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The Effect of Stress Level, Interleukin-10 Level, Neutrophil Percentage-Albumin Ratio on Severity in COVID-19 Patients

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Abstract:-
Background: COVID-19 is still a global problem today. In addition to causing physical disturbances, it also causes psychological disorders and stressful conditions for patients suffering from COVID-19. This study aimed to analyze stress level, IL-10 level, albumin level, neutrophil values and NPAR on severity in COVID-19 patients.

Methods: This study was an analytical observational study in a cohort prospective design. This research was conducted in June – September 2021, with patients who were confirmed to have COVID-19 in Infectious Emergency Department and Special Isolation Room of Dr. Soetomo General Hospital Surabaya as subjects. COVID-19 patients with mild, moderate and severe level according to WHO criteria 2020 were measured for stress level using DASS-21 questionnaire, interleukin level and also neutrophil and albumin level during treatment on the beginning of admission, the 3rd, 6th, and 12th day of admission.

Results: Stress levels and IL-10 levels had no significant effect on the severity of COVID-19 on day 0 and 3rd. Meanwhile, percentage of neutrophils, albumin levels, and NPAR had a significant effect on the severity of COVID-19 on day 0. Effect of neutrophil percentage, albumin level, and NPAR on severity of COVID-19 on day 0 was 41.5%, while 58.5% was due to other factors. On 3rd day, there was no significant effect of stress level, IL-10 level, neutrophil percentage, albumin level, and NPAR on the severity of COVID-19. On 6th day, there was no significant effect of stress level, IL-10 level, neutrophil percentage, albumin level, and NPAR on the severity of COVID-19.

Conclusion: Stress levels and IL-10 levels had no effect on severity in COVID-19 patients. Increase in NPAR had an effect on increasing severity in COVID-19 patients.

Keywords:- *Stress level, IL-10, Neutrophil Percentage-Albumin Ratio, COVID-19 Severity.*

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is still a global problem today. The current number of cases in Indonesia reaches 1.42 million and the death rate reaches 38,426, the number of cases in the world reaches 120,399,298. In addition to causing physical disturbances, COVID-19 also causes psychological disorders and stressful conditions for patients suffering from COVID-19.

Stress is a common word used to describe experiences that cause feelings of anxiety and frustration, because they push us beyond our ability to cope [1]. Stress is defined as any form of trauma, surgery, and infection that evokes a large number of neural and hormonal responses, resulting in disruption of the homeostatic mechanism of the patient, which aims to maintain and bring the patient to the healing process [2]. Exposure to traumatic or stressful events provides its own psychological stress. The clinical picture that appears can be a combination of anhedonic and dysphoric symptoms, anger and aggression, or dissociative [3]. Stress conditions will evoke a neuroendocrine response, namely activation of the Hypothalamus – Pituitary – Adrenal (HPA) axis [4].

COVID-19 patients undergoing treatment in hospitals will be treated in isolation rooms. The study conducted by Dziadzko et al, in 50 patients treated in intensive care, 70% experienced fear of death, 48% experienced hallucinations, and 38% experienced fear, especially focusing on uncertainty in the future and the possibility of failing to recover [5]. In Italy, as one of the European countries experiencing a severe COVID-19 pandemic, a study was conducted on the mental health conditions of patients and health workers. In patients undergoing isolation, there was an increased risk of mental disorders, such as anxiety, mood, addictive, and thought disorders. Feelings of loneliness due to isolation were associated with an increased risk of suicide [6]. In Indonesia, studies on the effect of stress levels, IL-10 levels, NPAR on severity and mortality in COVID-19 patients have not been widely carried out.

Theoretically, stress will have a negative impact on a person's condition. In a study conducted in the UK on an adult population aged over 35 years without cardiovascular disease and cancer, prolonged psychological stress was associated with mortality in a dose-response pattern [7]. From existing theories and research results, increased stress in COVID-19 patients is thought to have an effect on worse clinical outcomes in patients. In COVID-19 there is psychological stress and physical stress. There are not many studies that describe the relationship between the two. In this study, psychological stress is described by measuring stress levels, while physical stress is described by parameters of IL-10, neutrophils, and albumin.

