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RESEARCH ARTICLE

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Neutralizing Antibody Response by Inactivated SARS-CoV-2 Vaccine on Healthcare Workers

Nataniel Tandirogang[1], Evi Fitriany[2], Nursaci Mardania[2], Miftahul Jannah[2], Bilqis Faiqotun Nabilah Dilan[2], Sapta Rahayuning Ratri[1], Arfian Deny Prakoso[1], Meiliati Aminyoto[2], Yuliana Kartika Ningrum[3], Ika Fikriah[4], Yadi[1]

[1]*Department of Microbiology and Immunology, Faculty of Medicine, Universitas Mulawarman, Samarinda, Indonesia*
[2]*Department of Public Health, Faculty of Medicine, Universitas Mulawarman, Samarinda, Indonesia*
[3]*Prodia Clinical Laboratory, Samarinda, Indonesia*
[4]*Department of Pharmacology, Faculty of Medicine, Universitas Mulawarman, Samarinda, Indonesia*

Background: Currently, the key to combat coronavirus disease 2019 (COVID-19) as a global pandemic is relying mainly on vaccination, and several factors might affect the level of protection. This study aimed to determine the quantitative increase of neutralizing antibody titer against COVID-19 and the influence of gender, body mass index (BMI), routine consumption of vitamin C, D, and E towards the neutralizing antibodies after vaccination.

Materials and methods: One hundred nine health workers from various health facilities were recruited. Sinovac inactivated severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine was used in this study. Antibody titer measurements were carried out quantitatively using electrochemiluminescence immunoassay (ECLIA) on day 14 after the first and second doses administration of the vaccine.

Results: The average of antibody titers after the first and second doses were 109.1 and 191.6 U/mL, respectively. Antibody titer significantly increased (p=0.000) as much as 82.5 U/mL from the first to the second dose. There was a significant difference in the increase in antibody titer between respondents who consumed vitamin E regularly and those who did not (p=0.036). Routine consumption of vitamin C and D, gender, and BMI did not affect the increase in neutralizing antibody titer with p-values of 0.983, 0.337, 0.186, and 0.424, respectively.

Conclusion: Routine consumption of vitamin E is associated with post-SARS-CoV-2 vaccination neutralizing antibody response. Gender, BMI, and the routine consumption of vitamin C and D have no association with the immune response.

Keywords: *COVID-19, neutralizing antibody, inactivated SARS-CoV-2 vaccine*

Introduction

Coronavirus disease 2019 (COVID-19) was declared as a Global Pandemic on March 11, 2020 by the World Health Organization (WHO).[1] The total number of confirmed cases of COVID-19 by April 1, 2021, in the world, Indonesia and East Kalimantan, were 128,540,982, 1,517,854, and

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Corresponding Author:
Nataniel Tandirogang
Department of Microbiology and Immunology
Faculty of Medicine, Universitas Mulawarman
Jl. Kerayan, Kampus Gn Kelua, Samarinda 75119, Indonesia
e-mail: n.tandirogang@fk.unmul.ac.id

Cell and Biopharmaceutical Institute

63,877 cases, with a mortality rate of 2,808,308, 41,054, and 1,518 people, respectively.[2,3] Several vaccines have been developed worldwide in order to control COVID-19 rapid transmission, including Sinovac vaccine, which is one of the vaccines used in several countries, including Indonesia. The Ministry of Health of Republic of Indonesia considers health workers as the priority group to receive COVID-19 vaccine in the first period, as they are at a high risk when they come in contact with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) patients. Health workers' assistants, supporting staff, and students who are undergoing medical professional education and work in various health service facilities in January-April 2021 period are also considered as health workers.[3,4]

Micronutrients and nutritional status may play an important role in the management of viral infections, including SARS-CoV-2 infection. Vitamin C is essential in maintaining and enhancing the immune system, especially during an acute infection. Vitamin D is involved in augmentation of immune response and suppress cytokine storm, which often causes COVID-19 mortality. The importance of vitamin D supplementation is supported by the fact that vitamin D deficiency is common even in tropical areas, such as Indonesia, which may lead to poorer immune response to an infection. Similarly, lack of vitamin E can lead to impairment of both humoral and cellular immunity, adding the important role of vitamin E other than being a potent antioxidant. Supplementation of vitamin C, D, and E has been analyzed in multiple studies for their impact on reducing disease severity and mortality in COVID-19 patients. Obesity has long been linked to impairment of the immune system. A previous study confirms the negative association of body mass index (BMI) in COVID-19 antibodies, especially on humoral immunity. Obesity is also a risk factor of vitamin D deficiency as well as several metabolic diseases, with diabetes mellitus being one of the most prominent diseases, which would influence the immune response further in a negative manner.[5-9] Those factors might also influence the ability of an individual to produce more neutralizing antibodies after COVID-19 vaccination, which would result in a stronger protection against the virus.

