(RESEARCH ARTICLE)

Albumin levels, mean platelet volume, and neutrophil lymphocyte ratio as predictors of COVID-19 outcomes

Kristina Cecilia Widjaya [1], Dhani Redhono Harioputro [2, *], Agus Jati Sunggoro [2] and Arifin [2]

[1] Department of Internal Medicine, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
[2] Department of Internal Medicine, Dr. Moewardi Hospital, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.

Abstract

Coronavirus Disease 2019 (COVID-19) is a respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19 spreads very quickly to various countries and causes a high mortality rate. According to this urgency, a study was conducted on albumin levels, mean platelet volume (MPV), and neutrophil-lymphocyte ratio (NLR) as predictors of COVID-19 outcome. This research was an analytic observational study conducted cross-sectional at Dr. Moewardi Hospital Surakarta, Indonesia, from June-October 2021. Data analysis used the logistic regression test and ROC analysis to determine the cut-off point for each variable. The total samples used in this study were 123 samples, with 68 survival patients and 55 nonsurvival patients. Logistic regression test results received p values for MPV and NLR, respectively, 0.048 and 0.001, and OR values 1.369 and 1.186 with Nagelkerke R Square 0.186. The cut-off point of MPV is 9.05 (sensitivity 76.4%; specificity 48.5%; p=0.019), and the cut-off point of NLR is 3.27 (sensitivity 92.7%; specificity 55.9%; p=0.001). In conclusion, MPV and NLR can be used as predictors of COVID-19 outcomes.

Keywords: COVID-19; Predictors of Outcomes; Albumin Levels; Mean Platelet Volume (MPV); Neutrophil Lymphocyte Ratio (NLR)

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by *severe acute respiratory syndrome coronavirus 2* (SARS)-CoV-2) [1]. Many cases of unknown pneumonia in Wuhan at the end of December 2019 were later identified as a new variant of the coronavirus, SARS-CoV-2 [2]. Cases and deaths from COVID-19 continued to increase and spread to many countries until WHO declared it a pandemic [3].

Based on WHO data, as of March 13, 2022, there were more than 455 million confirmed cases globally, with an increase of 8% from the previous week's total cases and more than 6 million deaths. Meanwhile, Indonesia decreased the number of cases and deaths compared to the last week, but there were still 141,770 new cases and 1,994 deaths during the week [4]. The global COVID-19 mortality rate is 2.2%, with higher deaths occurring in patients who are elderly, have comorbidity, obesity, and acute respiratory distress syndrome severe (ARDS) [5, 6].

ARDS mainly causes the death of COVID-19 patients with cytokine storms and the presence of multi-organ failure, which is associated with coagulation disorders and systemic inflammation [2, 7]. Systemic inflammation increases capillary permeability and albumin transfer to extracellular, so albumin levels tend to decrease as a marker of endothelial damage [8, 9]. Cytokine storm conditions will reduce lymphocyte production in the bone marrow and increase the use of lymphocytes and neutrophil production as an inflammatory response increasing the neutrophil-lymphocyte ratio (NLR)

[7, 10, 11]. In addition, a cytokine storm will cause coagulation abnormalities and thrombus formation, characterized by an increase in the *mean platelet volume* (MPV) as a reflection of pro-inflammatory and prothrombotic [7, 12]. The three indicators, decreased albumin, increased MPV, and increased NLR, can predict the outcome of COVID-19 patients [9, 11, 12].

COVID-19 is still ongoing, with a relatively high mortality rate. Albumin levels, MPV, and NLR have good potential in predicting COVID-19 outcomes. There has been much research on this matter abroad, but not much has been done in Indonesia. For this reason, this research aims to determine how the outcome of COVID-19 can be predicted using the parameters of albumin, MPV, and NLR.

2. Material and methods

This research was an observational study conducted *cross-sectional* at Dr. Moewardi Hospital Surakarta, Indonesia, for June – October 2021. The research subjects were COVID-19 inpatients in room isolation who met the study criteria. The inclusion criteria were inpatients with COVID-19 that confirmed positive two times with PCR test and ranged from 18 to 60 years. In contrast, the exclusion criteria for this study were pregnant women, obese patients, and patients with a history of diabetes mellitus, hypertension, leukemia, lymphoma, multiple myeloma, stage 5 chronic *kidney* failure, and decompensated liver cirrhosis. The sample selection used purposive sampling with a minimum sample size was 78 people calculated using the *Lemeshow* formula with an unknown population size [13].