This research is expected to provide an understanding of the effect of stress on the pathophysiology of COVID-19. With a better understanding, interventions can be devised to reduce patient stress in isolation rooms in order to improve clinical outcomes of treated patients.

II. METHODS

This study was an analytical observational study in a cohort prospective design. This research was conducted in the period of June – September 2021, with the study population including patients who were confirmed to have COVID-19 in Infectious Emergency Department and Special Isolation Room 1,2,3,4,5 Dr Soetomo General Hospital Surabaya and met the inclusion and exclusion criteria.

The sample in the study was taken by total sampling. COVID-19 patients with mild, moderate and severe level according to WHO criteria 2020. Samples that met the inclusion and exclusion criteria were measured for stress level using DASS-21 questionnaire, interleukin level using ELISA kit, and also neutrophil and albumin level using flowcytometry and clinical chemical during treatment on the beginning of admission, the 3rd, 6th, and 12th days in the data collection sheet. The data was processed with the SPSS Statistic Ver 26.

III. RESULTS

The number of study samples that met the inclusion criteria were 45 patients (100.0%). The characteristics of the research subjects are presented in table 1. Data that are normally distributed are shown in the form of Mean ± SD, while those that are not normally distributed are shown in the form of Median (IQR).

From the characteristics of the research subjects, age was normally distributed with p = 0.172. The variables of BMI and duration of symptoms before MRS were not normally distributed with p 0.000 and 0.000, respectively.

Based on the completeness of the research data, an analysis of the research parameters was carried out on day 0 compared to day 3. The results of the analysis can be seen in table 2.

A. Stress levels, IL-10, neutrophil percentage, albumin, and NPAR based on severity on days 0,3rd , 6th, and 12th

There were significant differences in the mild, moderate, and severe severity groups of albumin level and NPAR levels (p = 0.003 and 0.014) on day 0 and (p = 0.044 and 0.026) on 3rd day. There were significant differences in the mild, moderate, and severe severity groups of neutrophil percentage, albumin level, and NPAR (p = 0.047, 0.004, and 0.010) on 6th day. There were no significant differences in the mild and moderate severity groups of all variables on 12th day.

B. The Effect of Stress Level, IL-10 and Albumin Level, Neutrophil Percentage Albumin Ratio (NPAR) on Severity in COVID-19 Patients

Statistical analysis was continued to assess the effect of stress levels, IL-10 levels, NPAR on the severity of COVID-19 on days 0, 3rd, and 6th. Severity was divided into two groups, namely mild-moderate and severe. The followings are the results of the logistic regression of the effect of stress levels, IL-10 levels, and NPAR on the severity of COVID-19 on days 0, 3rd, and 6th.

Partially, stress levels and IL-10 levels had no significant effect on the severity of COVID-19 on day 0 and 3rd. Meanwhile, the percentage of neutrophils, albumin levels, and NPAR had a significant effect on the severity of COVID-19 on day 0. The effect of neutrophil percentage, albumin level, and NPAR on the severity of COVID-19 on day 0 was 41.5%, while 58.5% was due to other factors.

On 3rd day, there was no significant effect of stress level, IL-10 level, neutrophil percentage, albumin level, and NPAR on the severity of COVID-19.

On 6th day, there was no significant effect of stress level, IL-10 level, neutrophil percentage, albumin level, and NPAR on the severity of COVID-19Characteristics	N (%) 45 (100,0%)	Mean ± SD/ Median (IQR)
Gender		
Male	25 (55,6%)	
Female	20 (44,4%)	
Comorbidities		
Hypertension	8 (17,8%)	
Diabetes mellitus	9 (20,0%)	
Age (years) – Mean ± SD		42,0 ± 10,9
BMI (kg/m2) – Median (IQR)		25,1 (6,5)
Normal (18,5 – 24,9)	22 (48,9%)	23,3 (2,0)
Overweight and Obesity (>25,0)	23 (51,1%)	29,5 (6,0)
Duration of symptom before admission (day) – Median (IQR)		4,0 (4,0)
Symptoms		
Fever	27 (60,0%)	
Cough	23 (51,1%)	
Out of Breath	13 (28,9%)	
Gastrointestinal symptoms (nausea, vomit, diarrhea)	6 (13,3%)	
Myalgia	3 (6,7%)	
Others (headache, anosmia, ageusia)	12 (26,7%)	
Mortality	1 (2,2%)	