A recently developed quantitative serological assay by Roche measures antibodies against the receptor-binding domain (RBD) of spike (S) protein, one of the vaccination targets. The Elecsys anti-SARS-CoV-2 S, an electrochemiluminescence immunoassay (ECLIA), is an *in vitro* test which able to determine total antibodies, including anti-SARS-CoV-2 S-RBD immunoglobulin G (IgG) quantitatively in human serum and plasma. The assay uses a recombinant protein which represents the RBD of the S antigen in a format of double-antigen assay. After the incubation process to form double antigen immune complexes (double antigen sandwich; DAGS), streptavidin-coated microparticles are added, and DAGS complexes bind to the solid phase. After that, the reagent mixture is transferred to the measuring cell where the microparticles are captured magnetically. Electrochemiluminescence is induced by applying a voltage, and the measurement is done with a photomultiplier. The increase of the signal yield is proportional to the antibody titer. This quantitative assessment for anti-SARS-CoV-2 antibodies can help to determine specific antibody titers and specifically monitor antibody responses towards vaccines, as well as facilitate longitudinal monitoring of antibody responses in each patient.[10-12] Both humoral and cellular immune responses towards vaccines could be influenced by several factors, including nutritional status, which can be measured with BMI, and micronutrients consumption.[13] This study observed the increase in antibody titers against the COVID-19 vaccine by performing serial measurement of neutralizing antibody titers in health workers after 14 days of the first vaccine dose and 14 days after the second vaccine dose, as well as its association with factors that may affect the antibody response towards COVID-19 vaccination in high-risk groups.

Materials and methods

Subjects Recruitment

This research was a cross sectional study conducted in January-April 2021 in Balikpapan, Samarinda, and Maumere involving 109 health workers who had been vaccinated with the first and second SARS-CoV-2 vaccine doses and filled an online questionnaire. The vaccine used in this study was Sinovac vaccine, an inactivated SARS-CoV-2 vaccine. The vaccine was given in 2 doses with the interval of 14 days between first and second dose administration. Purposive sampling method was used in this study. The inclusion criteria was all healthcare workers from various health facilities who were willing to get tested on day 14 after receiving the first dose and 14 day after second dose administration of SARS-CoV-2 vaccine. The exclusion criteria were subjects with history of COVID-19 infection

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before administration of the first vaccine dose, subjects exposed to COVID-19 before day 14 after the second dose administration, and subjects showing symptoms of COVID-19 infection with positive results of the SARS-CoV-2 polymerase chain reaction (PCR) examination. This study was approved by the Health Research Ethics Committee, Faculty of Medicine, Mulawarman University (No. 08/KEPK-FK/I/2021).

ECLIA

Neutralizing antibody titer measurements were carried out serially on day 14 after the first vaccine dose and day 14 after the second vaccine dose using Elecsys Anti-SARS-CoV-2 (Roche Diagnostics, Mannheim, Germany), an electrochemiluminescence immunoassay (ECLIA) method which measures neutralizing antibody against SARS-CoV-2 in blood serum of subjects. Blood serum samples were taken at the local Prodia Laboratory. Three mL of blood was taken from the vein at the cubital fossa. Blood samples were then set aside for 10-15 minutes in a vacutainer until the samples were perfectly clotted. The samples were centrifuged for 15 minutes at 3,000 rpm. The serum formed in this process should be made sure to be clear without fibrin. Serum samples were put into the sample rack in the ECLIA device to measure antibody titer. The value of more than 0.8 U/mL was considered as reactive.

Data Collection

The increase in antibody titer was determined as the dependent variable, while gender, routine consumption of vitamin C, D, and E, and BMI was determined as the independent variables. The increase in antibody titer was defined as the difference between the neutralizing antibody titer on the first and second serological tests. Gender was determined as male and female. History of routine consumption of vitamin C, D, and E was recorded based on consumption of these vitamins for the last 3 months with doses of 500 mg, 1,000-5,000 IU, and 100-400 IU, respectively. BMI was divided into 5 categories, which were severe underweight (<17.0 kg/m^2), mild underweight (17.0-18.4 kg/m^2), normal (18.5-25.0 kg/m^2), overweight (25.1-27.0 kg/m^2), obese (>27.0 kg/m^2). Online questionnaire was used for data collection. Questionnaires were distributed regarding availability to become respondents, personal identity – including gender, date of birth, vaccination date for each dose, body weight and height, and routine consumption of vitamin C, D, and E.

