Original Research Report

SPIKE-RECEPTOR BINDING DOMAIN (SRBD) ANTIBODIES SECRETION IN COVID 19 SURVIVORS AND NON-SURVIVORS POST-PRE-ENDEMIC VACCINATION

Museyaroh, Evy Diah Woelansari, Dwi Krihariyani

Department of Medical Laboratory Technology, Health Polytechnic Ministry of Health Surabaya, Surabaya, Indonesia

ABSTRACT

The development of a vaccine for SARS-COV-2 began in mid-2020 with the aim of stimulating an individual's immune response against SARS-CoV-2 infection. The purpose of this study was to determine the levels of post-vaccine SRBD antibody secreted in COVID-19 survivors and non-survivors. Antibodies are considered to play a more important role in evaluating immunity because antibody tests may provide information about a person's immune status against SARS-CoV-2. The study was conducted at Husada Utama Hospital, Surabaya, Indonesia, in April – May 2021. The samples were taken prospectively with a total sample of 60 patients, consisting of 40 non-survivors and 20 survivors of COVID-19 who had received Sinovac vaccine doses 1 and 2. Examination of Sars-CoV-2 SRBD antibody was conducted by using CL series of Mindray device by means of CLIA method. The average level of antibody was assessed in each sample group and the results were subjected to the Mann Whitney test. The mean SRBD antibody level in female patients was 428.24 ± 271.25, while in male patients it was 310.40 ± 113.71 U/mL. The results of the Mann Whitney test revealed a P-Value of 0.09 > 0.05, indicating no difference in post-vaccine SRBD antibody levels between females and males, but there were differences in SRBD antibody levels in COVID-19 survivors and non-survivors with a P-Value of <, i.e. 0.00 < 0.05 There was no difference in post-vaccine SRBD antibody levels between females and males in COVID-19 survivors and non-survivors, but there were differences in post-vaccine antibody levels between COVID-19 survivors and non-survivors.

Keywords: *COVID-19; SRBD; virus; good health and well-being; vaccine*

Correspondence: Museyaroh Muza, Department of Medical Laboratory Technology, Health Polytechnic Ministry of Health, Surabaya, Indonesia. Email: museyaroh21@gmail.com

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Highlights:

1. The research this for determine the presence of immune response post-vaccine
2. The results of this study indicate that there are differences in immune responses, in survivors patients have higher SRBD antibody levels than non-survivors

INTRODUCTION

Globally, the COVID-19 pandemic is still ongoing, including in Indonesia. As of April 13, 2022, the number of confirmed cases of COVID-19 in Indonesia was 6,036,909 people with recovered cases of 5,814,688 people (96.3%) and a death rate of 155,746 people (2.6%) (World Health Organization 2022). Clinical manifestations of COVID-19 can develop into pneumonia, respiratory failure, and even death (Özdemir 2020). About 80% of the cases are classified as mild or moderate and 13.8% experience severe illness, and 6.1% of patients fall into a serious critical condition (Han & Yang 2020). Deterioration and death generally occur in older people with the congenital disease (50-75%) (Özdemir 2020).

The spread of SARS-CoV-2 from human to human became the main source of transmission so the spread became more aggressive (Susilo et al 2020). Transmission of SARS-CoV-2 from symptomatic patients occurs through droplets released from a person infected with the SARS-CoV-2 virus when coughing or sneezing (Ong et al. 2020). The SARS-CoV-2 virus can transmit viable aerosols (generated via a nebulizer) for at least 3 hours (van Doremalen et al. 2020). Lung epithelial cells are the main target of the SARS-CoV-2 virus, in some cases, it has been reported that SARS-CoV-2 transmission from human to human occurs through the binding of the Receptor Binding Domain (RBD) and cellular receptors belonging to the host cell, namely the Enzyme Modifier. Angiotensin 2 (ACE2) (Rothan & Byrareddy 2020).

