International Journal of Research and Review
Vol. 9; Issue: 8; August 2022
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

The Relationship Between the Lymphocyte Value and the Neutralizing Antibody Titer Towards SARS-COV-2 in Residents of Internal Medicine Faculty of Medicine Universitas Sumatera Utara Who Had Received Covid-19 Vaccination

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DOI: https://doi.org/10.52403/ijrr.20220865

ABSTRACT

Background: Corona virus disease-19 (COVID-19) is a respiratory disease caused by SARS-COV-2 virus. COVID-19 vaccines were designed to produce neutralizing antibody towards the spike (S) protein of the SARS-COV-2 virus. The lymphocyte value has been known to influence the effectiveness of the vaccine. This research was conducted to assess the relationship between the lymphocyte value and the neutralizing antibody titer in residents of internal medicine in Faculty of Medicine, Universitas Sumatera Utara, who had received COVID-19 vaccination.
Method: This was an observational analytic study with cross-sectional design, conducted since February to May 2022. The research was performed on residents of internal medicine who had received COVID-19 vaccination. The lymphocyte value was based on the complete blood count, while the neutralizing antibody titer was based on the IgG-SARS-COV-2 titer that was measured using chemiluminescent immunoassay. The data was collected and analyzed using SPSS version 26.
Results: There were a total of 45 research subjects included in the study. The mean value of lymphocyte was 31.28% with a mean value of absolute lymphocyte count (ALC) of 2437.99. The mean value of IgG-SARS-COV-2 was 13864.44 AU/ml. The correlation test between lymphocyte value and IgG-SARS-COV-2 titer using Spearman correlation showed a p-valued of 0.476.
Conclusion: There was no significant relationship found between the lymphocyte value and the neutralizing antibody titer in residents of internal medicine in Faculty of Medicine, Universitas Sumatera Utara who had been vaccinated (*p-value* 0.476).

Keywords: Lymphocyte, Neutralizing antibody, IgG-SARS-COV-2, Internal Medicine Residents

INTRODUCTION

Corona virus disease-19 (COVID-19) is a respiratory disease caused by the SARS-CoV-2 (severe acute respiratory syndrome-Coronavirus 2) virus. The World Health Organization (WHO) first referred to this disease as Novel Coronavirus-Infected Pneumonia (NCIP) and the virus that caused it was named 2019-nCov (2019 novel coronavirus). In February 2020, WHO officially named this clinical condition as COVID-19 since the outbreak was first discovered in Hubei in December 2019. The COVID-19 disease itself was officially declared a pandemic since March 2020. (Hafeez, 2020) COVID-19 is an infectious disease that causes severe acute respiratory syndrome, followed by a characteristic hyperinflammatory response, vascular

damage, microangiopathy, angiogenesis and widespread thrombosis. (Stasi, 2021)

The COVID-19 vaccination has become the main effort that is currently being carried out globally in order to end the pandemic that has been going on since March 2020. (WHO, 2021) Almost all COVID-19 vaccines are designed to produce an immune response, which ideally is to produce neutralizing antibodies known as neutralizing antibodies (NABS) against the spike protein (S) of the SARS-CoV-2 virus. (Sadarangani, 2021) In one of the subunits of the S protein, there is a part called the receptor binding domain (RBD) that binds to the ACE-2 receptor. The immune response generated by targeting RBD has become a major focus in vaccine development

Based on a previously randomized study, the final outcome assessed as the basis for determining vaccine efficacy against SARS-CoV-2 was the onset of COVID-19 infection with symptoms. BNT162b2 and mRNA-1273 mRNA vaccines showed >90% efficacy at 5-6 months after the 2nd injection dose. The viral vector-based vaccine, AZD1222 had 70.4% efficacy against the Alpha variant for up to 3 months after the 2nd injection dose. The inactivated viral protein subunit-based vaccine, NVX-COV2373, had an efficacy of 86.3 – 93.2% against the Alpha variant and 60% against the Beta variant. The study stated that follow-up was only carried out until 90 days after the second dose of vaccination. (Fiolet et al, 2022) Several studies have shown that the number of antibodies formed after vaccination with BNT162b2, mRNA-1273 and also Ad26.COV2.S remained high for at least six months, and decreased gradually thereafter. (Pegu, 2021) Another study on health workers also found that 99.5% of those given the BNT162b2 vaccine had protective antibodies that persisted up to 250 days after the second vaccination dose. (Copetta, 2022) In a prospective study conducted on 4290 health workers it was found that after 13 months after being infected with COVID-19, anti-RBD antibodies still persisted in the body, and giving the booster vaccine just once was enough to increase the neutralizing antibody titer and reduce the risk of re-infection with SARS COV-2. (Gallais et al, 2021) All these studies showed that antibody titers against SARS-CoV-2 both post-vaccination and post-COVID-19 infection have decreased levels in the body at different timescales.

