and fatal cases of COVID-19, reported that NLR, PLR, and CRP were increased in the non-survive group compared to the survivor group, but there was no difference in the ESR values between the survivor group and the non-survival group.[23] When compared with a study conducted at Ulin Hospital itself, a significant increase in NLR and CRP values was also reported in the non-survive group compared to the survivors.[18] Regarding the differences in the elderly population with adults, a systematic review of clinical features in the elderly group by Neumann-Podczaska., et al, reported the incidence of lymphopenia with an increase in median CRP and ESR (> 10 mg/L and > 35 mm/hour) in various studies that were reviewed, although not accompanied by the results of the meaningfulness test.[24]

CRP is a non-specific acute phase reactant that is induced by IL-6 in the liver. Characteristics of CRP in the form of rapidly increasing levels within 6 to 8 hours and giving the highest peak within 48 hours from the onset of the disease and then decreasing when the inflammatory stage ends, making it an evaluation parameter of disease severity. Clinically, CRP is used as a biomarker of

various inflammatory and infectious conditions because elevated CRP levels are directly correlated with the degree of inflammation and disease severity. The meta-analysis findings of Malik., et al on the association of biomarkers with COVID-19 outcomes positively associated elevated CRP levels with disease severity and lung lesion formation in the early stages of COVID-19. Therefore, CRP is suggested to be the most effective and sensitive biomarker in predicting the progression of COVID-19 disease.[25]

In the elderly, a study on epidemiological, clinical, and laboratory characteristics by Ibrahim., et al in Saudi Arabia on the epidemiological, clinical, and laboratory features of several age groups in hospitals showed that there was no significant difference in CRP levels in the elderly compared to adults in the elderly. cases of COVID-19 and also there was no significant difference in the comparison between the surviving and non-surviving groups, but the researchers did not explain the possible cause of this phenomenon.[15] While another study by Villoteau., et al that specifically assessed the role of CRP in COVID-19 cases in the elderly population showed a role for CRP as a predictor of 14-day survival in elderly patients with elevated CRP levels associated with higher mortality in the 14 days in hospitalized COVID-19 cases.

The neutrophil-lymphocyte ratio (NLR), calculated as a simple ratio between the number of neutrophils and lymphocytes measured in peripheral blood, is a biomarker that conjugates two immune systems, namely the innate immune response, primarily neutrophils, and adaptive immunity supported by lymphocytes. In COVID-19, hematological examination characteristics were found in the form of leukocytosis, neutrophilia, and lymphocytopenia. Leukocytosis is common in critically ill patients because the damaged cells induce innate inflammation in the lung, mostly mediated by pro-inflammatory macrophages and granulocytes. Lymphocytopenia is also associated with disease progression, although it is not clear whether lymphopenia is associated with a critical illness. It is estimated that COVID-19 destroys T lymphocytes, thereby worsening the patient's condition.[27]

A study on NLR related to disease progression in the elderly population by Lian., et al reported that NLR was independently and significantly associated with the development of COVID-19 disease so NLR can be used as a prognostic tool to predict clinical outcomes of elderly patients suffering from the COVID-19.[28] This is in accordance with the results of this study which showed that there was a significant relationship between NLR levels and poor elderly patients' outcomes. The elderly group also obtained a higher relative coefficient than the adult group. This is indicated by the median NLR in the elderly is 8.85 while in adults it is 7.09.

NLR has been studied to have a positive correlation with age in both healthy women and men. This is because the number of granulocytes will increase and lymphocytes will decrease with age. The increase in NLR with age can be explained by the more frequent development of chronic infectious diseases and malignancies in the elderly. In addition, isolated neutrophil increases leading to increased NLR can be seen in several conditions such as bacterial or fungal infections, acute stroke, myocardial infarction, atherosclerosis, severe trauma, cancer, postoperative complications, and any condition characterized by tissue damage that activates systemic inflammatory response (SIRS). This is because the early hyperdynamic phase of infection is characterized by a proinflammatory state, which is mediated by neutrophils and other inflammatory cells. SIRS is associated with the suppression of neutrophil apoptosis, which promotes neutrophil-mediated elimination as part of the innate response.[29,30]

