Original Research Report

DURABILITY OF S-RBD IgG ANTIBODY LEVELS AFTER SINOVAC VACCINATION IN HEALTHCARE WORKERS

Jusak Nugraha[1], Cynthia Ayu Permatasari[2], Munawaroh Fitriah[1]

[1]Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
[2]Resident at Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

ABSTRACT

Since it was declared a pandemic in early 2020, Coronavirus Disease 2019 (Covid-19) has caused high morbidity and mortality in the world. In view of the urgency of the situation, vaccination efforts are needed to break the chain of disease transmission. Various types of vaccines have been successfully developed and obtained approval for emergency use. However, the effectiveness of these vaccines, both in the short and long term, has not been fully known. This study aimed to examine the effectiveness of vaccination through the kinetics of the antibody response to the administration of the SARS-COV-2 vaccine by examining IgG S-RBD levels. This study was an observational analytic study with a prospective cohort approach carried out between January and November 2021 at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Fifty health workers who received Sinovac vaccination in as many as 2 doses underwent venous blood taking and measurement of quantitative S-RBD antibody level. Then, quantitative S-RBD IgG antibody levels were measured and recorded in each subject. The mean S-RBD IgG antibody was found to have fluctuation. The titer was found to significantly increase on day 14 and dropped significantly in month 3 (p <0.001). There was a significant difference in S-RBD IgG levels 6 months after vaccination between Covid-19 uninfected groups and Covid-19 infected groups (p <0.001). In a conclusion, two doses of the Sinovac vaccine formed antibodies, although humoral immunity obtained tended to decrease in 3rd month after vaccination to healthy individuals. The average level of S-RBD IgG antibody in the sixth month post-vaccination was found to be significantly different between groups without history and groups with a history of with infection COVID-19.

***Keywords**: Sinovac; vaccination; covid-19; IgG S-RBD; cinetics; virus; coronavirus*

Correspondence: Jusak Nugraha, Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga/ Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. E-mail: jusak-n@fk.unair.ac.id

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Highlights:

1. The effectiveness of vaccination through the kinetics of the antibody response to the SARS-COV-2 vaccine administration by examining IgG S-RBD levels was aimed.
2. Two doses of the Sinovac vaccine formed antibodies in healthy individuals in the first 3rd month after vaccination.
3. An S-RBD IgG antibody in the 6th-month post-vaccination was significantly different between groups without a history and groups with a history of infection with COVID-19.

INTRODUCTION

Coronavirus disease (COVID-19) has spread to so many nations in such a short time that the World Health Organization (WHO) declared it a pandemic on March 11, 2020. Throughout the world, the ongoing COVID-19 infection has resulted in severe morbidity and mortality.On March 21, 2021, the WHO stated that 122,524,424 COVID-19 cases had been confirmed, with 2,703,620 patients died, or a Case Fatality Rate (CFR) of 2.20 percent (Jin et al. 2020, World Health Organization 2020). The Ministry of Health data on March 21, 2021, showed that 5,533,379 people had received vaccination (Ministry of Health 2020, Committee for COVID-19 Handling and National Economy Restoration 2021).

Given the severity of the situation, vaccination is absolutely important to break the disease transmission chain. In addition, vaccination is an effort to fulfill the Sustainable Development Goals (SDGs) to ensure a healthy life and promote prosperity for all. The keyword in the third point of the SDGs lies in the words 'healthy' and 'well-being'. The goal to be achieved is that all people will eventually have antibodies against the disease and the welfare of the people will be re-established when the pandemic has been overcome. Infections with SARS-COV-2 and vaccinations trigger an immunological response that includes the development of antibodies (binding antibodies) in the bloodstream. Vaccination-induced immunity is one of the options for reducing SARS-COV-2 disease morbidity and mortality. The Covid-19 vaccine is predicted to trigger a full immunological response, including cellular and humoral, as well as a high neutralizing antibody titer (Prekumar et al. 2020, Xia et al. 2020). NAbs are an antibody subset capable of blocking cellular infiltration and viral replication. The most essential target for neutralization is RBD in the S1 subunit. The COVID-19 vaccination is expected

