

D-dimer and NLR Levels as Potential Biomarkers to Predict Mortality in Patients with Covid-19

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Abstract

Introduction: Due to the high mortality of the coronavirus disease 2019 (Covid-19) pandemic that continues to strain healthcare systems, early and effective predictors of clinical outcomes are urgently needed to improve management of Covid-19 patients. The aim of this study was to evaluate whether elevated levels of D-dimer and NLR combination could predict mortality in patients with Covid-19. **Methods:** A total of 60 eligible patients with laboratory confirmed Covid-19 were retrospectively enrolled in Intensive Care Unit of Raden Mattaher Hospital from November 2020 to April 2021. D-dimer value on admission and death events were collected to calculate the optimum cutoff. **Results and discussions:** The optimum cut off values of D-dimer; NLR to predict in-hospital mortality were $\geq 2.1 \mu\text{g/ml}$; $\geq 8.09\%$ with both sensitivity 70.4% and specificity 72.7% ($P = 0.001$). There were 17 patients with D-dimer; NLR value $\geq 2.1 \mu\text{g/ml}$; $\geq 8.09\%$ on admission, and 15 deaths (88.2%) occurred during hospitalization. **Conclusions:** D-dimer; NLR values on admission $\geq 2.1 \mu\text{g/ml}$; $\geq 8.09\%$ could predict in-hospital mortality in patients with Covid-19, which indicated D-dimer and NLR could be an early and helpful markers to improve management of Covid-19 patients.

Keywords: coronavirus disease, D-dimer, NLR, mortality, prognosis

1. Introduction

On January 7th, 2020, a new type of coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2, SARS-CoV-2) that caused a series of respiratory infections (Coronavirus Disease 2019, COVID-19) was discovered in Wuhan, China.¹⁻³ In the next few days, 2019-nCoV spread rapidly in China and other countries. In Indonesia, up to August 23rd, 2021, a total of 3,989,060 cases have been confirmed, of which 127,214 have died, with a case fatality rate was 3.2%.⁴ In view of its seriousness and severity, Therefore, early and effective predictors of clinical outcomes are urgent needed, so that timely actions and reasonable interventions can be taken, in turn the cure rate and prognosis quality can be improved.⁵

A number of studies have shown that elevated D-dimer and NLR levels are prognostic factors for the adverse outcome of

respiratory diseases.⁶⁻⁸ The purpose of this study is to evaluate the prognostic value of D-dimer and NLR for initial testing of COVID-19 patients during hospital admission.

2. Method

This study was conducted in Intensive Care Unit of Raden Mattaher Hospital, Jambi. A total of 60 patients with laboratory-confirmed Covid-19 between November 2020 to April 2021 were retrospectively Enrolled. Demographic characteristics (age, gender), laboratory data, co-morbidities, and clinical outcomes were collected.

Adult (aged 18 years or older) patients with laboratory-confirmed Covid-19 who had a definite outcome (discharge or death) were included in the study. Excluded patients were who admitted to the ICU without D-Dimer, neutrophil and lymphocyte values.

Data were expressed as means \pm SD (standard deviation). Statistical analysis was performed using SPSS. Receiver operating characteristic (ROC) analysis was performed to determine the cutoff values of D-dimer and NLR to identify the outcomes of COVID-19 patients.

Independent sample t-test was used to compare between means. Chi-Square was used to determine significance for categorical variables. Independent variables having p-value <0.05 were used in Mann-Whitney test.

3. Results

Of 60 eligible patients, among which 36 (60%) were male and 24 (40%) were female, the mean age was 59.42 ± 8.353 years. Among all candidates, 30 (50%) patients had diabetes mellitus, 27 (45%) patients had hypertension, 5 (8.3%) patients had chronic kidney disease, 4 (6.7%) patients had coronary arterial disease, 3 (5%) patients had non-hemorrhagic stroke, 3 (5%) patients had congestive heart failure, 3 (5%) patients had acute kidney injury, 1 (1.7%) patient had hemorrhagic stroke, and 1 (1.7%) patient had bronchitis. 27 (45%) patients died during hospital stay.

The area under the curve (AUC) of ROC curve for D-dimer value on admission against patient outcome (Figure 1) was 0.679 (95% Confidence Interval [CI] 0.532–0.826, $p=0.018$). The optimal cutoff value of D-dimer was found to be 2.1 $\mu\text{g/ml}$ with a sensitivity of 70.4% and a specificity of 72.7%.

In 32 (53.3%) of 60 patients had D-dimer on admission less than 2.1 $\mu\text{g/ml}$, of which 8 (25%) patients died during hospital stay and 24 (75%) were discharged. Of the 28 patients who, on admission, had D-dimer of 2.1 $\mu\text{g/ml}$ and above, 19 (67.9%) died and 10 (32.1%) were discharged.