In this study, it was also found that PLR had a significant relationship with the outcome of patients with confirmed COVID-19 being treated. However, from the correlation

coefficient, the relationship is lower in the elderly group compared to the adult group. PLR is the ratio of platelet count to absolute lymphocyte count in peripheral blood and has been used as a sensitive indicator to reflect the control of infection and inflammation in the body, including COVID-19. Platelets are important immune cells that play a role in hemostasis, coagulation, maintenance of vascular integrity, angiogenesis, innate immunity, inflammatory response, tumor biology, and so on. Changes in the number and activity are closely related to various diseases. In a study by Qu., et al on the relationship of PLR with the prognosis of COVID-19 patients, it was explained that older patients with lower lymphocyte and platelet counts had more severe disease and longer hospital stays. The patient's age and platelet levels were positively correlated with length of stay, while lymphocyte levels were negatively correlated with length of hospitalization.[31]

In the elderly, there are changes in the number and function of platelets due to changes in hematopoietic tissue, blood composition, and blood vessel health. The number of platelets will remain relatively stable during adulthood but decreases in the elderly (> 60 years). With this condition, the PLR value in the elderly should decrease when compared to the adult group. However, there is no data on the comparison of PLR values between the elderly and adult groups that the researchers got, so it is hypothesized that the increase in PLR that occurred in this study was due to the decrease in lymphocytes in the elderly being more significant than the decrease in platelets. In addition, some of these studies also analyzed changes in platelet counts during treatment where it was found that platelets increased first and then decreased in patients who were severe during treatment and a significant increase in platelets generally occurred in elderly patients and stayed in the hospital longer. Therefore, it is thought that changes in platelets in the course of treatment may correlate with the progression and prognosis of COVID-19 and it is recommended that PLR assessment not only be performed at the outset but also be performed serially.[32-34]

In the ESR examination in this study, a significant relationship was found between ESR and the outcome of confirmed patients treated at Ulin Hospital Banjarmasin, but when divided by age, the elderly group did not have a significant relationship with patient outcomes while the adult group still had a significant relationship. ESR is an important index reflecting immunological disorders. This parameter was used more than a century ago but its clinical utility remains unchanged as an overall predictor of inflammation because it depends on the concentration of circulating acute-phase proteins, especially fibrinogen. Since the sensitivity and specificity of ESR are not very good, more specific inflammatory markers such as CRP and blood component ratios (NLR, PLR, etc.) have been developed.[35]

In a meta-analysis conducted by Mahat., et al on inflammatory markers in COVID-19 and Zeng., et al on the association of inflammatory markers with COVID-19 severity, it was found that higher ESR levels were associated with COVID-19 severity due to a higher inflammatory response.[14,36] Ibrahim., et al stated that there was a significant difference between the ESR values in the elderly group compared to the adult group.[15] However, from the results of a systemic review by Iwamura., et al that examined biomarkers of inflammation and the immune system, it was found that ESR values could be normal or elevated in COVID-19 patients. Normal ESR values can be caused by the absence of comorbidities in the patient or the examination carried out too early in the course of the disease because the ESR responds to inflammation slowly. After all, fibrinogen and immunoglobulin as the main contributors to ESR have different half-lives. This process resulted in a significant lag between clinical changes and ESR values. ESR is also elevated in active inflammatory diseases such as rheumatoid arthritis (AR),

chronic infections, collagen diseases, and malignancies. The presence of anemia also tends to increase ESR, because fewer red blood cells repel each other, while polycythemia has the effect of lowering ESR.[37,38]

Outcome predictive efficacy of confirmed COVID-19 inflammatory parameters NLR, PLR, CRP and LED

After knowing the significance of the relationship between the inflammatory parameters, the study was continued by looking for the cut-off value by selecting the best sensitivity and specificity. Using the ROC curve, the cut-off value is obtained with the consideration that AUC values above 0.7 are considered good. This was found in NLR in the general and adult groups, and CRP in all groups, so the sensitivity and specificity of the cut-off were above 60%.

