Factors Associated with SARS-CoV-2 Antibody Titer After Sinovac Vaccination Among Health Care Workers

Theresia Santi[1], Baringin De Samakto[2], Lina Kamarga[3], Feronica K. Hidayat[4], Ferry Hidayat[5]*

[1] Department of Pediatric, Siloam Hospitals Lippo Cikarang, Bekasi, Indonesia.
[2] Department of Internal Medicine, Siloam Hospitals Lippo Cikarang, Bekasi, Indonesia.
[3] Department of Neurology, Siloam Hospitals Lippo Cikarang, Bekasi, Indonesia.
[4] Department of Clinical Pathology, Siloam Hospitals Lippo Cikarang, Bekasi, Indonesia.
[5] Resident Medical Officer, Siloam Hospitals Lippo Cikarang, Bekasi, Indonesia.

Corresponding Author:
Theresia Santi, MD. Department of Pediatric, Siloam Hospitals. Jl. MH. Thamrin kav. 105, Lippo Cikarang, Bekasi, Indonesisa. Email: therezdaton@gmail.com.

ABSTRACT

Background: *One of the methods to record immunogenicity after vaccination is to measure antibody titer. This study aimed to get the value of antibody titer post Sinovac vaccination and to analyze factors that associate with it. The trend of titer changes within 3 months period and the incidence of COVID-19 were also observed.* ***Methods:*** *A prospective cohort study was conducted in March until May 2021 involving 250 health care workers of Siloam Hospitals Lippo-Cikarang who have completed two doses of Sinovac vaccination. We collected 3 titer data from each participant to observe the trend of changes. The incidence of COVID-19 among post-vaccinated subjects was also calculated.* ***Results:*** *From total of 250 participants, 88 (35.2%) were males and 162 (64.8%) were females. Fourteen days after vaccination, 248 subjects (99.2%) had seroconversion. The median antibody titer amounted to 63.58 U/ml (0.4->250 U/ml). The titer was higher in age group 26-39 years (85.1 U/ml, p=0.003) and in women (78.7 U/ml, p=0.007). Within 3 months period, 162 from 200 participants (81%) who completed 3 titer tests, had antibody titer reduction (p=0.231). In observation, 94 from 245 (38.3%) participants tested positive COVID-19, with only 5 out of 94 (5.3%) participants being hospitalized.* ***Conclusion:*** *The highest median titer was achieved 14 days after Sinovac vaccination (63.58 U/ml). Younger age group and women are associated with higher value. The reduction trend in titer within 3 months is insignificant. Among post-vaccinated infection subjects, the hospitalization rate is low, which shows that Sinovac vaccination still has a protective effect.*

Keywords**:** *Sinovac, SARS-CoV-2, COVID-19, antibody, vaccination, health care workers.*

INTRODUCTION

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is a novel corona virus that spreads Corona Virus Disease 2019 (COVID-19) worldwide, and vaccination to control the pandemic of COVID-19 has begun since December 2020.[1,2] Sinovac is an inactivated whole virus vaccine for COVID-19 developed by Sinovac Life Sciences which already completed its phase-3 clinical trials. Since January 11th 2021, Sinovac has already been approved by the Indonesian Food and Drugs Agency for emergency use of authorization in Indonesia, and the first target population was the health care workers as the front liners in fighting COVID-19.[3-9]

One of the methods to record immunogenicity after COVID-19 vaccination is the Anti-SARS-CoV-2 immunoassay which detects antibody titer of Spike protein (S-protein) from SARS-CoV-2.[10-12] There are many factors that affect the antibody titer after vaccination as stated in many journals and researches.[13] Age and gender has been already known to influence immune response after vaccination. Other factors such as body mass index, exercise, sleep duration had varied correlation with different types of vaccinations.[13-18] Correlation of those factors with Covid-19 vaccination is still unknown. In its clinical trial, Sinovac showed high immunogenicity among the subjects,[3-7] but the data about immune response post Sinovac vaccination among health care workers were still limited. It is important to have data on antibody titer, factors that influence the immunogenicity and incidence of infection after vaccination to monitor the impact of vaccination for health care workers and further get feedback for the next plan of their protection against COVID-19.

