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Complete blood count derived inflammation indexes predict outcome in COVID-19 patients: a study in Indonesia

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Abstract

Introduction: Inflammation plays a vital role in the pathophysiology of COVID-19. Complete blood count (CBC) is a routine test performed on patients. It provides information regarding the inflammatory process and can be used as a predictor of outcome. This study aimed to explore the correlation between different complete blood count (CBC)-derived inflammation indexes at hospital admission, such as neutrophil to lymphocyte ratio (NLR), derived NLR (dNLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte × platelet ratio (NLPR), aggregate index of systemic inflammation (AISI), systemic inflammation response index (SIRI), and systemic immune-inflammation index (SII), to in-hospital mortality in confirmed COVID-19 patients.

Methodology: A retrospective observational study was performed at Ulin Referral Hospital of South Kalimantan with 445 COVID-19 patients from April to November 2020. The patients were divided into two groups, non-survivor and survivor. A receiver operating characteristic (ROC) curve was used to determine the cut-off values. Bivariate analysis was performed using the Chi Square test, the risk ratio was calculated, and logistics regression was determined.

Results: Increase of NLR, dNLR, PLR, MLR, NLPR, MLR, AISI, SIRI, and SII from cut-off values were significantly correlated with patient survival outcome. The cut off values were 6.90, 4.10, 295, 0.42, 0.037, 1,422, 1.80, and 2,504 respectively. NLPR was dominant in predicting in-hospital mortality (OR: 6.668, $p = 0.000$) with a 28.1% sensitivity and 95.9% specificity.

Conclusions: CBC-derived inflammation indexes were associated with the survival outcome of confirmed COVID-19 patients and NLPR was a dominant variable.

Key words: COVID-19; CBC-derived inflammation indexes; NLPR; outcome.

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new coronavirus that first appeared in Wuhan, Hubei province, China in December 2019 causing the coronavirus disease 2019 (COVID-19) [1,2]. As of 28 August 2022, the World Health Organization (WHO) has reported over 598 million confirmed cases and over 6.4 million deaths globally [Case Fatality Rate (CFR) 1.08%]. The Ministry of Health of the Republic of Indonesia reported 6,358,808 confirmed cases of COVID-19 with 6,156,034 recovered and 157,566 deaths (CFR 2.47%). Meanwhile, South Kalimantan recorded 87,291 confirmed cases, with 84,424 cured cases and 2,581 deaths (CFR 2.95%), making South Kalimantan one of the provinces with a high COVID-19 death rate [3,4].

Complete blood count (CBC) is a regular pathological examination that is widely available, inexpensive, and easy to perform. It provides much necessary information about the inflammatory processes in COVID-19 [5]. While neutrophil, monocyte, lymphocyte, and platelet components in CBC can describe the inflammatory process, the ratio between those components can be a predictive parameter that is also considered significant for predicting the course and outcome of disease due to the interaction of complex immune processes in COVID-19 [6,7].

Complete blood count inflammation indexes that are reported to vary in several studies include neutrophil to lymphocyte ratio (NLR), derived NLR (dNLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte ×

platelet ratio (NLPR), aggregate index of systemic inflammation (AISI), systemic inflammation response index (SIRI), and systemic immune-inflammation index (SII) [6,7].

Given the limited research on CBC-inflammation indexes in relation to COVID-19 in Indonesia, this study explored a correlation between the different CBC-derived inflammation indexes at hospital admission and in-hospital mortality in confirmed COVID-19 patients at Ulin Regional Hospital Banjarmasin which was a COVID-19 referral hospital in South Kalimantan. This study aimed to provide early markers and aids for determining prognosis and providing optimal management to prevent poor outcomes, especially in countries with limited sources like Indonesia.

Methodology

Design and the samples for the study

A retrospective observational study was performed at the Ulin Referral Hospital of South Kalimantan with 445 patients who were confirmed COVID-19 admitted from April-November 2020. This research has received ethical approval from the Ethical Research Committee No. 881/KEPK-FK ULM/EC/X/2021.