Research on the COVID-19 vaccine also found that in the process of forming antibodies against SARS-Cov-2, the lymphocyte value was also an important parameter in assessing the effectiveness of the vaccine. Achiron et al explained that there was a correlation between the number of SARS-CoV-2 antibodies and the lymphocyte count in 1 month after the second dose of vaccination in 125 patients with multiple sclerosis who had received the BNT162b2 vaccination. In line with the results of this study, another study conducted on 427 patients with hematological malignancies who also received two doses of BNT162b2 vaccination, found that lymphocyte values were associated with higher seropositivity values and antibody titers formed. This observation is certainly not a new thing, considering the important role of lymphocytes in the formation of the immune response and specifically being an important instrument in the formation of antibodies. (Seban et al, 2021; Grothe, 2021; Herzog, 2021) Another study in patients with breast malignancy found that patients with normal lymphocyte count after COVID-19 vaccination, had a higher tendency for seropositivity and formation of antibody titers against SARS-CoV-2. (Seban et al, 2021) Another study that assessed the immune response to the SARS-CoV-2 variant after administration of two and three doses of vaccination in a group of patients with hematological malignancies found that the timing of vaccination with the time of treatment was associated with the antibody response formed. No antibodies were found after two doses, in 52.3% of respondents

who were vaccinated within 24 weeks of completing their treatment, compared to 8.7% who did not receive any systemic therapy within 24 weeks. Anti-CD20 therapy significantly impairs antibody response action for at least six months after therapy.

This is thought to be related to the disruption of the cellular system of T-cells and B-cells in their work to produce antibodies. (Lim, 2022) In a study that conducted immune profiling and examined its relationship to antibody responses in COVID-19 patients, it was found that the total number of T-cells, CD4 T-cells and the percentage of natural killer cells correlated with the serological response to antibody production of IgM and IgG against COVID-19, where specifically the results showed that there was an increased percentage of CD4 T-cells and natural killer cells in the group that showed an Ig-G antibody response compared to the group that did not show an antibody response. (Rezaei, 2021)

All of these parameters are very important in the work of the humoral immune response, however, the role of lymphocytes themselves in cell-related immune responses after COVID-19 vaccination is still being studied. (Seban et al, 2021) The existence of these different immune response mechanisms is, of course, influenced by many factors. The factors in question can include host intrinsic factors, extrinsic factors, behavioral factors, nutritional factors, environmental factors and also the vaccine itself. (Zimmerman, 2020)

The authors then have an interest in being able to assess lymphocytes and how the immune response is formed which is measured through the production of neutralizing antibodies (NABS) in internal medicine residents of USU who have received COVID-19 vaccinations. The basic mechanism of action of different vaccines accompanied by different host intrinsic factors, of course, will also provide varied immune responses, which theoretically will cause different antibody production.

METHODS

The research design used in this study was an observational analytic study with cross-sectional design. This research was conducted from February 2022 to July 2022. The population in this study were all residents of internal medicine at the Faculty of Medicine, Universitas Sumatera Utara with active educational status. The research sample is part of the affordable population that meets the inclusion and exclusion criteria. Inclusion criteria are male or female at least 18 years old, maximum 35 years old, have received at least two doses of Covid 19 vaccination and are willing to be included in the study. Exclusion criteria included a history of last vaccination previously less than three months or more than eight months. The sampling technique in this study used a non-probability sample design, namely a consecutive sampling technique. Subjects who are willing to participate, signed the informed consent form. Sample size was determined using the correlation coefficient (r) using a simple linear regression test for a single sample.

The normality test of numerical data was carried out by Kolmogorov Smirnov. Furthermore, a comparative and correlative sub-analysis was carried out. It is said that there is a significant difference between the two variables if the P value < 0.05. Statistical analysis was performed using the SPSS version 26 program.