This study observed the data of quantitative antibody response 14 days after the second dose of Sinovac vaccination followed by 1 month and 2 months later, among the health care workers of Siloam Hospitals Lippo Cikarang. The main purpose of this study is to get the value of antibody titer post Sinovac vaccination and to analyze factors that might correlate with the titer (i.e age, gender, exercise, sleep and Body Mass Index). The trend of titer changes and the incidence of COVID-19 after vaccination were also observed as an additional objective.

METHODS

This study used a cohort design held at Siloam Hospitals Lippo Cikarang from March to May 2021. To improve quality of reporting, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.[19] The subjects of this study were health care workers who have already got two doses of Sinovac vaccines, administered intramuscularly with 14 days interval, with the dose of 30 µg in a volume of 0.5 mL of aluminium hydroxide diluent solution per dose. In our hospital, there was a policy that all employees must undergo post vaccination evaluation of antibody titer using the Elecsys anti-SARS-CoV-2 S-antibody assay at the hospital's laboratory. The tests were taken 3 times, beginning at 14 days after getting the second dose of Sinovac vaccine, followed by 2 consecutive months afterward. During and after the study period, participants were observed for COVID-19 infection by the hospital surveillance team for approximately 5 months (March-July 2021).

All of the antibody titer data were collected to observe trend of changes. For correlation analysis of antibody titer with age, sex, BMI, duration of sleep and exercise, we used the first antibody data taken 14 days after completed vaccination. We collected data from our laboratory as secondary data that has already been saved in its database.

We distributed google form questionnaires via Whatsapps application to collect demographic data and the health status of the participants. The questionnaires asked about age, sex, body weight, body height, sleep duration per day, and routine exercise. Before filling the questionnaires, all participants were given written explanations and informed consent forms were attached to the questionnaires.

Antigen-specific humoral immune response was analyzed using quantitative Elecsys anti-SARS-CoV-2 S-immunoassay (Roche Diagnostics, Mannheim, Germany).[20] It is an electrochemiluminescence immunoassay used to detect antibodies (including IgG) to the SARS-CoV-2 spike protein receptor-binding domain (RBD) on the Cobas e411 module (Roche Diagnostics, Mannheim, Germany). In this study, we used a commercial test that was usually used among the community, with the measurement ranges from 0.4 U/ml to 250 U/ml (values higher than 250 U/ml will be stated as >250 U/ml). A concentration of < 0.80 U/ml considered negative and > 0.80 U/ml considered positive. The WHO international standard for anti-SARS-CoV-2 immunoglobulin is BAU/ml (Binding Arbitrary Units per mL). The correlation between U/ml and BAU/ml was: U = 0.972 BAU. According to the manufacturer, the correlation test between Roche Elecsys Anti- SARS-CoV-2 S units per mL and WHO International Standards for anti-SARS-CoV-2 immunoglobulins was excellent

(r^2 = 0.9992, slope =0.972, intercept = 0.0072), thus allowing to consider specific Roche Elecsys anti-SARS-CoV-2 S U/mL units equivalent to WHO International Standard BAU/mL.[21]

We excluded the participants with a history of confirmed COVID-19 on the reverse transcriptase polymerase chain reaction test (RT-PCR) before and during antibody titer examination. We also excluded participants with a history of reactive serology or rapid screening tests. The regular qualitative serological screening had been conducted by our hospital since July 2020 (7 months before the vaccination program), using the Elecsys anti-SARS-CoV-2 assay (Roche Diagnostics) which detected antibodies to nucleocapsid (anti-N). All health care workers had this serology screening every 10 days. If the result turned reactive, they would have to continue for RT-PCR test. The history of confirmed COVID-19 and reactive serological tests were obtained from laboratory data confirmed by the confession of the participants in the questionnaires.

Ethical Approval

This research was approved by The Mochtar Riady Institute for Nanotechnology Ethics Committee (Protocol No: 2104011-03).

The Sample Size Calculation

The sample size was determined using the formula for mean difference for two different groups. From a previous study from hospital workers in Geneve, Switzerland,[22] the mean difference for two groups was 49 U/ml and the deviation standard was 156, so the minimum sample size calculated was 158 subjects.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS 26.*0 (Statistical Package for the Social Sciences, IBM Corp,. Armonk, NY, USA*). Normality test was done using Kolmogorov-Smirnov, if the p-value were more than 0.05 then the data would be considered normally distributed. According to the data distribution, numerical data would be presented in mean and deviation standard or median and interquartile range. Values lower than 0.4 U/ml were assumed as 0.4, and values higher than 250 U/ml were calculated as 251 U/ml. p values <0.05 were considered statistically significant.