Statistical Analysis

Data was tested using Kolmogorov-Smirnov test to ensure that the data was normally distributed. Afterward, the data was analyzed using paired t-test, one-way analysis of variance (ANOVA), or linear regression to determine the significant relationship between the dependent variable and each independent variable. The significance level used in this study was $p<0.05$. All data was analyzed using SPSS 25.0.

Results

Characteristics of Subjects

From 109 subjects, 61.5% (n=67) of them were women, while 38.5% (n=42) were male. Subjects came from the age group of 22 to 60 years with an average age of 38.49±11.29 years. The percentage of obese subjects was 41.5% (n=45). The percentage of subjects with routine consumption of vitamin C, D, and E were 37.6% (n=41), 8.3% (n=9), and 9.2% (n=10), respectively (Table 1). Based on the ECLIA results, 56% (n=61) samples were reactive in the first serological test. This percentage then increased to 98.2% (n=107) after the second test. In the second serological test, there were two samples (1.8%) that had neutralizing antibody titers of <0.4 U/mL (non-reactive).

Neutralizing Antibodies Level After Vaccination

The average of antibody titers after the first and second doses administration were 109.1 and 191.6 U/mL, respectively (Figure 1). Antibody titer significantly increased (p=0.000) as much as 82.5 U/mL from the first to the second dose. One of the respondents showed a decrease in the neutralizing antibody titer from 327.0 U/mL by the first test to 235.4 U/mL on the second test. The respondent was a woman, with a normal BMI, and consumed vitamin C in her daily routine.

Effect of Gender, Vitamin C, D, and E Consumption, and BMI on Neutralizing Antibodies Titer

Paired t-test results showed a significant difference between antibody titers on the first and second serological test in each variable group, except for the group with routine consumption of vitamin E, the overweight BMI group, and the mild underweight BMI group (Table 2). The severe underweight group could not be tested, since there was only one subject in this group.

The independent variables were then tested by one-way ANOVA to assess the effect of these variables on the

Table 1. Characteristics of subjects.

Characteristics	Values	Neutralizing Antibody Titer (U/mL)		
		Day 14 post-vaccination dose I*	Day 14 post-vaccination dose II*	*p* -value
Age (years)*	38.49±11.29			
Gender, n (%)				
Man	42 (38.5)	89±327	145±418	0.001
Woman	67 (61.5)	121±606	220±747	0.000
BMI, n (%)				
Severe underweight	1 (0.9)			
Mild underweight	3 (2.8)	8±11	37±20	0.191
Normal	42 (38.5)	32±94	108±188	0.000
Overweight	18 (16.5)	260±1114	340±1306	0.091
Obesity	45 (41.5)	125±349	220±500	0.002
Routine consumption of vitamin C, n (%)				
Yes	41 (37.6)	53±142	136±291	0.006
No	68 (62.4)	142±643	224±774	0.000
Routine consumption of vitamin D, n (%)				
Yes	9 (8.3)	6±8	38±44	0.035
No	100 (91.7)	118±537	205±663	0.000
Routine consumption of vitamin E, n (%)				
Yes	10 (9.2)	92±189	265±507	0.127
No	99 (90.8)	112±539	184±650	0.000
Increase in neutralizing antibody titer (U/mL)*		82.54±164.15		

*Data is presented as average±standard deviation.

increase in antibody titer, which indicates the response of neutralizing antibodies towards COVID-19 vaccine. The results showed that there was no significant relationship between gender, vitamin C and D consumption, and BMI with an increase in neutralizing antibody titer with *p*-values of 0.186, 0.983, 0.337, and 0.424, respectively. Meanwhile, routine consumption of vitamin E was the only variable that showed a significant relationship with the increase in the neutralizing antibody titer (*p*=0.036). The average increase of antibody titer between the subjects who routinely consumed vitamin E (172.9 U/mL) and those who did not consume it (72.1 U/mL) was significantly different. It should be noted that in this study, there were only a small number of subjects who were included in the routine consumption

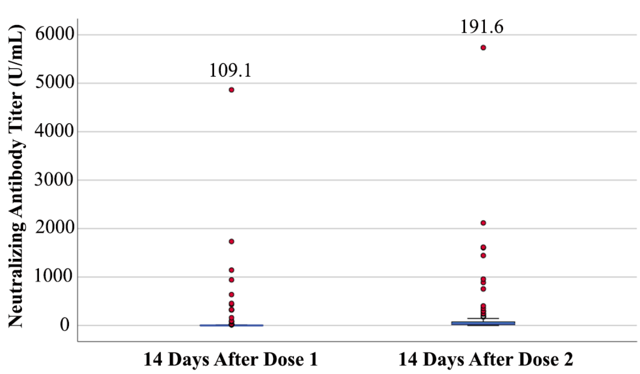

Figure 1. The average of antibody titers after administration of the first and second SARS-CoV-2 vaccine doses.