The sampling technique used total sampling of all patients with confirmed COVID-19 who had complete blood count test done at the beginning of hospital admission in Ulin General Hospital Banjarmasin. A confirmed diagnosis of COVID-19 is defined as a positive COVID-19 test result as evidenced by reverse transcriptase-polymerase chain reaction (RT-PCR) laboratory tests.

Data collection

The data included demographic variables, laboratory investigations including CBC and CBC-inflammation indexes, and outcome of patients (survive and non-survive). Demographic details included age, gender, comorbidities, and disease severity (non-severe or severe). Non-severe patients were defined as patients with mild and moderate degree [pneumonia (+), SaO_2 > 93 % room air] of severity of disease at the beginning of hospital admission. Severe patients were defined as those with SaO_2 < 93% room air or those who had acute respiratory distress syndrome (ARDS), sepsis, or septic shock. Complete blood count tests that were performed immediately after hospital admission for each patient included hemoglobin (Hb), leukocytes, platelets, neutrophils, lymphocytes, and monocytes. Complete blood count inflammation indexes included neutrophil to lymphocyte ratio (NLR), derived NLR (dNLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), neutrophil to lymphocyte × platelet ratio (NLPR), aggregate index of systemic inflammation (AISI), systemic inflammation response index (SIRI), and systemic immune-inflammation index (SII). Patients with incomplete medical records of the variables studied and those who had hematological malignancies were excluded from the sample subjects. The patients were divided into two groups: non-survivors, and survivors.

Statistical analysis

The data were tabulated using Microsoft Excel and statistically analyzed using SPSS 25 software [8]. The parametric analysis variables were analyzed by the independent sample t-test, and non-parametric variables were analyzed by the Mann-Whitney test. The variable was determined to be a significant difference if the *p* value was < 0.05. Receiver operating characteristic (ROC) curve and area under the curve (AUC) were used to analyze the optimal cut-off for prediction value. Bivariate analysis was performed using the Chi square test. Regression logistics tests were used to determine the dominant CBC-inflammation indexes associated with the survival outcome of confirmed COVID-19.

Table 1. Demographic and baseline characteristic patients.

Variable	Total	Non-Survivor n = 153 (34%)	Survivor n = 292 (66%)	*p* value
Age-years (median)	50 (40-57)	51 (41-59)	48 (38-56)	0.056†
Gender				
Men (%)	244 (54.8)	85 (55.6)	159 (54.5)	0.824‡
Women (%)	201 (45.2)	68 (44.4)	133 (45.5)	
Comorbidities				
Any comorbidities (%)	266 (59.8)	105 (68.6)	192 (65.6%)	0.587‡
No comorbidities (%)	179 (40.2)	48 (31.4)	100 (34.3%)	
Degree of severity				
Severe (%)	266 (59.8)	105 (68.6)	161 (55,1)	0.06‡
Non-severe (%)	179 (40.2)	48 (31.4)	131 (44.9)	

†T-2 tailed sample Test; ‡Mann-Whitney Test.

Table 2. Comparison of complete blood count between non-survivor and survivor group.