Table 1: The Characteristics of Study Sample

Variable	P value
Severity	0,07
Stress level	0,28
IL-10	0,78
Neutrophil	0,69
Albumin	0,008
NPAR	0,23

Table 2: Analysis of Research Variable 0 and 3rd Day

Variable	Severity											
	Mild (n=7)				Moderate (n=21)				Severe (n-17)			
	Day 0	3rd	6th	12th	Day 0	3rd	6th	12th	Day 0	3rd	6th	12th
Stress level	4,0	2,0	0,0	0,0	2,0	1,0	0,0	2,0	2,0	4,0	4,0	-
IL-10 level	44,8	88,4	148,3	48,2	77,5	66,0	110,6	114,7	183,6	155,3	143,3	-
Neutrophil percentage	78,0	65,2	67,9	80,3	72,4	78,7	67,2	74,0	78,3	78,1	77,8	-
Albumin	3,60	3,60	3,63	3,30	3,55	3,21	3,28	3,30	3,20	3,20	3,06	-
NPAR	21,7	17,6	18,6	24,3	20,7	23,9	23,4	22,4	24,9	25,1	26,0	-

Table 3: Stress levels, IL-10, neutrophil percentage, albumin, and NPAR based on severity on days 0, 3rd, 6th, and 12th

Variable	Regression coefficient	p	OR (95%CI)
Stress Level (X1)	0,046	0,573	1,047 (0.893 – 1,227)
IL-10 level (X2)	0,001	0,492	1,001 (0,998 – 1,003)
Neutrophil percentage (X3)	0,343	0,024	1,410 (1,047 – 1,899)
Albumin level (X4)	-11,598	0,008	0,000 (0,000 – 0,048)
NPAR (X5)	-0,993	0,036	0,370 (0,146 – 0,938)
Constanta	35,055	0,019	
Logistic regression equation	$\frac{1}{(1+e^{-(35,055+0,343\,X_3-11,598\,X_4-0,993\,X_5)})}$		
R Square	= 41,5%		

Table 4: The Effect of Stress Level, IL-10 and Albumin Level,
Neutrophil Percentage Albumin Ratio (NPAR) on Severity in COVID-19 Patients in Day 0

Variable	**Regression coefficient**	**p**	**OR (95%CI)**
Stress Level (X1)	0,123	0,124	1,131 (0,967 – 1,323)
IL-10 level (X2)	0,001	0,112	1,001 (1,000 – 1,003)
Neutrophil percentage (X3)	0,064	0,077	1,066 (0,993 – 1,145)
Albumin level (X4)	-0,155	0,880	0,857 (0,114 – 6,433)
NPAR (X5)	-0,461	0,332	0,630 (0,248 – 1,603)
Constanta	-5,641	0,045	

Table 5: The Effect of Stress Level, IL-10 and Albumin Level, Neutrophil Percentage Albumin Ratio
(NPAR) on Severity in COVID-19 Patients in 3rd day

Variable	**Regression coefficient**	**p**	**OR (95%CI)**
Stress Level (X1)	0,066	0,710	1,068 (0,756 – 1,509)
IL-10 level (X2)	0,005	0,144	1,005 (0,998 – 1,011)
Neutrophil percentage (X3)	0,879	0,123	2,409 (0,789 – 7,357)
Albumin level (X4)	-30,469	0,096	0,000 (0,000 – 215,964)
NPAR (X5)	-2,750	0,140	0,064 (0,002 – 2,472)
Constanta	94,065	0,127	