From the ROC curve, the cut-off value of NLR in this study was sequentially the highest in the elderly, overall, and adult groups (6.77; 5.97; and 5.36). When compared with a meta-analysis study by Simadibrata., et al regarding the prediction of NLR values for COVID-19 severity and mortality, the cut-off range for NLR for predicting mortality is in the range of 7.9 – 11.8 with study samples coming from China and the United States.[39] While researching NLR in Indonesia, Amiruddin., et al stated that the cut-off value of NLR in predicting the outcome of COVID-19 cases at RSUP dr. Wahidin Sudirohusodo is 3.4.[40] The mortality cut-off value in this study was not included in the above range. However, Simadibrata adds that the wide cut-off variation indicates that the absolute NLR values measured in different populations are hardly comparable and the optimal limit values may vary from one population to another.[39]

The cut-off value of NLR in this study was different between the elderly and adult groups. In the elderly group, the cut-off value of NLR which is significantly related to non-survive outcomes is 6.77; while in the adult group it was 5.36. This difference indicates that the elderly population with confirmed COVID-19 requires a higher cut-off value than adults to predict an adverse outcome. This could be because the NLR value has a positive correlation with age according to what was described by Li., et al who examined the NLR values of various age groups in a healthy population. It was reported in his research that NLR was positively correlated with age in both women and men because the number of granulocytes showed an increasing trend with age and the number of lymphocytes showed a decreasing trend with age. The increase in NLR with age may explain several phenomena such as chronic infectious diseases and malignancies that develop more frequently in the elderly.[29]

From the ROC curve, the cut-off value of PLR in this study was sequentially the highest in the elderly, adult, and overall groups (257.5; 227.5; and 226.5). When compared with a meta-analysis by Sarkar., et al on the role of PLR as a prognostic indicator in COVID-19, the cut-off range of PLR in predicting mortality is in the range of 233 – 274 with study samples from Italy, Iran, China, Pakistan, Turkey, Spain, India, Bangladesh, and the United States.[41] Meanwhile in Indonesia, Raihana., et al in a study on PLR as a predictor of mortality in COVID-19 stated that the cut-off value of PLR in predicting the outcome of COVID-19 cases in RSSA Malang was 356.13.[42] The mortality cut-off value in this study was not included in the above range. Yet despite the different PLR cut-off values, statistically increased PLR was associated with increased morbidity and mortality in COVID-19.

There is a difference in the PLR cut-off value in this study between the elderly and adult groups. In the elderly group, the cut-off value of PLR which is significantly related to non-survive outcomes is 257.5; while in the adult group it was 227.5. This difference indicates that a larger cut-off in the elderly population with confirmed COVID-19 is predicted to have an unfavorable outcome. The study of Mathur., et al. which examined

the value of PLR in all cases of death, not only COVID-19, in various age group,s stated that high PLR was an independent predictor of all-cause mortality in the elderly but not in the middle-aged or younger population.[43]

A high PLR can occur when a high platelet count and/or a low lymphocyte count is obtained. High platelet counts are thought to be affected by inflammation because of their ability to produce and secrete cytokines and chemokines under the control of specific intracellular pathways. Platelets are also able to intervene in tissue regeneration and repair because they can produce pro-angiogenic mediators. Due to their pro-inflammatory role, platelets are involved in the pathogenesis of several diseases such as atherosclerosis, arthritis, vasculitis, glomerulonephritis, sepsis, neuroinflammation, inflammatory bowel disease, and many others. Therefore, it is not uncommon to find an increase in the number of platelets in an inflammatory state. Meanwhile, if it is associated with age, the number of platelets is inversely proportional. A significant reduction of 10×103 /µL in individuals in the 60-69 year age group and 20×103 /µL in patients over 69 years of age. This shows that the decrease in platelet count with age is part of the biological aging process. Two hypotheses explain this phenomenon: (a) older individuals have lower stem cell reserves than younger individuals; and (b) decreased platelet count provides a biological advantage, so may have a better chance of reaching an older age. On the other hand, inflammatory states are often associated with high cortisol production, which can suppress lymphocyte production. Lymphocytes from the adaptive and immune compartments prevent tumor development, partly explaining why increased PLR is associated with high mortality and poor prognosis in malignant conditions.[44]