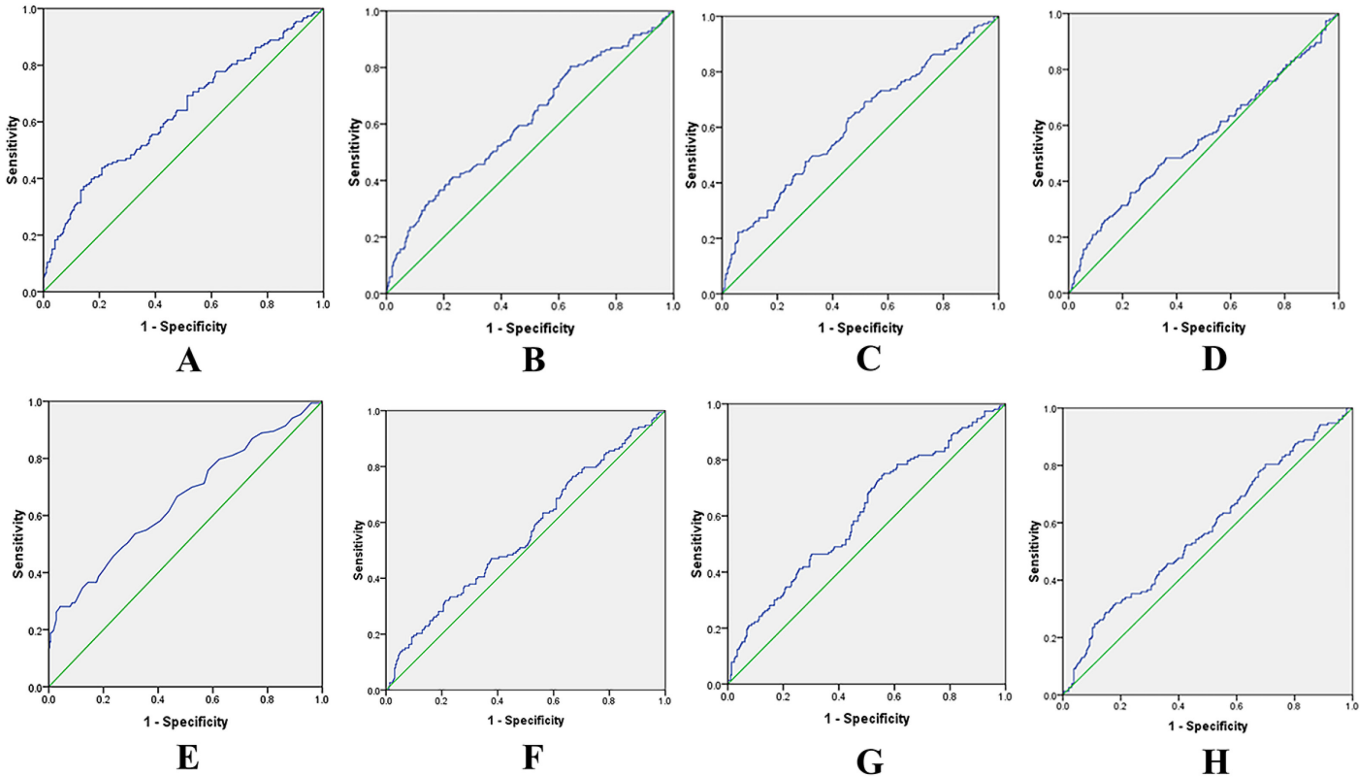
Variable	Non-Survivor n = 153 (34%)		Survivor n = 292 (65%)		*p* value
	Median	IQR	Median	IQR	
Haemoglobin (gr/dL)	13.2	11-14	13.3	11.6-14.7	0.579†
Leukocytes (× 10^9/L)	8.7	6.5-11.6	8	5.9-10.6	0.083†
Platelets (× 10^9/L)	256	190-350	278	245-368	0.012†*
Neutrophils (× 10^9/L)	6	4-9	5.9	3.71-8.26	0.018†*
Lymphocytes (× 10^9/L)	1.1	0.8-1.5	1.37	1.03-1.80	0.000†*
Monocytes (× 10^9/L)	0.58	0.44-0.74	0.58	0.41-0.78	0.911†

†Uji Mann Whitney; IQR: interquartile; * Significant variable.

Table 3. Cut off values of CBC-inflammation indexes.

