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Original Article

Effect of Immune Cell Ageing on Humoral Immunity Responses Post-COVID-19 Vaccination

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ABSTRACT

Background: COVID-19 pandemic has high incidence and mortality, including in Indonesia. One of the prevention efforts is the provision of vaccines, but the ageing of the immune system (immunosenescence) may reduce the immune response to vaccination. Studies reported the decline of interferon-gamma (IFN-γ) could be one of markers of immune cell ageing. Besides, the increases soluble CD28 (sCD28) reported has good correlation with membrane CD28 (mCD28), thus it could be used as an alternative marker for immunosenescence.
Objective: To determine the differences in levels of sCD28, IFN-γ and anti-S-RBD antibodies in the group suspected of having an ageing immune system with the control group after vaccination.
Methods: Sample consisted of 24 control (healthy adult) and 32 case (elderly and adult with comorbid) subjects. Blood samples were examined for anti-S-RBD antibody, IFN-γ, and sCD28 levels. Analysis of data performed by Median test and Spearman tests.
Results: Mean level of anti-S-RBD antibodies, IFN-γ, and sCD28 in case group compared to control group was 33.0 ±17.47 BAU/mL vs. 45.97 ± 23.13 BAU/mL (p = 0.007); 41.61 ± 38.79 ng/mL vs. 98.59 ± 94.31 ng/mL (p = 0.007); and 3.80 ± 3.68 ng/mL vs. 7.81 ± 7.97 ng/mL (p = 0.280), respectively. The anti-S-RBD antibodies and IFN-γ levels are lower in case group and sCD28 is lower in case group although not statistically significant.
Conclusion: Anti-S-RBD antibodies after COVID-19 vaccination are lower in elderly or comorbid people than in adults without comorbid because of ageing of immune system.

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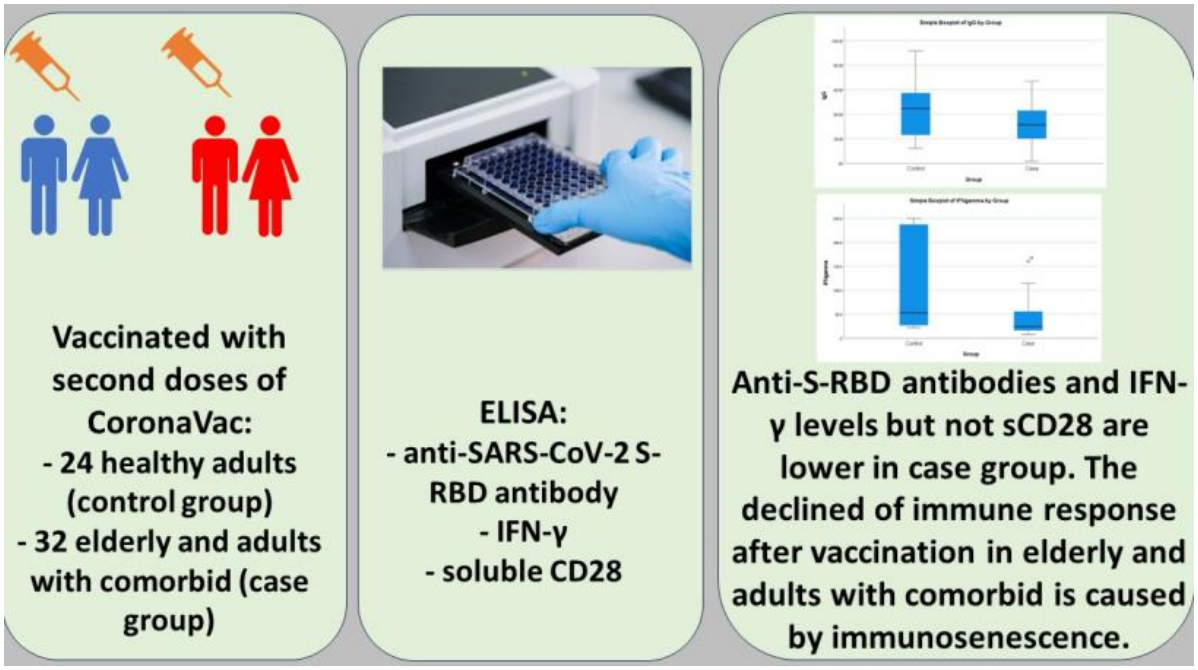
GRAPHICAL ABSTRACT