The study's independent variables included albumin levels, MPV, and NLR on a ratio scale. While the dependent variable is the outcome of COVID-19 in categorical form divided into survival and nonsurvival. Data analysis used the Statistical Program for Social Science (SPSS) application for Windows 25th version by conducting a bivariate test using Chi-Square for categorical data, namely age, sex, and comorbidities. Independent T-test for MPV variables and Mann-Whitney Test for albumin levels and NLR variables. The data analyzed were considered significant if the p-value <0.05. Multivariate analysis with *logistic regression test* to determine the effect of independent variables on the dependent variable and ROC test to determine the cut-off point of each variable.

3. Results

3.1. Sample Characteristics

The study found 123 COVID-19 patients at Dr. Moewardi Hospital Surakarta, Indonesia, from June-October 2021.

Table 1 Sample Characteristics

Characteristics	n	%
Age		
<50 years	74	60.2
≥50 years	49	39.8
Gender		
Female	78	63.4
Male	45	36.6
Comorbid		
Without comorbid	102	82.9
With comorbid	21	17.1
Cardiovascular disease	4	19.05
Kidney disease	4	19.05
Liver disease	2	9.52
Respiratory disease	3	14.29

Neurological disease	1	4.76	
Immunological and psychiatric diseases	2	9.52	
Hematological and oncological diseases	5	23.81	
COVID-19 Outcomes			
Survival	68	55.3	
Nonsurvival	55	44.7	

Table 2 Sample Characteristics Based on COVID-19 Outcomes

Characteristics	COVID-19 Outcomes				p
	Survival		**Nonsurvival**		
	N	**%**	**N**	**%**	
Age					
<50 years	47	38,2	27	22	0.038a
≥50 years	21	17,1	28	22.8	
Gender					
Female	54	43.9	24	19.5	0.001a
Male	14	11.4	31	25.2	
Comorbid					
Without comorbid	58	47.2	44	25.2	0.593a
With comorbid	10	8.1	11	8 .9	
Albumin					
<3.5 g/dL	19	15.4	23	18.7	0.024b
≥3.5 g/dL	49	39.8	32	26	
MPV					
≤12 fL	65	25.8	55	44.7	0.046c
>12 fL	3	2.4	0	0	
NLR					
1-3	26	21.1	3	2.4	0.001b
>3	42	34.1	52	42.3	

Bivariate analysis: a. Chi Square; b. Mann-Whitney test; c. Independent T-test

Table 1 shows the characteristics of the study subjects, including age, gender, comorbidities, and COVID-19 outcomes. Most of the research subjects were <50 years old (60.2%) and female (63.4%). Based on the comorbidities, more patients were without comorbidities (82.9%), and the three groups of comorbid that experienced the most were hematological and oncological diseases (23.81%), cardiovascular disease, and kidney disease (19.05%). Most of the patients in this study survived (55.3%).

Table 2 shows the characteristics of the research subjects and their relationships based on the COVID-19 outcomes. Based on age, more survival patients were aged <50 years (38.2%), while the nonsurvival patients were higher at the age of ≥50 years (22.8%). Patients who survived were dominated by women (43.9%), while nonsurvival patients were dominated by men (25.2%). Based on comorbidities, more patients without comorbidities survived (47.2%), while patients with comorbidities were more likely not survived (8.9%). Based on albumin levels, more patients with albumin

levels <3.5 g/d were not survived (18.7%), while patients with albumin levels ≥3.5 g/dL survived (39.8%). Based on the MPV value, survival patients who have MPV ≤12 fL were 65 patients (52.8%) and three patients (2.4%) with MPV >12 fL. On the other side, nonsurvival patients with MPV ≤12 fL were 55 patients. Based on NLR values, more patients with NLR 1-3 survived (21.1%), while NLR> 3 were not survived (42.3%). In this study, all variables were significantly related to the outcome of COVID-19 except for comorbidity.