Variable	Mean	AUC	95% CI	*p value*	*Cut-off*	Meaning	Spes
NLR	5.93	0.631	0.575-0.687	0.000	≥ 6.90	20.9	70.9
dNLR	3.55	0.609	0.553-0.666	0.000	≥ 4.10	41.2	77.1
PLR	246	0.552	0.494-0.611	0.069	≥ 295	35.9	77
MLR	0.50	0.611	0.555-0.667	0.000	≥ 0.42	63.4	54.5
NLPR	0.023	0.654	0.599-0.710	0.000	≥ 0.037	28.1	95.9
AISI	1,303	0.558	0.501-0.614	0.045	≥ 1,422	32	78.8
SIRI	3.92	0.606	0.551-0.661	0.000	≥ 1.80	75.2	44
SII	1,816	0.572	0.515-0.628	0.013	≥ 2,504	28.8	85.3

Figure 1. ROC curve of routine blood biomarkers for COVID-19 patient outcomes.



A: NLR; **B:** dNLR; **C:** PLR; **D:** MLR; **E:** NLPR; **F:** AISI; **G:** SIRI; **H:** SII.

Results

Patient demographics and baseline characteristics

Table 1 lists the demographics and baseline characteristics of the 445 patients confirmed for COVID-19 in the April-November 2020 period; the survivor group included 292 patients (66%), and the non-survivor group included 153 patients (34%). The median age in this study was 50 years, and the majority of males (54.8%) had comorbidity (59.8%) and severe degree illness (59.8%). The group of non-survivors had a median age higher than the patients who survived (median 51 years old, IQR: 41-59 vs. median 48 years old, IQR 38-56), males (55.6% vs. 54.5%), have comorbid (68.6% vs. 65.6%) and severe degree illness (68.6% vs. 55.1%). Comparisons made according to the outcome of patients showed that there was no statistically significant difference in age, gender, comorbidity, and severity of illness between the non-survivor and survivor groups (p value > 0.05).

The non-survivor group had some CBC parameters lower than survivors which included: haemoglobin (median 13.2 gr/dL, IQR 11-14 gr/dL vs median 13.3 gr/dL, IQR 11.6-14.7 gr/dL); platelets (median 256 × 10^9/L, IQR 190-350 × 10^9/L vs median 278 × 10^9/L, IQR 245-368 × 10^9/L); and lymphocytes (median 1.1 × 10^9/L, IQR 0.8-1.5 × 10^9/L vs median 1.37 × 10^9/L, IQR 1.03-1.80 × 10^9/L) (Table 2). Meanwhile, the number of leukocytes (median 8.7 × 10^9/L, IQR 6.5-11.6 × 10^9/L vs median 8 × 10^9/L, IQR 5.9-10.6 × 10^9/L) and neutrophils (median 6 × 10^9/L, IQR 4-9 × 10^9/L vs median 8 × 10^9/L, IQR 3.71-8.26 × 10^9/L) were higher in the non-survivor group compared to survivors. Statistical analysis for the comparison of CBC values in the groups showed significant differences in platelet, neutrophil, and lymphocyte counts with p value < 0.05.

Complete blood count inflammation indexes in confirmed COVID-19 patients

The optimal cut off values from the CBC-inflammation indexes were as follows: NLR, 6.90; dNLR, 4.10; PLR, 295; MLR, 0.42; NLPR, 0.037; AISI, 1,422; SIRI, 1.80; and SII, 2,504 (Table 3). After statistical calculations using the Youden index (Figure 1), it was determined that the increase in the value of NLR, dNLR, MLR, NLPR, AISI, SIRI, and SII increased risk of a non-survival outcome in COVID-19 confirmed patients.

Complete blood count inflammation indexes in non-survivor vs. survivor group COVID-19 patients

Comparisons made according to the outcome of patients indicated a statistically significant difference in CBC-inflammation indexes between non-survivor and survivor COVID-19 patient groups with p value > 0.05 (with the amount of risk corresponding to the prevalence rate column) (Table 4).

CBC-inflammation indexes logistic regression tests result concluded that NLPR was the dominant variable associated with the outcome in confirmed patients of COVID-19 with an Exp (B) value = 6,668 (Table 5). It was shown that when the NLPR was more than the cut-off value, there was an increased risk of (6,668 times higher) non-survival outcome of COVID-19 confirmed patients compared to the lower NLPR.

