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S-RBD IgG Response After Second Dose of CoronaVac; Prospective Study on Health Workers

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ABSTRACT

COVID-19 infection causes severe acute respiratory syndrome and requires immediate action. Therefore, developing safe vaccine efficacy and new therapies has become a global priority for achieving herd immunity. Vaccination is expected to form specific antibodies against the SARS-CoV-2 spike protein that can neutralize the virus, thus preventing it from binding to its specific receptor (ACE 2 receptor). This study aimed to analyze the kinetics of antibody response to the CoronaVac vaccine after administration of the second dose vaccine. An observational analytic study with a prospective cohort approach was conducted from January to November 2021 at Dr. Soetomo General Academic Hospital, Surabaya. Two hundred fifty specimens from 50 health workers who met the inclusion criteria were measured for S-RBD IgG levels using the indirect chemiluminescence immunoassay method on the Snibe Maglumi® device. The SARS-CoV-2 S-RBD IgG levels were measured five times, such as before vaccination (day 0) and day 14, day 28, month 3, and month 6 after vaccination of the second dose of CoronaVac. The median (min-max) of S-RBD IgG levels before and after vaccination of the second dose on day 14, day 28, month 3, and month 6 were 0.43 (0.43–4.07); 109,25 (30.71–1619,42); 136,46 (19.38–725,28); 26.56 (7.64–158,65); 13.11 (0.59–8666,00) BAU/mL, respectively. There was a significant difference in S-RBD IgG levels at six months post-vaccination between the group with COVID-19 infection and those without COVID-19 disease ($p < 0.001$). Vaccination of the second dose of CoronaVac resulted in antibody formation; however, there was a trend of decreasing humoral immunity in the 3rd month after the second dose of CoronaVac vaccination in healthy individuals.

Keywords: CoronaVac, antibody, COVID-19, S-RBD IgG, vaccination

INTRODUCTION

Coronavirus Disease (COVID-19) has spread to various countries quickly, triggering a statement by World Health Organization (WHO) on March 11, 2020, which later declared COVID-19 as a pandemic. Ongoing COVID-19 infection has caused high morbidity and mortality worldwide. WHO reported that as of March 21, 2021, there were a total of 122,524,424 confirmed cases of COVID-19; 2,703,620 cases with a death or Case Fatality Rate (CFR) of 2.20%; and as of March 19, 2021, there were 392,609,534 people.[1,2] In addition, The Ministry of Health of Indonesia recorded that as of March 21, 2021, there were a total of 1,460,184 confirmed cases of COVID-19, with 39,550 deaths and 5,533,379 vaccinations.[3,4]

Vaccination is a strategy to obtain adequate immunity to decrease the morbidity and mortality of SARS-CoV-2 disease. The COVID-19 vaccine induces both innate and adaptive immune responses, involving a cellular response (T cells) and an antibody response (B cells), leading to the production of antibodies directed against antigens distinct from SARS-CoV-2. Both SARS-CoV-2 infection and vaccination initiate an immune response, which results in the production of binding antibodies in blood circulation. Subpopulations of antibodies that can block cellular infiltration and viral replication are known as NAbs. RBD in the S1 subunit is the most critical target for neutralization. NAbs can interfere with the interaction of RBD and the hACE 2 receptor. Thus the levels of SARS-CoV-2 nAbs in human serum correlate with the immune response in individuals who have recovered from SARS-CoV-2 infection and participants receiving SARS-CoV-2 vaccination. The COVID-19 vaccine is expected to stimulate a complete immune response (cellular and humoral) with high neutralizing antibody titers.[5-7]

A similar study, which assessed the antibody response after BNT162b2 mRNA vaccine administration, showed a sharp increase in anti-IgG S-RBD levels in vaccinated recipients after day 22 and remained high on day 50.[8] However, data regarding antibody response to CoronaVac vaccine and durability of antibody levels after vaccination are still limited.