We used bivariate analysis to predict the association between variables. If the data were normally distributed, the association would use an independent t-test (for two groups), or One-way ANOVA (for more than 2 groups). If the data were not normally distributed, the Mann-Whitney test (for two groups) or the Kruskal Wallis test (for more than two groups) would be applied. The statistical significance was set to $p<0.05$.

RESULTS

We invited 503 health care workers who eligible for vaccination from January to February 2021. Twenty-seven of them were excluded because of being confirmed with COVID-19 infection within 3 months prior. Thus, as many as 476 participants who were vaccinated twice and had their antibody titer tests were eligible, but only 440 of them returned the questionnaires. Sixty five out of 440 participants were excluded due to confirmed COVID-19 (positive RT-PCR swab test) and 125 participants were excluded due to reactive serological or rapid antibody screening before vaccination. Finally, we enrolled 250 eligible participants (in accordance with the minimum sample size requirement). A summary of the sampling process can be seen in **Figure 1**.

250 health care workers were not homogeneously distributed, with age grouping based on the age quartile <25 years: 60 people (24%), age 26-39 years: 131 people (52.4%), and age >40 years: 59 people (23.6%). The youngest age of participants was 21 years old (4 subjects) and the oldest age of participants was 60 years old (2 subjects). 248 out of 250 participants (99.2%) who have received Sinovac vaccination twice were being tested for their first-month antibody titer had antibody titer >0.8 U/ml (reactive), while 2 subjects had antibody titer: 0.4 and 0.7 U/ml. The median antibody titer of 250 participants amounted to 63.58 U/ml (minimum 0.4 U/ml, maximum >250 U/ml). The description of HCW who participated in the study can be seen in **Table 1**.

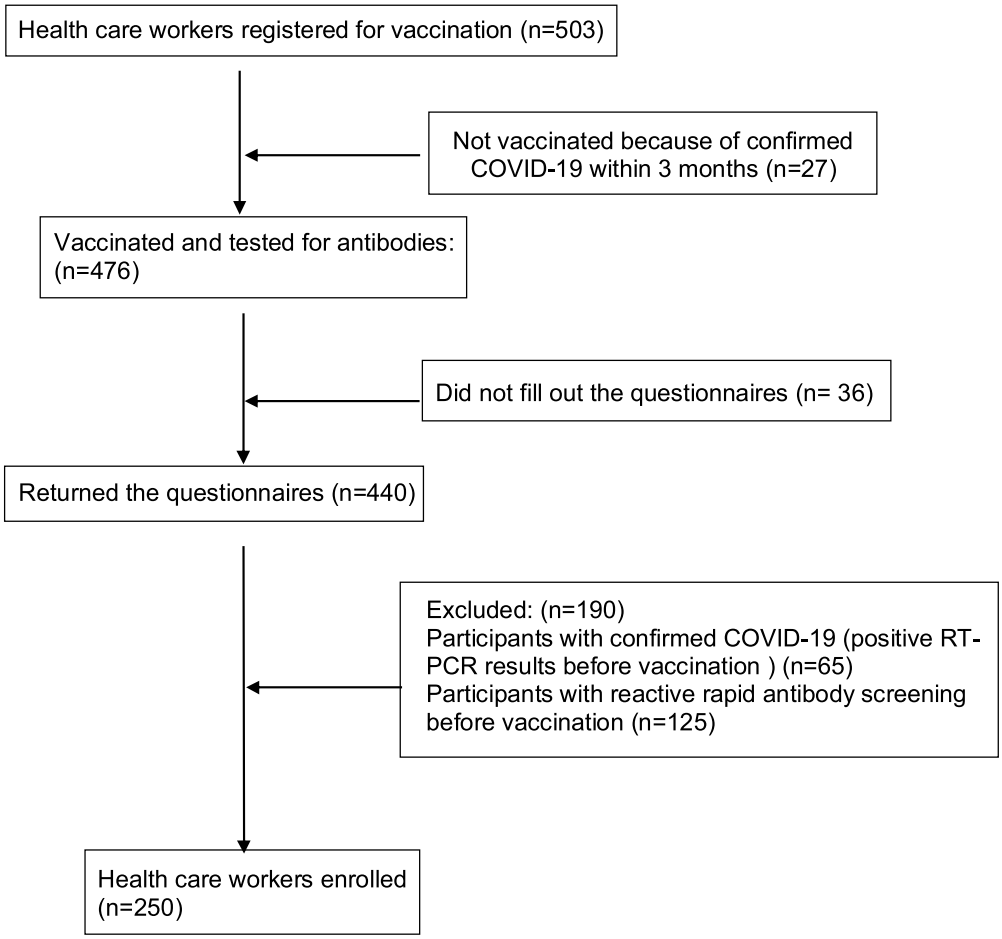

Figure 1. The overview of the research sampling process and participation rate

Table 1. Demographics of health care workers who participated in the study (N= 250).