to trigger an immunological response with a high neutralizing antibody titer. Several types of vaccinations have been successfully produced and approved for use in emergencies. However, the vaccines' usefulness in the short and long term has yet to be fully recognized (Amanat et al. 2020, Natarajan et al. 2021, Nile et al. 2020). Although COVID-19 serological diagnostic tests have been developed, antibody responses in vaccinated people, particularly those who received the Sinovac vaccination, remained largely unknown. This study aimed to determine the levels of anti-IgG S-RBD kinetics by taking samples on day 0 (before vaccination), day 14, day 28, 3 months, and 6 months following the second dose vaccination. By identifying the antibody response, the SARS-CoV-2 disease can be prevented and the time when the booster vaccine should be given can be determined.

MATERIALS AND METHODS

This prospective cohort observational study was carried out in January-November 2021 and involved fifty healthcare workers of Dr. Soetomo Hospital, Surabaya, Indonesia. This study had received ethics approval from the Health Research Ethics Committee, Dr. Soetomo General Academic Hospital, Surabaya, number: 0141/KEPK/II/2021. Participants who approved this study had received two doses of Sinovac vaccination between January 1 - March 31, 2021.

All subjects involved in this study had signed informed consent and were willing to participate in this study for blood taking before vaccination on day 0, after the second dose vaccination on day 14, day 28, after 3 months, and 6 months. Blood was taken from the cubital vein with a volume of 2.5 ml and collected in a serum separator tube (SST) and the plasma was stored at -80^{o}C until the measurement was carried out. The kit used was Abbott SARS-COV-2 IgG II Quantitative and run on the Architect I-1000 instrument.

The kinetics of the antibody response was obtained by observing the ups and downs or the pattern of S-RBD IgG antibodies depicted on the line diagram. The comparative test values of S-RBD IgG at each measurement time were analyzed using the non-parametric statistical test of the Friedman test followed by the Wilcoxon signed-rank test.

RESULTS

This study involved fifity health workers from Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, who had received two doses of the SARS-CoV-2 vaccine (Sinovac). During the trial, 10 (20%) of the individuals were infected with COVID-19 after month 3 and before month 6 of sampling. The median CT-value of the infected patients was 10.58 (3.96 - 21.93). After booster vaccination, the median day of being confirmed or infected with COVID-19 was day 151. (144-164) (Table 1).

The sex of the patients receiving the Sinovac vaccine in the two sample groups (with and without a history of COVID-19 infection) revealed that females outnumbered males. Females made up a total of 25 patients (57.5%) in the group without a history of COVID-19 infection and 8 patients (80%) in the group with a history of COVID-19 infection. Among the male vaccine recipients, there were 17 patients (42.5%) in the group without a history of COVID-19 infection and 2 (80%) in the group with a history of COVID-19 infection.

The age range in both groups was 20-40 years, with 8 patients (80%) having a history of COVID-19 infection and 36 patients (90%) not having a history of COVID-19 infection. Comorbidities were discovered in 19 of the participants, with hypercholesterolemia being the most common, which was found in ten patients.

Table 2 shows the levels of S-RBD IgG antibodies in the two study groups before and after SARS-CoV-2 (Sinovac) vaccination. It is clear from Table 2 that the total median value has increased. In contrast to the fluctuation on day 0 (pre-vaccination), the median value of subjects who were not infected with COVID-19 during the study was 0.2 AU/mL (IQR 0.0-38.4), increased on day 14 to 655.4 AU/mL (IQR 154.1-5920.1), then started to decrease on day 28 to 606.2 AU/mL (IQR 94.4-4065.3), and then continued to decrease further.

Figures 1 and 2 illustrate the kinetics of the S-RBD IgG antibody response from before vaccination to 6 months after the second dose of vaccination. Figure 1 shows the kinetics of S-RBD IgG levels in patients without a history of COVID-19. The median level of IgG S-RBD continued to rise until observation day 14, which was the highest median. From observation day 28 onwards, this amount gradually decreased.

Figure 2 shows the fluctuation of IgG S-RBD levels for each group with a history of COVID-19 infection. The only alterations in the median peak point in many levels on day 14 and others on day 28 were the same as in the prior profile. The kinetics of S-RBD IgG values in patients with a history of COVID-19 infection revealed that the median of S-RBD IgG fluctuated, increasing and decreasing until month 3 of observation, and then increasing until a higher median value of more than 70,000 Au/mL was recorded starting from month 6.