RESULT AND DISCUSSION

Based on the minimum size calculation, 45 subjects were taken to be examined for lymphocyte levels and SARS-COV-2 neutralizing antibody titers. Sampling was carried out at the Prodia Medan Laboratory and complete blood counts and IgG-SARS-CoV-2 examinations were performed on all subjects. In this study, the overall average age of the subjects was 29.53 years with the highest age range being 26-30 years old, as many as 29 people (64.4%). Male research subjects consisted of 19 people (42.2%) while women were 26 people (57.8%). The average body mass index (BMI) in the

research subjects as a whole was 23.14 ± 5.56 kg/m2 with the highest BMI category being normal, as many as 34 people (75.6%). The average value of hemoglobin in all study subjects was 13.59 mg/dL, with a mean leukocyte value of 7926 mg/dL, and a mean platelet value of 287,866. The mean value of lymphocytes measured based on the examination of complete blood counts was 31.28% with the mean absolute lymphocyte count (ALC) of 2437.99.

Based on the results in Table 1., it can be seen that the average value of IgG-SARS-COV-2 measured was 13864.44 AU/ml. For the last vaccine schedule before the subject was examined for lymphocytes and IgG-SARS-CoV-2, 9 subjects (20%) received the last vaccine since the previous 3 months, 1 subject (2.2%) since the previous 4 months, 4 subjects (8.9%)) since the previous 5 months, and as many as 31 (58.9%) subjects since the previous 6 months. The previous history of Covid-19 was found in 37 subjects (82.2%) and as many as 8 subjects (17.8%).

Based on Table 2., it was found that research subjects with a history of previous Covid-19 infection had an average lymphocyte value of 31.48 ± 7.23, while for those who had no previous history of infection with Covid-19, the lymphocyte value was found to be lower at a slight value of 30.35 ± 7.59. The ALC value based on the presence or absence of a history of being infected with Covid-19 is 2407.58.

In contrast, the group with no history of being infected with Covid-19 actually had a slightly higher ALC value compared to those with a history of Covid-19.

Based on Table 4., it can be seen that the mean value of the SARS-CoV-2 IgG antibody titer in subjects with a previous history of covid-19 (+) was higher than subjects with a history of covid-19 (-) with a mean of 17136.77 and 13156.93, respectively. Based on Table 5., correlation test of lymphocyte value variable with IgG-SARS-CoV-2 titer has been carried out using the Spearman correlation test. The significance value showed that there was no relationship between the lymphocyte value and the IgG-SARS-CoV-2 titer with a p-value of 0.476.

Table 1. Subjects Characteristics

Characteristics	Mean	n (%)
Age 21 – 25years 26 – 30 years 31 – 35 years	29,53 (25-35)[b]	 3 (6.7) 29 (64.4) 13 (28.9)
Sex Male Female Body Mass Index (kg/m^2) Severe underweight Underweight Normal Overweight Obese	23,14 ± 5,56 [a]	 19 (42.2) 26 (57.8) 1 (2,2) 2 (4,4) 34 (75.6) 3 (6.7) 5 (11.1)
Hemoglobin	13.59 ± 1.59[a]	
Leucocyte	7926 (5100 - 14700)[b]	
Trombocyte	287.866 (190.000 - 428.000)b	
Lymphocyte	31.28 ± 7.22[a]	
Absolute Lymphocyte Count (ALC)	2437.99 ± 722.36[a]	
Neutrophil	2 (0,8 - 16,5)[b]	
Monocyte	7.24 (4.4 - 10.8)[b]	
Eosinofil	3.03 (0.5 - 8.9)[b]	
Basofil	0.48 (0.0 - 1)[b]	
Erythrocyte Sedimentation Rate	16.2 (2 - 56)[b]	
IgG SARS COV-2	13864.46 (1388.6 - 37419)[b]	
Last Vaccination 3 months 4 months 5 months 6 months		9 (20) 1 (2.2) 4 (8.9) 4 (8.9) 31 (58.9)
History of confirmed Covid-19 previously Yes No		 37 (82.2) 8 (17.8)

[a]normal distribution, mean±SD
[b]distribution not normal, median (min-max)

Table 2. Lymphocyte Value in Internal Medicine Residents based on History of Covid-19