Variables	n (%)
Age	
- ≤ 25 years old	60 (24.0)
- 26-39 years old	131 (52.4)
- ≥ 40 years old	59 (23.6)
Gender	
- Male	88 (35.2)
- Female	162 (64.8)
Body Mass Index	
- Underweight (≤18.5)	28 (11.2)
- Normoweight (18.51–22.99)	90 (36)
- Overweight (23–24.99)	48 (19.2)
- Obesity I (25–29.99)	65 (26)
- Obesity II (≥30)	19 (7.6)
Sleep Duration	
- <7 hours/day	144 (57.6)
- ≥7 hours/day	106 (42.4)
Physical Exercise	
- Not Routine	177 (70.8)
- Routine	73 (29.2)
1st Antibody titers, U/ml	63.58 (0.4 – >250)

Category variables: n(%)
Numeric variables: median (min-max)

When the bivariate analysis was performed to analyze the association between the first month antibody titer with age, there was a significant difference among antibody levels of the age groups ≤ 25 years, 26-39 years, and ≥ 40 years (64.1 U/ml, 85.1 U/ml, and 38.2 U/ml, respectively), Kruskal Wallis Test, p=0.003, <0.05). Antibody titer was also significantly different between men and women, which were higher in women (78.7 U/ml vs 49.6 U/ml respectively). Antibody titer was not significantly associated with BMI, sleep duration and exercise. (**Table 2**).

In addition, data about vitamin consumption of the participants were also collected. There was no association between vitamin D, C, and E consumption and antibody titer of the participants (p-value were 0.700, 0.270 and 0.223, respectively). We also collected the data of the participant's blood type and found no association between blood type and antibody

Table 2. Association of first month antibody titer with factors of age, sex, BMI, sleep duration and exercise (N=250).

	Antibody Titer (median, range, U/ml)	P Value
Age		
- ≤25 years old (n=60)	64.1 (0.7->250)	0.003 [a]
- 26-39 years old (n=131)	85.1 (1.02–>250)	
- ≥40 years old (n=59)	38.2 (0.4–>250)	
Gender		
- Male (n=88)	49.6 (0.4->250)	0.007 [b]
- Female (n=162)	78.1.02–>250)	
Body mass index		
- Underweight (≤18.5) (n=28)	44.1 (0.4–>250)	0.383 [c]
- Normoweight (18.5–22.99) (n=90)	58.29 (0.7–>250)	
- Overweight (23–24.99) (n=48)	70.65 (7.41->250)	
- Obesity I (25–29.9) (n=65)	90.9 (1.02–>250)	
- Obesity II (≥30) (n=19)	44.9 (7.73->250)	
Sleep duration		
- <7 hours/day (n=144)	62.2 (0.4–>250)	0.245 [b]
- ≥7hours/day (n=106)	64.5 (3.8–>250)	
Physical exercise		
- <3x/week (n=177)	64.7 (0.4–>250)	0.450 [b]
- ≥3x/week (n=73)	55.6 (0.7–>250)	

[a]Kruskall-Wallis test, Post-hoc Mann Whitney group <25 years vs group 26-39 years, p-value = 0.814, group 26-39 years vs. group >40 years, p-value = 0.001, group <25 years vs group >40 years , p value= 0.009
[b] Mann Whitney test
[c]Kruskall-Wallis test

titers of the participants (p=0.364). History of influenza vaccination also showed no significant association with the antibody titer (p=0.884).