This study aimed to assess the antibody response

kinetics to the SARS-CoV-2 vaccine by monitoring the IgG S-RBD levels of vaccine recipients by sampling at five different times: one day before vaccination, day 14, day 28, 3rd month, and 6th month after a booster injection or second dose of vaccine.

METHODS

This research was an observational analytic study with a prospective cohort approach carried out in the Clinical Pathology laboratory unit, Central Laboratory Installation, Dr. Soetomo Hospital, Surabaya, from January to November 2021. Samples were taken consecutively only on health workers at Dr. Soetomo General Academic Hospital who have received two doses of the SARS-CoV-2 (CoronaVac) vaccine and never had a history of COVID-19 (based on medical history and medical records and PCR test results performed before vaccination). The research has obtained ethical approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital with the number 0141/KEPK/II/2021.

All subjects involved in this study have signed informed consent and underwent five times of blood collections consisting of pre-vaccination (day 0) and post-vaccination on day 14, 28, month 3, and month 6 after receiving the second dose of vaccine (booster). The blood was collected in a serum separator tube. Serum samples collected from research subjects were categorized into the pre-vaccination group (day 0) and the CoronaVac booster vaccine group (day 14, 28, month 3, month 6). S-RBD IgG levels were measured in all subjects by indirect chemiluminescence immunoassay method on a Maglumi 800 device (SNIBE-Shenzhen New Industries Biomedical Engineering Co., Ltd, Shenzhen, China). The reference range value used in this study was 0.180-100 Au/mL, and the detection limit was 0.180 Au/mL. Antibody levels <1.00 Au/mL indicated that no antibody was produced, and antibody levels of 1.00 AU/mL indicated antibody production. Based on the WHO International standard study results, the mathematical relationship of the AU/mL Snibe unit to the BAU/mL unit will follow the equation: 1 AU/mL is equivalent to 4.33 BAU/mL.

The kinetics of the antibody response was evaluated by monitoring the ups and downs or the pattern of S-RBD IgG depicted on the line diagram. The difference in S-RBD IgG levels at each measurement time was analyzed using non-parametric statistical methods, Friedman's test followed by the Wilcoxon signed-rank test.

RESULTS AND DISCUSSIONS

This study collected a total of 250 specimens which were obtained from 50 subjects of health workers at Dr. Soetomo General Academic Hospital who received two doses of CoronaVac. Characteristics of the research subjects are shown in Table 1. The subjects in this study comprised a higher number of females, as many as 31 (62%) female subjects and 19 (32%) male subjects. The mean age in this study was 35.74±6.99 years, with a median of 34.5 years, the lowest age was 25 years, and the highest age was 57 years. During the study period, specifically after the 3rd month of sampling and before the 6th month of sampling, there were 10 (20%) subjects infected with COVID-19. The median of days confirmed or infected with COVID-19 after booster vaccination was day 151 (144-164), which coincided with the second wave of COVID-19 infections.

Table 1. Characteristics of research subjects

Variable	Value (n)
Total subjects	50
Age	
Mean±standard deviation	35.74±6.99
Median	34.50
Range	25-57
Gender [n(%)]	
Male	19 (38%)
Female	31 (62%)
Comorbid	
Yes	23 (46%)
No	27 (54%)
Type of comorbid	
Diabetes mellitus	3 (6%)
Hypertension	10 (20%)
Overweight-obesity	7 (14%)
Hypercholesterolemia	10 (20%)
COVID-19 infection after blood sampling on 3rd month	
Yes	10 (20%)
No	40 (80%)

The results of the measurement of pre-vaccinated and post-vaccinated S-RBD IgG levels for CoronaVac research subjects in this study are shown in Table 2. Differences in S-RBD IgG levels were analyzed using the non-parametric statistical method Friedman test followed by Wilcoxon signed rank test.