3.2. Data analysis

Table 3 shows the multivariate test results using logistic regression tests. The result variables that affect the outcome of COVID-19 are MPV and NLR, with p-values of 0.048 and 0.001, respectively. Meanwhile, albumin levels were eliminated, so they were considered not to affect the outcome of COVID-19. The *Odds Ratio* (OR) indicates the strength of the effect between variables. MPV and NLR with OR 1.369 and 1.186, respectively, meaning that every unit increase in each variable will increase the risk of an event equal to the OR value. *Nagelkerke R Square* is 0.186, which means that the tested variable has an 18.6% influence on the dependent variable (COVID-19 outcomes), while other variables outside the research analysis influence the additional 81.4%.

Table 3 Logistic Regression Test

Variable	*Nagelkerke R Square*	B	p	OR
MPV		0.314	0.048	1.369
NLR	0.186	0.170	0.001	1.186
Constant		-4.326	0.006	0.013

ROC analysis was performed on MPV and NLR to determine the performance of variables in predicting COVID-19 outcomes. Based on Figure 1, an overview of the AUC is obtained from the two variables, with the NLR curve higher than the MPV curve.
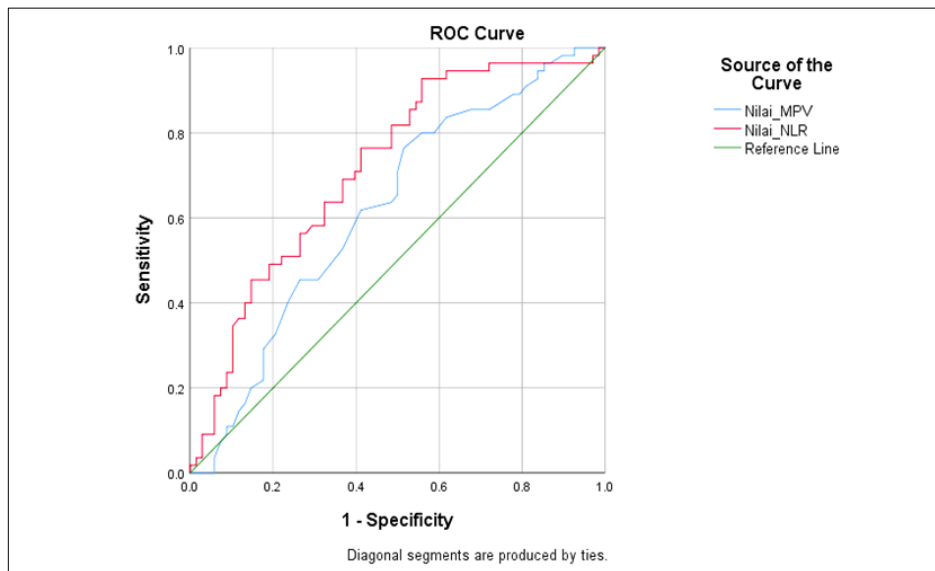

Figure 1 ROC Curves for COVID-19 Outcomes

Table 4 shows MPV has an AUC of 0.623, which is classified as having a weak level of accuracy with a cut-off point of 9.05 based on the best sensitivity and specificity (sensitivity 76.4%; specificity 48.5%; p = 0.019). NLR has AUC, which is classified as having a moderate level of accuracy, namely 0.718, with a cut-off point of 3.27 based on the best sensitivity and specificity (sensitivity 92.7%; specificity 55.9% p = 0.001).

Table 4 Interpretation of the ROC Curve

Variable	AUC	Cut-off point	Sensitivity	Specificity	p
MPV	0.623	9.05	76.4	48.5	0.019
NLR	0.718	3.27	92.7	55.9	0.001

4. Discussion

The characteristics of the subjects of this study, based on age, survival patients were higher in the age group <50 years (38.2%), while nonsurvival patients were more in the age group >50 years (22.8%). These results follow the research that age >50 years have a higher risk of death [14, 15]. Patients older than 50 years have higher ACE2 expression, experience decreased immunity and organ function, and the presence of comorbidities will increase the risk of death [14].

Based on gender, women were more likely to survive (43.9%), while the group who not survived was dominated by men (25.2%). The effect of gender on COVID-19 is related to genetics and sex hormones [14, 16, 17]. Women have a more robust adaptive immune system compared to men. The female hormone estradiol increases immune cells' response and production of antibodies, which can help fight COVID-19 infection. In contrast, testosterone suppresses the immune system and increases inflammatory cytokines [16].