Table 1. Sample profile

Groups	Profile	n (%)
Not infected with COVID-19 during the study	Sex	
	Male	17 (42.5)
	Female	23 (57.5)
	Age	
	2 0–30 years	7 (17.5)
	31–40 years	29 (72.5)
	> 40 years	4 (10.0)
	Comorbidity	
	None	25 (62.5)
	Present	15 (37.5)
	Hypercholesterolemia	5 (12.5)
	Hypertension	3 (7.5)
	Obesity	1 (2.5)
	DM & Hypertension	3 (7.5)
	Hypercholesterolemia & Obesity	1 (2.5)
	Hypercholesterolemia & Hypertension	2 (5.0)
Infected with COVID-19 after sampling in month 3 of the study	Sex	
	Male	2 (20.0)
	Female	8 (80.0)
	Age	
	20 – 30 years	4 (40.0)
	31 – 40 years	4 (40.0)
	> 40 years	2 (20.0)
	Comorbidity	
	None	6 (60.0)
	Present	4 (40.0)
	Hypercholesterolemia	1 (10.0)
	Hypertension	2 (20.0)
	Hypercholesterolemia & Obesity	1 (10.0)

Table 2. Pre- and post-vaccination S-RBD IgG antibody levels

Groups	Variables	n (%)	Range	Median	Mean	St. Dev
Not infected with COVID-19 during the study	S-RBD IgG	40 (80.0)				
	Day 0		0.0 – 38.4	0.2	3.1	7.2
	Day 14		154.1 – 5920.1	655.4	1194.4	1269.3
	Day 28		94.4 – 4065.3	606.2	888.7	795.0
	Month 3		32.6 – 2897.1	204.0	315.5	453.1
	Month 6		0.0 – 1607.5	104.5	182.6	285.1
Infected with COVID-19 after sampling in month 3 of the study	S-RBD IgG	10 (20.0)				
	Day 0		0.0 – 43.1	0.7	8.3	16.3
	Day 14		618.6 – 3319.5	1237.8	1401.8	768.3
	Day 28		433.3 – 2530.1	895.3	1085.6	656.1
	Month 3		98.0 – 610.9	257.6	286.7	185.7
	Month 6		1868.7 – 80000.0	77027.8	56552.7	30996.5

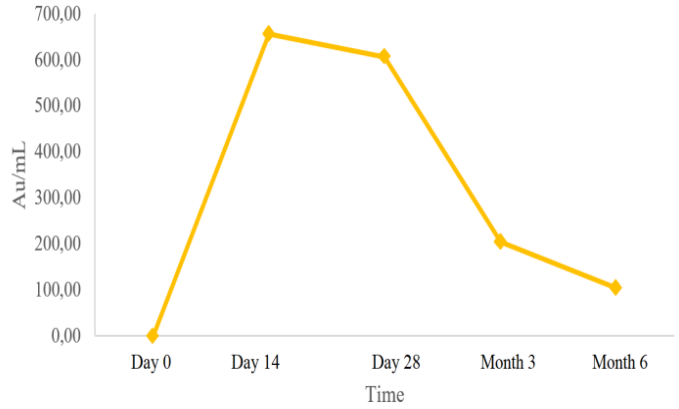

Figure 1. The fluctuation of S-RBD IgG median in the group without a history of COVID-19 infection

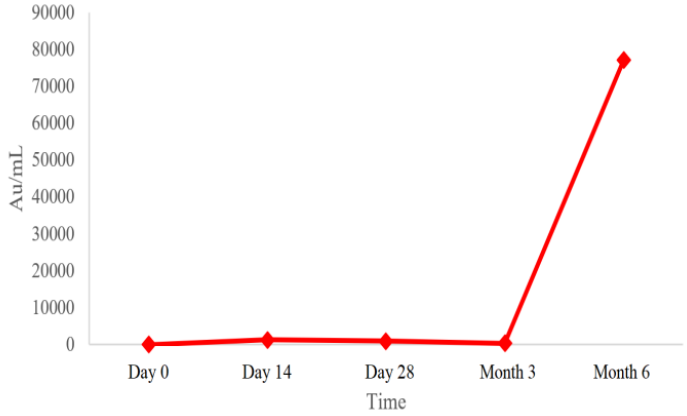

Figure 2. The fluctuation of IgG S-RBD median in a group with a history of COVID-19 infection after month 3 of the study