Variables	Lymphocyte Mean (Mean ± SD)[a]
Historty of Covid-19 (+)	31.48 ± 7.23
History of Covid-19 (-)	30.35 ± 7.59

[a]Data in normal distribution presented in mean ± SD

Table 3. Absolute Lymphocyte Count in Internal Medicine Residents based on History of Covid-19

Variables	ALC (Mean ± SD)[a]
History Covid-19 (+)	2407.58 ± 658.21
History Covid-19 (-)	2578.63 ± 1012.07

[a]Data in normal distribution presented in mean ± SD

Table 4. IgG-SARS-COV-2 in Internal Medicine Residents based on History of Covid-19

Variables	IgG-SARS-COV-2 Titer (Mean (min-max))[a]
History Covid-19 (+)	17136.77 (1782 – 37419)
History Covid-19 (-)	13156.93 (1388.6 – 35757.6)

[a]Data in normal distribution presented in mean ± SD

Table 5. Relationship between lymphocyte and neutralizing antibody titer towards SARS-COV-2 in Internal Medicine Residents

Significance (p-value)	**IgG SARS CoV-2 Titer**
Lymphocyte Value	0.476[a]

[a]p value is declared significant if <0.05

In this study, the values of lymphocytes and IgG-SARS-COV-2 were measured in healthy adult research subjects, namely residents of internal medicine at the USU Faculty of Medicine. The basic characteristics of the research subjects were pursued in homogeneous conditions, where all research subjects were young adults and without any comorbid diseases such as diabetes mellitus, hypertension, heart disease or other chronic disease conditions. Efforts to equalize these characteristics are expected to provide an overview of samples with immune systems that are considered to be similar to each other. However, for the genetic part or certain immune disorders in each individual it cannot be definitely ruled out so that the homogeneity of all research subjects is still not perfect.

The results showed that the mean lymphocyte value in the form of a percentage of the leukocyte value was 31.28% of the total leukocyte mean value of 7926/µL. Normally, lymphocytes are found as much as 20-40% of the total number of leukocytes. From a total of 45 research subjects, there were 2 subjects with lymphocyte values below normal values, respectively 18.8% (ALC 1710.80) and 16.9% (ALC 1521). However, in each of the subjects of this study there was no use of certain drugs that might suppress the immune system or disease states that might be associated with low lymphocyte values.

For the number of IgG-SARS-CoV-2 antibody titers in this study, the average antibody value was 13864.46 AU/mL with a minimum value of 1388.6 AU/mL and a maximum of 37419 AU/mL. All study subjects had received the Covid-19 vaccination 3 times, with the last vaccine dose 3-6 months before the blood sample was taken in this study. In the research subject with the lowest titer value, it was found that the lymphocyte value was still in the normal range. Of the 45 research subjects, after division based on their quartiles, there were 11 research subjects with the lowest antibody titer range, which was below equal to 4857.1 AU/mL. Of these 11 subjects, 9 people have been confirmed to have Covid-19 at least once previously, and of these 9 people, observations have been made since sampling was carried out until this research was carried out, and there was 1 research subject who was found to be confirmed Covid-19 again. Of all other research subjects with antibody titer values above the previous quartile, none were found to be confirmed to have Covid-19 again. From these results, although statistically it has not been proven that there is a significant relationship between the number of antibody titers and the confirmation of a person with Covid-19, it can provide an illustration that with an antibody titer in this range, there is still a risk of experiencing a Covid-19 infection compared to if the antibody titer is in higher range. Furthermore, the results of the correlation test between lymphocyte variables and IgG-SARS-CoV-2 titers in internal medicine residents as research subjects, showed that there was no significant relationship between the two. This is not in line with several previous studies that also assessed lymphocyte and neutralizing antibody levels against SARS-CoV-2. In the literature, previous studies that assessed the relationship between lymphocytes and a person's immune response, which were shown based on the antibody value to SARS-CoV-2, illustrate that in a statistically low lymphocyte condition, it is found that the individual will produce antibody production. which is also low.