Table 2. ANOVA test results between risk factors of COVID-19 and an increase in neutralizing antibody titer.

Risk Factors	*p* -value
Gender	0.186
Vitamin C consumption	0.983
Vitamin D consumption	0.337
Vitamin E consumption	0.036
BMI	0.424

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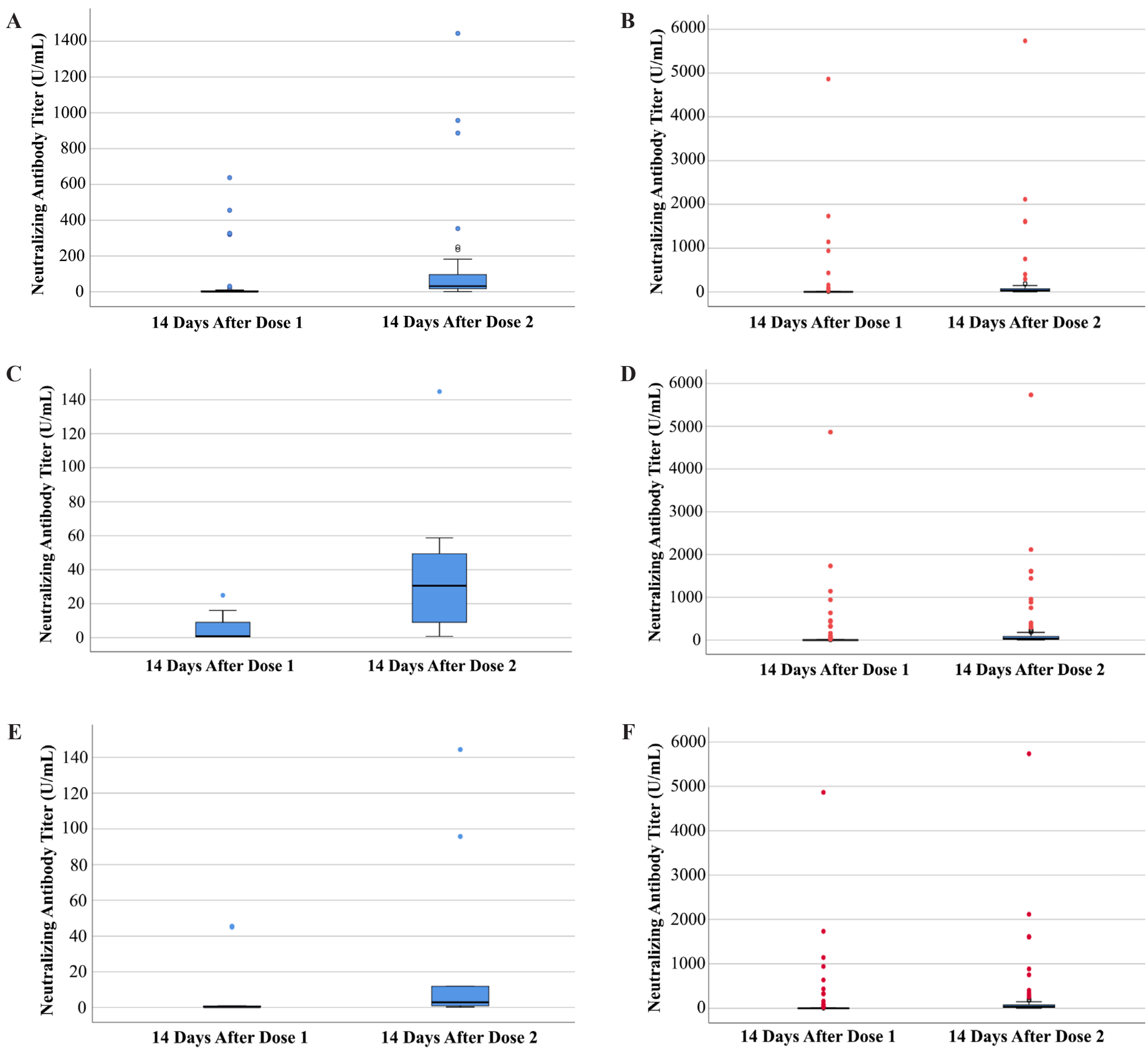

Figure 2. Antibody titers after administration of the first and second SARS-CoV-2 vaccine doses based on the routine consumption of vitamin C, D, and E. A: Routine consumption of vitamin C; B: No routine consumption of vitamin C; C: Routine consumption of vitamin D; D: No routine consumption of vitamin D; E: Routine consumption of vitamin E; F: No routine consumption of vitamin E.

of vitamin E group (n=10). Figure 2 showed the neutralizing antibody titers of subjects in the group with or without routine consumption of vitamin C, D, and E. Figure 3 showed the neutralizing antibody titers of subjects in each gender group. Figure 4 showed the neutralizing antibody titers of subjects in each BMI group.

