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Original Article

# Predictive accuracy of blood inflammatory markers on COVID-19 mortality

Visuddho Visuddho[1], Agus Subagjo[2], Retno Asih Setyoningrum[3*], Alfian Nur Rosyid[4]

## Abstract

**Background:** The impact of COVID-19 may be more severe in developing countries. Our study aims to analyze the accuracy of several inflammatory biomarkers in predicting COVID-19 mortality, providing information about the most suitable markers for developing countries.

**Methods:** A retrospective cohort study was conducted at Dr. Soetomo General Hospital, Indonesia, from March to June 2020. White Blood Cells (WBC) count, Neutrophil-Lymphocyte Ratio (NLR), Procalcitonin (PCT), D-Dimer, and C-Reactive Protein (CRP) have been collected from the electronic medical records. We performed survival analysis to provide the hazard ratio and Receiver Operating Characteristic (ROC) curve analysis to test for accuracy for each parameter.

**Results:** A total of 423 patients who met the criteria for participating had a median age of 54 (IQR 45-61) years. Patients in the death group are characterized by older age and shorter length of hospitalization. The WBC, NLR, PCT, D-Dimer, and CRP are found significantly higher in the death group (*P*=0.000). The WBC, NLR, PCT, D-Dimer, and CRP have an Area Under the Curve (AUC) of 0.709, 0.773, 0.738, 0.721, and 0.769, respectively moderate accuracy in predicting COVID-19 patient mortality. We found that NLR is significantly more accurate than the age parameter (Z=3.527; *P*=0.000) but has equal accuracy with other laboratory parameters.

**Conclusion:** Since NLR obtained the highest accuracy, we still recommend routine complete blood count tests as prognostic biomarkers with the highest feasibility to be performed in developing countries.

**Keywords:** Covid-19, Infectious Disease, Laboratory, Inflammatory, Marker, Predictive, Indonesia

## Background

Coronavirus Disease 2019 (COVID-19) has been one of the most significant global pandemics. Recently, on July 27th, 2021, Indonesia contributed the third-highest number of new COVID-19 cases in the world [1]. The exponential increase of COVID-19 patients is also found in Indonesia, with 3,532,567 cases and 100,636 deaths as of August 4th, 2021 [2]. Therefore, Indonesia, and other developing countries, must increase awareness and develop the most well-suited guidelines for COVID-19 management. The early identification can provide necessary information for managing COVID-19 patients [3,4]. A previous study showed an association between several biomarkers to the severity and mortality of COVID-19 patients [5–7]. Early laboratory examinations are necessary to predict worsened outcomes and prepare the most advisable management for patients [5,8]. However, few studies from a large developing country like Indonesia reported early

laboratory examination on predicting survival and mortality. The white blood cell count (WBC) and neutrophil-lymphocyte ratio (NLR) have been recognized as routine hematological markers that have been used widely in clinical settings [9,10]. The WBC and NLR have good predictive accuracy in predicting poor clinical outcomes [11,12]. However, previous studies show that only the newer inflammatory biomarker, procalcitonin (PCT), has high accuracy in predicting COVID-19 poor outcomes in critical conditions [13]. The findings were also supported by one meta-analysis, showing the accuracy of PCT was 90.5%, while other markers (WBC, NLR, and C-Reactive Protein (CRP)) have accuracy below 85% [14]. The newer inflammatory marker seems promising but has a higher cost and difficulty implementing primary or secondary medical care in developing countries. Therefore, there is a need for information on the difference in accuracy between the newer inflammatory marker and the routine, low-cost, complete blood count test. Our study aims to analyze the accuracy of WBC, NLR, PCT, D-Dimer, and CRP in predicting COVID-19 mortality. These findings may support the decision of clinical management protocols in developing countries.

**\*Correspondence:** retno-a-s@fk.unair.ac.id

[3]\*Department of Pediatrics, Faculty of Medicine, Universitas Airlangga Jl. Mayjen Prof. Dr. Moestopo 47, Surabaya, East Java 60132, Indonesia.

A full list of author information is available at the end of the article.

## Methods

### Study Design and Participants

This study was a retrospective cohort study of hospitalized patients with COVID-19 enrolled at Dr. Soetomo General Hospital (Surabaya City, East Java Province, Indonesia). All confirmed COVID-19 patients were screened, and those who had definite outcomes (death or discharged) between March 1st, 2020, and June 30th, 2020, were listed. From the total of 423 patients, then 28 pregnant patients, 8 patients with no Real-Time Polymerase Chain Reaction (RT-PCR) test record, and 46 patients with no early laboratory tests were excluded, leaving 341 patients included in this study. Not all the patients received all parameters tests because of physicians' feasibility and clinical decision.

