

# Relationship between Neutrophil Lymphocyte Ratio (NLR) and Anxiety Levels among COVID-19 Patients at H. Adam Malik General Hospital Medan

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## ABSTRACT

**Background:** COVID-19 caused great anxiety and stress in patients, especially those treated in isolation wards. SARS-CoV-2 infected respiratory tract and caused acute respiratory syndrome with the consequent release of pro-inflammatory cytokines, such as IL-1 $\beta$  and IL-6, resulting in a "cytokine storm". These cytokines were also elevated in psychiatric disorders such as depression, anxiety, schizophrenia, and post-traumatic stress disorder. Therefore, this study aimed to determine the relationship between NLR and anxiety levels in COVID-19 patients at RSUP. H Adam Malik.

**Methods:** This was an analytic observational study using cross-sectional design. This study was conducted from February to August 2021 on confirmed COVID-19 patients being treated at H. Adam Malik Hospital. The patient's anxiety scale was measured using the Beck Anxiety Inventory (BAI) questionnaire. The NLR value were taken from the results of a blood test performed when patient was first admitted to the isolation room. The data were coded, tabulated, and analyzed using SPSS 23.00 software. The magnitude of the desired deviation ( $\alpha$ ) was 0.05, with p value of <0.05.

**Results:** The median NLR ratio among 50 confirmed COVID-19 patients in each group respectively was 2.18, 5.03, 3.57 and 8.37. The median NLR ratio increased accordingly to the level of anxiety in COVID-19 patients, with p-value of <0.05 (p = 0.034).

**Conclusion:** NLR ratio was significantly related to anxiety level among COVID-19 patients.

**Keywords:** NLR, Anxiety Level, COVID-19, Neutrophil Lymphocyte Ratio

## INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). When SARS-CoV-2 infects the respiratory tract, it causes an acute respiratory syndrome with consequent release of pro-inflammatory cytokines, such as IL-1 $\beta$  and IL-6, resulting in a "cytokine storm". These cytokines can be elevated in psychiatric disorders such as depression, anxiety, schizophrenia, and post-traumatic stress disorder (PTSD).<sup>[1]</sup>

As a new and life-threatening disease, COVID-19 causes great anxiety and stress in patients, especially those treated in isolation wards. Several sociodemographic variables are associated with the prevalence of clinically relevant mental symptoms. A previous meta-analysis stated the prevalence of anxiety symptoms in COVID-19 cases to be 46% (95% CI 33.9% - 58.2%), with statistically significant evidence of heterogeneity between studies (Q = 154953, I<sup>2</sup> = 99.99 %, p<0.001). Women were pointed out to be one of the main variables of anxiety disorder. The same finding had also been reported in other studies. Moreover, patients whose family members were diagnosed and died of COVID-19 had

higher prevalence of somatic and anxiety symptoms. [2,3]

Earlier studies hinted those levels of inflammatory markers might be associated with mental problems in COVID-19 patients. The results showed that patients with mental symptoms had higher levels of IL-1 $\beta$  and NLR, lower levels of IL-10, and lower lymphocyte counts than those without mental symptoms. [4,5] Neutrophil Lymphocyte Ratio (NLR) is useful to measure inflammatory response, which reflects the intensity of systemic stress, inflammation, and the following cytokine cascade. Previous studies had also found significant association of NLRs with established inflammatory markers such as CRP and other pro-inflammatory cytokines, supporting NLRs as a useful marker. [6,7] Furthermore, NLR value greater than 6.5 at the time of hospital admission was found to be related in cases of clinically relevant depression and anxiety symptoms in COVID-19 patients. [8,9] This was the first study of the topic at North Sumatra. Therefore, this study aimed to determine the relationship between NLR and the level of anxiety in COVID-19 patients at H. Adam Malik Hospital Medan.