The development of a vaccine for SARS_COV-2 began in mid-2020 with the aim of stimulating an individual's immune response to SARS-CoV-2 infection. In early 2021, the government began implementing a community vaccine program with the priority for the health workers. In this first stage, the vaccine used was an inactivated vaccine platform (Irsan et al. 2022). Viruses that infect the body will carry antigens that will be recognized by the body's immune system. Vaccines containing attenuated viruses or parts of viruses that are not pathogenic (antigens) can trigger an immune

response in the body that receives the vaccine 2 by the formation of antibodies (Rotty et al. 2022).

The antibody test for SARS-CoV-2 aims to detect the body's immune response to infection with the SARS-CoV-2 virus either naturally or due to vaccination (Röltgen & Boyd 2021). The antibodies that can be detected are antibodies to the spike protein (S) and the nucleocapsid protein (N) of the SARS-CoV-2 virus, while based on their effects, the antibodies are divided into two. The first one is the Neutralizing Antibody (NAb), which is an antibody that works by blocking the bond between the pathogen and the host cell, while the second one is the non-neutralizing antibody (non-NAb) is an antibody that acts by other mechanisms (opsonization, complement activation, antibody-dependent cellular cytotoxicity (ADCC). These non-NAbs include antibodies to proteins N (anti-N) and against S proteins other than RB. In SARS-CoV-2 infection, NAb primarily refers to antibodies to the Receptor Binding Domain (RBD) subunit of the Spike-Receptor Binding Domain (S-RBD). However, not all S-RBD antibodies have a neutralizing effect. Neutralizing SARSCoV-2 antibodies are found in the form of IgG, IgM, and IgA (Pang et al. 2021).

Monitoring antibody levels in post-vaccinated patients is very important to determine the effectiveness of the vaccine, especially for health workers at the frontline of the COVID-19 pandemic (Choi & Cheong 2021). However, the current protective resistance of existing vaccines is unknown and the nature of the antibody cycle decreases over time. Therefore, the purpose of this study was to determine the difference in the levels of post-vaccine Spike-Receptor Binding Domain (S-RBD) antibody in COVID-19 survivors and non-survivors because Spike-Receptor Binding Domain (S-RBD) antibody examination is considered to play a more important role for the purpose of evaluating immunity as this test is capable to provide information about a person's immune status against SARS-CoV-2 (Xu et al. 2020).

MATERIALS AND METHODS

This was a descriptive-analytic study using the cross-sectional method. This study was conducted at Husada Utama Hospital Surabaya, Indonesia, in May – June 2021. The samples were taken prospectively with a total sample of 60 samples consisting of 40 non-surviving and 20 surviving COVID-19 patients. Sixty patients had received Sinovac vaccine doses 1 and 2. The samples were taken ± 3 weeks after vaccine dose 2 and Sars-CoV-2 SRBD antibody examination using CL series of Mindray device with Chemiluminescent Immunoassay (CLIA) method. Assessment of the average level of antibody in each sample group was performed, and the results were subjected to Mann Whitney statistical test using IBM SPSS Statistics 26.

RESULTS

Of 60 COVID-19 patients involved as samples in this study, 40 were non-survivors, consisting of 31 females and 9 males, while 20 were survivors consisting of 16 females and 4 males (Figure 1).

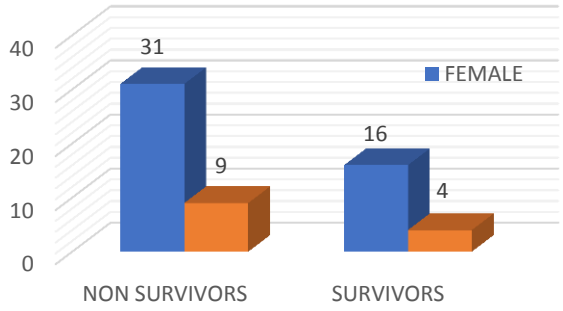

Figure 1. COVID-19 survivors and non-survivors' gender

Table 1 explains post-vaccine SRBD antibody levels for survivors of COVID-19. The average SRBD antibody level in females was 428.24 ± 271.25 U/mL with a maximum level of 1000.00 U/mL and a minimum level of 172.10 U/mL, while in males, the average SRBD antibody level was 310.40 ± 113.71 U/mL with the maximum level of 458.80 U/mL and the minimum level of 187.22 U/mL.