Discussion

The ongoing COVID-19 pandemic has caused immense social and economic burdens. This causes a global priority of rapid development of a safe and protective vaccine against this disease. CoronaVac is a vaccine prototype based on inactivated SARS-CoV-2, which has showed promising results both in safety and immunogenicity profiles in preclinical studies, as well as phase 1 and 2 clinical trials in China, while phase 3 clinical trials are underway in Brazil, Indonesia, Turkey, and Chile where emergency use authorization (EUA) has been released in these countries. Sinovac vaccine has fulfilled EUA criteria to be used as a vaccine against COVID-19.[14,15]

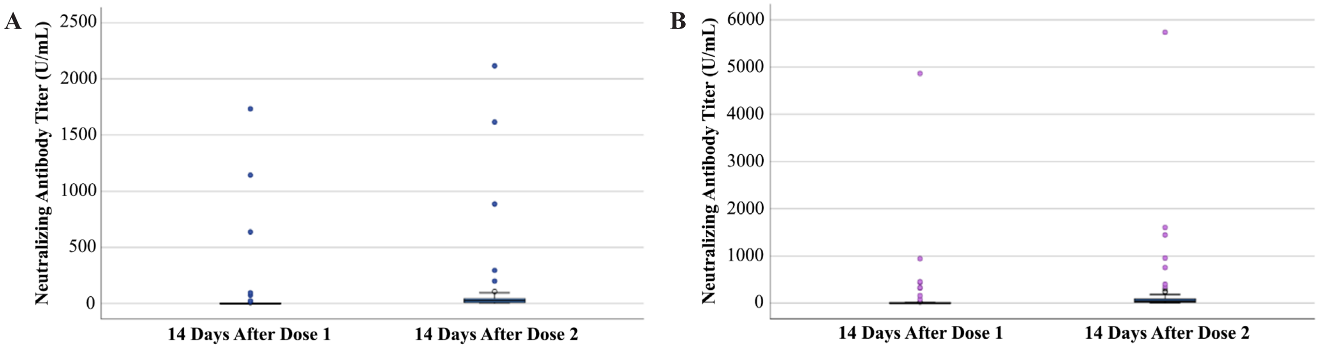

Figure 3. Antibody titers after administration of the first and second SARS-CoV-2 vaccine doses based on the gender of the subjects. A: Male; B: Female.

COVID-19 vaccine has been evaluated for its ability to enhance humoral immunity and antibody response against SARS-CoV-2. Neutralizing antibodies are highly correlated with the immune system and vaccination success. Vaccination can increase neutralizing antibody titers in most individuals, but its efficacy and level of protection are still questionable. This is most likely related to high mutation rate in SARS-CoV-2 genome.[16-18]

In this study, the first neutralizing antibody titer examination was carried out on day 14 after administration of the first vaccine dose. The second antibody titer examination was also carried out 14 days after the second dose administration to equalize the time of the first and second examinations.[3]

This study showed that only 56% of subjects had reactive results of ECLIA in the first serological test. In the second serological test, almost all subjects (98.2%) had reactive results. This is in line with research that conducts a study on the efficacy, tolerance, and immunogenicity of inactivated virus vaccines in a group of healthy adults in