Table 3. Differences in pre- and post-vaccination S-RBD IgG antibody levels in subjects without a history of COVID-19 infection

Time	Participants (n)	Median	Friedman test χ^2 (p-value)	Wilcoxon test Z (p-value)				
				D 0	D 14	D 28	M 3	M 6
D 0	40	0.20	142.34 (< 0.001)	-	-5.51 (<0.001)	-5.51 (<0.001)	-5.51 (<0.001)	-5.50 (<0.001)
D 14	40	655.35		-	-	-3.79 (<0.001)	-5.01 (<0.001)	-5.24 (<0.001)
D 28	40	606.15		-	-	-	-5.00 (<0.001)	-5.09 (<0.001)
M 3	40	203.95		-	-	-	-	-4.48 (<0.001)
M 6	40	104.45		-	-	-	-	-

Notes: D: Day
M: Month

The purpose of this study was to see if there were any variations in S-RBD IgG levels in SARS-CoV-2 vaccine recipients from pre-vaccination (day 0) to month 6 in each group. Friedman's non-parametric statistical test was used to compare S-RBD IgG levels, followed by Wilcoxon Sign Rank Test if the Friedman test revealed a significant difference. The results of comparative test results on S-RBD IgG levels in SARS-CoV-2 vaccine (Sinovac) recipients in a group without a history of COVID-19 infection are shown in Table 3.

Table 4. Differences in pre- and post-vaccination S-RBD IgG antibody levels in group with a history of COVID-19 infection

Time	Participants (n)	Median	Friedman test χ^2 (p-value)	Wilcoxon test Z (p-value)				
				D 0	D 14	D 28	M 3	M 6
D 0	10	0.65	39.280 (< 0.001)	-	-2.80 (0.005)	-2.80 (0.005)	-2.80 (0.005)	-2.80 (0.005)
D 14	10	1237.80		-	-	-1.89 (0.059)	-2.80 (0.005)	-2.80 (0.005)
D 28	10	895.25		-	-	-	-2.80 (0.005)	-2.80 (0.005)
M 3	10	257.60		-	-	-	-	-2.80 (0.005)
M 6		77027.75		-	-	-	-	-

Notes: D: Day
M: Month

Table 5. Comparison of pre- and post-vaccination S-RBD IgG antibody levels between groups without and with a history of COVID-19 infection

S-RBD IgG (AU/mL)	Mean ± SD Median (min-max)		p
	Not infected with COVID-19 (n = 40)	Infected with COVID-19* (n = 10)	
Pre-vaccination (D 0)	0.2 (0.0 – 38.4)	0.7 (0.0 - 43.1)	0.834[b]
Post-vaccination			
Day-14	1194.4 ± 1269.3	1401.8 ± 768.3	0.607[a]
Day-28	888.7 ± 795.0	1085.6 ± 656.1	0.337[a]
Month-3	315.5 ± 453.1	286.7 ± 185.7	0.701[a]
Month-6	104.5 (0.0–1607.5)	77027.8 (1868.7 – 80000.0)	< 0.001[b]

Notes: *Subjects were infected with COVID-19 during the study (after month 3 and before month 6 of sampling). A two independent samples T-test; Mann-Whitney test.

The findings of Friedman and Wilcoxon tests on pre- and post-vaccination S-RBD IgG levels in patients not infected with COVID-19 revealed significant differences. S-RBD IgG levels were observed to have increased between pre- and post-vaccination and then decreased as post-vaccination time progressed.

Table 4 shows the findings of a comparative test on S-RBD IgG levels in recipients of the SARS-CoV-2 vaccine (Sinovac) in a group with a history of COVID-19 infection.

