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Original Article

Inflammatory Markers upon Admission as Predictors of Outcome in COVID-19 Patients

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) may cause dysregulation of the immune system, leading to hyperinflammation. Inflammatory markers can be used to predict in-hospital mortality in COVID-19 patients. This research was aimed to investigate the association between the levels of various inflammatory markers and mortality in COVID-19 patients.*
Methods: *This study was conducted at Persahabatan National Respiratory Referral Hospital, Indonesia. Blood tests were performed upon admission, measuring the C-reactive protein, PCT, leukocyte, differential counts, and platelet count. The outcome measured was the mortality of hospitalized COVID-19 patients. Statistical analysis methods included the Mann–Whitney U test, receiver operating characteristic (ROC) analysis, and area under the curve (AUC) test.*
Results: *Total 110 patients were included, and the laboratory values were analyzed to compare survivors and non-survivors. The non-survivor group had significantly higher leukocyte count, lower lymphocyte count, higher CRP and PCT levels, higher neutrophil-to-lymphocyte ratio (NLR), higher platelet-to-lymphocyte ratio (PLR), and lower lymphocyte-to-CRP ratio. As predictors of mortality, AUC analysis revealed that PCT, CRP, NLR, and PLR had AUCs of 0.867, 0.82, 0.791, and 0.746, respectively.*
Conclusions: *Routine and affordable inflammatory markers tested on admission may be useful as predictors of in-hospital mortality in COVID-19 patients requiring hospitalization.* ***(J Respirol Indones 2021; 41(4): 252–9)***
Keywords: *biomarkers; COVID-19; mortality; prognosis*

Penanda Inflamasi saat Masuk Sebagai Prediktor Luaran pada Pasien COVID-19

Abstrak

Latar Belakang: *Coronavirus Disease 2019 (COVID-19) dapat menyebabkan disregulasi sistem imun yang berujung pada hiperinflamasi. Penanda inflamasi dapat digunakan untuk memprediksi mortalitas dan kesintasan pada pasien COVID-19. Penelitian ini bertujuan untuk menyelidiki hubungan antara berbagai penanda inflamasi dengan mortalitas pada pasien COVID-19.*
Metode: *Penelitian ini dilakukan di Rumah Sakit Persahabatan, Indonesia. Uji laboratorium pada sampel darah yang meliputi C-reactive protein (CRP), procalcitonin (PCT), jumlah dan hitung jenis leukosit, dan jumlah trombosit diukur pada saat masuk rawat. Luaran yang dievaluasi adalah kematian pada pasien rawat inap dengan COVID-19. Analisis statistik meliputi uji Mann-Whitney U, analisis karakteristik operasi penerima (ROC), dan uji area di bawah kurva (AUC).*
Hasil: *Data laboratorium dan luaran dari 110 pasien yang dirawat di RS Persahabatan dengan COVID-19 dianalis. Kelompok non-survivor memiliki jumlah leukosit yang lebih tinggi secara signifikan, jumlah limfosit yang lebih rendah, tingkat CRP dan PCT yang lebih tinggi, rasio Neutrofil-ke-Limfosit (NLR) yang lebih tinggi, serta Rasio Platelet-Limfosit (PLR), dan rasio Limfosit / CRP yang lebih rendah. Sebagai prediktor mortalitas, analisis AUC menunjukkan bahwa PCT, CRP, NLR, dan PLR masing-masing memiliki AUC 0,867, 0,82, 0,791, dan 0,746.*
Kesimpulan: *Penanda inflamasi rutin dan terjangkau yang diuji selama masuk mungkin berguna sebagai prediktor kematian di rumah sakit pada pasien COVID-19 yang membutuhkan rawat inap.* ***(J Respirol Indones 2021; 41(4): 252–9)***
Kata kunci: *penanda inflamasi; COVID-19; mortalitas; prognosis*

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a novel disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously called the novel coronavirus (2019-nCoV). It was first identified following an increase in respiratory illness with an unknown cause.[1,2] The disease spread rapidly throughout multiple countries and was declared a public health emergency of international concern by the World Health Organization (WHO) on 30 January 2020. The WHO escalate the status to be a global pandemic on 11 March 2020. The first two cases of COVID-19 in Indonesia were reported on 2 March 2020, and the number has been increasing since then. As of 23 February 2021, there have been more than 117 million confirmed cases of COVID-19 globally causing disruption in normal healthcare routine.