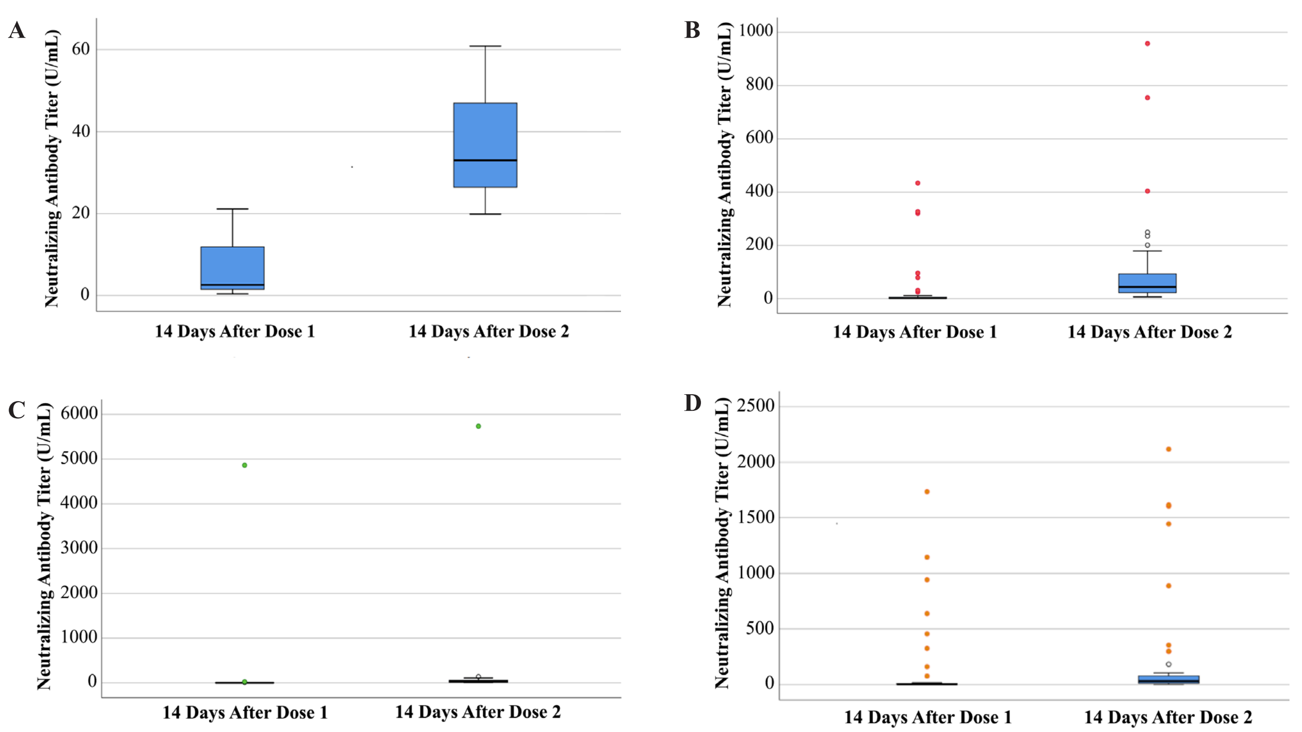

Figure 4. Antibody titers after administration of the first and second SARS-CoV-2 vaccine doses based on the BMI of the subjects. A: Mild underweight; B: Normal BMI; C: Overweight; D: Obesity.

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phase 1 and 2 clinical trials.[19] This study shows that the increase in antibody titers is more significant at the second dose. The study also states that the vaccine dosing interval also affects the quality of the antibody response, in which the administration of vaccine doses at 14 day intervals provides a faster immune response than the 28 day intervals, making it suitable for emergency use during the COVID-19 pandemic. This may be the reason of why vaccine doses are given to health workers at 14 day intervals.[19]

Similar results of immunogenicity of SARS-CoV-2 vaccine are also obtained in phase 2 randomized, double-blind, placebo-controlled trial (NCT04352608) of Sinovac vaccine to 600 healthy adults aged 18–59 years, which demonstrates that Sinovac vaccine is well-tolerated, safe, and shows no serious adverse event (SAE). Good immunogenicity has been demonstrated by this vaccine, with at least 92.4% seroconversion with various vaccination schedules in the low dose group (3 μg/dose). The range of geometric mean titer (GMT) of the neutralizing antibody is 24-65 among different doses and vaccination schedules. In a phase III trial conducted in Brazil, this vaccine shows an effectiveness of 78%.[20]

A systematic review shows that IgG titers peak between the third and seventh week after symptom onset and begin to decline after the eighth week. Immunoglobulin M (IgM) titers increase 2-5 weeks after symptom onset and decrease gradually. Neutralizing antibodies are detected between 7-15 days after the onset of symptoms, then increase in 14-22 days before stabilizing and decrease after six weeks. These indicating that SARS-CoV-2 infection-induced neutralizing antibodies increase and peak at around the similar time as vaccination-induced neutralizing antibodies.[21]

Information regarding the efficacy of Sinovac vaccine in phase 3 clinical trial is still limited because the studies are still ongoing. A study that has completed a phase 3 clinical trial of Sinovac vaccine in Chile reports that immunization with the inactivated virus is safe and could induce strong humoral and cellular immune responses, characterized by increased antibody titers against RBD with neutralizing capacity.[14] The study detects a seroconversion of more than 90% for RBD-specific IgG and neutralizing antibodies at 28 and 42 days post-immunization. This statement is in line with a phase 2 trial conducted in China with results of 100% for RBD-specific IgG and 99.2% for neutralizing antibodies.[14,19] Although seroconversion rates are slightly lower in participants aged 60 years at 42 days post-immunization, these results still suggest that the vaccine provides protection in elderly population. Differences in seroconversion rates and antibody-neutralizing capacity are observed among various methodologies that may be tested directly related to the intrinsic characteristics of each methodology.[16]