Friedman's comparative tests showed a p-value of 0.001 in S-RBD IgG levels in patients receiving the SARS-CoV-2 vaccine with a history of COVID-19 infection, indicating a significant difference in S-RBD IgG levels in those patients. The Wilcoxon test revealed that the majority of the patients had a p-value of less than 0.05, except for the S-RBD IgG level test on days 14 and 28, which had a p-value of 0.059. The Wilcoxon test revealed differences in S-RBD IgG in patients receiving the SARS-CoV-2 vaccine with a history of COVID-19 infection on days 0 to 6, while a non-significant difference was only found on observation day 14 and day 28.

Differences in pre-vaccination and post-vaccination SARS-CoV-2 IgG S-RBD antibody levels between subjects without and with a history of COVID-19 infection during the study period are shown in Table 5. S-RBD IgG antibody levels differed significantly in 6 months post-vaccination between the uninfected group and the group with COVID-19 infection history ($p < 0.001$).

DISCUSSION

This study aimed to examine the kinetics pattern of S-RBD IgG antibodies against the administration of the SARS-CoV-2 (Sinovac) vaccine up to 6 months post-vaccination. Vaccination can stimulate the production of various antibodies. The antibody formed against RBD is considered to be the most relevant one to assess the effectiveness of a vaccine concerning its neutralizing effect (Azkur et al. 2020, Liu et al. 2020).

This study on the kinetics of S-RBD IgG levels obtained a median pre-vaccination antibody level of 0.2 (0.0 –38.4), which means that it was non-reactive or did not have antibodies. This value indicates that all subjects had never been infected with COVID-19 before receiving the vaccination.

During this study, after sampling in month 3 and before sampling in month 6, 10 subjects developed COVID-19 infection. The infection of several of these subjects coincided with the presence of the second wave of the cases in Indonesia. The COVID-19 infection in these subjects caused an increase in the average level of IgG S-RBD in month 6 as many as 32 times. Therefore, this study made different observations between the group that was not infected with COVID-19 and the group with a history of COVID-19 infection. In month 6, there were differences in kinetic patterns between the group not infected with COVID-19 and the group with a history of COVID-19 infection. In the uninfected group, antibody levels tended to decrease, while in the group with a history of infection, the antibody levels increased very drastically.

The antibody kinetics described in this study were following the response to antibody formation in patients with COVID-19. Three seroconversion patterns in SARS-CoV-2 have been observed in previous studies. IgM, IgG, and NAb peak 2–3 weeks post-symptom onset and decline to undetectable levels within 6 weeks for IgM, whereas IgG and NAb titers pass through a plateau before falling within 2–3 weeks (Hamady et al. 2022).

Antibodies are formed from exposure of the immune system to vaccine antigens which stimulates the formation of memory B cells, which then differentiate into antibody-secreting cells. These antibody-secreting cells produce IgG molecules that are responsible for vaccine-induced immunity. The results of this study were consistent with several other studies which also found that immediately after vaccination, antibody titers tended to increase significantly until day 36 or the first-month post-vaccination (Terpos et al. 2021). A similar study assessing antibody response kinetics after vaccine administration has also been carried out on BNT162b2 mRNA vaccination, which found a sharp increase in S-RBD anti-IgG levels in vaccinated recipients after day 22 and remained high on day 50 (Trougakos et al. 2021).

A significant decrease in S-RBD IgG levels in this study was obtained from day 28 to month 3 post-vaccination ($p < 0.05$), and then decreased slowly until month 6 post-vaccination. The decrease in antibody levels that occurred in month 3 still showed levels above the threshold of positivity, which indicated that the immune response against SARS-CoV-2 was still active until month 6. These results were in agreement with a study which found that more than 90% of individuals infected with SARS-CoV-2 developed antibodies within one week of symptom onset and the antibody titers tended to persist for at least three months post-infection (Hall et al. 2021).

This study found a significant difference in S-RBD IgG antibody levels at month 6 between the group without a history of COVID-19 infection and the group with a history of COVID-19 infection, which was not followed by a significant difference in antibody levels at 3 months after the booster. In the two groups, the mean levels resulted in 3 months after booster (315.5 ± 453.1 vs. 286.7 ± 185.7; p=0.701). This finding showed that although antibody levels persisted in month 3, these levels did not reach the optimal value that was considered to have a neutralizing effect.