In this study, more patients without comorbidities recovered, while more patients with comorbidities died. Several studies show that comorbidities increase the risk of death from COVID-19 [15, 18]. This risk will improve with age and the number of comorbidities you have [19]. All variables in this study were significantly related to the outcome of COVID-19, except for comorbidities. The reason is that common comorbidities often found in COVID-19, such as diabetes mellitus and hypertension, have been excluded from this study, so the number of patients with comorbidities is small [18, 19].

The outcomes of COVID-19 are associated with decreased albumin, increased MPV, and increased NLR. In critically ill patients, the change of albumin, MPV, and NLR increases the risk of patients not surviving their disease [20–22]. Each 1 g/dL decrease in albumin levels increases 137% mortality, 87% morbidity, and 71% longer hospital stay [23]. On the other side, the increase of 1 MPV unit between the first and third days during treatment is inseparable from thrombocytopenia, which is experienced by 58-95% of severe cases of COVID-19 and increased by 1.76 times the risk of mortality [24, 25]. Then significantly increased NLRs are also commonly found in patients treated in intensive care units with severe disease, with each unit increase in NLR associated with an 8% increase in the risk of death from COVID-19 [10, 26].

4.1. Effect of Albumin Levels on the Outcome of COVID-19

The results of this study showed that there was no significant effect between albumin levels and the outcome of COVID-19. This study is in line with Utariani et al., 2022, which used albumin to predict COVID-19 outcomes, especially the occurrence of multi-organ dysfunction syndrome (MODS). The results showed no effect of albumin on COVID-19 mortality, with a p-value = 0.899 [27]. Another study by Putranta et al., 2022, also showed that hypoalbuminemia did not have a significant relationship with mortality even though it was common in severe cases of COVID-19, with a p-value = 0.12 [28]. An insignificant effect of albumin on COVID-19 mortality was also obtained after controlling for other factors such as age, gender, and body mass index (BMI) [23].

In contrast, several studies showed an effect of albumin levels on the outcome of COVID-19 [9, 29]. Albumin plays a role in physiological functions, including maintaining colloid osmotic pressure, binding to various compounds, and plasma antioxidant activity. The decrease in albumin levels is associated with the magnitude of the inflammatory response. Decreased albumin levels due to plasma leakage, increased degradation, and reduced albumin synthesis during the inflammatory response to COVID-19 [9]. Hypoalbuminemia is unlikely caused by decreased albumin synthesis in severe COVID-19 because the onset of illness to admission is only three days, far shorter than the half-life of albumin [29].

These results differences may be due to the administration of albumin therapy given to COVID-19 patients while undergoing treatment and the limitation of the definition of death only in the hospital [23, 28]. In addition, low albumin levels are usually found in severe or critical patients, whereas this study did not differentiate patients based on symptoms or severity [27, 29].

4.2. Effect of MPV on COVID-19 Outcome

This study shows the effect of MPV on the outcome of COVID-19. These results align with studies showing that increased MPV impacts COVID-19 outcomes [12, 30]. A study by Serbat, 2021 [30] showed that the patients' initial and final MPV values were significantly higher in the group that did not survive than the survivors with p<0.001. Another study showed that increased MPV significantly predicts COVID-19 mortality, and the use of low-dose acetylsalicylic acid along with anticoagulants when MPV increases may improve clinical outcomes [12].

The mechanism of increasing MPV caused by the condition of thrombocytopenia in COVID-19 patients makes the body respond by producing more extensive and younger platelets [21, 24]. This mechanism is mediated by an increase in pro-inflammatory cytokines, especially IL-6, which causes an increase in megakaryocytic nuclear ploidy and cytoplasmic platelet volume [21]. These large platelets have a greater cell granule content and higher expression of adhesions, resulting in platelet hyperactivity and an increased risk of clot formation and adverse outcomes [31].

However, several studies show no significant relationship between MPV and the outcome of COVID-19 [25, 32]. A study in Italy on 119 patients found no statistically significant difference in MPV values between patients who died and those alive, with a p-value = 0.37 [32]. Another study by Güçlü et al., 2020 [25] reported that COVID-19 patients who died had MPV, which was insignificant compared to patients who survived on the first day of hospital admission (p = 0.005).