Friedman test results showed a significant difference in the S-RBD IgG levels before and after vaccination with p-value < 0.001 (p< 0.05). Differences in S-RBD IgG levels before and after booster

Table 2. S-RBD IgG levels before and after SARS-CoV-2 (CoronaVac) vaccination

S-RBD IgG (BAU/mL)	n	Minimum	Maximum	Median	p
Before vaccination	40				
Day 0		0.43	4.07	0.43	
After vaccination	40				
Day 14		30.71	1619.42	95.28	**< 0.001**
Day 28		19.38	725.28	110.24	
Month 3		7.64	158.65	26.42	
Month 6		0.59	11.76	9.73	

Table 3. The difference in S-RBD IgG levels before and after vaccination (Wilcoxon signed-rank test)

Variable	Time	Median	Friedman Test χ^2 (p-value)	Wilcoxon Test Z (p-value)				
				D 0	D 14	D 28	M 3	M 6
S- RBD IgG	H 0	0.43	142.680 (< 0.001)	-	-5.51 (<0.001)	-5.51 (<0.001)	-5.51 (<0.001)	-5.22 (<0.001)
	H 14	95.28		-	-	-0.07 (0.946)	-5.23 (<0.001)	-5.51 (<0.001)
	H 28	110.24		-	-	-	-5.46 (<0.001)	-5.51 (<0.001)
	B 3	26.42		-	-	-	-	-4.70 (<0.001)
	B 6	9.73		-	-	-	-	-

vaccination on day 14, day 28, month 3, and month 6, at the two-time measurements, were analyzed using the Wilcoxon signed rank test, as shown in Table 3.

Based on the Wilcoxon signed-rank test, there were significant differences between pre-vaccinated S-RBD IgG levels on day 14, day 28, month 3, and month 6 before vaccination ($p < 0.001$); day 14 with month 3 and month 6 after vaccination ($p < 0.001$); day 28 at month 3 and month 6 after vaccination ($p < 0.001$); month 3 to month 6 after vaccination ($p < 0.001$). Most of the obtained p-values were smaller than 0.05, except for the different tests of S-RBD IgG levels on the 14th day and 28th day of observation. Therefore, based on the results of the Wilcoxon test, it was concluded that there were differences in S-RBD IgG levels in patients receiving the pre-vaccinated SARS-CoV-2 vaccine until month 6.

After the 3rd month of sampling and before the 6th month of sampling during this study, 10 (20%) subjects were reported to be infected with COVID-19. The kinetics of the S-RBD IgG response from before vaccination to 6 months after vaccination of the 2nd dose of both groups are shown in Figure 1 and Figure 2.

Generally, S-RBD IgG levels in the group without a history of COVID-19 infection increased significantly until day 14 after the second vaccination dose, then decreased slowly until the 6th month. Contrastingly, in the group with a history of COVID-19 infection, a significant increase of S-RBD IgG levels was found on day 14 and month 6 after vaccination (45 days after COVID-19 infection).

S-RBD IgG titers in this study were compared between 23 (46%) subjects in the group with comorbid and 27 (54%) subjects in groups without comorbid. The types of comorbidities found in this study were 3 (6%) diabetes mellitus, 10 (20%) hypertension, 7 (14%) overweight-obesity, and 10 (20%) hypercholesterolemia. Based on these data, it was suggested that there was no significant difference in S-RBD IgG levels between the group with comorbid and without comorbid on day 14, day 28, month 3, and month 6 after vaccination ($p > 0.05$) (Table 4).

This study aimed to evaluate the kinetics pattern of S-RBD IgG against the administration of the CoronaVac up to 6 months after vaccination. Vaccination can stimulate the production of various antibodies. Antibodies formed against RBD are