Table 6: The Effect of Stress Level, IL-10 and Albumin Level, Neutrophil Percentage Albumin Ratio
(NPAR) on Severity in COVID-19 Patients in 6th day

IV. DISCUSSION

A. Characteristics of Research Subjects

This study, which involved all COVID-19 patients treated at the Infectious Emergency Department and Special Isolation Room Dr Soetomo General Hospital Surabaya, aimed to analyze the effect of stress levels, IL-10 levels, albumin levels, and neutrophil percentage-albumin ratio on the severity of COVID-19 patients. There were 45 patients who met the inclusion and exclusion criteria. The research subjects were then followed from admission to the hospital through the Infectious Emergency Department to the Special Isolation Room treatment room. Data on stress levels, IL-10 levels, neutrophil levels, albumin levels and neutrophil percentage-albumin the ratio and severity of COVID-19 were measured periodically on treatment days 0, 3rd, 6th, and

12th. Research subjects were followed until their condition improved (out of hospital, transfer to regular inpatient care, intensive care or death).

From the research data, 55.6% of the patients were male. COVID-19 cases in Indonesia are dominated by male patients. Several studies indicate similar findings, including by Surendra, as many as 54.6% of male patients were infected with COVID-19 [8]. Female patients are known to be more resistant to viral infections. This is related to the protection of the X chromosome and the hormone estrogen, which has an important role in the mechanism of adaptive immunity. The X chromosome is associated with several genes that play a role in immunological processes, such as cytokine receptors, which are associated with T cell and B cell activity, as well as transcriptional and translational regulatory factors. In addition, women have more estrogen receptors that can protect the body and help the immune system, including T cells, B cells, macrophages, neutrophils, dendritic cells and natural killer cells [9].

Another characteristic observed was the patient's body mass index, where patients who had a body mass index 25 kg/m2 were 51.1%. This is in accordance with a previous study, by Bello-Chavolla et al., which stated that obese patients had an increased risk of death, hospitalization, pneumonia, ICU admission and invasive ventilation compared to non-obese patients[10]. Obesity can cause abnormalities in the secretion of adipokine cytokines and interferon which will cause disruption of the immune system in the human body. In addition, there is a dysregulation in the expression of tissue leukocytes and macrophages that play a role in the natural inflammatory and lymphoid response, which leads to impaired immune response. Obesity induces chronic inflammation with a consistent increase in circulating IL-6 and TNFα. Il-6 and TNFα concentrations in serum are predictors of increasing severity and risk of death in COVID-19 patients. Impaired immune response due to obesity reduces the response of cytotoxic cells to immunocompetent cells that play a major role as anti-virals. ACE-2 receptors are expressed more in adipose tissue than in the lungs, so obesity with an increase in adipose tissue mass causes an increase in the number of ACE-2 receptor expressions. This is the reason COVID-19 patients with obesity are at risk of increasing the severity of infection [9].

Symptoms experienced by patients in this study included fever (60.0%), cough (51.1%), and shortness of breath (28.9%). Respiratory symptoms such as cough, shortness of breath or fever increase the risk of COVID-19 positive patients dying compared to those without respiratory symptoms. These symptoms arise as a form of the body's response to COVID-19 infection. Cell destruction that occurs due to the viral replication process will stimulate the body's defence system to start the inflammatory process which will cause various symptoms experienced by the patient. These symptoms are a sign, where the infection process has taken place and the virus has begun to replicate and spread to other cells. Previous studies have found that if patients have respiratory symptoms such as shortness of breath or coughing up phlegm, the risk of dying can increase to 7.35 times higher [11].

The data description of the research variables in table 5.2 shows a significant difference in severity levels on days 0, 3rd, 6th, and 12th with p value = 0.03, while for data on stress levels, IL-10 levels, neutrophil levels, albumin levels and values. NPAR showed no significant difference on examination days 0, 3rd, 6th, and 12th. Furthermore, the research variables that could be compared were data on days 0 and 3rd, where the variable that showed a significant difference was the severity level (p=0, 07) and albumin levels (p=0.008).