## MATERIAL AND METHOD

This was an analytic observational study using cross-sectional design to assess relationship between NLR ratio to anxiety level among COVID-19 patients treated at H. Adam Malik Hospital. It was conducted from February to August 2021. Total of 50 respondents were confirmed COVID-19 patients with minimum age of 18 years old. Diagnose was made through history taking, physical examination and supporting examinations such as RT-PCR swab, chest X-ray or thorax CT scan. Patients with comorbidities like severe infections, history of malignancy, other chronic diseases such as heart failure, chronic kidney disease, psychiatric disorders, neurovascular disorders and in treatment of corticosteroid were excluded.

In prior of study, every respondent gained information regarding the overall research and gave informed consent via phone call. Anxiety level was measured using Beck Anxiety Inventory (BAI) questionnaire by nurse on duty while NLR value was taken from previous blood test performed at the time of admission to isolation room. NLR value was the absolute value of neutrophils divided by lymphocyte count.

## Statistical Methods

Univariate, bivariate and multivariate analysis were performed. Univariate analysis was done to gain overview of respondents' demographic data. Bivariate analysis was performed to determine relationship between NLR ratio to anxiety level among respondents. Multivariate analysis using Fisher exact was conducted to look for correlation between each anxiety group to respondents' demographic data. Normalization test was carried out using Shapiro-Wilk while correlation between the two variables were done with Kruskal-Wallis test. Post hoc study was also performed using Mann-Whitney test. All data was tabulated and analyzed using SPSS 23.00 software with standard deviation of 95%. Result was considered significant if p value <0.05 was found.

## RESULT

Table 1. Characteristics of research sample

Characteristics	n = 50
<b>Age, (years)</b>	
Mean $\pm$ SB	53.1 $\pm$ 13.89
Median (minimum-maximum)	56.0 (22.0-82.0)
<b>Gender, n (%)</b>	
Male	23 (46)
Female	27 (54)
<b>Education, n (%)</b>	
Primary School	1 (2)
Junior High School	1 (2)
Senior High School	31 (62)
Bachelor	17 (34)
<b>Married Status, n (%)</b>	
Married	47 (94)
Not married	3 (6)
<b>Anxiety Level (BAI), n (%)</b>	
Minimal anxiety	2 (4)
Mild anxiety	2 (4)
Moderate anxiety	13 (26)
Severe anxiety	33 (66)

Fifty subjects met the inclusion criteria. The proportion of male and female was almost the same, with most of them

being married. Most respondents also studied until senior high. (Table 1.)

**Table 2. Characteristics of supporting examination parameters**

Parameter	Mean	Standard Deviation	Median	Minimum Value	Maximum Value
Neutrophils	77.17%	11.79%	76.45%	52.00%	96.20%
Lymphocytes	14.88%	9.79%	15.20%	1.50%	40.6%
NLR	11.84	14.05	5.03	1.28	62.47

Based on statistical test, there was a significant correlation between NLR and anxiety level among COVID-19 patients ( $p=0.034$ ) (Table 3). However, a post-hoc follow up study showed not all groups were

related to NLR ratio (Table 4.) Moreover, no correlation was found between study sample demographic characteristics and anxiety level among COVID-19 patients (Table 5).

**Table 3. Analysis between NLR and anxiety levels in COVID-19 patients**

Parameter	Minimum (n=2)	Mild (n=2)	Moderate (n=13)	Severe (n=33)	p-value
NLR	2.18 (1.28-3.08)	5.03 (4.97-5.08)	3.57 (1.96-16.47)	8.37 (1.63-62.47)	0.034*

\*Kruskal-Wallis non-parametric test, significant  $p<0.05$ .

**Table 4. Post-hoc analysis of between NLR and each level of anxiety**

Anxiety Level	p-value	
NLR	Minimal vs Mild	0.121
	Minimal vs Moderate	0.089
	Minimum vs Severe	0.039*
	Mild vs Moderate	0.234
	Mild vs Heavy	0.522
	Moderate vs Severe	0.035*

\*Post-hoc Mann-Whitney test, significant  $p<0.05$ .