### Data Collection

The age, length of hospitalization, and early laboratory test (WBC, neutrophil percentage, lymphocyte percentage, procalcitonin, D-Dimer, and CRP) were collected from secondary data from electronic medical records using a standardized data collection form. All data were checked twice to ensure the data retrieve correctly before being entered into a computerized database. .

### Definitions

The diagnosis of COVID-19 was defined according to the Indonesian Ministry of Health COVID-19 prevention and control guidelines (version 5.0) [15]. Detection of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is done using real-time RT-PCR methods from nasopharyngeal swab specimens. The confirmative examination was conducted by the Diagnostic Center of Dr. Seotomo General Hospital, Surabaya. The criteria for discharge were complete isolation for ten days from the date of onset with a minimum of 3 days after an absence of fever and respiratory problems (for mild and moderate patients) or has obtained a negative one-time RT-PCR follow-up examination plus a minimum of 3 days after an absence of fever and respiratory problems (for severe and critical patients). The laboratory examination was conducted

based on Dr. Soetomo General Hospital Clinical Practice Guidance. Neutrophil-Lymphocyte Ratio (NLR) was calculated by dividing the neutrophil percentage by the lymphocyte percentage.

### Statistical analysis

The age, length of hospitalization, and laboratory data were presented as the median and interquartile range (IQR), while sex variables were presented as count (n) and percentage (%). The Mann-Whitney U test and Chi-square test compared differences between the discharge and death groups. Survival analysis was performed using the Kaplan-Meier survival curve to measure survival probability during hospitalization, showing the Log Rank p-value. We use the Cox proportional hazard regression model to determine the hazard ratio (HR) during hospitalization. Receiver Operating Characteristic (ROC) curves were conducted to measure the Area Under the Curve (AUC) value, sensitivity, and specificity of a predictivevariable. All statistic was performed individually for each variable. Since the difference in the sample size of each laboratory data, we can not perform multivariable analysis to show the most influencing variables. We do Z-test between NLR to other laboratory parameters to compare the accuracy. Statistically significant was considered using two-sided $\alpha$ less than 0.05. Statistical analysis was done using the IBM SPSS software (version 13).

## Results

### Patients Characteristic and Comparative Test

The patient's baseline characteristics, early laboratory test, and comparative test results are presented in Table 1. A total of 423 patients who met the criteria for participating had a median age of 54 (IQR 45-61) years. Patients in the discharge group have lower age (51.00 vs. 55.00; $P$ =0.000) and higher length of hospitalization (15.00 vs. 5.00; $P$ =0.000) than patients in the death group. There is no significant difference in mortality between male and female patients ($P$ =0.514). The discharge group has significantly lower value than death group for WBC (7.71 vs 10.80; $P$ =0.000), NLR (4.43 vs 9.32; P=0.000), PCT (0.13 vs 0.39; $P$ =0.000), D-Dimer (1010.00 vs 2560.00; $P$ =0.000) and CRP (6.00 vs 15.00; $P$ =0.000) parameters.

**Table 1**. Baseline Characteristic and Early Laboratory Test of The Study Cohort

| Variables | Total (n=341) | Discharge (n=193) | Death (n=148) | p-value |
|---|---|---|---|---|
| Age (year) | 54.00 (45.00-61.00) | 51.00 (40.50-59.00) | 55.00 (47.25-65.00) | 0.000** |
| Sex | | | | 0.514 |
|    Male | 189 (55%) | 104 (54%) | 85 (57%) | |
|    Female | 152 (45%) | 89 (46%) | 63 (43%) | |
| Length of Hospitalization (days) | 11.00 (5.00-17.00) | 15.00 (11.00-20.00) | 5.00 (2.00-9.00) | 0.000** |
| White Blood Cell Count ($10^3$/uL) (n=325 Patients) | 8.73 (6.42-12.06) | 7.71 (5.86-9.77) | 10.80 (7.88-15.02) | 0.000** |
| Neutrophil Lymphocyte Ratio (n=325 Patients) | 6.02 (3.48-10.64) | 4.43 (2.79-6-95) | 9.32 (5.81-15.12) | 0.000** |
| Procalcitonin (ng/ml) (n=249 Patients) | 0.19 (0.09-0.69) | 0.13 (0.08-0.26) | 0.39 (0.16-1.71) | 0.000** |
| D-Dimer (ng/ml) (n=184 Patients) | 1390.00 (712.50-5537.50) | 1010.00 (520.00-2400.00) | 2560.00 (1185.00-11395.00) | 0.000** |
| C-Reactive Protein (mg/dL) (n=111 Patients) | 9.70 (3.80-15.90) | 6.00 (1.50-11.90) | 15.00 (9.78-19.45) | 0.000** |