B. Stress levels, IL-10, neutrophil percentage, albumin, and NPAR based on severity on days 0, 3rd, 6th, and 12th

Furthermore, the data were analyzed based on the severity level assessed based on the WHO 2020 criteria, which were divided into 3 groups, namely severe, moderate, and mild severity on days 0, 3rd, 6th, and 12th. In this study, mild severity increased on day 0, 3rd, and 6th. Meanwhile, the severity of the severity decreased on days 0, 3rd, and 6th. The stress levels observed in this study were then compared based on the severity on days 0, 3rd, 6th, and 12th. The p value = 0.475 on days 0, then the 3rd day (p=0.155), the 6th day (p=0.318), and the 12th day (p=0.346), which showed that there was no significant difference in the level of stress experienced by patients with mild severity, medium and heavy. In a 2003 study of patients with SARS, it was found that stress levels (assessed using the Perceived Stress Scale) and negative psychological effects (sleep disturbances, decreased concentration ability, depressed mood, nightmares) were higher when compared to healthy subjects [12]. In a study in the United States, acute stress disorder was only detected after 2 weeks of treatment in 25% of study subjects [13]. Meanwhile, another study on COVID-19 patients in Iran found 97% of research subjects experienced symptoms of stress, with 84.9% of subjects experiencing severe and very severe stress (based on the DASS-21 questionnaire) during treatment [14].

The level of stress in this study used the DASS-21 questionnaire, which is a self-report questionnaire with Likert-style answer choices. Several things that can affect the bias in the results of this study include (1) being dishonest in answering questions, especially sensitive questions; the respondent answers according to socially applicable norms (social desirability bias); (2) the tendency to answer yes or no, answering in extreme ratings on all questions given (response bias); (3) interpret the data differently; (4) the presence of the researcher when completing the questionnaire; (5) the questionnaire is less flexible [15, 16].

In this study, one of the laboratory parameters that was also observed was albumin and NPAR levels. On day 0 obtained p = 0.003, then p = 0.044; p=0.004; p=0.564 on days 3rd, 6th, and 12th. Albumin levels on days 0, 3rd, and 6th showed a significant difference between mild, moderate and severe severity. While on day 12th there was no significant difference in the degree of mild and moderate severity. Albumin which is a protein that secretes important haemostatic effects such as maintenance of colloid osmotic pressure, intravascular transport molecules, lipid metabolism, thrombosis and inflammation [17]. Albumin levels are referred to as one of the laboratory markers associated with

disease severity. Hypoalbumin status is associated with critically ill patients and the degree of mortality. The pathophysiology that causes decreased albumin levels in certain diseases (pancreatitis, infection, trauma, burns and organ dysfunction) is due to increased capillary permeability, decreased protein synthesis, decreased serum albumin half-life, decreased total serum albumin, increased volume of distribution, and increased expression of vascular endothelial growth factor. A meta-analysis study and a systematic review of a total of 11 studies (910 patients in total) on the relationship between albumin levels and the severity of COVID-19 stated that there were significant differences in albumin levels in the severe patient group compared to non-severe patients. This study concluded that low albumin levels have the potential to cause disease severity [18]. Another meta-analysis of 76 studies (a total of 19,760 subjects), stated that low albumin concentrations were associated with disease severity and poor clinical outcome in COVID-19 patients [17].

In addition to albumin levels, an analysis of the neutrophil percentage-albumin ratio (NPAR) was performed, where p-values on days 0, 3rd, 6th, and 12th were 0.014, respectively; 0.026; 0.010; and 0.180. These values indicate a significant difference in neutrophil percentage-albumin ratio (NPAR) values at days 0, 3rd, and 6th. Neutrophils affect the initial inflammatory response caused by acute infection, and a high neutrophil count value indicates systemic infection. Meanwhile, albumin is a negative acute-phase reactant and decreases in value in acute infection. Low albumin levels are associated with the risk of mortality in hospitalized patients. Neutrophil percentage-albumin ratio (NPAR) is one of the combined biomarkers that has prognostic value in septic patients, while also indicating systemic inflammation and mortality. A study conducted on 144 patients, by analyzing the ratio of neutrophil-albumin values as a predictor of new mortality in COVID-19 patients, stated that there was a significant difference between the severe COVID-19 patient group compared to the non-severe group. The neutrophil-albumin ratio value of 201.5 indicates mortality in all patients with a sensitivity value of 71.1% and a specificity of 71.7% [19].