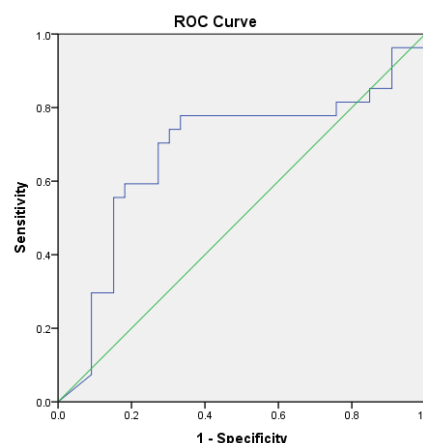


Figure 1. ROC curve for D-dimer as a predictor of in-hospital mortality

The mean of D-dimer on admission among patients who discharged was 2.3 $\mu\text{g/ml}$ (± 2.705 $\mu\text{g/ml}$), whereas that among patients who died was 3.7 $\mu\text{g/ml}$ (± 2.851 $\mu\text{g/ml}$). D-dimer means differed significantly between groups, $p=0.018$.

The AUC of ROC curve for NLR on admission against patient outcome (Figure 2) was 0.728 (95% CI 0.597–0.860, $p=0.002$). The optimal cutoff value of NLR was found to be 8.09% with a sensitivity of 70.4% and a specificity of 72.7%.

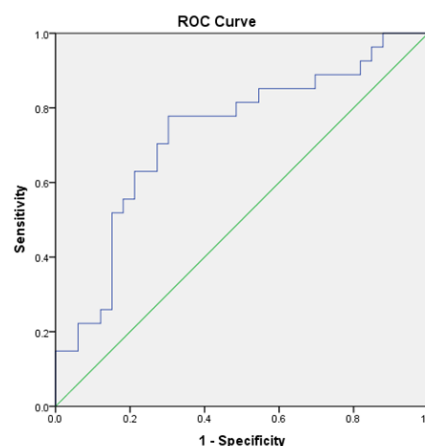


Figure 2. ROC curve for NLR as a predictor of in-hospital mortality

In 32 (53.3%) of 60 patients had NLR on admission less than 8.09%, of which 8 patients

(25%) died during hospital stay and 24 (75%) were discharged. Of the 28 (46.7%) patients who on admission, had NLR of 8,09% and above, 19 (67.9%) died and 9 (32.1%) were discharged.

The mean of NLR on admission among patients who discharged was 7.18 % (± 4.52 %), whereas that among patients who died was 12.57 % (± 8.98 %). NLR means differed significantly between groups $p=0.002$.

Based on the cutoff value of two predictors, all patients were categorized into two groups for comparison, summarized in

Table 1. Comorbidities, age and gender were not differed significantly.

There were significant difference between D-dimer value; NLR value on admission and mortality with $p=0.001$ (OR: 6.333, 95% CI 2.053-19.540); $p=0.001$ (OR: 6.333, 95% CI 2.053-19.540), respectively.

Of the 17 patients with both D-dimer; NLR value ≥ 2.1 $\mu\text{g/ml}$; ≥ 8.09 % on admission, 15 (88.2%) deaths occurred during hospitalization. There was a higher risk of mortality in patients with D-dimer; NLR value ≥ 2.1 $\mu\text{g/ml}$; ≥ 8.09 % on admission, $p=0.000$ (OR: 19.375, 95% CI 3.838-97.797) (Table 2).

Table 1. Demographic Characteristics of COVID-19 Patients

Variables	Total (n)	D-dimer <2.1 $\mu\text{g/ml}$ (n)	D-dimer ≥ 2.1 $\mu\text{g/ml}$ (n)	p-value	NLR < 8.09% (n)	NLR > 8.09% (n)	p-value
Age (Mean \pm SD)	59.42 \pm 8.353	58.88 \pm 8.979	60.04 \pm 7.691	0.592	58.56 \pm 8.625	60.38 \pm 8.075	0.400
Gender	60	32	28	0.916	32	28	0.916
- Female	24	13	11		13	11	
- Male	36	19	17		19	17	
Comorbidities							
- Hypertension	27	16	11	0.405	15	12	0.755
- Diabetes Mellitus	30	16	14	1.000	17	13	0.605
- Stroke Hemorrhage	1	0	1	0.281	0	1	0.281
- Stroke Non-Hemorrhage	3	2	1	0.635	1	2	0.476
- Coronary Artery Disease	4	3	1	0.369	3	1	0.369
- Acute Kidney Injury	3	0	3	0.057	1	2	0.476
- Chronic Kidney Disease	5	1	4	0.119	2	3	0.533
- Congestive Heart Failure	3	3	0	0.096	3	0	0.096
- Bronchitis	1	1	0	0.346	1	0	0.346
Mortality	60	32	28	0.001	32	28	0.001
- Death	27	8	19		8	19	
- Discharged	33	24	9		24	9	

Table 2. D-dimer and NLR Values of COVID-19 Patients

Variables	Total (n)	Death	Discharged	p-value
D-dimer (Mean ± SD)	2.9 ± 2.837 µg/ml	3.7 ± 2.851 µg/ml	2.3 ± 2.704 µg/ml	0.018
NLR (Mean ± SD)	9.60 ± 7.34 %	12.57 ± 8.98 %	7.18 ± 4.52 %	0.002
D-dimer X NLR				0.000
- Both ≥ cutoff point	17	15	2	
- One or Both < cutoff point	43	12	31	

4. Discussion

In this study, we found that high levels of NLR and D-dimer were significantly associated with COVID-19 mortality. This indicates that when D-dimer and NLR values exceeded the cutoff point, the risk of mortality increased.

