

## Neutrophil Lymphocyte Ratio (NLR) in COVID-19 Patients Receiving Convalescent Plasma Therapy

Desyani Ariza<sup>1</sup>, Andi Maya Kesrianti<sup>1</sup>, Tazya Anggraini Ruslan<sup>1</sup>

<sup>1</sup>D-IV of Medical Laboratory  
Technology, MegaRezky  
University, Makassar, Indonesia

Correspondence:  
Desyani Ariza, Jl. Antang Raya  
No.43, Makassar, Indonesia  
Zip Code: 90234

Email: desyaniariza@yahoo.co.id

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### Abstract

Recently, a new RNA virus from the Coronaviridae family was discovered, known as SARS-Cov-2. This virus causes pneumonia and inflammation in the body. One of the laboratory tests used to see inflammation in the body is the Neutrophil Lymphocyte Ratio, or often abbreviated as NLR. NLR is one of the markers of inflammation that can be used simply, efficiently, and reliably because of its high stability and sensitivity. Higher NLR values tend to lead to a severe and poor prognosis, so this test can be done by monitoring patients with confirmed Corona Virus Disease 2019 (COVID-19). The purpose of this study was to determine the neutrophil lymphocyte's ratio in COVID-19 patients receiving convalescent plasma therapy. This research method is a quantitative observation using a descriptive approach. Quantitative observational research is used to analyze data in the form of numbers from the results of laboratory tests. The results obtained from 17 research subjects, namely the NLR values before convalescent plasma therapy were obtained in as many as 6 patients (35%) with normal NLR values below 3.13 and NLR values are increasing above 3.13 in as many as 11 patients (65%). Meanwhile, after convalescent plasma therapy, there were 8 patients (47%) with normal NLR below 3.13 and NLR values increasing above 3.13 as many as 9 patients (53%). This research concerns about changes in NLR values before and after convalescent plasma therapy, which before convalescent plasma therapy there were 6 patients with normal NLR values and after convalescent plasma therapy increased to 8 patients with normal NLR values which indicate a better good prognosis.

### Keywords

Convalescent Plasma Therapy, Corona Virus Disease 2019, Neutrophil Lymphocyte Ratio.



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## INTRODUCTION

At the end of 2019, the whole world was shocked by the news of the spread of disease outbreaks such as pneumonia, the cause of which was not yet known. This disease was discovered for first time in China, specifically in the city of Wuhan. Patients infected with this pneumonia-like disease are mainly animal dealers at the Huanan market located in the city of Wuhan. On January 7, 2020, several researchers successfully identified the cause of the spreading pneumonia epidemic, the new type of Novel Coronavirus. Over 800 confirmed cases, including health workers infected by COVID-19 have been identified in Wuhan. A number of other confirmed cases have been discovered in other provinces in China, South Korea, Thailand, Japan and the United States (1). The World Health Organization (WHO) has officially named the disease COVID -19 (2019 Coronavirus Disease) and the virus called SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) (2).

Initially the symptoms of COVID-19 were not so severe and only occurred with fever and cough symptoms which then spontaneously recovered. In some individuals, it doesn't even produce symptoms (3). However, these symptoms can develop shortness of breath, dyspnea, pneumonia, which can cause Acute Respiratory Distress Syndrome (ARDS), kidney failure, coagulation dysfunction,

multiple organ failure and can even cause death (4). The cytopathic effect of the virus and its ability to control the immune response determines how severe the infection is. A diminished and weak immune response can lead to rapid reproduction of the virus, resulting in tissue damage (5).

A number of other treatments have been offered to treat patients with COVID-19. One of them is a Convalescent Plasma Therapy (TPK). Convalescent Plasma Therapy is a therapy or treatment that uses plasma from donors who have rescued patients with COVID-19 patients to COVID-19 patients who are still suffering from the disease. Previously, convalescent plasma therapy had been applied to treat diseases Ebola-related illnesses and was a recommended by the WHO in 2014 (6).