The mortality rate of COVID-19 is approximately 2–7% and varies Among the countries.[3] Approximately 20% of patients with COVID-19 develop severe symptoms, including acute respiratory distress syndrome requiring hospitalization.[4] As the number of patients with COVID-19 increases, an imbalance between demand and availability of medical assistance may occur.[5–7] This may explain why the mortality rate remains relatively low in developed countries and gradually increase in overburdened countries. Worsen situation emerges urgent need prioritizing healthcare resources to save more lives, for example deciding patient to get advance care in Intensive Care Unit (ICU). Above all, the foremost goal is to keep a low mortality.[8,9]

Along with substantial evidence that COVID-19 may cause dysregulation of the immune system, allows the development of hyperinflammation. Severe cases of COVID-19 tend to have lower lymphocyte counts, higher leukocyte counts, and higher neutrophil-to-lymphocyte ratios (NLR).[10] The NLR is a well-known biomarker of systemic inflammation and infection. Higher NLR values have been associated with poor prognosis in inflammatory diseases, such as sepsis and cancer.[11,12] In COVID-19, the NLR has been suggested as a predictor of poor prognosis. This study aimed to investigate the association between several inflammatory markers tested upon admission and mortality rates in patients hospitalized with severe COVID-19.

METHODS

This was a retrospective cohort study conducted at the Persahabatan National Respiratory Referral Hospital in Jakarta, Indonesia, which is one of the major hospitals responsible for COVID-19 management, assigned by the government. A total sampling method was used. All hospitalized patients aged 18 years and older with confirmed COVID-19 between March and April 2020 were included in this study. The diagnosis of COVID-19 was based on WHO guidelines and confirmed by positive results of SARS-CoV-2 RNA. A total of 110 patients with COVID-19 who had a definite outcome (survivors vs. non-survivors) were included. Outcomes were measured at the time of death or discharge. The patient was discharged after at least 14 days of observation and two consecutive negative reverse transcription polymerase chain reaction (RT-PCR) tests.

Collected data including demographic data (age and sex) as well as laboratory findings (white blood cells [WBCs], neutrophils, lymphocytes, monocytes, platelets, C-reactive protein [CRP], and procalcitonin [PCT]). Using these data, we calculated the NLR, platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-CRP ratio (LCR). All data were extracted from electronic medical records using a standardized data collection form.

Blood samples were obtained within 24 hours after admission to perform routine laboratory tests, such as complete blood count, electrolytes, serum biochemical tests, and coagulation profiles. All measurements were performed within 1 hour after blood sampling. Complete blood count was analyzed using the Sysmex XN-2000 hematology analyzer. The CRP assay was performed using the Abbott Architect c8000. The PCT assay was performed using the Abbot Architect i2000.

Data analysis was conducted using IBM SPSS Statistics for Windows, version 20.0. Descriptive analysis was performed using frequencies and percentages for categorical variables and median (minimum–maximum) for quantitative variables. Bivariate analysis of the associations between various inflammatory markers and in-hospital mortality was performed. Normally distributed data were analyzed as independent samples using the independent sample t-test, while skewed distribution data were analyzed using the Mann–Whitney U test. Comparison of categorical variables between survivors and non-survivors were performed using the chi-square test. The optimal cutoff points for various inflammatory markers were evaluated using receiver operator characteristic (ROC) curves. To minimize observer bias, personnel directly involved in patient care were not involved in the statistical analysis.

This study was approved by the Ethics Committee of the Persahabatan National Respiratory Referral Hospital on 30 March 2020, in Jakarta, Indonesia.

RESULTS

A total of 110 hospitalized patients aged 28–84 years were included in this study. The overall mortality rate was 58.2%. No statistically significant difference in mortality was observed between men and women. The mean age was significantly higher in the non-survivor group (*P*=0.035).

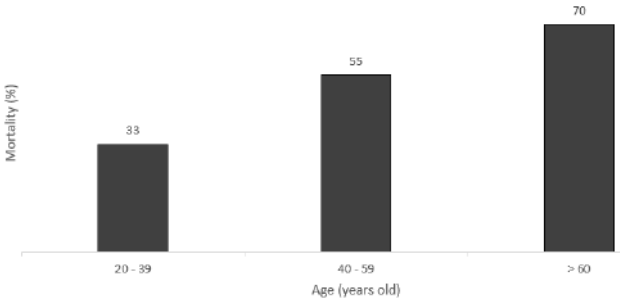

Figure 1. Mortality rate in different age groups (%).

We further divided the subjects into the following three age groups: 20–39, 40–59, and >60 years (Figure 1). Mortality was higher in the older age groups than in the younger, as shown in Figure 1. Differences in the mean values of inflammatory markers between COVID-19 survivors and non-survivors were significant for leukocyte count, neutrophil count, lymphocyte count, CRP, PCT, NLR, PLR, and LCR (Table 1).