On 6th day, there was a significant difference in neutrophil values with p value = 0.047 based on mild, moderate and severe severity. One of the parameters that become the laboratory examination protocol for COVID-19 patients is the examination of neutrophils. Neutrophils are the main component of leukocytes that actively migrate to the immune system or organ. Neutrophils release large amounts of ROS (reactive oxygen species) which induce damage to cell DNA and cause free viruses to leave the cell. Then ADCC (antibody-dependent cell-mediated cell) can kill viruses directly and trigger humoral immunity [20]. A study of the neutrophil profile in COVID-19 patients was conducted on 113 patients, which stated that a significant increase in neutrophils was obtained in the study subjects. An increase in neutrophil value may occur when the body's defence by neutrophils that takes place during infection from COVID-19 causes emergency granulopoiesis, a hematopoietic response program that rapidly increases neutrophil production to cope with increased demand. This mechanism results in the presence of neutrophils in the peripheral blood, which act as immunosuppressive or proinflammatory [21]. The pathophysiology of severe COVID-19 is characterized by changes in neutrophil abundance, phenotype and functionality. After SARS-CoV-2 infection, an increase in the number of neutrophils has been observed in the nasopharyngeal epithelium and then in more distal parts of the lung [22].

Levels of IL-10 which is one of the anti-inflammatory cytokines were also observed in this study. Based on the results of statistical analysis, there was no significant difference for IL-10 levels on examination days 0, 3rd, 6th and 12th. IL-10 is a cytokine that acts as an anti-inflammatory during infection, the main function of IL-10 is to inhibit the production of several cytokines. proinflammatory, inhibiting the function of macrophages and dendritic cells in helping T cell activation, so that it is immunosuppressive and limits the occurrence of tissue injury due to excessive immune responses [23]. A meta-analysis and systematic review study stated that IL-10 has great potential as a biomarker of severity and mortality in COVID-19 patients [24]. Another study conducted on 52 COVID-19 patients in the United States stated that IL-10 was a predictor in determining the severity of COVID-19 infection. The presence of increased levels of IL-10 is associated with clinical outcomes when compared to IL-6 or IL-8 [25].

C. The Effect of Stress Level, IL-10 and Albumin Level, Neutrophil Percentage Albumin Ratio (NPAR) on Severity in COVID-19 Patients

Statistical analysis was continued to assess the effect of stress levels, IL-10 levels, NPAR on the severity of COVID-19 on days 0, 3rd, and 6th. Severity was divided into two groups, namely mild-moderate and severe severity. In this study, the effect of neutrophil levels, albumin levels and neutrophil percentage-albumin ratio (NPAR) values on the severity of COVID-19 was only found on day 0. Meanwhile, on day 3rd, and 6th, there was no significant effect of all parameters on severity. COVID-19. In general, the results obtained in this study are caused by: (1) almost all stress levels in the subjects of this study were normal, so there was no effect on the severity of COVID-19, (2) on days 6th and 12th some of the research parameter data were incomplete so that further analysis could not be carried out, and (3) the criteria for the severity of COVID-19 used refers to the criteria for the patient's respiratory function. Changes in IL-10 levels, neutrophil values, albumin levels and NPAR values that describe the subject's inflammatory process cannot be described completely with the severity criteria.

V. CONCLUSION

Changes in stress levels were not associated with IL-10 levels and NPAR in COVID-19 patients. Stress levels and IL-10 levels had no effect on severity in COVID-19 patients. An increase in NPAR between days 0, 3rd, and 6th had an effect on increasing severity in COVID-19 patients.

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