The characteristics of recipients of convalescent plasma therapy are COVID-19 patients who have been confirmed by throat swabs using Reverse Transcription Polymerase Chain Reaction (RT-PCR) examinations, show signs and symptoms towards the progression of illness, and have critical conditions. Those who are entitled or able to donate or as donors are patients who have recovered from COVID-19 infection, which has been proven by conducting a negative swab examination with RT-PCR. In addition, the donor has no signs and symptoms in the last 10 days. The donor also tests seronegative is for hepatitis B virus

(HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and syphilis and has high polyclonal antibody titers (IgM and IgG), and neutralizing antibody titers >40 (7).

In addition to treatment and therapy for patients with COVID -19, several medical measures to detect SARS-CoV-2 have been widely extensively implemented. Many initial tests are carried out so that people infected with this virus are immediately treated and isolated so that this virus does not spread to a large extent. Abnormal laboratory results play an important role in classifying and assessing a patient's prognosis so that early treatment is given, which is should lead to better outcomes. Laboratory tests may describe inflammation and immune status, which may be useful as a possible predictors of the prognosis for patients with COVID -19 (8). One of the parameters that are simple, rapid, and widely available is the hematological parameter that can determine the number and ratio of inflammatory cells (9).

Neutrophils are the most common type of leukocyte, the greatest number, and play a significant role in the body's response to inflammation (10). Neutrophils have an affinity for immune complexes, as well as phagocytosis capacity (11). One of the inflammatory markers which may be used is the Neutrophil Lymphocyte Ratio (NLR) (12). According to Fuad et al., (13), an

increase in the NLR was found in patients with confirmed COVID-19. NLR provide an illustration of the balance between the innate immune response (neutrophils) and adaptive immunity (lymphocytes). The NLR value is calculated by dividing the absolute number of neutrophils cells by the absolute number of lymphocytes. The NLR value is also calculated from the percentage of neutrophils divided by the percentage of lymphocytes. The NLR calculation can be used as an important point in COVID-19 patients care at intake. Higher levels of NLR tend to have a severe and poor prognosis, requiring particular care and treatment (13). In the study above, we have not examined the value in COVID-19 patients undergoing treatment or therapy, whether or not there are changes. Therefore, in this study, we are examining the specificities of the neutrophil lymphocyte ratio value in patients with COVID-19 undergoing Convalescent Plasma Therapy.

## MATERIALS AND METHODS

The method used in this study is a quantitative observation using a descriptive approach to determine the value of neutrophil lymphocyte ratio (NLR) in patients with COVID-19 undergoing Convalescent Plasma Therapy. Quantitative observational research aims to analyses and process data in the form of figures derived from the laboratory test results. The NLR value is calculated by dividing the neutrophils percentage by the

lymphocytes percentage (17) and then record the results of the data obtained. Data obtained in the raw data via laboratory examinations, then processed and presented in tables and descriptions.

Tools and materials used in this study included total blood samples, EDTA vacuum tubes, Spout, Alcohol and cotton, and the use of the Sysmex XN-10™ Automated Hematology Analyzer as an examination tool. The method of the tool is flowcytometry. In this study, blood was collected twice, namely blood collection before therapy and blood collection after therapy.

The collection of COVID-19 healing plasma is based on routine plasma collection by plasmapheresis. Plasma products are processed in the form of as fresh frozen plasma. The convalescent COVID-19 plasma transfusion dose is approximately 4 -13 mL/kg of the recipient's body weight. The ABO type of the transfused convalescent plasma is consistent with the patient's ABO type. In addition, the convalescent plasma is intersected with the patient's red blood cells to ensure compatibility. A conventional plasma transfusion is given at approximately 10 mL during the first 15 minutes, which is then increased to approximately 100 mL per hour with careful monitoring (14).

The study population in this study were COVID-19 patients confirmed by a physician. Patients were subjected to routine

blood sampling prior to and following convalescent plasma therapy to see the value of the neutrophil-lymphocyte ratio. The interval between blood collection before and after treatment was 1-2 days, but there was no measurement of the amount of treatment given to patients who received convalescent plasma donors. This research was completed in 2021 in the clinical laboratory of RSUP. DR. Wahidin Sudirohusodo, Makassar, Indonesia. This research was approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University and bears the letter number 685/UN4.6.4.5.31/PP361 2021.