Discussion

The relationship of demographic and clinical characteristics with the outcome in COVID-19 patients has been established in many studies with different results. Based on demographic and baseline characteristics of patients in our study, the non-survivor

Table 4. Comparison CBC-inflammation indexes between non-survivor and survivor group.

Variable		Non-Survivor (153)	Survivor (292)	Prevalence Rate (PR)	p value
NLR	≥ 6.9	67 (52.3 %)	61 (47.7%)	1.929	0.000*
	< 6.9	86 (27.1%)	231 (72.9%)		
dNLR	≥ 4.1	63 (46.7%)	72 (53.3%)	1.251	0.000*
	< 4.1	90 (29%)	220 (71.0%)		
PLR	≥ 295	53 (44.2%)	67 (55.8%)	1.435	0.008*
	< 295	100 (30.8%)	225 (69.2)		
MLR	≥ 0.42	97 (42.2%)	133 (57.8%)	1.619	0.000*
	< 0.42	56 (26.0%)	159 (74.0%)		
NLPR	≥ 0.037	43 (75.4%)	14 (23.6%)	2.661	0.000*
	< 0.037	110 (28.4%)	278 (71.6%)		
AISI	≥ 1,422	48 (43.6%)	62 (56.4%)	1.392	0.019*
	< 1,422	153 (31.3%)	230 68.7%)		
SIRI	≥ 1.80	115 (41.2%)	164 (58.8%)	1.801	0.000*
	< 1.80	38 (22.9%)	128 (77.1%)		
SII	≥ 2,504	44 (50.6%)	43 (49.9%)	1.661	0.000*
	< 2,504	109 (30.9%)	249 (69.9%)		

* Significant variable.

group was older (51 years old), males (55.6%), had comorbidities (68.6%) and severe illness (68.6%) compared to the survivor group. However, there was no statistically significant difference between the two groups. Research by Adem *et al.* reported that age has a significant relationship with mortality of COVID-19 patients but there was no significant relationship with gender [9]. Prado *et al.* concluded that older age, male gender, and the presence of comorbidities were related to deaths in COVID-19 patients [10]. Another study by Liu *et al.* reported that severe COVID-19 more often causes death (32.5%) than mild COVID-19. In addition to age, comorbidities, and the severity of the disease, other factors such as race, genetics, and habits like a healthy lifestyle are suspected of playing a role in COVID-19 infection [11].

This study showed significant differences in increased neutrophils and decreased platelets, and lymphocytes count in the non-survivor group compared to the survivor group. Neutrophils are part of the leukocytes that play a role in the innate and adaptive immune system. During COVID-19 infection, there is an increase in neutrophils induced by the rise in CXC-3. Neutrophilia can induce neutrophil extracellular traps (NETs), and neutrophilic mucositis cause immunotrombosis and ARDS. This increases mortality in COVID-19 patients [12,13]. Research by Zhao *et al*. is in line with this study that significant increases in the number of neutrophils are observed in non-survivor patients compared to survivor patients ($p < 0.001$) [14]. The platelets function as part of the immune system by contributing to the inflammatory process and maintaining hemostasis. Decreased platelet count is often found in COVID-19 patients and is caused by the complex process of direct destruction of megakaryocytes in the bone marrow, activation of renin-angiotensin-aldosteron-system (RASS) pathways, and formation of the immune-autoantibodies complex. Our results are similar to research by Yang *et al*. who reported that non-survivor COVID-19 patients had lower platelet counts than survivors (72.7% vs. 10.7%, $p < 0.001$) [15]. The study by Lippi *et al*. also concluded that patients with thrombocytopenia conditions experienced worsening during the patient's hospitalization [16]. Zhao *et al*. reported a decrease in lymphocytes in non-survivor patients compared to survivor patients; similar observations were made in this study. Reduction in the number of lymphocytes during COVID-19 infection occurred through several mechanisms, including direct destruction of COVID-19 virus particles in lymphoid tissue and increased expression of *Fas*, excessive expression of *CXCL10* and *CCL2* resulting in direct suppression of lymphopoiesis from hematopoietic stem cells (HSC), an increase of serum proinflammatory cytokine levels such as TNF-α and IL-6, lactic acidosis that interferes with lymphocyte proliferation, increased expression of apoptosis-related genes in peripheral blood, decreased lymphocyte-related gene expression (*MAP2K7* and *SOS1*) and reduced interaction of soluble form from CD25 (SCD25) with IL-2 leading to impaired clonal expansion of T cells [14,17].