Another study shows that individuals who are naturally infected with SARS-CoV-2 develop an antibody response primarily to the S and N proteins at a similar level. However, studies of immunization with inactivated viruses in mice and nonhuman primates showed that the induced antibodies mostly targeted glycoprotein S and RBD, and a lesser extent to protein N.[20] A previous study states that antibodies against protein S are more abundant than antibodies against protein N. Thus, it may lead to a significant consideration to select a technique for confirming SARS-CoV-2 infection, as anti-N antibodies may not be detectable in most immunized individuals. The same study also conducts an evaluation of specific IgG against RBD and N protein of SARS-CoV-2 using enzyme-linked immunosorbent assay (ELISA). The seroconversion rates for RBD-specific IgG are 47.8% after 14 days of immunization in participants aged 18-59 years (GMT of 23.1) and 18.1% in participants aged ≥60 years (GMT of 45.1). On the other hand, the seroconversion rate is 95.6% in participants aged 18-59 years (GMT of 1,755 and 1,878) at days 28 and 42 post-immunization. The seroconversion rates in participants aged 60 years reach 100% on day 28 post-immunization (GMT of 1,860.2) and 87.5% on day 42 post-immunization (GMT of 1,878). Interestingly, the seroconversion rates for protein N specific IgG on 14 days after immunization are 8.7% for participants aged 18-59 years (GMT of 5.3) and 0% for participants aged 60 years (GMT of 5.5). The seroconversion rates are 17.4% for the 18-59 year age group and 20.0% for the 60 years age group (GMT of 8.0 and 9.6) on day 28 post-immunization, which increases to 37.5% for the 60 years age group (GMT of 32.6) and decreases to 13.0% in participants aged 18-59 (GMT of 9.2) 42 days after immunization. The results show that Sinovac vaccine induces notable production of RBD-specific IgG after immunization with the 0-14 day scheme but induces weak specific IgG production against N protein. Research confirms that doses of Sinovac vaccine contain large amounts of N protein.[14]

Our study found that 2 respondents did not show reactive ECLIA results. In a previous study, approximately 30% of patients do not have detectable antibody levels.[16] Another study mentions that some subjects may not produce a high titer response, so that antibody titers may diminish with time.[23] We suggest conducting further research to explain in detail why some subjects had undetectable antibody levels.

We found that gender did not affect the increase in neutralizing antibody titers after administration of two doses of the COVID-19 vaccine. Nevertheless, in another study, gender may affect the antibody response to the vaccine. This study states that some vaccines, such as dengue, hepatitis A (HepA), hepatitis B (HepB), rabies, *Haemophilus influenzae* type b (Hib), inactivated poliovirus vaccine (IPV), and trivalent influenza vaccine (TIV) cause a better antibody response in women, while some others, such as diphtheria, tetanus, and pneumococcal conjugate vaccine (PCV) have a better response in men.[13] Differences in hormone composition can cause differences in immune responses between men and women. A study shows that estrogen plus antiandrogen decrease the number of natural killer (NK) cells and increase the expression of type 1 T helper (Th1)-associated chemokine receptors in men. In addition, sex hormones cause differences in T cell differentiation pathways in peripheral blood cells. For example, testosterone in men tends to determine towards Th1 cells, whereas estrogen in women tends to determine towards type 2 T helper (Th2) cells.[24]

Several studies conducted in adults show that the increase in BMI is inversely correlated with antibody response to HepA and HepB vaccination. Initially, the group with the higher BMI number is correlated with higher antibody response. However, a greater decrease in antibodies is reported in 12 months after vaccination in that group.[13] However, in this study, there was no significant difference of neutralizing-antibodies on each BMI group.

There was also no significant effect of consuming vitamin C routinely on the level of neutralizing antibody. This study did not measure the serum level of vitamin C, so the differences in vitamin levels between subjects who regularly consume vitamin C and those who did not were unknown. Several factors affect the effectiveness of vitamin C in the body. Exposure to pollution, especially air pollution, such as cigarette smoke and polluted air, and microorganisms infection can cause vitamin C depletion. This may be due to the increase in oxidants, which makes the cells undergo oxidative stress, so vitamin C has to work extra in its role as an antioxidant. Another factor is the difference in the mechanism of vitamin C absorption, *i.e.* passive diffusion, facilitated diffusion, and active transport. These mechanisms strongly influence the dosage form of vitamin C. Different dosage forms will affect its absorption in the intestine.[25,26] However, in COVID-19 treatment guidelines therapy, vitamin C is given as an epithelial barrier against pathogens. High doses of vitamin C decrease the cytokine storm in acute respiratory distress syndrome (ARDS) that may occur in COVID-19.[27] It has the potential to protect against oxidative stress. In COVID-19 patients, there is a rapid improvement of chest radiographs after a few days of vitamin C consumption. Vitamin C deficiency increases the susceptibility to infection, weak immune response, and increased risk of pneumonia.[28] Vitamin C increases the production of immunoglobulins by peripheral blood lymphocytes, with supplementation of 200 mg/day for 1-3 months increases serum IgG and IgM levels and improves humoral immune responses in the elderly.[29] Another study states that vitamin C (25-250 mg/kg/day) during the early stages of malaria infection may better enhance host protective immunity.[30]