For all inflammatory markers described in Table 1, we evaluated their predictive values for mortality using ROC curves (Figure 2). We excluded patients who did not have all inflammatory markers tested on admission. A total of 94 patients were included in the ROC analysis.

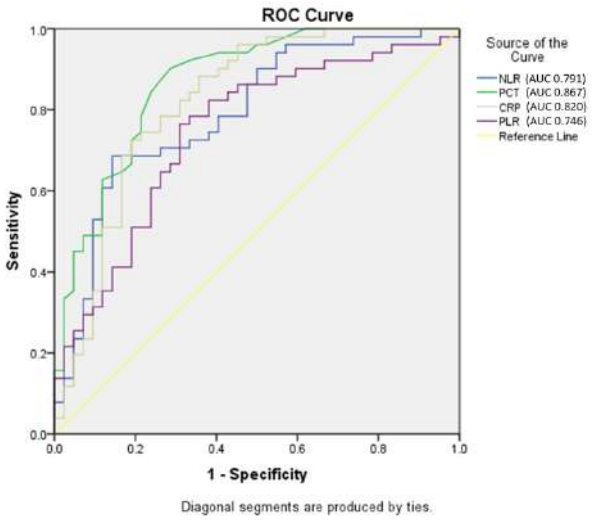

Figure 2. Performance of various inflammatory markers in predicting mortality in COVID-19 patients

These results demonstrated the great predictive capacity of PCT, CRP, NLR, and PLR as possible clinical predictors of mortality in hospitalized COVID-19 patients (Table 2). The optimum cutoff values of various inflammatory markers for the prediction of mortality as well as their sensitivity and specificity are summarized in Table 3.

The predictive capacity of the LCR was evaluated using an area under the curve (AUC) analysis. The LCR AUC as a predictor of good outcome was 0.852 (*P*<0.001; 95% confidence interval [CI]: 0.772–0.932) (Figure 3).

The optimal cutoff point of LCR for the prediction of good outcome was set at 0.086, and the corresponding calculations for sensitivity and specificity as well as the positive and negative predictive values were 81.4%, 77.8%, 84%, and 74.74%, respectively.

Table 1. Characteristics of subjects

Variable	Non-survivor, n (%)	Survivor, n (%)	*P*	RR (95% CI)
Age (years ± SD)	58,11±12,058	52,76±14,054		
Young adult (20–39)	5 (4,5%)	10 (9.1%)		
Adult (40–59)	28 (25,5%)	23 (20.9%)	0,035	
Elderly (>60)	31 (28,2%)	13 (11.8%)		
Gender				
Male	46 (60,5%)	30 (39,5%)	0,456	1.143 (0.793–1.647)
Female	18 (53%)	16 (47%)		
Laboratory findings				
Leucocyte (10^3/µL)	10,74 (3,54–24,18)	6.99 (3.21–17.06)	<0,001	
Neutrophil (%)	86,75 (51,20–95,60)	75,30 (36,40–94,70)	<0,001	
Lymphocyte (%)	7,75 (1,00–39,30)	17,25 (3,20–51,50)	<0,001	
Monocyte (%)	5,80 (1,00–16,10)	6,50 (1,10–14,40)	0,111	
Platelet (10^3/µL)	241,50 (100,00–564,00)	262,00 (43,00–451,00)	0,533	
CRP (mg/L)	164,20 (22,50–449,80)	49,70 (1,50–348,90)	<0,001	
Procalcitonin (ng/mL)	0,29 (0,05–17,66)	0,06 (0,01–1,15)	<0,001	
NLR	11,27 (1,30–94,10)	4,42 (0,71–29,59)	<0,001	
PLR	29,24 (3,42–198,00)	15,34 (3,61–85,00)	<0,001	
LCR	0,04 (0,01–0,73)	0,28 (0,01–14,53)	<0,001	

Note: RR=relative risk; NLR=neutrophil-to-lymphocyte ratio; PLR=platelet-to-lymphocyte ratio; LCR=lymphocyte-to-CRP ratio

Table 2. AUCs of inflammatory markers for predicting mortality in severe, hospitalized COVID-19 patients

Variable	Area under the curve	*P*	95% CI
Neutrophil-to-lymphocyte ratio (NLR)	0.791	<0.001	0.698–0.884
Platelet-to-lymphocyte ratio (PLR)	0,746	<0,001	0,645–0,847
Procalcitonin	0,867	<0,001	0,793–0,941
C-reactive protein	0,820	<0,001	0,730–0,911