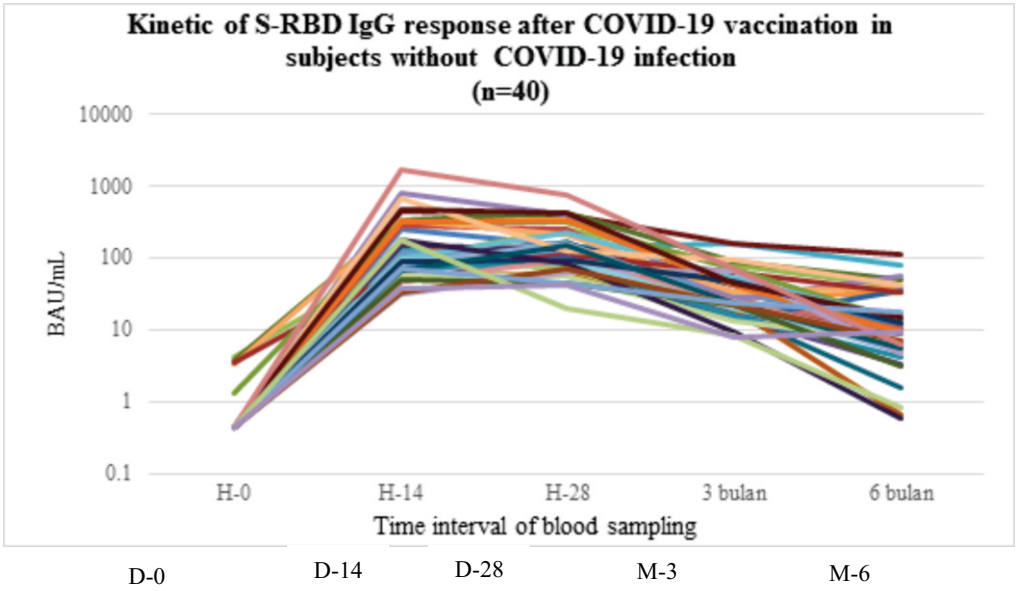

Figure 1. Kinetic of S-RBD IgG response after COVID-19 vaccinations in subjects without COVID-19 infection

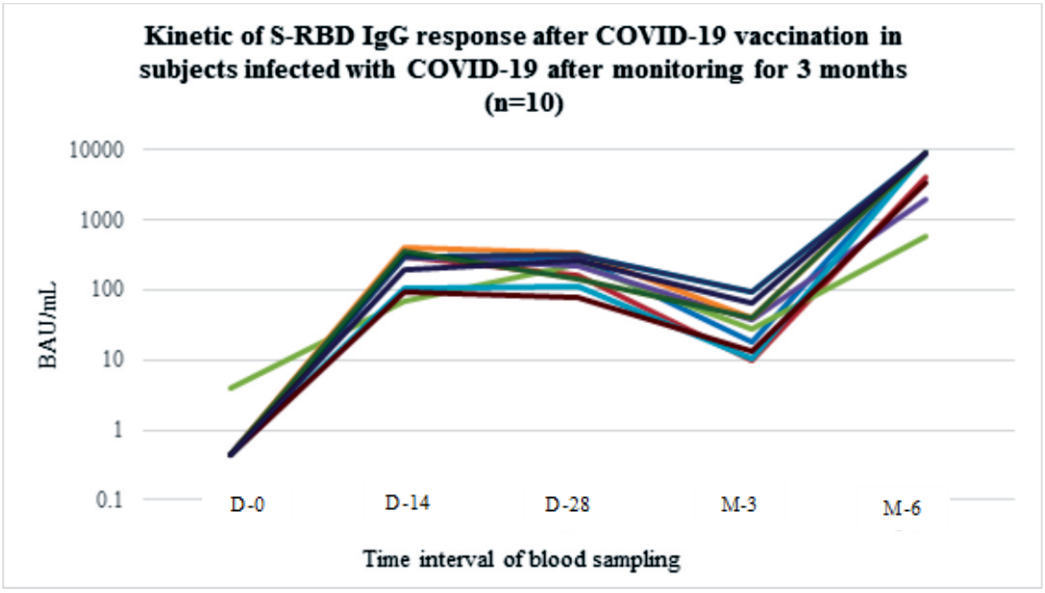

Figure 2. Kinetic of S-RBD IgG response after COVID-19 vaccinations in subjects infected with COVID-19 after monitoring for 3 months

considered the most relevant antibodies to determine the effectiveness of a vaccine concerning its neutralizing effect.[9,10]

Forty-six percent of the subjects in this study had comorbidities. The predominant comorbidities in this study were hypertension found in 10 subjects (20%) and hypercholesterolemia found in 10 subjects (20%), obesity found in 7 subjects (14%), diabetes mellitus, and hypertension found in 3 subjects (6%).