The oral vitamin D is converted in the liver into 25(OH)D, which plays a role in reducing the risk of infection and death, including from influenza, COVID-19, and pneumonia. Generally, 25(OH)D with a concentration of 20-30 ng/mL reduces the risk of upper respiratory tract infection. To achieve this concentration, it is recommended that each individual consume vitamin D at least 2,000-5,000 IU/day for 3 months. Several studies classify the mechanism of Vitamin D in reducing the risk of flu into three categories, including a physical barrier, natural cellular immunity, and adaptive immunity.[31] Vitamin D is able to decrease the production of Th1 proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFNγ) which respond to bacterial and viral infections, including SARS-CoV-2 infection.[32] However, there was no significant correlation between routine consumption of vitamin D and the increase in neutralizing antibodies after administration of first and second doses COVID-19 vaccine. Similar to vitamin C, serum levels of vitamin D were not measured, so it could not be ascertained whether there was a difference in serum levels in subjects who regularly consumed vitamin D and those who did not. Vitamin D absorption is known to have the same pathway as vitamin E and K, hence these micronutrients need to compete for absorption by enterocytes. Vitamin A is also a vitamin D antagonist, and it is known that high vitamin A concentrations can reduce vitamin D bioavailability by up to 30%. These factors cause the bioavailability of vitamin D to remain low in the body

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despite adequate vitamin D supplementation.[33] The result of this study is consistent with other studies which suggest that vitamin D supplementation promotes higher plasma levels of transforming growth factor (TGF) in response to influenza vaccination without increasing antibody production.[34]

A meta-analysis study stated that in one study, daily consumption of vitamin E 100-400 mg/day for 3 months affects the immune system by increasing lymphocyte proliferation and skin hypersensitivity responses, such as delayed-type hypersensitivity (DTH) in the elderly group (≥65 years). However, another study that is conducted in the adult group (20-50 years) with daily consumption of Vitamin E 200 mg/day for 56 days does not show a significant difference in their immune system. These measurements are performed in healthy adults. It may give different results if there are immunogenicity challenges, such as vaccination. Another study states that the elderly group who had received tetanus and HepB vaccination shows a better DTH response and vaccine efficacy in the group with vitamin E consumption of 200 IU/day for one month compared to the 60 mg dose and 900 IU/day group.[35] This supports the results of our study which showed that the routine consumption of vitamin E for at least 3 months had a significant relationship with an increase in neutralizing antibody titers after administration of the vaccine.

Other factors can affect the humoral and cellular immune responses in an individual after being vaccinated, including the intrinsic host, extrinsic, environmental, and behavioral factors. In addition, types and dose of vaccine, the presence of adjuvant, as well as schedule, place, route and time of vaccination are important to be considered further. These factors may lead to different immune responses in each individual. Therefore, these factors might indirectly influence each variable that affects the increase in neutralizing antibodies in this study.[12]

In this study, the levels of vitamins C, D, and E in the blood serum of subjects were not measured quantitatively, thus becoming a limitation in this study. The dose of vitamins taken by each subject was also different, so this could also affect the immunity of the subject. The number of subjects who took vitamin E routinely was too small. In addition, we measured neutralizing antibody titers without distinguishing them specifically, making it difficult to identify types of target antibody that have been formed. Further research on the association between neutralizing antibody response after administration of inactivated SARS-CoV-2 vaccine with other factors should be conducted.

Conclusion

Routine consumption of vitamin E is associated with post-SARS-CoV-2 vaccination neutralizing antibody response. Gender and other nutritional factors, such as BMI and the routine consumption of vitamin C and D have no association with the immune response. Therefore, vitamin E has a potential to increase immune response to SARS-CoV-2 vaccination.

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Authors Contribution

NT, EF and IF were involved in concepting and planning the research. EF, NM, MJ, BFND, and YKN performed the data acquisition. NT, MA, YKN and Y calculated the experimental data and performed the analysis. NM, MJ, BFND, SRR and ADP drafted the manuscript and designed the figures and tables. NT, MA and Y aided in interpreting the results. All authors took parts in giving critical revision of the manuscript and have read and approved the final manuscript.

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