The high PLR value in the elderly can be caused by a higher decrease in lymphocytes than the decrease in platelets in the elderly and as a result, even though there is a decrease in platelets, the PLR value in the elderly group is still high. In addition, this could be caused by chronic inflammatory conditions that are more dominant in the elderly causing platelets to increase so that the PLR value also increases. There is also a tendency for changes in PLR values to increase from day 0 of treatment and reach a peak on day 3 or day 6 of treatment and then decrease gradually until day 14 of treatment as reported by Wijaya, et al in their research on the trend. PLR and ALC on the severity of COVID-19 patients, so PLR is considered more meaningful if it is carried out serially to monitor inflammation that occurs in COVID-19 patients.[45]

From the ROC curve, the cut-off value of CRP in this study was sequentially the highest in the elderly, overall, and adult groups (95.65; 63; and 47.9). When compared with the meta-analysis study by Hariyanto., et al., it was stated that the cut-off range for CRP to predict mortality was 33.55 mg/L with study samples from Kuwait, Oman, Germany, and China.[46] While researching CRP in Indonesia, Prasetya., et al reported that the cut-off value of CRP in predicting the outcome of COVID-19 cases at three Siloam hospitals in Indonesia was 47 mg/L.[47] The cut-off value of mortality in this study itself is above the results of these studies. The high variability of the CRP cut-off across these studies may be due to an age distribution factor, with the median age in this study being relatively higher than in the previously mentioned studies. In addition, several studies assess the cut-off for predicting disease severity which is certainly lower than the cut-off for predicting patient outcomes. In addition, other factors that affect the CRP value are known, such as differences in the characteristics of the population studied including age, sex, smoking status, hypertension, diabetes, and the presence of other conditions that have the potential to affect the concentration of CRP in the blood, including polymorphisms of the CRP or IL-6 gene.[46]

There is a difference in the CRP cut-off value between the elderly and adult groups in this study. In the elderly group, the cut-off value of CRP which was significantly related to non-survive outcomes was 95.65; while in the adult group of 47.9. This difference indicates that a larger cut-off in the elderly population with confirmed COVID-19 is predicted to have an unfavorable outcome. The association of CRP with decreased survival in the elderly with COVID-19 is not fully understood. Several possibilities that could underlie the association of CRP are: (a) CRP in the early stages of COVID-19 has been reported to be positively correlated with lung lesions so that it becomes a biomarker of disease severity; (b) CRP levels reflect IL-6 secretion due to activation of SARS-CoV-2, which is involved in cytokine storm, contributing to greater vascular permeability, arterial hypotension, organ failure and ARDS, with risk of fatal outcome; (c) an inflammatory state illustrated by increased CRP inducing a prothrombin state with an increased risk of stroke or venous thromboembolic events such as pulmonary embolism; (d) increased CRP is also associated with a higher risk of death by inducing hypercatabolism of respiratory muscle proteins so that the compensatory response in respiratory distress is impaired; and (e) CRP levels are a marker of the pre-COVID-19 health status of the elderly and reflect chronic disease burden, most of which are risk factors for severe COVID-19 and inflammation. Inflammation is the chronic activation of the innate immune system as we age, which results in controlled chronic inflammation in older adults. Inflammation is represented by an increase in the number of NK cells and an increase in the production of pro-inflammatory cytokines, especially IL-6 and CRP. This chronic inflammatory state has detrimental effects on health, contributes to biological aging, and may explain the frequency of severe and fatal forms of COVID-19 in the elderly population.[26]

The LED cut-off values in this study were sequentially the highest in the elderly, overall, and adult groups (64.5; 58.5; and 55.5). It was reported by Ji., et al in a study of increasing inflammatory markers in severe COVID-19, that the cut-off value for predicting mortality was 10.94 mm/hour with the study sample coming from China.[48] The cut-off LED in this study was 58.5 mm/hour, with the difference in values in the elderly group being 64.5 and 55.5 in the adult group. However, the LED cut-off value in the elderly group was not statistically significant. This is because ESR is an acute inflammation parameter that is less sensitive and specific due to the influence of various factors that can influence it.[35]

