

# The Relationship Between Neutrophil-to-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP) with the Severity of COVID-19 Patients Hospitalized at RSUP H. Adam Malik Medan

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## Abstract

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). COVID-19 infection triggers an inflammatory response characterized by an increase in Neutrophil-Lymphocyte Ratio (NLR) and C-Reactive Protein (CRP). This study aims to determine the relationship between NLR and CRP levels and the severity of COVID-19 patients treated at Haji Adam Malik General Hospital in Medan.

This study is a retrospective observational analytic study with a cross-sectional design, conducted at Haji Adam Malik General Hospital in Medan from January 1 to December 1, 2022. The study sample included all patients aged 18 years and above who were treated in the COVID-19 isolation ward at Haji Adam Malik General Hospital, tested positive for COVID-19 via PCR swab, and underwent NLR and CRP examinations upon their initial admission to the hospital.

A total of 98 patients tested positive for COVID-19 via PCR swab, with 49 cases of moderate severity, 32 cases of severe severity, and 17 cases of mild severity. The increase in NLR and CRP was significantly associated with the severity of COVID-19 ( $p < 0.001$ ). Comorbid conditions such as diabetes mellitus and chronic kidney disease were not associated with increases in NLR and CRP ( $p > 0.005$ ). Patients with a history of vaccination showed a significant increase in NLR ( $p = 0.01$ ) and CRP ( $p = 0.001$ ).

Keywords: COVID 19; Infection; NLR; CRP

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## 1. Background

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)<sup>1</sup>. Indonesia has become the country with the highest number of COVID-19 cases in Southeast Asia, with 6 million cases.<sup>2</sup> Medan is the province in North Sumatra with the most COVID-19 cases as of December 2022, accounting for 321 out of 771 cases reported in the province.<sup>3</sup>

COVID-19 infection leads to an inflammatory response. Neutrophils, which are polymorphonuclear phagocytes, become activated and destroy microbes through both oxygen-independent pathways (e.g., lysozyme, lactoferrin, reactive oxygen intermediates, proteolytic enzymes, cathepsin G, and cationic proteins) and oxygen-dependent pathways. Viral stimulation and the production of pro-inflammatory cytokines cause neutrophils to release Neutrophil Extracellular Traps (NETs), which can lead to lung tissue damage.<sup>4-5</sup>

Lymphocytes, which include CD8<sup>+</sup> T lymphocytes and natural killer (NK) cells, kill virus-infected cells, while CD4<sup>+</sup> T lymphocytes assist B cells in producing antiviral antibodies. Lymphopenia, an immunological disorder, occurs in 96.1% of COVID-19 cases, especially severe cases, affecting the proportion of CD3<sup>+</sup>,

CD4+, CD8+ T cells. Hyperinflammation and lymphopenia are important indicators of immune system dysregulation in COVID-19 patients.<sup>4</sup> The Neutrophil-Lymphocyte Ratio (NLR) is used as an inflammatory biomarker to indicate a systemic inflammatory response. An increase in NLR is associated with the progression of COVID-19 and is significantly correlated with disease severity.<sup>8</sup>

Another inflammatory biomarker is C-Reactive Protein (CRP), an acute-phase protein synthesized by hepatocytes. COVID-19 infection is also associated with an increase in CRP. Recent studies have reported that elevated NLR and CRP levels can serve as predictive biomarkers for COVID-19 severity.<sup>9-11</sup> Both biomarkers are widely available, relatively inexpensive, and quick to measure, making them potentially accurate clinical parameters for early management and prognosis.

## 2. Methods

This study is a retrospective observational analytic study with a cross-sectional design, conducted at Haji Adam Malik General Hospital in Medan from January 1 to December 1, 2022. The study sample included all patients aged 18 years and above who were treated in the COVID-19 isolation ward at Haji Adam Malik General Hospital, tested positive for COVID-19 via PCR swab, and underwent NLR and CRP examinations upon their initial admission to the hospital.

The exclusion criterion for this study was patients with autoimmune diseases. The samples were selected using consecutive sampling. Data analysis was performed using the Kolmogorov-Smirnov normality test and the Mann-Whitney U test, due to the non-normal distribution of the data.

## 3. Result

The study subjects consisted of 98 patients who tested positive for COVID-19 via PCR swab and were treated in the COVID-19 isolation ward at Haji Adam Malik General Hospital. Among these, there were 49 cases of moderate COVID-19, 32 cases of severe COVID-19, and 17 cases of critical COVID-19. The study found no significant differences in the average age or gender across the different severity levels of COVID-19. However, there was a significant relationship between comorbidities such as diabetes mellitus, chronic kidney disease, and vaccination status.

Table 1. Sample Characteristic

Characteristic	Covid-19 Severity			P Value
	Moderate (n=49)	Severe (n=32)	Critical (n=17)	
Age (Years), Mean $\pm$ SD	51,88 $\pm$ 16,56	53,84 $\pm$ 16,09	53,24 $\pm$ 16,49	
Sex, n (%)				0,522
Male	20 (40,8)	17 (53,1)	7 (41,2)	
Female	29 (59,2)	15 (46,9)	10 (58,8)	
Diabetes Mellitus, n (%)				0,015*
Yes	28 (57,1)	10 (31,3)	12 (70,6)	
No	21 (42,9)	22 (68,8)	5 (29,4)	
Hypertension, n (%)				0,417
Yes	26 (53,1)	17 (53,1)	12 (70,6)	
No	23 (46,9)	15 (46,9)	5 (29,4)	
Stroke, n (%)				0,146
Yes	22 (44,9)	14 (43,8)	12 (70,6)	
No	27 (55,1)	18 (56,2)	5 (29,4)	
Coronary Artery Disease, n (%)				0,428