D-dimer is a fibrin degradation product and its fundamental utility is in the diagnosis and management of thrombotic disorders. Before the 2019 COVID-19 pandemic, D-dimer was not considered a useful biomarker for bacterial or viral pneumonia despite some evidence to the contrary.⁹ Since then, however, elevated D-dimer and thrombotic complications have been widely reported in COVID-19 patients.

Elevation of D-dimer indicates that patients with Covid-19 are in a hypercoagulable state, which might be attributed to the following reasons. First, virus infections are usually accompanied by an aggressive pro-inflammatory response and insufficient control of an anti-inflammatory response.¹⁰ It may cause endothelial cell dysfunction, leading to excessive thrombin production.¹¹ Second, the hypoxia found in severe Covid-19 can stimulate thrombosis through blood viscosity, and hypoxia-inducible transcription factor-dependent signaling pathway.¹²⁻¹³ As evidence, the lung organ dissection of critical patient with Covid-19 have reported occlusion and micro thrombosis formation in pulmonary small vessels.¹⁴

Several studies have been conducted to analyze the association between initial D-

dimer measurements and disease severity and outcome. A study done by Zhang et. al. in China including 343 patients found the optimal cutoff point for D-dimer to be 2 µg/ml could be an early useful marker for predicting in-hospital mortality in patients.¹⁵ Another study in China found that D-dimer value at the time of admission of more than 2 µg/ml was associated with increased odds of mortality (Odds Ratio 10.17 (95% CI 1.10–94.38)).¹⁶ A similar study in India found the optimal cutoff value for admission D-dimer to predict hospital mortality to be 1.44 µg/ml, whereas the optimal value for highest D-dimer measurement during hospital stay for predicting hospital mortality was 2.01 µg/ml.¹⁷ The AUC of the ROC for D-dimer on admission in our study was 0.679 is generally considered to indicate 'poor accuracy' of the test, however 2.1 µg/ml D-dimer cut-off value was associated with increased odds of mortality (OR: 6.333, 95% CI 2.053-19.540) P<0.05) and in accordance with most of published research on the topic.

In other hand, Immune dysfunction also plays an important role in the severity of COVID-19.¹⁸ Recent studies have shown that neutropenia and lymphopenia can be observed in severe COVID-19 patients.¹⁹⁻²⁰

COVID-19 severity is primarily affected by the innate inflammatory response of the body, where more severe cases were attributed to cytokine storm, a condition when there is an excessive immune response.²¹ NLR is a known indicator of systemic inflammation that has been widely

used. The biological mechanism underlying this association is that high NLR indicates an imbalance in the inflammatory response, which resulted from increased neutrophil and decreased lymphocyte counts. Inflammatory factors related to viral infection, such as interleukin-6, interleukin-8, and granulocyte colony-stimulating factor, could stimulate neutrophil production.²² In contrast, systemic inflammation accelerates lymphocyte apoptosis, depresses cellular immunity, decreases CD4+, and increases CD8+ suppressor T-lymphocytes.²³⁻²⁴

A study conducted by Yang et al in 93 patients with COVID-19 demonstrated that NLR value 3.3% can be used as an independent indicator for poor clinical outcome with 63.6% specificity and 88% sensitivity.²⁵ Another study by Cheng B et al found the optimal cutoff point for NLR to be 7.9% could be an early useful marker for predicting in-hospital mortality in patients with COVID-19.²⁶ The predictive value of NLR in our study was 8.09% and the AUC was 0.728 (OR: 6.333, 95% CI 2.053-19.540, $P < 0.05$) which are considered to indicate 'fair accuracy'. NLR values were previously reported to vary with age, sex and race; thus, NLR value found in our study is different from the other study in different populations.²⁷⁻²⁸

Therefore, our study suggests that combination of D-dimer and NLR values as predictive factors of mortality in COVID-19 is more efficient than using D-dimer or NLR alone as independent factor. It shown with increased odds of mortality by 19 times higher.

This study has some limitations. First, selection bias because of its retrospective nature. Second, owing to the different disease severities among the patients, the time from onset to admission might not be representative, which could have affected the

level of the parameters considered on admission. Third, some otherwise eligible cases also had to be excluded due to incomplete laboratory tests and medical records, specifically D-dimer on admission. And lastly other clinical data and test results were not included in the analysis, which may have caused bias, weakening the reliability of the results. In the future research, it is necessary to conduct dynamic research on indicators and combine more indicators to meet different clinical needs.

5. Conclusion

D-dimer; NLR values on admission ≥ 2.1 $\mu\text{g/mL}$; $\geq 8.09\%$ could predict in-hospital mortality in patients with Covid-19, which indicated D-dimer and NLR could be an early and helpful marker to improve management of Covid-19 patients.

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