In this study, the trend of antibody titer was observed in 3 months. The number of participants who were examined for the first antibody titer was 250, the second was 234 and the third was 200. Based on the results of 200 participants who completed the laboratory tests within 3 months, we identified that the antibody titer of 162 participants (81%) were gradually reduced. As many as 31 participants (15.5%) had increased antibodies, and 7 participants (3.5%) were stable. The median of the first antibody titer in 200 health care workers was 68.65 U/ml (1.02- >250 U/ml), the second one was 57.65 U/ml (6.13->250 U/ml), and the third one was 55.59 U/ml (4.80->250 U/ml). The reduction of median antibody titer from the first month until the third-month post-vaccination were 16% and 3.5%, respectively. However, the reduction was not statistically significant (Kruskal Wallis test, p=0.231). The trend of antibody titer reduction can be seen in **Figure 2**.

We observed the incidence of COVID-19 among participants within 4 months after completed vaccination, and after completing the monitoring of antibody titer trends (between

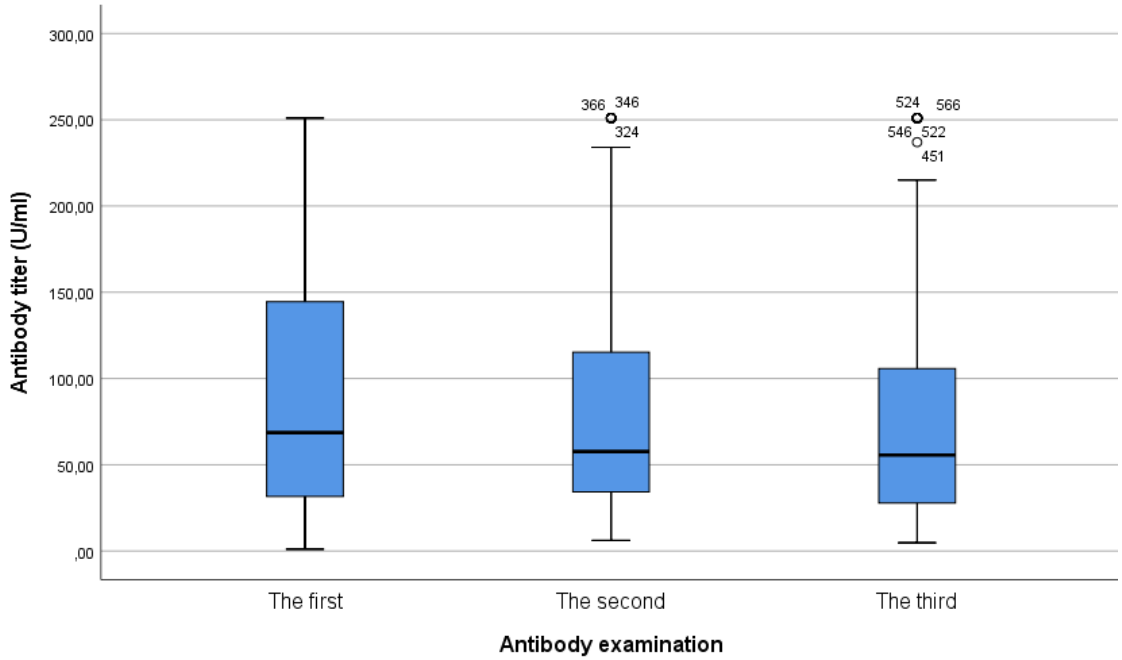

Figure 2. Reduction trend of antibody titer (n = 200).

June-July 2021). Five out of 250 participants were resigned from the hospital, leaving 245 remaining participants. The incidence of COVID-19 infections among the participants was 94 cases (38.3%): 9 cases (9.6%) were asymptomatic, 80 cases (85.1%) had mild symptoms, and 5 cases (5.3%) were admitted to the hospital due to moderate symptoms. We did not find any severe-symptom cases nor death cases among the infected participants. Thirty seven out of 94 infected participants (39.3%) had the first median antibody titer higher than baseline value (>63.58 U/ml), and 20 out of 37 participants still had high antibody titer 1 month before the infection.

DISCUSSION

The Anti-SARS-CoV-2 S-immunoassay is one the methods of serology testing which detects antibodies, including IgG antibody titers of Spike protein- Receptor Binding Domain (S-RBD) SARS-CoV-2.[20,23] Assessment of immunogenicity in clinical trials of COVID-19 vaccines were conducted using immunoassays that detect binding antibody titer, and also neutralizing antibody examination as the gold standard of functional antibody, which requires laboratory facilities with biosafety level 3.[7,10] The assays of S-RBD which detect antibodies against the S-protein of the SARS-CoV-2 virus have a strong correlation with neutralizing antibodies.[7,22,23] Due to the strong correlation between S-RBD and neutralizing antibody, the examination of antibody S-RBD titer is a good choice in further research on the immune response to vaccination, and may help to monitor the antibody response in patients after vaccination.