Introduction

COVID-19 is a disease caused by the severe acute respiratory syndrome corona virus 2 (SARS CoV-2), which is a worldwide pandemic. Symptoms experienced by each infected person vary significantly from no symptoms, mild, moderate to severe symptoms [1]. The absence of effective drugs for COVID-19 has prompted the rapid development of vaccines that are considered capable of preventing the spread of COVID-19, although in people with ageing of immune system there is possibility that the vaccine will be less effective [2-4]. In Indonesia, COVID-19 mortality is still high especially in older people. Research by Surendra *et al.* found that mortality of people ≥ 70 years old was 21% and increased if they had two or more comorbidities (51%) [5]. To control the pandemic in Indonesia, the government imported COVID-19 vaccine from Sinovac Life, CoronaVac, and it administered first for people with high risk to spread COVID-19 (medical staff, people that work in public services) or people with high risk of mortality and morbidity in COVID-19 (older people) [6].

CoronaVac (Sinovac Life Sciences, Beijing, China) is an inactivated virus-based vaccine administered to most Indonesians. A study in China reported that vaccination with Sinovac produced 92% neutralizing antibodies after four weeks and peaked at 6-8 weeks. Adverse events from Sinovac were seen in 29% of participants without severe circumstances, which indicates that the vaccine is relatively safe [7].

Several innate and adaptive immune cells respond to SARS-CoV-2, such as alveolar macrophages, dendritic cells, neutrophils, and lymphocytes [8-10]. The immune response to administration of the Sinovac vaccine is analogous to the natural response when SARS-CoV-2 enters the host's body through the Angiotensin Converting Enzyme (ACE)-2 receptor [11-13]. Viruses in host cells are recognized as damage-associated molecular patterns (DAMPS) and pathogen-associated molecular patterns (PAMPs) by alveolar macrophages. Furthermore, macrophages induce an effector mechanism played by B lymphocyte cells, which can secrete antibodies and bind specifically to pathogens. Cytotoxic T cells limit virus spread, and helper T cells secrete specific anti-viral cytokines [14,1 5].

There are four structural proteins in SARS-CoV-2, namely S (spike), N (nucleocapsid), M (membrane), and E (envelop) proteins. Protein S is one of the targets for developing vaccines to form antibodies against the receptor-binding domain (RBD) protein S to prevent the virus entry into host cells and protect against Coronavirus infection [16-18].

Some considerations in assessing the vaccination success are the formation of humoral immune responses and cellular immune responses to viruses that appear after vaccination. The evaluation of humoral immune response after vaccination is essential to assess the production of neutralizing antibodies. Neutralizing antibodies are antibodies that can inhibit the interaction between SARS-CoV-2 and the ACE-2 receptor, thereby effectively preventing the SARS-CoV-2 entry into the host. Anti-S-RBD is currently used to evaluate the neutralizing antibody [19-21].

Many factors influence the formation of post-vaccination antibodies, one of which is the immune system ageing. Immune ageing is found commonly in older people, but it can be found in many conditions, such as patients with autoimmune diseases, chronic infections, malignancies, and other inflammatory diseases, that accelerate immune ageing (premature ageing of the immune system). Individuals with ageing immune systems are reported to have an inadequate response to vaccination [22-24]. Markers of immune system ageing include an inverted CD4/CD8 T-cell ratio, a decrease in the number of naive T cells (TCD4+CD45RA and TCD8+CD45), a decrease in the number of activated T cells (TCD4+CD28+ and TCD8+CD28+), senescent/memory T cells (TCD4+CD45RO and TCD8+CD45RO), and memory T cells that were neither activated nor proliferated (CD4+CD28null and TCD8+CD28null). In addition, decreased proinflammatory cytokine IFN-γ [25, 26] and increased soluble CD28 (sCD28) in the blood was also reported [27, 28].

Currently, research on the effectiveness of the Sinovac vaccine, especially in the Indonesian population, has not been widely carried out. In addition, the role of ageing of the immune system in the emergence of humoral responses after Sinovac vaccination has not been studied, but it is understandable that the ageing of immune ageing will affect immune response after vaccination make it less effective. Therefore, this study was conducted to evaluate the relationship between markers of immune system ageing (IFN-γ and sCD28) and the humoral immune response (neutralizing antibody) after CoronaVac (Sinovac) vaccination.

Materials and Methods

The design of this study was analytic observational, and sample was taken one time (cross sectional). Subjects were taken from medical staffs in Dr. Saiful Anwar General Hospital Malang who are willing to participate in this study.