**p-value<0.001

## Survival Analysis

As seen in Figure 1, by using old age criteria and prespecified cut-off (obtained from the diagnostic tools) for laboratory parameters, we compare the survival probability between discharge and death group using Kaplan-Meier Survival Curve. Patients with older age (>59 years), higher WBC (>10.000/ul), NLR(>5), PCT (>0.5 ng/ml), d-dimer (>440 ng/ml), and CRP (>1 mg/dl) seem more vulnerable with lower survival during hospitalization. Patients older than 59 years have a significantly lower survival than patients younger than 59 years. Table 2 shows that all laboratory parameters predict patient mortality during hospitalization. Each addition of one year's age would increase 1.027 (95% CI: 1.013-1.040; P=0.000) times of mortality risk. The HR of other laboratory parameters are 1.041 (95% CI: 1.025-1.057; P =0.000) for WBC, 1.020 (95% CI: 1.010-1.030; P =0.000) for NLR, 1.047 (95% CI: 1.024-1.070; P =0.000) for PCT, 1.000 (95% CI: 1.000-1.000; P =0.012) for d-dimer, and 1.004 (95% CI: 0.998-1.009; P =0.209).

**Table 2.** COX Regression Analysis of Predictive Variables

| Variables | HR (95% CI) | p-value |
|---|---|---|
| Age (year) | 1.027 (1.013-1.040) | 0.000** |
| White Blood Cell Count (103/uL) (n= 325 Patients) | 1.041 (1.025-1.057) | 0.000** |
| Neutrophil Lymphocyte Ratio (n= 325 Patients) | 1.020 (1.010-1.030) | 0.000** |
| Procalcitonin (ng/ml) (n= 249 Patients) | 1.047 (1.024-1.070) | 0.000** |
| D-Dimer (ng/ml) (n= 184 Patients) | 1.000 (1.000-1.000) | 0.012* |
| C-Reactive Protein (mg/dL) (n= 111 Patients) | 1.004 (0.998-1.009) | 0.209 |

HR = Hazard Ratio; *p-value<0.05; ** p-value<0.01

## ROC Analysis and Comparison of AUC value

The AUC value of all variables is shown in Figure 2. Age has an AUC value of 0.633, a low accuracy category (0.6-0.7). The early laboratory parameter, WBC, NLR, procalcitonin, d-dimer, and CRP, have moderate accuracy (0.7-0.8). NLR accuracy is significantly greater than age in predicting patient mortality with a Z-test score of 3.527 (p=0.000). As shown in Table 3, we found a more excellent AUC value on NLR but no significant Z-test in other comparisons. As a result, NLR was comparable to other laboratory parameters in predicting COVID-19 patient mortality.

**Table 3.** Comparison of area under the curve of neutrophil-lymphocyte ratio to other parameters

| Variables | AUC of NLR | AUC of Comparator | Z-test | *p*-value |
|---|---|---|---|---|
| NLR vs Age | 0.773 | 0.633 (0.574-0.692) | 3.527 | 0.000** |
| NLR vs. WBC | (0.722-0.824) | 0.709 (0.652-0.767) | 1.643 | 0.100 |
| NLR vs PCT | | 0.738 (0.674-0.802) | 0.833 | 0.405 |
| NLR vs D-Dimer | | 0.721 (0.649-0.794) | 1.150 | 0.250 |
| NLR vs CRP | | 0.769 (0.679-0.858) | 0.076 | 0.939 |

AUC = Area Under the Curve; CRP = C-Reactive Protein; NLR = Neutrophil-Lymphocyte Ratio; PCT = Procalcitonin; WBC = White Blood Cells; **p-value<0.001