Table 5. CBC-inflammation indexes with COVID-19 outcome using logistic regression analysis.

Variable	Sig	Exp (B)
Stage I Regression Test		
NLR	0.158	2.017
dNLR	0.061	0.431
PLR	0.709	1.117
MLR	0.605	1.155
NLPR	0.000	6.997
AISI	0.293	0.678
SIRI	0.092	1.635
SII	0.227	1.753
Stage II Regression Test		
NLR	0.122*	2.120
dNLR	0.040*	0.407
NLPR	0.000*	7.192
SIRI	0.049*	1.627
SII	0.295	1.467
Stage III Regression Test		
NLR	0.022	2.686
dNLR	0.043	0.412
NLPR	0.000*	6.668*
SIRI	0.042	1.651

* Significant variable.

NLR, dNLR, and NLPR ratios are obtained by comparing the number of leukocytes, neutrophils, and lymphocytes. In this study, NLR ≥ 6.9 (sensitivity 20.9% and specificity 70.9%) increased risk 1.721 times of reaching the non-survival outcome in patients with confirmed COVID-19 (p value = 0.000). NLR is an inflammatory biomarker obtained by dividing the absolute neutrophil value by the absolute lymphocyte value. A meta-analysis by Li *et al*. concluded that NLR can predict the mortality of patients with confirmed COVID-19 [18]. dNLR modifies NLR by including the number of leukocytes in the ratio calculation. dNLR is a biomarker that is often used as a predictor in malignancy. The cut-off dNLR value ≥ 4.1 (sensitivity 41.2% and specificity 77.1%) increased the risk of non-survival outcome in confirmed COVID-19 patients 1.251 times. Research by Fois *et al.* demonstrated higher dNLR values in non-survivor patients. Other research by Aly *et al*. concluded that dNLR is a CBC-inflammation index with the highest specificity value compared to NLR, PLR, and MLR to predict the

prognosis of COVID-19 patients (cut-off > 2.86, sensitivity 67.20% and specificity 89.19%, p value < 0.001). An increase in NLR and dNLR values indicate an increased neutrophil-dependent inflammatory condition followed at the same time with decreased lymphocyte-mediated immune response [6,19]. In this study, NLPR ≥ 0.037 (sensitivity 28.1% and specificity 95.9%) increased the non-survival risk in patients with confirmed COVID-19 by 2.661 times. NLPR is a CBC-inflammation index that describes the interaction of neutrophils, lymphocytes, and platelets. In research by Fois *et al*., NLPR scores were higher in non-surviving patients [6]. In other studies, conducted by Gameiro *et al.,* NLPR values were higher by > 0.14 (sensitivity 33.1% and specificity 79.7%) in non-survivors with sepsis and acute kidney injury (AKI) [20].

This study showed that PLR value of ≥ 295 (sensitivity 35.9% and specificity 77%) increased the non-surviving outcome in patients with confirmed COVID-19 by 1.435 times. Research by Aly *et al.* and Fois *et al*. also obtained similar results that increased PLR is an independent risk factor of increased mortality in COVID-19 patients [19]. The increase in the value of PLR in COVID-19 patients is still unclear. It is suspected that a significant decrease in the number of lymphocytes compared to the decline in platelet count is the main cause of an increase in PLR value in various diseases [6].