Subjects were divided into two groups, namely the case group (elderly and patients with comorbidities) while the control group were healthy adults. All subjects already got vaccinated with CoronaVac twice and after 6-7 weeks from second dose vaccine, blood sampling is taken. The inclusion criteria for the case group were individuals aged more 60 years old or patients diagnosed with chronic diseases with pathogenesis chronic inflammation who had received the second dose of COVID-19 vaccination. We put elderly and patients with chronic inflammation in one group because both suffered from immunosenescence due to continues activation of the immune system. The inclusion criteria for the control group were healthy adults who had received the second dose of COVID-19 vaccination. Both groups are gender matched. The research subjects were taken by consecutive sampling at 6-8 weeks after the second dose of COVID-19 vaccination. The venous blood sample was collected, and serum stored at -80 °C before being examined. The anti-S-RBD antibody examination was carried out using the fluorescent immunoassay (FIA) method with FREND™ COVID-19 SP.

The procedure is put 35 µl blood sample to cartridge then place It into FREND™ system. Once samples react to reagents, analysis is begun and done within 3-4 minutes. Anti-S-RBD

antibody is measured based on ratio of fluorescence detected by FREND™ system. The magnitude of fluorescent ratio is proportional to the presence of anti-S-RBD antibody [29]. Soluble CD28 and IFN-γ were measured by enzyme-linked immunosorbent assay (ELISA) kit from BT Lab. ELISA plate already coated with human sCD28 or IFN-γ antibody. Substrate in the sample will bind to the antibody coated in wells, and then biotinylated antibody is added to bind substrate. Thereafter, streptavidin-HRP is added to bind biotinylated antibody. After incubation, streptavidin-HRP is washed, and then color develops in proportion to the amount of the substrate. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm [30, 31].

Data analysis in this study was carried out using IBM SPSS version 24 software. The unpaired t-test or Mann-Whitney test was used to compare the levels of anti-S-RBD, sCD28, and IFN-γ antibodies between the two groups. While the correlation between anti-S-RBD antibodies with sCD28 and anti-S-RBD antibodies with IFN-γ was carried out with the Pearson or Spearman test. The data is considered statistically significant if the p-value < 0.05. The research will be carried out after obtaining an Ethics Certificate obtained from the Ethics Committee of Dr. Saiful Anwar Hospital, Malang.

Results and Discussion

Table 1 presents characteristics of the subjects in both groups. The sexes in the two groups were not significantly different but the ages in the two groups were significantly different because one of the research variables used was the age difference so that the distribution of the sample was as expected. The comorbid diseases in the cases group are hypertension, type 2 diabetes mellitus, dyslipidaemia, obesity, asthma, cancer, and lung TB infection (Table 1).

The data normality test with Shapiro-Wilk showed that the distribution of anti-S-RBD, sCD28, and IFN-γ antibodies had an abnormal data distribution. Therefore, the different test used is Mann-Whitney test. There were no significant differences in the levels of anti-S-RBD antibodies, sCD28, and IFN-γ between the case group and the control group (Table 1 and Figure 1).

Table 1: Patient characteristics health subject and disease control

Characteristics	Control group (n = 24)	Case group (n = 32)	*P*-value
Age, median (min-max)	24 (26-49)	32 (27-76)	< 0.001*
< 60-year-old, n	24	17	
≥ 60-year-old, n	-	15	
Gender, female (%)	16 (66.7)	18 (56.3)	0.581
Vaccine type	CoronaVac	CoronaVac	
Time between 2nd dose vaccine to sampling	6-7 weeks	6-7 weeks	
Comorbid Disease			
Hypertension	-	12	
Type 2 Diabetes Mellitus	-	4	
Dyslipidaemia	-	6	
Obesity	-	3	
Asthma	-	5	
Cancer	-	1	
TB infection	-	1	
IFN-ɣ (ng/mL), mean ± SD	98.59±94.31	41.61±38.79	0.007*
sCD28 (ng/mL), mean ± SD	7.81±7.97	3.80±3.68	0.280
Anti-S-RBD (BAU/mL), mean ± SD	45.96±23.14	33.00±17.47	0.007*