**Table 5. Analysis between patient demographic characteristics and anxiety levels**

Characteristics	Anxiety Level			p-value
	Minimal-Mild	Moderate	Severe	
Age				0.20
60 years	4	11	21	
>60 years	0	2	12	
Gender				0.74
Woman	3	7	17	
Man	1	6	16	
Married status				1.00
Marry	4	12	31	
Not married	0	1	2	
Education				0.094
Primary School	2	6	25	
Junior High				
Senior High				
Bachelor	2	7	8	

\*Fisher exact test

## DISCUSSION

Immune system disorders triggered by COVID-19 infection can lead to psychopathology. Psychiatric sequelae may also be found. COVID-19 causes public panic and mental health stress, where symptoms of anxiety and depression are considered as common psychological reactions to the COVID-19 pandemic and associated with sociodemographic factors

and sleep quality. The overall global prevalence of anxiety disorders is estimated at 7.3%, but anxiety levels in the general population could even be more than 3 times higher during the COVID-19 pandemic. Approximately 28% of patients had posttraumatic stress disorder (PTSD), 31% had depression, 42% had anxiety, 20% had an obsessive-compulsive disorder, and 40% had insomnia. [10,11]

Based on the results of the study, the average age of respondents was 53 years, with the youngest being 22 years old and the eldest being 82 years old. Majority of subjects were women with 27 female (54%) and 23 male (46%). In the study by Li et al. (2020), it was found that the overall prevalence of anxiety was 13.67%. The prevalence was higher in women than in men (13.89% vs. 12.93%). [12] The highest prevalence of anxiety was 14.06% (SE 2.51%) at age 60 to 100 years in men, and 14.70% (SE 0.56%) at age 50 to 60 years in women. Age, gender, educational status, sources of information, level of concern, level of fear, and behavioral status are related to anxiety. [11]

Based on the BAI scoring to assess the anxiety level in COVID-19 patients, it was found that 33 respondents experienced severe anxiety (66%), followed by 13 with moderate anxiety (26%), 2 with mild anxiety (4%) and 2 with minimum anxiety

(4%). Similar study by Basheti et al. (2021) found that 43.8% and 40.0% of the subjects had normal anxiety scores, while 22.4% showed abnormal anxiety scores. Smoking ( $p = 0.022$ ), lower family income ( $p = 0.039$ ), and drug use ( $p = 0.032$ ) were positively associated with higher (worse) anxiety scores.<sup>[13]</sup>

Enhance cytokine levels was one of the mechanisms responsible in the manifestation of mental health problems during COVID-19 infection. In addition, biological factors such as advanced age, female gender, and obesity along with other factors related to COVID-19 including social isolation, financial stress, and adverse effects of medication can influence the progression of psychiatric disease. Therefore, the psychiatric symptoms observed in COVID-19 patients are due to a combination of processes involving the virus-host relationship, psychosocial factors and therapeutic process along the disease course. Based on laboratory examination, the mean of neutrophils was  $10,025.80 \pm 8832.35$  cell/mm<sup>3</sup> while the mean of lymphocytes was  $1397.76 \pm 887.42$  cells/mm<sup>3</sup>. Average of NLR ratio was 11.84, and the mean score of BAI is 27.46. The median NLR ratio in COVID-19 patients with minimal, mild, moderate and severe anxiety respectively was 2.18, 5.03, 3.57 and 8.37. The number increased accordingly to the anxiety level. Based on statistical test, there was a correlation between the NLR ratio and groups of anxiety level among patients with COVID-19 with  $p$  value of 0.034. ( $p < 0.05$ ).