The odds ratio of inflammation parameters to the outcome of patients with confirmed COVID-19

In this study, the odds ratio (OR) of COVID-19 outcomes for each parameter in each age group was investigated. All parameters, in all age groups, had statistical significance except PLR and ESR in the elderly group. So it can be concluded based on the OR value, the most significant parameters in the elderly group to predict the risk of non-survive outcomes, respectively, are CRP and NLR, PLR and LED. While in the adult group are CRP, NLR, PLR, and LED. OR predictions for each parameter between age groups for non-survive outcomes were also considered equivalent because the 95% confidence ranges overlap.

Conclusions

The results showed that there are differences in inflammatory parameter values between the elderly and adult groups to predict the outcome of COVID-19 cases. The inflammatory parameter that has the best sensitivity and specificity to predict the patient outcome is CRP in the elderly group while in the adult group it is NLR. Meanwhile, the inflammatory parameters as a risk predictor for the outcome of confirmed COVID-19 patients in the elderly group, respectively, the most significant, were CRP, NLR, and PLR. Meanwhile, LED was found to

be insignificant in predicting non-survive outcomes.

In this study, there were several limitations, including the study was still a single-center, no treatment was carried out to homogenize the sample, or further analysis of confounding factors such as gender, comorbidities, vaccination status, severity, complications, and treatment so that it could bias the results of the parameters. inflammation and outcome of confirmed COVID-19 patients.

References

1. MINISTRY OF HEALTH OF THE REPUBLIC OF INDONESIA. PENYELENGGARAAN PELAYANAN GERIATRI DI RUMAH SAKIT. Jakarta; 2014.
2. Sari N, Maylasari I, Dewi F, Putrianti R, Nugroho S, Wilson H. Statistik penduduk lanjut usia 2020. Jakarta: Badan Pusat Statistik; 2020.
3. Werner H, Kuntsche J. Infektionen im Alter - was ist anders?. Z Gerontol Geriat. 2000;33(5):350-356.
4. He W, Xiao K, Fang M, Xie L. Immune Cell Number, Phenotype, and Function in the Elderly with Sepsis. Aging and disease. 2021;12(1):277.
5. Esakandari H, Nabi-Afjadi M, Fakkari-Afjadi J, Farahmandian N, Miresmaeili S, Bahreini E. A comprehensive review of COVID-19 characteristics. Biological Procedures Online. 2020;22(1).
6. Data Visualization | COVID-19 Deaths by Age | The Heritage Foundation [Internet]. Data Visualizations | The Heritage Foundation. 2022 [cited 1 March 2022]. Available from: https://datavisualizations.heritage.org/public-health/covid-19-deaths-by-age/
7. Distribution Map | Covid19.go.id [Internet]. covid19.go.id. 2022 [cited January 5, 2022]. Available from: https://covid19.go.id/peta-sebaran
8. Haryati H, Isa M, Assagaf A, Nurrasyidah I, Kusumawardhani E. Clinical Characteristics of Hospitalized Individuals Dying with COVID-19 in Ulin Regional Hospital Banjarmasin. Jurnal Respirasi. 2021;7(1).
9. Felsenstein S, Herbert J, McNamara P, Hedrich C. COVID-19: Immunology and treatment options. Clinical Immunology. 2020;215:108448.
10. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, D'Agnano V, et al. COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. Aging Clinical and Experimental Research. 2020;32(8):1599-1608.
11. Pietrobon A, Teixeira F, Sato M. Immunosenescence and Inflammaging: Risk Factors of Severe COVID-19 in Older People. Frontiers in Immunology. 2020;11.
12. Chan AS, Rout A. Use of Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in COVID-19. J Clin Med Res. 2020;12(7):448-453.
13. Pakos IS, Lo KB, Salacup G, Pelayo J, Bhargav R, Peterson E, et al. Characteristics of peripheral blood differential counts in hospitalized patients with COVID-19. Eur J Haematol. 2020;105(6):773-778.
14. Mahat R, Panda S, Rathore V, Swain S, Yadav L, Sah S. The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: A systematic review and meta-analysis. Clinical Epidemiology and Global Health. 2021;11:100727.
15. Ibrahim M, AL-Aklobi O, Abomughaid M, Al-Ghamdi M. Epidemiological, clinical, and laboratory findings for patients of different age groups with confirmed coronavirus disease 2019 (COVID-19) in a hospital in Saudi Arabia. PLOS ONE. 2021;16(4):e0250955.
16. Shirani K, Ashraf M, Sherafat A, Naderi Z, Sami R, Soltaninejad F, et al. Association of systemic complications with mortality in coronavirus disease of 2019: A cohort study on intensive care unit patients.