**SD = standard deviation; TB = tuberculosis*

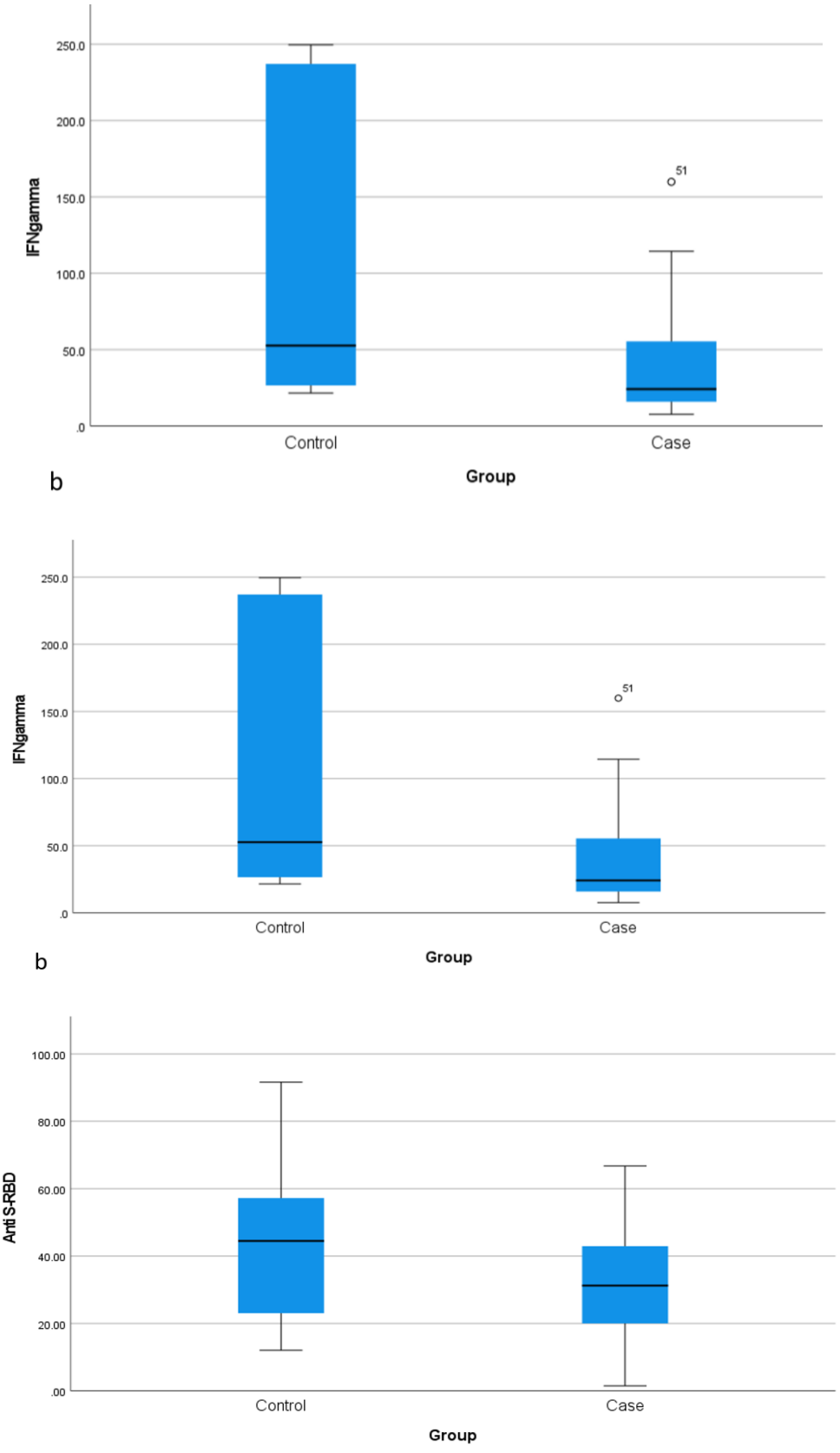


Figure 1: Boxplot of (a) IFN-γ, (b) sCD28, and (c) anti-S-RBD antibody levels between control and case group

Table 2: The correlation between anti-S-RBD antibody with sCD28 and IFN-γ

Variables	*P*-value	r value
Anti S-RBD antibody with sCD28	0.206	0.172
Anti S-RBD antibody with IFN-γ	0.283	0.180

Table 3: Correlation between age of the subject with sCD28, IFN-γ, and anti-S-RBD

Correlation	p value	r
Age with sCD28	0.169	-0.186
Age with IFN-γ	0.064	-0.249
Age with anti-S-RBD	0.634	-0.065

The correlation test is the Spearman correlation test because the data distribution is not normal. The correlation test was carried out between anti-S-RBD antibody levels with sCD28 and IFN-γ with the results, as presented in Table 2. Correlation between age of the subject with sCD28, IFN-γ, and anti-S-RBD is summarized at Table 3.