Table 1. Levels of post-vaccine SRBD antibodies among COVID-19 survivors based on gender

	Mean ± SD (U/mL)	Maximum (U/mL)	Minimum (U/mL)
Female	428.24 ± 271.25	1000.00	172.10
Male	310.40 ± 113.71	458.80	187.22

Post-vaccine SRBD antibody levels in COVID-19 non-survivors showed that the average SRBD antibody levels in female patients were 60.06 ± 30.94 U/mL with a maximum level of 117.99 U/mL and a minimum level of 14.53 U/mL, while in males, the average level of SRBD antibody was 37.38 ± 17.82 U/mL with the maximum level of 72.81 U/mL and the minimum level of 7.30 U/mL (Table 2)

Table 2. Levels of post-vaccine SRBD antibody among COVID-19 non-survivors by gender

	Mean ± SD (U/mL)	Maximum (U/mL)	Minimum (U/mL)
Female	60.06 ± 30.94	117.99	14.53
Male	37.38 ± 17.82	72.81	7.30

Mann Whitney test revealed the p-value of 0.09 > 0.05, indicating no difference in post-vaccine SRBD antibody levels in female and male COVID-19 survivors, while for non-COVID-19 survivors the P-value was 0.75 > 0.05, indicating no difference in post-vaccine SRBD antibody levels between female and male patients.

Table 3. Levels of post-vaccine SRBD antibody in doses 1 and 2

	Mean ± SD (U/mL)	Maximum (U/mL)	Minimum (U/mL)
COVID-19 survivals	404.67 ± 55.88	1000	172
COVID-19 non-Survivals	54.96 ± 4.72	117.99	7.30

The average post-vaccine SRBD antibody level in COVID-19 survivors was 404.67 ± 55.88 U/mL with a maximum value of 1000 U/mL and a minimum value of 172 U/mL while the post-vaccine SRBD antibody level in non-COVID-19 survivors was 54.96 ± 4.72 U/mL with a maximum value of 117.99 U/mL and a minimum value of 7.30 U/mL. Kolmogorov-Smirnov normality test revealed a p-value of 0.03 < 0.05, indicating that the data were not normally distributed so it was followed with the Mann Whitney test and the results of the p-value were 0.00 < 0.05, indicating differences in the levels of post-vaccine SRBD antibody between COVID-19 survivors and non-survivors. COVID-19 survivors had higher SRBD antibody levels than non-COVID-19 survivors.

DISCUSSION

In this study, among COVID-19 survivors and non-survivors who had received Sinovac 1 and 2 vaccines, there were more female than male patients. This could be because there were more female than male populations who had received the vaccines. In contrast, Hidayati (2020) found that in Indonesia male-dominant population confirmed positive COVID-19. They made up more than half of the total patients confirmed with COVID-19. Clinical manifestations in male patients were much worse than in female patients. The percentage of male patients who died was much higher than of female patients. This may be related to cigarette smoking habit, which was more often in males than in females, resulting in worse respiratory tract disease among male patients (Rothe et al. 2020). Mann Whitney statistical test showed no differences in post-vaccine SRBD antibody levels between females and males, but there were differences in post-vaccine SRBD antibody levels in COVID-19 survivors and non-survivors. The Average post-vaccine SRBD antibody levels were higher in COVID-19 survivors.

SARS-COV-2 has 4 structural proteins Spike (S), Membrane (M), Envelope (E), and Nucleocapsid (N) proteins. S protein role in receptor binding and fusion. This protein is encoded by the S gene and is functionally divided into 2 subunits, namely S1 role in binding to ACE2 receptors while S2 role in fusion. N protein has an important role in viral pathogenesis, replication, and RNA packaging. Antibodies to N protein are frequently detected in COVID-19 patients (Tang et al. 2020, Chen et al. 2021).