The difference in the results may be due to the difference in MPV measurement time, where the MPV value used in this study is the result of the first measurement performed on the patient when he was just admitted to the hospital. The increase in MPV was significantly higher in nonsurvival patients on the third or seventh day after the onset of symptoms and was mainly associated with chronic renal failure [25, 33]. Despite these differences, in this study, increasing the MPV will increase the risk of death from COVID-19.

4.3. Effect of NLR on COVID-19 Outcome

The results of this study show a significant effect of NLR on the outcome of COVID-19. This result is in line with studies that higher NLR at admission is associated with an increased risk of death [34, 35]. The study by Kheyri et al., 2022, showed that the first results of NLR upon admission to the hospital were independently significant (p < 0.0011) with death and care in the intensive care unit [35]. A retrospective cohort also showed significant results (p = 0.0147), where each unit increase in NLR was associated with an 8% increase in the risk of death [26].

The increase in NLR was caused by an increase in neutrophils and a decrease in lymphocytes during the COVID-19 infection. The body's inflammatory response tends to increase neutrophil production and accelerate lymphocyte apoptosis [22, 34]. Lymphocytes express ACE2 receptors, which are the targets of the COVID-19 virus, especially during cytokine storm conditions, so the number of lymphocytes tends to decrease [35]. Meanwhile, an increase in neutrophils is also associated with bacterial co-infection, which usually accompanies viral infections due to a decrease in the overall immune system [22, 26]. Dysregulation of the immune response would result in an excessive inflammation that the body couldn't handle, related to adverse outcomes, including death [26]. So, an increase in NLR will increase the risk of death from COVID-19.

4.4. MPV and NLR as Predictors of COVID-19 Outcome

This study shows that as COVID-19 outcome predictors, MPV has a weak accuracy (AUC=0.623) with a cut-off point of 9.05 (sensitivity 76.4%; specificity 48.5 %; p = 0.019). In comparison, NLR has a moderate accuracy (AUC = 0.718) with a cut-off point of 3.27 (sensitivity 92.7%; specificity 55.9%; p = 0.001).

Research by Sertbas, 2021 [30] states that MPV can be a predictor of COVID-19 mortality with a 4.62-fold increased risk of death after an increase in the initial MPV value of 2.18% (OR=4.62; 95% CI = 3.455-6.203, p<0.001). Another study conducted in Turkey also made MPV a predictor of COVID-19 mortality with a cut-off point of 10.45 fL (AUC = 0.750; 95% CI = 0.693-0.807; p<0.001), which has a sensitivity of 66.3% and specificity 62.8% [12].

NLR can be used as a predictor of COVID-19 outcomes [11, 35]. A study in Wuhan established that the cut-off point of NLR was 3.338 (AUC=0.963; 95% CI = 0.911–1.000; p<0.001) with a sensitivity of 100% and a specificity of 84% [11]. In Iran, the cut-off point of NLR was 4.27, which has a sensitivity of 70.2% and a specificity of 60.22% [35].

Compared with previous studies, the results of this study have lower accuracy and the cut-off point for both MPV and NLR. These differences may be due to differences in the characteristics of the research subjects and the number of

samples used. However, increasing the MPV and NLR beyond the existing cut-off point will increase the risk of death and can be used as a predictor of COVID-19 outcomes.

Our study has several limitations. First, this research was conducted with a Unicenter study in a hospital, so it has not generalized all conditions of COVID-19. The characteristic distribution might change statistically. Secondly, this study only assesses and analyzes the initial values from albumin, MPV, and NLR laboratory tests. It makes the progress of the parameters in each COVID-19 patient unclear. In addition, this study did not analyze other data that might affect the outcome of COVID-19, such as clinical symptoms, length of stay, and interventions are given.

5. Conclusion

This study concludes that MPV and NLR can be used as predictors of COVID-19 outcomes.

Compliance with ethical standards

Disclosure of conflict of interest

This study has no conflicts of interest.

Statement of ethical approval

The Research Ethics Committee at Dr. Moewardi Hospital, Surakarta, Indonesia, issued the ethical clearance approval letter, No. 818/VI/HREC/2022.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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