## Discussion

The increasing demand for managing COVID-19 cases has burdened medical healthcare systems. Implementing good triage by early identification of a patient's prognosis is essential to improve COVID-19 patient management. In this study, the high mortality percentage (43.4%) might be caused by higher severe cases in Dr. Soetomo General Hospital due to its function as a national referral hospital. We found that all the variables involved in the patients' survival can be a predictor with low-moderate accuracy. We also found that NLR was comparable to other laboratory parameters in predicting COVID-19 patient mortality. Previous studies have reported the association between older age and COVID-19 mortality [16–18]. We confirmed that patients with older age have lower survival during hospitalization. The decrease of immunity function due to immunosenescence may be involved in a patient's condition [19]. In addition, the elderly appears to develop sub-clinical chronic inflammation conditions, called inflame-aging, after viral or other pathogens infections [20]. The consequence of inflame-aging is deleterious effet to organ leading to a higher risk of mortality [21]. Consistent with other studies, our findings reported that patients with higher WBC count, NLR, PCT, D-Dimer, and CRP had higher odds of COVID-19 mortality [5,22,23]. Although several studies declare no significant result on the association of higher WBC with the severity, higher WBC may impact higher neutrophils cells which have a role in inflammation [23,24]. The higher NLR reflects the increase in pro-inflammatory cells and decreased lymphocytes and regulatory T cells, which have a role in controlling inflammation [22,25]. The use of PCT and CRP in COVID-19 patients may be based on their capability in detecting sepsis conditions [26,27]. The PCT showed high accuracy, while the CRP showed moderate accuracy in predicting sepsis [28]. Interestingly, these are also similar to the accuracy of both parameters in predicting COVID-19 severity, with the high accuracy for PCT and moderate accuracy for CRP [13]. D-dimer is also one of the standard parameters tested in COVID-19 patients. The significant association may be based on the potency of D-dimer to detect coagulopathy, the risk for venous thromboembolism, and excessive inflammation in COVID-19 infection [29]. The survival analysis shows the significance of all variables in determining the patient's mortality risk.
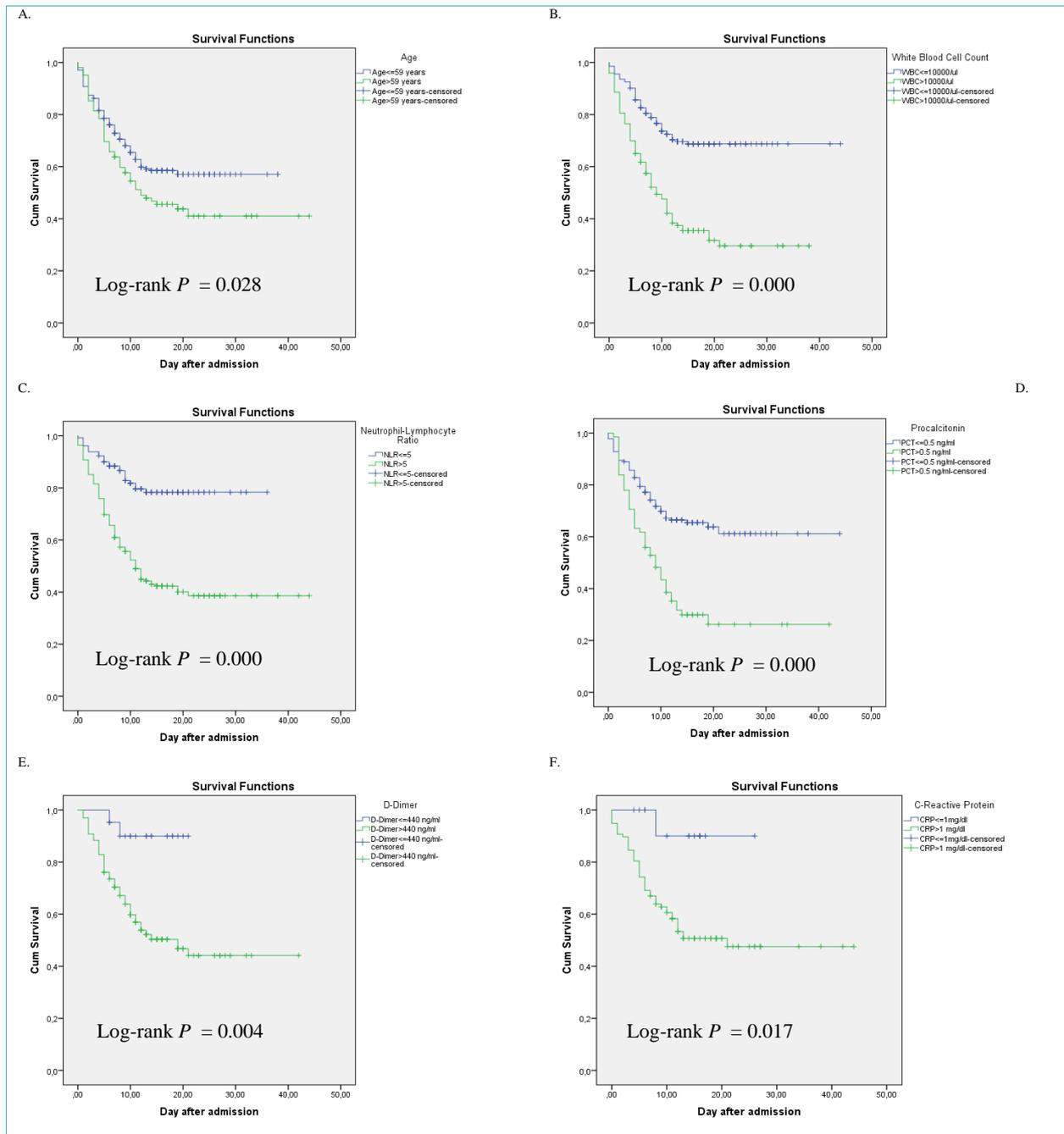
**Figure 1.** Kaplan-Meier Survival Curve of (A) Age (B) White Blood Cell Count (C) Neutrophil-Lymphocyte Ratio (D) Procalcitonin (E) D-Dimer (F) C-Reactive Protein for COVID-19 Patients Survival