This study did not find any difference in S-RBD IgG levels before and after vaccination or in antibody levels between the comorbid and non-comorbid groups. These results differed from previous studies, which found differences in the immune response after SARS-CoV-2 vaccination between groups with DM and groups without a history of DM. A study by Ali *et al.* found lower SARS-CoV-2 NAb and IgG levels in the DM group after administration of the BNT162b2 vaccine (79.7±19.5 vs. 87.1±11.6).[11] According to a study by Terpos *et al.*, the presence of comorbidities can interfere with immunogenicity, and relatively lower NAbs levels were reported among individuals with DM after COVID-19 vaccination.[12]

Table 4. Comparison of S-RBD IgG levels before and after vaccination based on the history of comorbid disease

S-RBD IgG (BAU/mL)	Mean±SD Median (min-max)		p
	Without Comorbid (n=27)	With Comorbid (n=23)	
Before vaccination	2.04±2.99	12.38±3.39	0.451[a]
After vaccination			
Day 14	109.24 (30.71-1619.42)	188 (50.01–303.57)	0.971[b]
Day 28	173.70±137.90	202.36±68.84	0.685[a]
Month 3	26.56 (7.64–158.65)	31.75 (20.49–75.77)	0.567[b]
Month 6	50.07±91.09	13.45±29.13	0.589[a]

[a] Independent sample T-test; [b] Mann-Whitney test

Various comorbidities such as diabetes mellitus, hypertension, obesity, metabolic syndrome, and hypercholesterolemia can contribute to innate and adaptive immunity disorders. For example, a low-grade chronic inflammatory state in patients with metabolic syndrome can disrupt the macrophage activation process and interfere with proinflammatory mechanisms and/or cytokine production before exposure to antigens.[13,14] No finding of significant difference in each comorbid group with the group without a comorbid history in this study might be due to the low number of subjects with comorbid diabetes mellitus, obesity, hypertension, and hypercholesterolemia. A more significant number of individuals in each subgroup may be required to reveal other significant differences in antibody kinetics over time.

Pre-vaccinated S-RBD IgG levels with a median kinetic of 0.43 (0.43-0.47) were obtained in this study, indicating non-reactivity or no production of antibodies. This study provides information that all subjects have never been infected with COVID -19 before vaccination. The kinetics of S-RBD IgG levels later increased on day 14 after immunization, then tended to develop into a plateau phase until day 28, then began to decrease significantly on the 3rd month after vaccination ($p < 0.05$) (Table 3).

The antibody kinetics described in this study were following the antibody-forming response in patients with COVID-19, which revealed three seroconversion patterns in SARS-CoV-2 that have been successfully observed in previous studies. IgM, IgG, and NAb peaked 2-3 weeks after symptom onset, and IgM declined to undetectable levels within 6 weeks, whereas IgG and NAb titers developed into a plateau phase before decreasing in 2-3 weeks.[15]

The antibody kinetics depicted in this study were also in accordance with the response to antibody formation in general vaccination. The antibody is formed after exposure of the immune system to vaccine antigens, which will stimulate the formation of memory B cells, which then differentiate into antibody-secreting cells. Antibody-secreting cells produce IgG molecules, which are responsible for vaccine-induced immunity. The results of this study were consistent with several other studies, which also found a tendency of a significant increase of antibody titers immediately after vaccination until day 36 or the first month after vaccination.[12] A similar study evaluating the kinetic of antibody response after mRNA BNT162b2 vaccination has also reported a sharp increase of S-RBD IgG levels after day 22 and stable on high levels until day 50.[8]