In Sinovac phase 1 and 2 clinical trials, seroconversion rates were defined as a change from seronegative at baseline to seropositive on day 14 after vaccination or a 4-fold increase antibody titer in those who were already seropositive.[8] The seroconversion rate of Sinovac vaccination in phase 2 clinical trial in China was 97%,[8] and in the interim report of phase 3 clinical trial in Indonesia was 99.7%.[6] In our study, we found that 99.2% of participants had detectable antibody on day 14 after the second Sinovac vaccination.

Previous studies have shown that antibodies to SARS-CoV-2 S-RBD would also increase after infection and could be detected until several months.[24,25] Although our study did not obtain antibody titer before the Sinovac vaccination, we tried to make sure that the antibody was not influenced by the past COVID-19 infection by excluding subjects who had been confirmed COVID-19 based on the history of RT-PCR results and subjects who had reactive rapid or serological tests before vaccination. Our hospital has already screened all health care workers routinely for early detection of COVID-19 with rapid serological tests and periodic RT-PCR examinations, so it was possible to exclude prior infection status of our participants.

Age has been shown to have a major influence on a person's response to vaccination. Vaccines response showed suboptimal effects in the elderly, who also have more rapid waning of antibodies.[13] Causes of a decreased immune response to vaccination include changes in cellular immunity, changes in humoral immunity, and the structure of lymphoid tissue.[26] Previous studies have shown a decrease in cellular and humoral immunity with age, thus affecting the response to vaccination.[13,26] Sinovac vaccine administration protocols are also different in those over 60 years of age, using a vaccination schedule of 0-28 days.[27] Research by Pellini et al[14] showed that the antibody titer after BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 vaccination was related to age, i.e. young people had the highest antibody levels compared to other age groups. Research on health care workers in Israel after BNT162b2 (Pfizer-BioNTech) vaccination also showed that antibody levels decreased with age.[15] Our study showed similar results, that antibody titer post-Sinovac vaccination differed significantly according to age, which was higher in the age group 26-39 years.

Gender has been known to have different effects on immunity in general. Women tend to have antibody responses, basal immunoglobulin levels and B cell counts higher than men.[16] The causes of the different immune responses between women and men are related to the X chromosome which regulates more immune

functions, and the presence of hormonal factors that play a role in the regulation of the immune system. Gender has been known to produce differences in antibody titer after COVID-19 vaccination. Research on health care workers in Italy found that post-BNT162b2 vaccination, antibody levels in women were higher than in men.[14] Research by Jabal et al[15] on workers in Israel also showed significant differences in antibody levels post BNT162b2 vaccination in women and men. Our study results were in accordance with the two studies above that antibody titer in women was higher than men.

Systematic review from Zimmerman[13] stated that body mass index, sleep and exercise can be associated with immune response after immunization, but in our study, those factors were not associated with antibody titers after Sinovac vaccination. Body mass index has long been known to correlate with the immune response to vaccination due to some influences in the increased body fat and production of leptin.[13] According to Asia Pacific Criteria, body mass index is classified as underweight (<18.5), normoweight (18.5-22.9), overweight (23-24.9), and obese (>25).[28] Obesity is a product of biological and environmental influences that leads to an increase of excess adipose tissue, which correlates with an increase in debilitating conditions associated with increased morbidity and mortality.[29] The pro-inflammatory hormone leptin, which has many immunologic functions, has been shown to correlate with body fat mass since it is produced and secreted from adipocytes. Adipocytes also produce signaling molecules, such as TNFα, IL-6, and resistin, together with leptin induce a chronic state of inflammation.[29] The chronic inflammatory state has been shown to interfere with a proper vaccine-induced immune response through several mechanisms, including altered production of cytokines and T cells, diminished natural killer cell activity, and poor response to antigens, which leads to a dysregulated immune system.[29] So that, obesity may interfere with an obese individual's ability to mount an effective immune response to vaccination or infection due to increased body fat and increased leptin production.[29] Many kinds of researches show that there is a correlation between obesity and decreased vaccine-induced immune response for example hepatitis B vaccine, influenza, tetanus and rabies.[30,31] In our research, there was no correlation between antibody serum level and Body Mass Index. This finding is in accordance with the phase III trial of the SARS-CoV-2 vaccine from BNT162b2[32] and mRNA-1273[33], whereas no difference in immunogenicity between the normal BMI group and the obese group.