## RESULTS

Clinical laboratory tests are conducted to confirm the diagnosis of patients with confirmed COVID-19. Among these are performed by out by various examination methods, namely Rapid Diagnostic Test (RDT) Antigen, RDT Antibodies, polymerase chain reaction (PCR) and culture. In the diagnosis COVID-19, the RT-PCR exam is the gold standard recommended due to its high sensitivity and specificity (15).

The subjects of this study were mainly patients with COVID-19 with moderate to severe symptoms. These patients were treated at the RSUP DR. Wahidin Sudirohusodo. 14 of the 17 patients who had convalescent plasma therapy made a full recovery and were permitted to continue receiving ambulatory care (26).

According to the study results, 17 subjects obtained samples of COVID-19 patients that met the inclusion criteria. Table 1 presents the general characteristic of the subjects after data processing.

**Table 1.** Patient Characteristics (n=17)

Characteristics	Criteria	n	%
<b>Age (years old)</b>	12-25	1	5.9
	26-45	2	11.76
	46-65	8	47.05
	>65	6	35.29
<b>Gender</b>	Man	11	64.70
	Woman	6	35.30
<b>Total</b>		17	100%

Table 1 shows the age characteristics and obtained by the age of 12-25 years there is

one patient (5.9%). Subjects at the age of 26-45 years there are two patients (11.76%), at the age of 46-65 years there are eight patients (47.05%) and aged over 65 years there are 6 patients (35.29%). Meanwhile, gender characteristics revealed that among males there were 11 patients (64.70%) and among females there were 6 patients (35.30%).

Table 2 shows the normal pre-treatment NLR values lower than 3.13 in 6 patients (35%) and increasing above 3.13 before therapy in 11 patients (65%). Whereas the NLR value after therapy was obtained that was normal below 3.13 on 8 patients (47%) and increased by 9 patients (53%).

**Table 2.** Overview of NLR Values Before and After Convalescent Plasma Therapy

Check Indicator		Before therapy		After therapy	
		N	%	n	%
<b>NLR</b>	$\leq 3,13$	6	35%	8	47%
	$\geq 3,13$	11	65%	9	53%
<b>Total</b>		17	100%	17	100%

## DISCUSSION

An investigation was conducted at RSUP Dr. Wahidin Sudirohusodo on 17 investigate subjects. These subjects have undergone an NLR examination to see a description of the NLR value in patients with COVID-19 receiving convalescent plasma therapy using the Sysmex XN-10™ Automated Hematology Analyzer. The most amount of subject is between age of 46-65 years with up to eight patients (47.05%). As a result, we can infer that growing older also contributes to an

increase in the number of COVID-19 instances that have been confirmed. This study is in line with research undertaken by Liu et al., (18), where the age of people symptomatic COVID-19 is older than 40 years old (84%). This is due to the relationship between age and immunity level, where older people are at greater risk of infection than body immunity decreases (18).

With regard of gender criteria, 11 subjects (64.70%) had more COVID-19 infection than women. This study is



consistent with research of Liu et al., (18) which lead us to believe that man with COVID-19 are more infected than women (18). This is due to the fact that men are known to have superior ACE2 expression. It is related to sex hormones that cause men to be more likely to be infected more easily. Furthermore, men's daily activities are more predominant when they work outside for long hours. However, in fact, both of men and women have a high risk of contracting COVID-19 when performing day to day activities without implementing the health protocols established by the government.

In Table 2, pre-treatment NLR results for 6 patients with NLR values are normal or below 3.13. As many as 11 patients indicated that NLR values increased above 3.13 post-therapy. Currently, there is a change for 8 patients with normal NLR values and 9 patients with higher NLR values. A high NLR value describes the prognosis of the disease in the direction of severe and poor behavior in order for it to require more intensive treatment. Additionally, the value of the NLR can serve as a simple test to help determine the severity of the illness and predict the outcome of COVID-19. The results of Table 2 demonstrate that the normal NLR values are higher therapy, which means that there is a change. This study is in line with the research of Maulana (19) which indicates that convalescent plasma therapy has potential to reduce mortality in COVID-

19 patients and help reduce hospitalizations. It also indicates that there is a change or a better prognosis after plasma therapy. However, this requires even more research with larger research subjects to see changes that occur in the NLR value or other examination parameters performed in patients with COVID-19 receiving convalescent plasma therapy.