The study by Kahve et al. in 2021 among hospitalized COVID-19 patients showed that age ( $p < 0.001$ ), neutrophil levels ( $4540 \pm 2750$ ,  $p = 0.036$ ) and BAI scores ( $14.26 \pm 11.24$ ,  $p = 0.046$ ) were significantly higher in patients with comorbidities like hypertension, diabetes mellitus, coronary heart disease and lower education level.<sup>[14]</sup> Previous study by Hu et al. in 2021 in China revealed that patients with anxiety symptoms had higher levels of IL-1 $\beta$  (2.5 (2.5, 6.2) vs 2.5 (2.5, 2.5)),  $p =$

0.045), NLR (2.1 (1.5, 3.2.) vs. 1.7 (1.3, 2.2),  $p = 0.049$ ), and lower mean lymphocyte count ( $1.6 \pm 0.4$  vs.  $1.9 \pm 0.7$ ,  $p = 0.015$ ). GAD-7 scores for anxiety were positively correlated with length of stay ( $r = 0.22$ ,  $p < 0.05$ ), IL-1 $\beta$  levels ( $r = 0.46$ ,  $p < 0.001$ ), NLR ( $r = 0.30$ ,  $p < 0.05$ ), self-perceived disease severity ( $r = 0.44$ ,  $p < 0.01$ ), and ISI scores ( $r = 0.75$ ,  $p < 0.01$ ).<sup>[15]</sup>

The study of Huarcaya-Victoria et al. a year before also found that high NLR ( $\geq 6.5$ ) was associated with clinically relevant anxiety symptoms (PRa=1.82; 95% CI: 1.18-2.81) compared to those with low NLR ( $< 6.5$ ).<sup>[16]</sup> Furthermore, an observational study conducted by Li et al. in 2021 had of 0.283 between SAS (Self-Rating Anxiety Scale) and NLR, with  $p$  value of 0.052. There was also significant difference between NLR and viral negative conversion time (NCT) between anxiety and non-anxiety groups ( $p = .021, .024$ ).<sup>[12]</sup>

This study also analyzed demographic characteristics such as age, gender, education, and marital status. Age, gender, education, and marital status were found not to be associated with anxiety levels in COVID-19 patients. This result goes along with a meta-analysis study by Deng et al. in 2020 which revealed that gender ( $p = 0.68$ ) and age ( $p = 0.44$ ) were not significantly related to anxiety.<sup>[17]</sup> In the following year, Guan et al. conducted a study on factors that influenced anxiety during COVID-19 pandemic in students in China. From that study it was found that gender, place of residence, level of concern, level of fear, cognitive level, and behavioral status were related to anxiety ( $p < 0.05$ ). Students with positive preventive behavior showed a protective effect on anxiety symptoms compared to those with negative preventive behavior. In contrast to high cognitive levels, participants with low cognitive levels 14.9% experienced more anxiety symptoms.<sup>[18]</sup>

In 2020, Hou et al. found that women experienced more stress and anxiety symptoms than men. The severity of anxiety symptoms decreases with higher education

and better resilience. However, anxiety levels increased in women who read information about COVID-19 for more than 60 minutes. They were also assumed as less adaptable and were feeling more stressed.<sup>[19]</sup> The study of Kibret et al. in 2020 elaborated risk factors associated with higher stress such as age between 30-39 years (AOR, 3.05; 95% CI, (1.70, 5.47) and 40 years (AOR, 11.32; 95% CI (3.37, 37.98), married (AOR, 3.56; 95% CI, (2.30, 6.38), had a chronic disease (AOR, 3.43; 95% CI, (1.59, 7.43), had a family member family with suspected COVID-19 (AOR, 5.20; 95% CI, (2.11, 12.78), and limited access to personal protective equipment (AOR, 2.55; 95% CI, (1.43, 4.56).<sup>[20]</sup> In the same year, Dai et al. also found poor sleep quality (odds ratio [OR], 3.655, 95% confidence interval [CI], 1.074-12.433;  $p=0.038$ ) and two current physical symptoms (OR, 3.504; 95% CI, 1.919–6.398;  $p<0.01$ ) as independent risk factor for anxiety symptoms.<sup>[10]</sup>

## CONCLUSION

There was a significant relationship between the Neutrophil Lymphocyte Ratio (NLR) between groups on the anxiety level of COVID-19 patients with  $p < 0.05$  ( $p=0.034$ ). There is a significant relationship between the NLR ratio in COVID-19 patients with minimal vs. severe anxiety with  $p$ -value = 0.039 and moderate vs severe anxiety with  $p=0.035$ .

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