This can be explained since all the variables are associated with inflammation [30]. Inflammation is responsible for the progression of tissue damage and organ injury, from mild to severe organ dysfunction leading to poor outcomes [31,32]. Sepsis and other organ dysfunction appear as complication and mortality cause in COVID-19 patients [33,34]. ROC curve analysis reveals low accuracy of age and moderate accuracy of all laboratory markers on predicting mortality of COVID-19 patients. The NLR has the highest accuracy with AUC 0.734 (95%CI 0.675-0.793). This result is quite different from other studies reporting higher accuracy of PCT than other parameters [13], even though all the markers still show a significant accuracy to predict COVID-19 patient mortality. Z-test also showed no significant difference in accuracy between all

laboratory markers, interpreted as all these markers have the same moderate accuracy in predicting COVID1-9 mortality. Hence, our study still recommends using conventional parameters, like WBC and NLR, for predicting the mortality of COVID-19, with better accessibility, feasibility, and affordable price, especially in developing countries. Until now, there are still few studies focused on analysis survival and predictive factors for COVID-19 mortality from developing countries in Southeast Asia. Our strength is to show the survival and predictive value of the conventional and "advanced" laboratory parameters. Therefore, our result can be used as a reference, especially for the developing countries which needed effective parameters with relatively low-cost expenditure.

### Limitation of study

Several limitations exist in our study. First, due to the limited sample tested by the "advanced" laboratory parameters, our accuracy comparison only can be conducted indirectly using the Z-test. Second, we cannot do the multivariate analysis due to the unequal sample size of each parameter. Finally, the investigators could not include other variables that may influence the result due to limited data on electronic medical records.

## Conclusion

In conclusion, our study found a significant association between age and all laboratory markers (WBC, NLR, PCT, D-Dimer, and CRP) and COVID-19 patient mortality. All laboratory markers showed moderate accuracy as early predictors.

However, our study still suggests routine complete blood count tests as prognostic biomarkers with moderate accuracy and the highest feasibility to be performed in developing countries. Further research may look into comparing all these parameters with radiological markers or specific clinical conditions to improve the management of COVID-19, especially in developing countries.