Convalescent Plasma Therapy has previously been applied to treat diseases caused by virus, such as 1918 Influenza, avian influenza A (H5N1), Ebola, and other viral infection. This therapy has also been used in Hong Kong for the outbreak of SARS-CoV-1 in 2003, H1N1 in 2009-2010 and MERS-CoV in 2012. Convalescent Plasma Therapy was also performed in Wuhan, China and in New York, United States (US). The US Food and Drug Administration (FDA) has issued a decision allowing Convalescent Plasma Therapy to for patients with COVID-19 (20).

Although it still requires further research with larger research subjects, the results of the study indicated that there was a shift in the NLR value to a better prognosis. What is known if the normal NLR value means describe the successful completion of therapy. Because the NLR value describes how severe the inflammation is in the body.

In severe infections or systemic inflammation, the neutrophil/lymphocyte ratio will increase so that it may be used for

clinical assessment of patients with systemic inflammation. This description shows that in severe systemic inflammation there is a greater increase in neutrophil lymphocytes ratio compared with mild systemic inflammation conditions (21). The sample of subjects in this study were COVID-19 patients with severe symptoms and hospitalized. This is indicated that the NLR value was increasing. From this finding, it may be indicated that the body's immune system reacts by increasing the neutrophil-lymphocyte ratio. This ratio is higher for severe inflammation than for mild systemic inflammation. It's just that there aren't any other studies that compare the NLR value in patients with COVID-19 with various categories of symptom.

An increased number of neutrophils compared with lymphocytes ratio is one of the immune system's physiological responses to systemic inflammation (22). This is due to changes in the dynamics and regulation of apoptosis in the systemic inflammatory versus non-inflammatory condition (21).

The delay in the mechanism of neutrophil apoptosis will have an impact on the prolonging the function of neutrophil in the inflammatory process. In addition, it also delays the production of toxic metabolites. On the other hand, increased lymphocyte apoptosis may have an impact on reducing inflammatory effectors and causing

immunosuppression (23,24). Activated neutrophils and inflammatory cytokines will damage the function of tissues and organs as a result of the effects of the toxic metabolites produced. In addition, the process of lymphocyte apoptosis can lead to immunosuppression of the adaptive immune system, making it more susceptible to infection which will trigger a further systemic inflammatory response (25).

Finally, the occurrence of high neutrophil counts and decreased lymphocyte counts will increase the absolute ratio of neutrophils to lymphocytes relative to patients without a systemic inflammatory response. An rise in the neutrophil-lymphocyte ratio will raise the patient's risk of morbidity and mortality, which are characterized by organ damage and dysfunction (21).

This study is strengthening the theoretical basis and other studies that the ratio of neutrophil to lymphocyte or NLR changes when appropriate therapy or treatment is carried out. It also indicates a change or improved prognosis after convalescent plasma therapy. However, this requires even more research with larger research subjects to see changes that occur in the NLR value or other examination parameters carried out in COVID-19 patients receiving convalescent plasma therapy.

For information other than the laboratory tests results from 17 patients undergoing convalescent plasma therapy, 14 patients

were able to recover and were allowed to be outpatients (26).

## CONCLUSIONS

This study emphasizes how secure NLR treatment is. There is a change to the NLR values before and after convalescent plasma therapy. In pre-treatment, up to 6 patients with normal NLR values. Afterwards, after therapy grew to 8 patients with normal NLR values. This suggests a positive prognosis.

## AUTHOR CONTRIBUTIONS

Desyani Ariza: processing data, conceptualizing, writing and submitting

articles, supervision, administration. Andi Maya Kesrianti: sample and data collection, data verification and validation. Tazya Anggraini: article revision, field review, reviewing and editing articles.

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## CONFLICT OF INTEREST

According to the author there is no conflict.

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