Antibodies to the SARS-CoV-2 virus are acquired either naturally by SARS-CoV-2 virus infection or due to vaccination. The difference in antibody levels between COVID-19 survivors and non-survivors is related to the immune response to COVID-19 when the virus enters the host (Takita et al. 2022). Spike protein portion of the virus binds to the ACE2 receptor after replicating in the viral host cell and then detaches itself and is phagocytosed by Antigen Presenting Cells (APCs), such as macrophages or dendritic cells, then antigens from SARS-CoV-2 are presented to helper T cells which then will activate B cells. The activated B cells will proliferate and differentiate into plasma B cells and memory B cells. The plasma B cells then release specific receptors in the form of antibodies, the IgM, IgG, or IgA. SARS-CoV-2 (Lee et al. 2010). The significant increase in SRBD antibodies in COVID-19 survivors could be due to memory B cells having recognized antigens from SARS-CoV-2 vision so that when a similar antigen enters the body, the body's immune response will quickly release antibodies. Examination of SRBD antibody levels after vaccination can be one way of monitoring antibody responses in individuals, especially in someone who has a high risk of being exposed (Deshpande et al. 2021).

The S (spike) and RBD (receptor binding domain) proteins in SARS-CoV-2 are the main targets for vaccine manufacture, because the specific antibodies formed against these proteins can prevent the virus from binding to the Angiotensin-Converting Enzyme 2 (ACE2) receptor as a port of entry into the immune system in the host cell. This has resulted in the development of various antibody titer tests using protein S and RBD targets. In Indonesia, in the early stages of the government's public vaccination program, vaccines with an inactivated vaccine platform were

used. This vaccine is known to exhibit good immunogenicity by inducing neutralizing antibodies against SARS-CoV-2, and this vaccine has been effectively preventing COVID-19 and death caused by SARS-CoV-2 infection. B and plasma cells are some important keys in the immune system against SARS-CoV-2 infection (Jin et al. 2020). According to several studies, there are differences in the speed of antibody formation in each individual. According to Barbosa et al. (2020), the rate of increase in SARS-CoV-2 antibodies is different for each individual. In patients with mild clinical symptoms, specific antibodies appear earlier, usually on day 7 when IgM is lower and IgG continues to increase. In patients with severe clinical symptoms of SARS-CoV-2, antibody seroconversion appears longer usually on day 12 and IgM continued to increase. Meanwhile, in COVID-19 patients, it occurs between 7-12 days after the onset of symptoms, generally IgM is produced first and IgG is produced later. The presence of IgG lasts a long time in the body (Hoffman et al. 2020). Hsueh et al. (2004) emphasized that the increase in IgG occurred on average 10 days after the onset of clinical symptoms in COVID-19 patients and the peak of this antibody seroconversion was in 15 days. According to Dohla et al. (2020), seroconversion occurs sequentially for IgM and then IgG with a median time of 11 and 14 days, respectively, so if the sample is taken less than that time, it is likely that antibodies have not been formed and the test results will be false negative. IgM can be detected in the blood of a person infected with the SARS-CoV2 virus for 3-6 days after the onset of clinical symptoms and IgG can be detected 8-13 days after infection with the SARS-CoV-2 virus (Long et al. 2020). Therefore, it is important to monitor the antibody levels of post-vaccinated patients to determine the effectiveness of the vaccine, especially for health workers who are at the forefront of handling COVID-19 and as an evaluation of whether an individual should be re-vaccinated or not (Li et al. 2020).

Stregth and limitation

This study stimulates an individual's immune response against the virus. The methods used to examine the SRBD antibody levels add to the scientific rigor of the study. The study was conducted at a single hospital in Indonesia, which may limit the generalizability of the findings to other populations.

CONCLUSION

There are no differences in post-vaccination Spike-Receptor Binding Domain (SRBD) antibody levels between females and males. There were differences in SRBD antibody levels in post-vaccination between survivors and non-survivors. COVID-19, COVID-19 survivors have higher SRBD antibody levels than non-COVID-19 survivors.

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Conflict of interest

None.

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Author contribution

M: conceptualization, methodology, investigation, writing-reviewing editing, software, data curation, and writing-editing, methodology, EDW: Validation and Editing–reviewing, DK: validation.

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