Based on the results of the study by Seban et al in 2021, a retrospective study was conducted on a population of patients with malignancies including breast cancer, hematologic malignancies, gastrointestinal cancer, head and neck cancer, gynecological cancer and other types of cancer such as thyroid gland, sarcoma or melanoma. All

research subjects were currently on various types of treatment, ranging from groups that are currently on chemotherapy treatment, targeted-therapy¸ endocrine therapy, or those who were not on any treatment. The Covid-19 vaccination was carried out using an mRNA-based vaccine. Then the ALC data was taken based on the results of a complete peripheral blood examination carried out at least 1 month before the patients underwent an F-FDG-PET/CT scan imaging examination to determine the presence or absence of vaccination-induced hypermetabolic lymph nodes or vaccine-induced hypermetabolic lymph nodes (V-HLN) to assess how the immune response after vaccination. The results showed that ALC significantly affected the occurrence of V-HLN and the absence of a normal ALC value significantly caused the absence of V-HLN on the F-FDG-PET/CT scan. (Seban et al, 2021)

In contrast to the current study, in this study, as previously described, the population was healthy adults and not a group with immunosuppressed status as in the study of Seban et al. In this study, there was also no treatment or intervention that caused lymphocyte levels in the blood to decrease or their values to low, so that a direct relationship between ALC values and the immune response as measured by antibody titers as in previous studies was not proven. In addition, the absence of infectious factors or triggers that cause a person's immune response to be activated, so that later lymphocytes will be used to produce antibodies, was also absent in this study. This caused when the measurement was carried out, the majority of lymphocyte levels were actually in normal conditions, and the researcher assumed that because of this, the previous linear relationship could not be applied in this study.

In the current study, it was found that the majority of research subjects described high antibody values. This is in line with the previous theory because most of the subjects in this study received the last vaccination dose within 6-8 months, so that the antibody titer had not changed and the amount had not decreased in plasma. However, the high antibody titer value cannot fully reflect that this is due to the high level of lymphocytes, which are the basic ingredients for making antibodies.

Correlation test which showed insignificant value between lymphocyte value and antibody titer explained that even in low lymphocyte conditions, high antibody titer values could be found. On the other hand, even in normal lymphocyte conditions, antibody titers may still be normal or even low. In addition, another theory that was adopted by the researcher to explain the results obtained is based on previous literature studies which show that the measured lymphocyte levels may still be new lymphocytes, which do not produce antibodies that are currently measured, but new lymphocytes that have undergone regeneration. The life span of lymphocytes is still not fully known. Lymphocytes will circulate in the blood circulation and lymphatic circulation, and also remain in the lymphoid organs in all parts of the body. The continuous course of lymphocytes in their circuits makes it difficult for researchers from time to time to predict with certainty the age or life span of these lymphocytes. Based on studies that have been carried out, it is said that the variation in the life span of lymphocytes ranges from 85 days to 300 days until the lymphocytes will undergo destruction, turn into a subset of other types of cells or recirculate through the lymphatic flow and will later return to the blood plasma circulation. (Gowans, 1995; Weissman, 2010; Baliu, 2018)

CONCLUSION

Based on the analysis of the data obtained in this study, the following conclusions were found that the value of lymphocytes is not related to the neutralization antibody titer of SARS-CoV-2 in internal medicine residents, Faculty of Medicine USU who have received the Covid-19 vaccination. The mean value of lymphocytes in the internal medicine residents, Faculty of Medicine

USU who had received the Covid-19 vaccination did not show a significant difference between the group with a history of Covid-19 infection (+) and the group with a history of Covid-19 infection (-). The mean value of neutralizing antibody for internal medicine residents, Faculty of Medicine USU who had received Covid-19 vaccination did not show a significant difference between the group with a history of Covid-19 infection (+) and the group with a history of Covid-19 infection (-). Suggestions for further research can consider a population that resembles the population in previous studies. The relationship of lymphocytes to SARS-CoV-2 neutralizing antibody titers may have clinical relevance in assessing the immune response to the unexplained action of Covid-19 vaccination in a healthy population as in this study.

Acknowledgement: None

Conflict of Interest: None

Source of Funding: None

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How to cite this article: Giovani Christin Faitino Purba, Dairion Gatot, Heny Syahrini et.al. The relationship between the lymphocyte value and the neutralizing antibody titer towards SARS-COV-2 in residents of internal medicine faculty of medicine universitas Sumatera Utara who had received Covid-19 vaccination. *International Journal of Research and Review*. 2022; 9(8): 775-783.
DOI: *https://doi.org/10.52403/ijrr.20220865*

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