Journal of Research in Medical Sciences. 2022;27(1):34.
17. Passarelli-Araujo H, Pott-Junior H, Susuki A, Olak A, Pescim R, Tomimatsu M, et al. The impact of COVID-19 vaccination on case fatality rates in a city in Southern Brazil. American Journal of Infection Control. 2022; S0196-6553(22)00095-5.
18. Haryati H, Isa M, Assagaf A, Nurrasyidah I, Kusumawardhani E, Suhartono E, et al. Clinical and Laboratory Features of COVID-19 in Ulin Referral Hospital of South Kalimantan: Predictors of Clinical Outcome. Journal of Tropical Life Science. 2021;11(3):299-307.
19. Shi C, Wang L, Ye J, Gu Z, Wang S, Xia J et al. Predictors of mortality in patients with coronavirus disease 2019: a systematic review and meta-analysis. BMC Infectious Diseases. 2021;21(1).
20. Booth A, Reed A, Ponzo S, Yassaee A, Aral M, Plans D, et al. Population risk factors for severe disease and mortality in COVID-19: A global systematic review and meta-analysis. PLOS ONE. 2021;16(3):e0247461.
21. Saletti G, Gerlach T, Jansen J, Molle A, Elbahesh H, Ludlow M, et al. Older adults lack SARS-CoV-2 cross-reactive T lymphocytes directed to human coronaviruses OC43 and NL63. Scientific Reports. 2020;10(1).
22. Cunha L, Perazzio S, Azzi J, Cravedi P, Riella L. Remodeling of the Immune Response With Aging: Immunosenescence and Its Potential Impact on COVID-19 Immune Response. Frontiers in Immunology. 2020;11.
23. Qin R, He L, Yang Z, Jia N, Chen R, Xie J, et al. Identification of Parameters Representative of Immune Dysfunction in Patients with Severe and Fatal COVID-19 Infection: a Systematic Review and Meta-analysis. Clinical Reviews in Allergy & Immunology. 2022;1(33).
24. Neumann-Podczaska A, Al-Saad S, Karbowski L, Chojnicki M, Tobis S, Wieczorowska-Tobis K. COVID 19 - Clinical Picture in the Elderly Population: A Qualitative Systematic Review. Aging and disease. 2020;11(4):988.
25. Malik P, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, et al. Biomarkers and outcomes of COVID-19 hospitalizations: systematic review and meta-analysis. BMJ Evidence-Based Medicine. 2020;26(3):107-108.
26. Villoteau A, Asfar M, Otekpo M, Loison J, Gautier J, Annweiler C. Elevated C-reactive protein in early COVID-19 predicts worse survival among hospitalized geriatric patients. PLOS ONE. 2021;16(9):e0256931.
27. Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. Journal of Translational Medicine. 2020;18(1).
28. Lian J, jin C, Hao S, Zhang X, Yang M, Jin X et al. High neutrophil-to-lymphocyte ratio associated with progression to critical illness in older patients with COVID-19: a multicenter retrospective study. Aging. 2020;12(14):13849-13859.
29. Li J, Chen Q, Luo X, Hong J, Pan K, Lin X et al. Neutrophil-to-Lymphocyte Ratio Positively Correlates to Age in Healthy Population. Journal of Clinical Laboratory Analysis. 2015;29(6):437-443.
30. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. International Journal of Molecular Sciences. 2022;23(7):3636.
31. Qu R, Ling Y, Zhang Y, Wei L, Chen X, Li X et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. Journal of Medical Virology. 2020;92(9):1533-1541.
32. Jones C. Platelet function and ageing. Mammalian Genome. 2016;27(7-8):358-366.