Table 3. The cutoff points of PCT, CRP, NLR, and PLR for predicting mortality in severe and critical COVID-19 patients

Cutoff Points	Sensitivity	Specificity	PPV[a]	NPV[b]
Procalcitonin ≥0.155 ng/mL	76.5%	78.6%	82.35%	72.34%
C-reactive protein ≥94,750	80,4%	69%	75,86%	74,36%
Neutrophile/ lymphocyte ratio ≥7,08	70,6%	71,4%	76,36%	60,00%
Platelet/lymphocyte ratio ≥ 19,57	76,5%	69%	75,41%	63,27%

Note: [a]PPV positive predictive value; [b]NPV negative predictive value

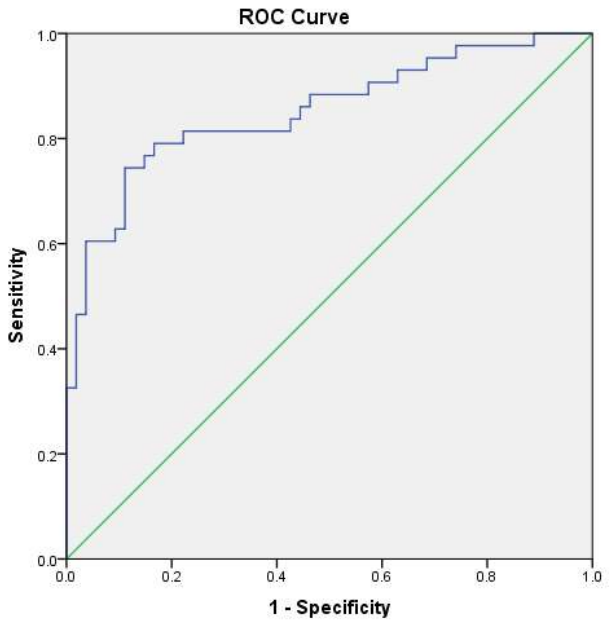

Figure 3. Performance of lymphocyte-to-CRP ratio in predicting good outcome in COVI1D-19 patients with an AUC of 0.852

DISCUSSION

As clinicians in a developing country, we often face the dilemma of deciding which patients would be given the limited health resources, for example, ICU bed, ventilator or high flow oxygen therapy. The particular significance in this study is the fact that we only analyzed inflammatory markers that are affordable and readily available in most hospitals. More importantly, these markers are routinely assessed for every patient during admission, rendering them ideal for screening COVID-19 patients with a higher mortality rate.

In this study, the mortality rate was higher than that reported in other studies. This can be attributed to the fact that the Persahabatan National Respiratory Referral Hospital was a COVID-19

referral hospital; therefore, only patients with severe and critical COVID-19 were hospitalized. This analysis only included patients who were hospitalized and had a final outcome on the day of data analysis. Ongoing treatment patients without final outcome (survival or death) were not included in this study.

This study revealed that older patients had higher mortality rates than younger patients. Increased mortality among elderly might have been caused by the impairment of the immune system characterized by the low-grade and chronic systemic inflammatory state associated with aging.[13] Older patient also tend to have more comorbidities, such as diabetes and hypertension.[14] Diabetes is a chronic inflammatory state disease characterized by multiple metabolic abnormalities that potentially affect the body's response to pathogens. Insulin resistance and the resulting hyperglycemia promote the synthesis of pro-inflammatory cytokines and oxidative stress, which may worsen outcomes in patients with COVID-19.[15,16] Hypertension has also been shown to increase the mortality of patients with COVID-19 through the involvement of vascular damage, although the exact mechanism is still largely unknown.[17]

Based on an analysis of 110 patients with COVID-19, we found that leukocyte and neutrophil counts increased significantly, whereas lymphocytes significantly decreased in non-survivors when compared to those in survivors. According to a study by Qin et al.(10), the decreased lymphocyte subsets are regulatory cells and CD4+ cells, which have vital role in suppressing inflammation. This condition may lead to a hyperinflammatory immune response in patients with severe COVID-19. Well-coordinated immune responses are important in defending against viral infections. However, when the immune system is dysregulated, excessive inflammation may occur, resulting in injury and even death. An increased NLR also suggests that an excessive innate immune response, unbalanced by a dysregulated adaptive immune response, may be the cause of higher severity in COVID-19. The innate immune system plays a major role in the development of sepsis and systemic inflammatory response syndrome (SIRS).[18]

In normal and healthy population, reference ranges have not been established yet; however, several studies suggest the normal NLR value within healthy population within healthy population is approximately 1–3.[19] In line with this study, Yang et al. revealed that increased NLR was associated with poor outcome and resulted in similar AUC value. Yang et al. used 3.3 as the cutoff value to differentiate patients with good and poor outcomes. This yielded higher sensitivity (88%) but lower specificity (63.6%).[20] In this study, the optimal threshold for normal and increased NLR was 7.08, which yielded 70.6% sensitivity and 71.4% specificity.