Studies have found that shorter sleep duration (measured naturally) was related to reduced influenza and hepatitis B vaccine response in healthy young and middle-aged adults.[17] Sleep on the night after experimental vaccinations against hepatitis A produced a strong and persistent increase in the number of antigen-specific T helper cells and antibody titer.[34] The impact of sleep on immune response after COVID-19 vaccination so far is still unknown. Data from the phase 3 trial COVID-19 vaccine from BNT162b2 did not show a clear role of sleep in modulating vaccine efficacy.[35] In our study, we did not find an association between sleep duration and antibody titer after Sinovac vaccination. So far we have not yet found any studies about association between sleep and Sinovac vaccination. Further study to investigate association between certain duration and sleep quality around the time of vaccination with antibody titer needs to be explored for further insight.

Exercise has been identified as a behavioral factor that can increase immune function, possibly acting as an adjuvant for the immune response after vaccination. A meta-analysis from Chastin et al[18] from 6 studies about the interventional effect of physical activity to the result of H1N1, H3N3, influenza B, pneumococcus, and Varicella zoster vaccination, concluded that routine moderate to high-grade physical activity (3 times a week, 60 minutes duration, within 20 weeks before vaccination) related with increase vaccine potency. However, there was a different result between young adult and old age population. The young adult had a lesser effect of exercise on immune response after vaccination compared to the older age.[36] Our study did not find any significant correlation between regular exercise and antibody titer

after vaccination. It was probably affected by the greater percentage of young age subjects compared to the old ones and we also did not know about the intensity (mild/moderate/high) or duration of the exercise. In the future, we need a specific study with a certain type and duration of exercise on the homogenous population to better elucidate the association.

Concerns had been raised about the factors that affect the immunogenicity of vaccines against SARS-CoV-2. Studies from different platforms of SARS-CoV-2 vaccines showed several common influencing factors on humoral response, that were assessed by antibody titer or neutralizing antibody. The publications which showed correlation between age, gender and body mass index with immunogenicity after SARS-CoV2 vaccination were summarized in **Table 3**.

The observation of antibody titer trend within 3 months duration in our study showed reduction tendency. This finding is in line with the interim report of clinical trial phase 3 of Sinovac vaccine in Bandung which showed a reduction trend of IgG seropositive rate and neutralization antibody until 44.1% within 6 months after the second dose of Sinovac vaccination.[6] The interim report of phase 2 CoronaVac trial in Jiangsu, China, also showed that neutralizing antibody titer induced by the first two doses declined after 6-8 months to below the seropositive cutoff.[41] Prior shreds of evidences that showed waning antibody titers indicate that SARS-CoV-2 vaccines induced humoral immunity might not be as durable as that of other virus vaccines. But some studies showed that antigen-specific CD4 and CD8 T cells responses had an association with reduced disease severity while neutralizing antibody titer did not.[7,10-12]

Table 3. Summary of the previous studies about association between age, gender and body mass index with immunogenicity after SARS-CoV-2 vaccination.

Study	Methods/Samples	Results
Obesity May Hamper SARS-CoV-2 Vaccine Immunogenicity Pellini R et al, 2021.[14]	248 Health Care Workers (HCW) antibody titres ,7 days after second dose of BNT162b2 (Pfizer)	Higher antibody in female, young age and lean body weight.
Impact of Age,Ethnicity,Sex,and Prior Infection Status on Immunogenicity Following A Single Dose of The BNT162b2 mRNA COVID-19 vaccine: Real-World Evidence from Health Care Workers, Israel, December 2020 to January 2021 Jabbal et al, 2021.[15]	514 HCW antibody titres, 21 days after first dose of BNT162b2 (Pfizer)	Reduction of antibody titer with increasing age. No correlation of antibody titer with sex.
Assesment of Factors Affecting Inactivated COVID-19 (CORONAVAC) Vaccine Response and Antibody Response in Healthcare Proffesionals Ozdemir HO et al, 2021.[37]	264 HCW antibody titres, 28 days after second dose of CoronaVac	Lower immunogenicity in advanced age and male
Safety and Immunogenicity of An Inactivated SARS-CoV-2 Vaccine, BBIBP-CorV: A Randomized, Double-Blind, Placebo-Controlled, Phase 1/ 2 Trial.Xia S, et al.[38]	320 participants antibody titers, day 0, day 28, and day 56 after first dose of BBIBP-CorV (Sinopharm) a randomised, double-blind, placebo-controlled trial	People age 60 and above produced significantly fewer antibody than those aged 18-59.
Antibody Persistence Through 6 Months After The Second Dose of mRNA-1273 Vaccine for COVID-19 Doria-Rose N, et al.[39]	33 participants neutralizing antibodies at 180 days after second dose of mRNA-1273 (Moderna)	Age group 18 to 55 had higher antibody titer compared to older age groups
Safety and Immunogenicity of ChAdOx1 nCoV-19 Vaccine Administered in A Prime-Boost Regimen in Young and Old Adults (COV002) Ramasamy et al.[40]	560 participants neutralizing antibodies at 28 days after second dose of ChAdOx1 (Astra-Zeneca) A single-blind, randomized, controlled trial	The neutralizing Antibody titer did not differ significantly between the vaccinated population aged 18 to 55 years and those over 55 years of age.