Yes	16 (32,7)	15 (46,9)	7 (41,2)	
No	33 (67,3)	17 (53,1)	10 (58,8)	
Chronic Kidney Disease, n (%)				0,007*
Yes	20 (40,8)	11 (34,4)	0	
No	29 (59,2)	21 (65,6)	17 (100)	
Hematology Malignant				0,545
Yes	2 (4,1)	1 (3,1)	0	
No	47 (95,9)	31 (96,9)	17 (100)	
Lung Tumor				0,649
Yes	1 (2)	1 (3,1)	0	
No	48 (98)	31 (96,9)	17 (100)	
Vaccination Status				0,001*
Yes	9 (18,4)	18 (56,3)	8 (47,1)	
No	40 (81,6)	14 (43,8)	9 (52,9)	

Research indicates that there is a significant relationship between NLR and CRP levels and the severity of COVID-19, with  $p < 0.001$ . The more severe the disease, the higher the NLR and CRP values.

Table 2. Analysis of the Relationship Between NLR and COVID-19 Severity

	Median	Min-Max	P Value*
Moderate, n=49	4,58	0,6-68,79	<0,001
Severe, n=32	10,55	0,17-58,81	
Critical, n=17	12,17	6,45-38,40	

\*Kruskal-Wallis test

Table 3. Analysis of the Relationship Between CRP and COVID-19 Severity

	Mean $\pm$ SD	P Value*
Moderate, n=49	3,01 $\pm$ 1,4	<0,001
Severe, n=32	11,62 $\pm$ 2,88	
Critical, n=17	25,02 $\pm$ 3,42	

\*Analysis of Variance test

This study also shows that there is no relationship between diabetes mellitus and chronic kidney disease with NLR and CRP levels in COVID-19 patients, with  $p > 0.05$ .

Table 4. Analysis of the Relationship Between Diabetes Mellitus and NLR Value in COVID-19 Patients

	Median	Min-Max	P Value*
DM (+), n=50	8,29	0,6-45,19	0,887
DM (-), n = 48	7,03	0,17-68,79	

\*Mann-Whitney U test

Table 5. Analysis of the Relationship Between Diabetes Mellitus and CRP Value in COVID-19 Patients

	Median	Min-Max	P Value*
DM (+), n=50	4,7	1,1-29,8	0,683
DM (-), n = 48	8,65	0,8-29,9	

\*Mann-Whitney U test

Table 6. Analysis of the Relationship Between Chronic Kidney Disease and NLR Value in COVID-19 Patients

	Median	Min-Max	P Value*
CKD (+), n = 31	8,61	1,07-68,79	0,456
CKD (-), n = 67	7,16	0,17-44,89	

\*Mann-Whitney U test

Table 7. Analysis of the Relationship Between Chronic Kidney Disease and CRP Value in COVID-19 Patients

	Median	Min-Max	P Value*
DM (+), n=50	4,1	0,8-19,5	0,683
DM (-), n = 48	9	1-29,9	

\*Mann-Whitney U test

COVID-19 patients who have been previously vaccinated have significantly higher CRP and NLR levels compared to patients who have not been vaccinated.

Table 8. Analysis of the Relationship Between Vaccination Status and NLR Value in COVID-19 Patients

	Median	Min-Max	P Value*
Vaccine (+), n=35	15,25	1,49-58,81	0,01
Vaccine (-), n = 63	6,67	0,17-68,79	

\*Mann-Whitney U test

Table 9. Analysis of the Relationship Between Vaccination Status and CRP Value in COVID-19 Patients

	Median	Min-Max	P Value*
Vaccine (+), n=35	12,6	0,8-28,8	0,001
Vaccine (-), n = 63	4,6	1-29,9	

\*Mann-Whitney U test

#### 4. Discussion

This study demonstrated a significant relationship between NLR and CRP levels with the severity of COVID-19, with a p-value of <0.001. This finding aligns with the research by Tjandra et al., which found that an increase in NLR corresponds with the progression of pneumonia and a higher risk of mortality in COVID-19 patients. Similarly, research by Kermali et al. found that CRP levels positively correlate with the degree of inflammation in COVID-19 patients and can be used for the early detection of pneumonia. Liu et al.'s study

also showed that the combination of NLR and CRP can predict the severity of COVID-19 within the first seven days of treatment and forecast the likelihood of COVID-19 worsening, as well as the need for ICU care.

The study observed an increase in NLR among patients with moderate COVID-19 severity, while a significant increase in CRP was found in those with severe and critical cases. This suggests that CRP may be associated with excessive inflammatory cytokine production in patients with severe and critical COVID-19.

Comorbid conditions such as diabetes mellitus and chronic kidney disease were not found to have a significant relationship with NLR and CRP levels. This finding is consistent with the study by Russell et al., which also found that comorbidities do not significantly correlate with COVID-19 severity. However, another study by Ng et al. indicated that the severity of COVID-19 could be influenced by factors such as hypertension, obesity, and diabetes mellitus. Other characteristics that may affect COVID-19 outcomes include patient age, female gender, and living in urban areas.

Patients who had received COVID-19 vaccination before infection had higher NLR and CRP levels compared to those who were not vaccinated. This finding is in line with research by Subramanian et al., which indicated that some countries with a high percentage of fully vaccinated individuals had more cases of severe COVID-19 at the time of admission.

## 5. Conclusion

This study shows that there is a relationship between the increase in NLR and CRP values with the severity of COVID-19 patients treated at Haji Adam Malik General Hospital in Medan. Comorbidities such as diabetes mellitus and chronic kidney disease did not affect NLR and CRP values. Patients who had previously received COVID-19 vaccination had significantly increased NLR and CRP values.

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