MLR values of ≥ 0.42 (sensitivity 63.4% and specificity 54.5%) increased the non-survival risk in COVID-19 confirmed patients by 1.619 times in this study. Fois *et al.* also reported that high MLR cut-off values (≥ 0.37) were found in non-survivors [6]. Another research by Yang *et al.* reported high MLR results in non-survivors who had ARDS in the first 28 days of hospitalization. Monocytes have an essential role in initiating inflammatory processes and as infection effectors. There is no exception in COVID-19. COVID-19 causes rapid recruitment of monocytes in the lungs. It makes monocytes differentiate rapidly to perform many functions, such as increasing phagocyte activity and forming proinflammatory cytokines, causing monocytosis conditions and may affect the rise in MLR ratio [21].

AISI (MLR × neutrophil absolute × platelet), SIRI (MLR × neutrophil absolute), and SII (NLR × platelets) values were associated with survival in patients with confirmed COVID-19. Research by Fois *et al*. reported non-survivors to have a higher AISI, SIRI, and SII value than survivors [6]. In our study, AISI, SIRI, and SII with a cut-off value of ≥1,422; ≥1.8 and ≥ 2,504, respectively increased 1335; 1.801 and 1.661 times non-surviving risk outcome in COVID-19 confirmed patients, respectively.

CBC inflammation indexes logistic regression tests with outcome in COVID-19 confirmed patients in this study concluded that NLPR is a dominant variable in predicting in-hospital mortality (OR: 6.668, p = 0.000) with 28.1% sensitivity and 95.9% specificity.

NLPR research on COVID-19 is very limited, particularly in Indonesia. However, NLPR is reported to be one of the routine CBC-inflammation indexes studied in certain diseases. For example, in research by Koo *et al.,* high NLPR values was a risk factor for mortality in the first five years of heart surgery, and Fonseca *et al*. studied high NLPR as a risk factor for acute kidney injury in abdominal surgery [22,23]. In the case of COVID-19, research by Fois *et al.* obtained NLPR values among non-survivors as higher than among survivors (median: 0.0121; IQR: 0.0075–0.0194 vs median: 0.0215; IQR: 0.0142–0.0508, p-value 0.0009). NLPR describes the interaction of acute processes of the immune system and immunoembolism involving neutrophils, lymphocytes, and platelets [6].

Another important point is the relationship between age, inflammatory indexes, and poor outcomes. Despite the fact that there was no statistically significant difference in age between the survivor and non-survivor groups in our study, the non-survivor group was older. The disparity between the mortality rates of elderly and non-elderly patients indicates the possibility that a range of various risk factors may be responsible for this discrepancy. Elderly patients have a higher risk for severe COVID-19. This is due to changes in the immune system that limit their capacity to fight infection. A study by Ghobadi *et al.* demonstrated that in comparison to non-elderly patients, elderly patients had more severe laboratory findings and systemic inflammatory indexes (NLR, PLR, dNLR, SIR-I, SII, AISI, and NLPR) at the time of admission [24]. The exact mechanisms underlying the association between inflammation indexes and mortality in elderly individuals are not certain [24,25].

Our study has some limitations; it is a single-center research, retrospective study, and no further analysis, such as the type of comorbidities, complications, and treatment were done. This biased the CBC-inflammation indexes and outcome in patients with confirmed COVID-19. Further prospective studies are needed to construct data and provide insights into this ongoing pandemic, especially in Indonesia.

Conclusions

CBC-derived inflammation indexes during hospital admission are associated with and can predict poor outcomes in confirmed COVID-19 patients. The increase of NLR, dNLR, PLR, MLR, NLPR, MLR, AISI, SIRI, and SII from cut-off values was significantly correlated with patient survival and NLPR was dominant in predicting in-hospital mortality. Therefore, this study established that CBC is an inexpensive and simple test for an early marker in determining poor outcomes and is potentially helpful for doctors and medical personnel in countries with limited resources to determine when the treatment should be aggressive in COVID-19 patients.

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