An increase in CRP level was also observed in non-survivors. The increase in CRP level was positively correlated with COVID-19 severity. Another study demonstrated that the CRP level was higher in critically ill COVID-19 patients than in severe patients, and in severe patients than in moderate patients. It was also revealed that CRP levels were positively correlated with the size of lung lesions. These findings support the assumption that mortality is higher in patients with wider lung lesions.[21] This increase in CRP is also consistent with findings from another study by Yan et al.[22] in which machine learning was used to select inflammatory markers with the highest value in predicting mortality. According to Yan's study, inflammatory markers can be used to predict mortality up to 7 days before the outcome. In this study, we demonstrated that inflammatory-marker testing on hospital admission can accurately predict mortality, regardless of the duration from admission to outcome.

We also examined the LCR as a predictor of good outcome. Similar to NLR, LCR is a marker that reflects systemic inflammatory responses.[23] LCR has been used as a prognostic predictor in several diseases. Lower levels of LCR have been shown to indicate poor prognosis in patients with colorectal and gastric cancers.[24,25] A recent meta-analysis demonstrated that lower LCR was associated with poor prognosis in patients with COVID-19.[26] In this study, a higher LCR was associated with better

outcome. As shown in a previous study, regulatory and CD4+ lymphocyte cells were decreased in COVID-19 patients.[10] These two lymphocyte subsets play an important role in maintaining a normal inflammatory response. On the other hand, CRP has long been known as a marker for systemic inflammation.[27] Therefore, this may indicate that dysregulation of the immune response in patients with high LCR is less severe thus resulting lower mortality.

However, in this study, the strongest predictor was PCT. Procalcitonin is routinely tested in patients with pneumonia and other critical conditions to determine whether a patient has a concomitant bacterial infection leading to sepsis. In COVID-19, bacterial infection, indicated by an increase in PCT, may be the strongest predictor of mortality in patients with COVID-19.[28] However, PCT levels may also be elevated in the absence of bacterial infection, typically during tissue injury. Currently, we know that COVID-19 may induce coagulopathy, resulting in wide tissue injury. The elevated PCT in COVID-19 patients may reflect this condition. The cutoff for poor prognosis in this study (0.155 ng/mL) was similar to the well-established cutoff for elevated PCT (0.15–0.2 ng/mL).[29,30]

Through these results, we may predict which patient have poorer prognosis. In the clinical setting during pandemic, the decision made using this newfound knowledge may goes both ways. In the setting of overwhelming number of patients, typical in disaster situation, clinician may prioritize patient with better odds of survival. However, in healthcare center with adequate medical resources, clinician should prioritize patient with more severe COVID-19.

The limitation of this study is the lack reporting of different antibiotic use during hospitalization. Due to limited data, we also Did not foresee comorbidities and bacterial coinfection as potential confounding factors in predicting mortality. Further studies to assess the efficacy of antibiotic administration and the role of comorbidity in increasing mortality in patients with COVID-19 are paramount. Another limitation of this study is that it was conducted in national respiratory referral hospital during the first phase of COVID-19 pandemic. The patients referred to this hospital were relatively in more severe condition compared to other hospital. Therefore, the result of this study may not be applicable in community setting That have generally milder symptoms.

The authors would like to thank the COVID-19 team of Persahabatan General Hospital for their valuable suggestions. The authors declare no competing interests. This study was privately funded by the authors.

CONCLUSION

Routine and affordable inflammatory markers tested on admission may be useful as predictors of mortality in COVID-19 patients requiring hospitalization and help clinician prioritize patient according to the availability of medical resources. This screening method can be used both in referral healthcare center and peripheral hospital. The markers reviewed in this study, especially peripheral blood sampling, is routinely checked. Procalcitonin gave the best prediction, however it may not be available in rural hospital.

This study does not include several important variables such as antibiotic use, the presence of concomitant bacterial infection, and comorbidity due to constraint of resources during the early days of pandemic. The result of this study may not accurately reflect the pandemic situation in the current days. On the other hand, this study may also prove that continuous research is needed to accurately assess the ever-changing COVID-19 situation. We encourage fellow researcher to further investigate this subject of interest.

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