The increase in S-RBD IgG levels began on day 14 after the second dose of Sinovac vaccination. The highest increase was seen in the mean antibody levels on day 14 post-vaccination with two doses of Sinovac, which were 1194.4 ± 1269.3 Au/mL (169.6 ± 184.07 BAU/mL) in a group without a history of COVID-19 and 1401.8±768.3 Au/mL (199.05 ±109.09 BAU/mL) in a group with a history of COVID-19 infection. In the internal research by Abbott ARCHITECT 2021 and as listed on the SARS-CoV-2 IgG II Quant reagent kit, the equivalence of the PRNT50 titer (1:80) to the IgG S-RBD result was 1050 AU/mL (149.1 BAU/mL) (based on Abbott ARCHITECT 2020 and Abbott ARCHITECT 2021). The highest increase on day 14 was considered to have an optimal neutralizing effect against the SARS-COV-2 virus because the increase was more than 1050 AU/mL (149.1 BAU/mL). In 2021 the FDA has also published a test table of several reagents and tools that are acceptable for use in the manufacture of COVID-19 convalescent plasma, one of which is for Abbott SARS-CoV-2 IgG II Quant with qualifying results $\geq$ 840 AU/mL ($\geq$ 119.28 BAU/mL) (Bratcher-Bowman 2021).

Sinovac is effective in generating a faster and higher humoral immune system in the next Covid infection. This shows that memory cells in the immune system, either obtained from vaccination or previously infected, still survive for 10 months and will cause faster and higher antibody formation when the body is invaded by the same antigen (Ontañón et al. 2021).

Similar results were obtained by the study of Ontañón et al. (2021) on vaccinated health workers. The study revealed that antibody titers at two months post-vaccination were higher in a group with a previous history of SARS-CoV-2 infection than in a group that had never been infected. The study found that within 7 days after the first dose of vaccination, the group with a

history of SARS-CoV-2 infection experienced a 126-fold increase in antibody levels ($p < 0.001$). In the group without a history of infection, only 5 subjects showed positive antibody levels. Observations two months later found that antibody levels were still higher in the group with a history of previous infection.

Goel et al. (2021) examined the response of B and T lymphocytes in individuals receiving the SARS-CoV-2 mRNA vaccine by conducting a 6-month longitudinal study. Vaccination had 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 important components of the resistance response to viral antigens and have protective mechanisms in individuals who have acquired pre-existing immunity. When the same antigen enters the body, memory T cells proliferate very rapidly and provide a stronger immune response. These antibodies are useful for the control of early viral replication and limiting the spread of the virus in the host. Cellular immunity has the role of reducing or even preventing disease symptoms (that is, preventing hospitalization and death) and reducing the ability to spread the virus to others.

It can therefore be assumed that the underlying reason for the increase in S-RBD IgG antibody levels at 6 months post-vaccination between the uninfected group and the group with a history of COVID-19 infection in this study might be due to high viral load and the role of B and T memory cells from previous vaccination.

Strength and limitation

As the pandemic is still ongoing, this research serves to shed light on how the COVID-19 vaccine works. This study can demonstrate that two doses of Sinovac vaccine are effective in boosting S-RBD IgG antibody levels, even though other factors may reduce the efficacy. A limitation of this study was that it only evaluated the humoral immune response and did not evaluate the cellular immune response. Previous studies have proven a correlation between humoral and cellular immunity after vaccination (Lozano-Ojalvo et al. 2021). Other limitations of this study were that it was only conducted in a single-center, the small sample size, and the narrow age range of the subjects which might have limited the generalizability of the results.

CONCLUSION

Two doses of the Sinovac vaccine did produce antibodies, although the obtained humoral immunity tended to decrease in 3 months post-vaccination in healthy individuals. There was a significant difference in the mean S-RBD IgG antibody levels at 6 months post-vaccination between the group without a history of COVID-19 infection and the group with a history of COVID-19 infection. Further studies are recommended by conducting further observations on antibody kinetics after the 3rd booster vaccination and by conducting further multicenter studies using a larger sample size to obtain a better generalization of the results.

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Conflict of interest

None.

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Author contribution

JN, and CAP contributed to the conceptualization study design and methodology. CAP and MF were data collection, data analysis. MF were contributed to the final revise.

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