A significant decrease in S-RBD IgG levels in this study was found from day 28 to the 3 months after vaccination ($p < 0.05$) and then decreased slowly until 6 months after vaccination. The reduced antibody levels in the 3rd month were still above the positive threshold (positivity threshold), indicating a protective immune response to SARS-CoV-2 until the 6th month. These results were by a study by Hall *et al.*, which suggested that more than 90% of individuals infected with SARS-CoV-2 develop antibodies within one week of the onset of symptoms. In contrast, antibody titers persist for at least three months post-infection.[16]

During the study, after the 3rd month of sampling and before the 6th month of sampling, there were ten subjects infected with COVID-19. The infection of those subjects coincided with the presence of the second wave of cases in Indonesia, which was mostly caused by a new variant of the SARS-CoV-2 virus known as the delta variant. In the 6th month, there were different kinetic patterns between the group without COVID-19 infection and those with a history of COVID-19 illness. There was a tendency for a decrease in antibody levels in the group without COVID-19 infection. Contrastingly, antibody levels increased drastically in the group with a history of the condition (Figures 1 and 2).

The increase in S-RBD IgG levels began on day 14 after the second dose of the CoronaVac vaccination. The highest increase was reported on the 14th day after two doses of CoronaVac vaccination with mean antibody levels of 212.97±261.16 BAU/mL. Research by

Padoan *et al*. found the equivalence of the PRNT50 titer (1:160) to the S-RBD IgG levels. S-RBD IgG levels, equivalent to PRNT50 with reagents from Snibe Maglumi are 75 AU/mL (324.75 BAU/mL).[17] It was presumed that the highest increase on the 14th day was unable to provide an optimum neutralizing effect to SARS-COV-2 because the increase did not exceed 324,75 BAU/mL. However, CoronaVac in this study effectively evoked a faster and stronger humoral immune system in subsequent COVID infections. These results indicated that memory cells in the immune system either obtained from vaccination or previously infected still persist for 10 months and will cause faster and higher antibody formation when the same antigen invades the body.[18] CoronaVac is thought to have low immunogenicity concerning its type as an inactivated virus vaccine, which has antigen multivalence and changes in the S antigen that occur due to the virus inactivation process.[19-21]

Similar results were obtained in a study by Ontañón *et al.* on vaccinated health workers. The study revealed that antibody titers two months after vaccination were higher in the group with a history of previous SARS-CoV-2 infection compared to the group that had never been infected. The study found that the group with a history of SARS-CoV-2 infection experienced a 126-fold increase in antibody levels within 7 days after the first dose of vaccination ($p < 0.001$). In contrast, only five subjects in the group without a history of infection showed positive antibody levels. Observations two months later showed that antibody levels were still higher in the group with a history of previous infection.[18]

Goel *et al*. evaluated the response of B and T lymphocytes in individuals receiving the SARS-CoV-2 mRNA vaccine by conducting a longitudinal study for 6 months. Vaccination has been shown to produce spike-specific memory CD4 and CD8 T cells. Although antibodies often correlate with the effectiveness of vaccines, memory B cells, and memory T cells are essential components of the immune response to viral antigens. They have protective mechanisms in individuals who have acquired pre-existing immunity. Memory T cells will proliferate quickly when the body is invaded with the same antigen and provide a more robust immune response. These antibodies are helpful for the control of initial viral replication and limiting the spread of the virus in the host. Cellular immunity can reduce disease symptoms (i.e., preventing hospitalization and death) and reduce the ability to spread the virus to others.[22]

The mere evaluation of humoral immune response without that of cellular immune response remained one of the limitations of this study. Previous studies have demonstrated a correlation between humoral and cellular immunity after vaccination.[23] Another limitation of this study was single-centered research and the involvement of a narrow age range of subjects that might limit the generalization of the results.

CONCLUSIONS AND SUGGESTIONS

There were differences in S-RBD IgG levels before and after vaccination. The kinetics of S-RD IgG levels were found to significantly increase from before vaccination to day 14 after vaccination, horizontally from the 14th to the 28th day, and continued to decrease significantly from the 28th day to the 6th month.

It was recommended to perform further research for observations on antibody kinetics after the 3rd booster vaccination.

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