In this study, the levels of anti-S-RBD antibody and IFN-γ were lower in the case than control groups. However, sCD28 level is lower in case group although is not statistically significant. The level of anti-S-RBD antibody was lower in case group indicating that there was declining immune response after vaccination. This is supported by the lower level of IFN-γ in case group which reflect ageing in immune system. Some factors may influence the result of the study like the comorbid conditions in the case group varied and were likely to be under controlled conditions. Until now, the comorbid factors that play an essential role in antibody formation are unclear. The result of the study is in line with some studies that conclude elderly people tend to have lower antibody levels after vaccination than adult [32-34]. Meanwhile, various factors can affect the body's immune response to vaccines, such as microbiota conditions, lifestyle (smoking, sleep, exercise, and alcohol consumption), and birth weight or other maternal factors that were not evaluated in our study [35]. The IFN-γ examination in our study was intended to indicate ageing in the immune response that might affect the response after the second dose of Sinovac was given. There was a higher level of IFN-γ in the control group than in the case, but the difference was not significant. This result is in line with previous findings that a decrease in IFN-γ is found in elderly people [36-38], also IFN-γ is one of the immune risk profiles which indicates an immunosenescence [22]. The research on IFN-γ levels with chronic diseases such as hypertension, diabetes mellitus, and dyslipidemia has also not found an increase in IFN-γ levels in comorbid conditions compared to healthy controls. Niu *et al*. (2013) found lower IFN-γ levels in the hypertension group than in the control group [39]. Research by Nosratabadi *et al*. (2009) found an increase in IFN-γ in patients with diabetes mellitus with nephropathy. It is unknown whether there is a difference of IFN-γ levels between healthy individuals with diabetes mellitus without nephropathy [40].

Based on our study, the sCD28 levels were lower in the case group than the control group but not significantly different. Decreased expression of CD28 is one of the markers of the ageing process of the immune system. Various studies have shown that in the elderly and autoimmune diseases, there is an ageing condition of the immune system (a decrease in CD28 expression). An increase in the population of CD28null T lymphocytes in the aging process of the immune system, especially in $CD8^+$ T cells ($CD8^+$CD28 null T cells) [41]. Research by Youn *et al*. (2013) found a decrease in CD28 in hypertension [42], but research on sCD28 levels in hypertension has never been done. Research by Li *et al*. (2021) found an increase in sCD28 levels in patients with diabetic nephropathy compared to diabetes mellitus alone. There is not known comparison of sCD28 levels in diabetes mellitus compared to healthy controls [43]. The elevated levels of sCD28 in chronic disease are found mainly in autoimmune or chronic infectious diseases [44-47] but not in metabolic diseases. According to the study by Feehan *et al*. (2021), the research found a decrease in CD28 count cells with age but did not examine soluble CD28 levels [48]. The correlation between anti-S-RBD antibodies with sCD28 and IFN-γ showed no correlation. This is probably due to the many confounding factors that were not such as psychological stress, microbiota, sleep quality, sedentary lifestyle, as well as smoking and alcohol drinking habit [35]. In addition, various factors that may influence the

immune response to vaccines were not evaluated in this study. Some studies on IFN-γ and sCD28 have mainly been carried out in chronic autoimmune diseases or chronic infectious diseases and not in chronic metabolic diseases as in the sample used in this study. Therefore, it is necessary to conduct further research on the differences in levels of anti-S-RBD antibodies, IFN-γ, and sCD28 in healthy populations compared to the patients with uncontrolled comorbid conditions. Anti-S-RBD antibody levels and IFN-γ levels in elderly individuals or chronic metabolic diseases were lower than healthy adults showed that in elderly and or adult with comorbid there is ageing of immune system process that responsible for declining of the immune response after vaccination. However, sCD28 levels were lower in elderly individuals or chronic metabolic disease than healthy adults but not significantly different. Furthermore, this study has some limitations that may impact the result. This study lacks information about confounding factors that may impact immune-senescence, for example, gut dysbiosis, smoking habits, alcohol consumption, physical activity, etc. Likewise, this study only examines subjects once, thus the decreased of the antibody are unknown between two groups. We suggest that a cohort study needed to assess more accurate about the immunosenescence effect on immune responses after vaccination.

Conclusion

Anti S-RBD antibodies after COVID-19 vaccination is lower in elderly and adult with comorbid. IFN-γ is lower in case group because of the ageing of immune system. However, the sCD28 levels between two groups are not different.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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