In our study, we had 200 subjects who had 3 complete antibody titer data within 3 months period, 162 of them (81%) showed a reduction of antibody titer. The titer on the third examination showed a 19% reduction compared to the first one (55.59 U/ml vs 68.65 U/ml). Although we found the downward trend, it was statistically insignificant, probably due to the short period of observation. Thus, a study with a longer period of observation is needed policy makers about the timing of vaccine boosters in the community.

The observation about COVID-19 among our participants showed that vaccination protected 61.7% of participants from infections. This finding was similar to a prospective national cohort study in Chile, which also used Sinovac in a large number of participants, which had 65.9 % adjusted vaccine effectiveness.[42] Vaccination in our study also prevented 94.7% of infected participants from being hospitalized (only had mild or no symptoms at all), whereas the study in Chile had 87.5 % for the prevention of hospitalization and 90.3 % prevention of ICU admission. Data on the hospitalized participants in our study revealed no severe-symptom cases or death (0%) and no ICU admission. It shows that although there are many persons infected with COVID-19 after completed vaccination, it still has protective effects on morbidity and mortality, which is in line with the findings of a study in Chile.[42]

In order to reveal the variant of virus which infected participants, we did a whole-genome sequencing of 3 participants' samples (2 with moderate symptoms and 1 with mild symptoms). The results showed that three of them were infected by SARS-CoV-2 delta variants. Delta variants which were initially detected in India have been predominant in Indonesia, as the COVID-19 surged up since June 2021. Indonesian Ministry of Health reported that until 7 August 2021, there were 1477 cases of new SARS-CoV2 variants, whereas Delta variants were predominant with 1368 cases.[43] From our study, we thought that SARS-CoV-2 delta variants might reduce Sinovac vaccine efficacy which impacts on many infections among our participants.

The strengths of our study are that we used the Elecsys Anti-SARS-CoV-2 assay which its unit of measurement is equivalent to WHO International standard BAU (Binding Arbitrary Unit per mL) and our participants were selectively screened to be free from COVID-19. However, this study had some limitations. Firstly, that we used the assay without dilution (for commercial purposes, budget restriction) which could only detect the highest titer up to 250 U/ml. Other limitations are: the observation period of antibody titer trend is not long enough and we only did whole-genome sequencing to 3 of our subjects who got COVID-19 after completed vaccination due to access and time limitation.

This study showed the immune response of health care workers who have been vaccinated with 2 doses of Sinovac vaccine in the real world, outside clinical trials which have been done in Indonesia. To the authors' knowledge, there has not yet been any published Indonesian study about SARS-CoV2 antibody titer and incidence of COVID-19 after competed Sinovac vaccination. We got the basic data of antibody titer after vaccination which can be used as a comparison for other research in the future. Up till now, the optimal protective value of antibody against SARS-CoV-2 is still unknown, many studies with a bigger scale and longer duration are needed to reveal it.

CONCLUSION

The highest median antibody titer occurs 14 days after the Sinovac vaccination (63.58 U/ml). Age group 26-39 years and women are associated with the higher antibody titer. The antibody titer within 3 months after vaccination is not significantly reduced in all participants. COVID-19 incidence post-vaccination is quite high but the hospitalization rate is low with no mortality, which shows that Sinovac vaccination still has a protective effect.

CONFLICT OF INTEREST

The authors report no conflict of interest

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