33. Bedel C, Korkut M, Armağan H. NLR, d-NLR and PLR can be affected by many factors. International Immunopharmacology. 2021;90:107154.
34. Karimi A, Shobeiri P, Kulasinghe A, Rezaei N. Novel Systemic Inflammation Markers to Predict COVID-19 Prognosis. Frontiers in Immunology. 2021;12.
35. Zhang W, Yuan Y, Zhang S, Jin C, Wu L, Mei H et al. Erythrocyte Sedimentation Rate in COVID-19 Infections. 2020.
36. Zeng F, Huang Y, Guo Y, Yin M, Chen X, Xiao L et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. International Journal of Infectious Diseases. 2020;96:467-474.
37. Lapić I, Padoan A, Bozzato D, Plebani M. Erythrocyte Sedimentation Rate and C-Reactive Protein in Acute Inflammation. American Journal of Clinical Pathology. 2019;153(1):14-29.
38. Alende-Castro V, Alonso-Sampedro M, Vazquez-Temprano N, Tuñez C, Rey D, García-Iglesias C et al. Factors influencing erythrocyte sedimentation rate in adults. Medicine. 2019;98(34):e16816.
39. Simadibrata D, Calvin J, Wijaya A, Ibrahim N. Neutrophil-to-lymphocyte ratio on admission to predict the severity and mortality of COVID-19 patients: A meta-analysis. The American Journal of Emergency Medicine. 2021;42:60-69.
40. Amiruddin A, Nurdin H, Arif S, Musba A, Salahuddin A, Palinrungi A. Hubungan Penanda Infeksi, Penanda Oksigenasi, dan Faktor Risiko Lainnya terhadap Mortalitas Pasien COVID-19 dengan Pneumonia Saat Admisi di Unit Perawatan Intensif RSUP Dr. Wahidin Sudirohusodo. JAI (Jurnal Anestesiologi Indonesia). 2021;13(2):114-124.
41. Sarkar S, Kannan S, Khanna P, Singh A. Role of platelet-to-lymphocyte count ratio (PLR), as a prognostic indicator in COVID-19: A systematic review and meta-analysis. Journal of Medical Virology. 2021;94(1):211-221.
42. Raihana D, Iskandar A, Seskoati P. Platelet, Limfosit Absolut, dan PLR (Platelet Lymphocyte Ratio) Sebagai Prediktor Mortalitas Pada Pasien COVID-19 di RSSA Malang [Bachelor]. Universitas Brawijaya; 2021.
43. Mathur K, Kurbanova N, Qayyum R. Platelet-lymphocyte ratio (PLR) and all-cause mortality in general population: insights from national health and nutrition education survey. Platelets. 2019;30(8):1036-1041.
44. Le Blanc J, Lordkipanidzé M. Platelet Function in Aging. Frontiers in Cardiovascular Medicine. 2019;6.
45. Wijaya M, Utariani A, Hamzah H, Semedi B, Airlangga P. The Trend of Platelet-To-Lymphocyte Ratio (PLR) and Absolute-Lymphocyte-Count (ALC) in the Severity of Covid-19 Patients. International Journal Of Scientific Advances. 2021;2(4).
46. Hariyanto T, Japar K, Kwenandar F, Damay V, Siregar J, Lugito N et al. Inflammatory and hematologic markers as predictors of severe outcomes in COVID-19 infection: A systematic review and meta-analysis. The American Journal of Emergency Medicine. 2021;41:110-119.
47. Prasetya I, Cucunawangsih, Lorens J, Sungono V, El-Khobar K, Wijaya R. Prognostic value of inflammatory markers in patients with COVID-19 in Indonesia. Clinical Epidemiology and Global Health. 2021;11:100803.
48. Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B et al. Association of elevated inflammatory markers and severe COVID-19. Medicine. 2020;99(47):e23315.