### Abbreviation

COVID-19: Coronavirus Disease 2019; WBC: White Blood Cells; NLR: Neutrophil-Lymphocyte Ratio; PCT: Procalcitonin; CRP: C-Reactive Protein; AUC: Area Under the Curve; RT-PCR: Real-Time Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; IQR: Interquartile Range; HR: Hazard Ratio
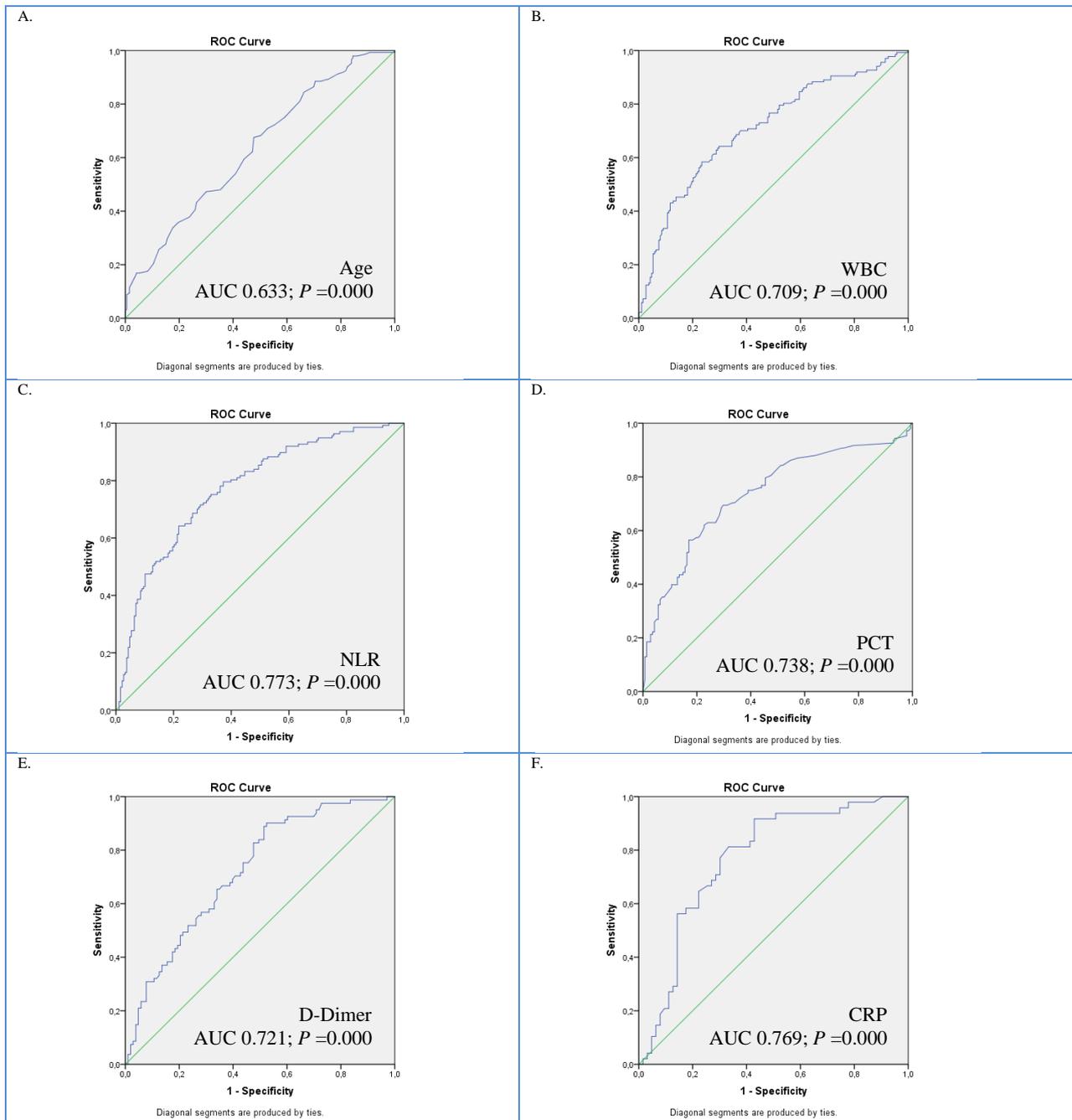


**Figure 2.** Receiver Operating Characteristic Curve of (A) Age (B) White Blood Cell Count (WBC) (C) Neutrophil-Lymphocyte Ratio (NLR) (D) Procalcitonin (PCT) (E) D-Dimer (F) C-Reactive Protein (CRP) for Prediction of COVID-19 Mortality

## Declaration

### Availability of data and materials
Data will be available by emailing visuddho2018@fk.unair.ac.id

### Authors' contributions
Visuddho Visuddho (VSD), Agus Subagjo (AGS), and Retno Asih Setyoningrum (RAS) are responsible for the study concept, design, data acquisition, and writing the original draft. VSD also performed the data analysis. Alfian Nur Rosyid (ANR) is responsible for editing and reviewing the manuscript. The approval of the final manuscript is done by all authors.

### Ethics approval and consent to participate
We conducted the research following the Declaration of Helsinki. The ethical protocol was approved by the Research Ethics Commission of Dr. Soetomo General Hospital (Ref. No: 0257/LOE/301.4.2/XII/2020).

### Consent for publication
Not applicable

### Competing interest
The authors declare that they have no competing interests.

### Author Details
[1]Medical Programme, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Department of Pediatrics, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[4]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

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