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RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2022;27(1):142-150 • doi: 10.5578/flora.20226161

SARS-CoV-2 Seropositivity Level in a Cohort of Turkish Health Care Professionals After COVID-19 Vaccine (CoronaVac) and Assessment of Factors Affecting the Antibody Response

COVID-19 Aşısı (CoronaVac) Sonrası Türk Sağlık Çalışanlarından Oluşan Bir Kohortta SARS-CoV-2 Seropozitiflik Düzeyi ve Antikor Yanıtını Etkileyen Faktörlerin Değerlendirilmesi

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Cite this article as: *Özkan Özdemir H, Tosun S, Coşkuner SA, Demir S. SARS-CoV-2 seropositivity level in a cohort of Turkish health care professionals after COVID-19 vaccine (CoronaVac) and assessment of factors affecting the antibody response. FLORA 2022;27(1):142-50.*

ABSTRACT

Introduction: *Although Phase III trial results of many COVID-19 vaccines were reported, the literature regarding community results is inadequate for CoronaVac. This study aims to evaluate the experience gained during the vaccination process among health care workers (HCWs), the measured antibody responses and the factors affecting the response. These findings will contribute to the literature in this field.*

Materials and Methods: *Anti-SARS-CoV-2 (anti-spike) antibodies were measured by ELISA in blood samples taken at least 28 days (28-32) after the second CoronaVac among 264 HCWs vaccinated twice with an interval of 28 days. Information from individuals was collected with an online participation form.*

Results: *A total of 264 HCWs (166 females (63%), 98 males (37%) whose ages werebetween 23-69 (mean 44.22 ± 11.58) were included independent of their COVID-19 history in the study. After vaccination, 22HCWs (8.3%) were unresponsive, 25 (9.5%) HCWs among responders had a weak antibody response, and 217 (82.2%) had afull antibody response according to the test kit manufacturer. For HCWs with and without a COVID-19 infection history, the full antibody response rates were 91.7% and 77.5%, respectively. The antibody titres tended to be lower in HCWs with no prior COVID-19 infection (p= 0.046). In our study, antibody response was found to be significantly lower in males (p= 0.043).There was a significant decrease in antibody response with advancing age (p= 0.002 Chi-square test, p= 0.030 Spearman coefficient), and the difference was highly significant (p= 0.017) above the age of 60.*

Conclusion: *In this study, it was determined that 91.7% of healthcare workers (weak in 9.5% and full in 82.2%) developed anti-spike antibodies with CoronaVac. It was determined that the factors affecting the development of antibodies were gender, age, and the state of having COVID-19.*

Key Words: *COVID-19; CoronaVac; Inactivated COVID-19 vaccine; Antibody*

Received/Geliş Tarihi: 31/01/2022 - Accepted/Kabul Ediliş Tarihi: 03/03/2022

Available Online Date: 24.03.2022

ÖZ

COVID-19 Aşısı (CoronaVac) Sonrası Türk Sağlık Çalışanlarından Oluşan Bir Kohortta SARS-CoV-2 Seropozitiflik Düzeyi ve Antikor Yanıtını Etkileyen Faktörlerin Değerlendirilmesi

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Giriş: *Birçok COVID-19 aşısının Faz III deneme sonuçları bildirilmiş olsa da CoronaVac için toplumdan gelen sonuçlarına ilişkin literatür yetersizdir. Bu çalışmada, sağlık çalışanları arasında aşılama sürecinde kazanılan deneyimleri, ölçülen antikor yanıtlarını ve yanıtı etkileyen faktörleri değerlendirmek amaçlanmaktadır. Bulgular bu alandaki literature katkı sağlayacaktır.*

Materyal ve Metod: *Yirmi sekiz gün ara ile iki kez aşılanan 264 sağlık çalışanından, ikinci CoronaVac uygulamasından en az 28 gün sonra (28-32) alınan kan örneklerinden ELISA ile anti-SARS-CoV-2 (anti-spike) antikorları ölçüldü. Kişilerden bilgiler online katılım formu ile toplanmıştır.*

Bulgular: *Çalışmaya COVID-19 geçmişinden bağımsız olarak yaşları 23-69 (ortalama 44.22 ± 11.58) arasında olan toplam 264 sağlık çalışanı [166 kadın (%63), 98 erkek (%37)] dahil edildi. Aşılamadan sonra kit üreticisi firma tarafından önerilen antikor yanıtı düzeylerine göre 22 sağlık çalışanı (%8.3) yanıtsız, yanıt verenler arasında 25 (%9.5) sağlık çalışanı zayıf antikor yanıtına ve 217'si (%82.2) tam antikor yanıtına sahipti. COVID-19 infeksiyon geçmişi olan ve olmayan sağlık çalışanları için tam antikor yanıt oranları sırasıyla %91.7 ve %77.5'ti. Antikor titreleri, önceden COVID-19 infeksiyonu olmayan sağlık çalışanları için daha düşük olma eğilimindeydi (p= 0.046). Çalışmamızda antikor yanıtı erkeklerde anlamlı olarak daha düşük bulundu (p= 0.043). İlerleyen yaşla birlikte antikor yanıtında anlamlı bir azalma oldu (p= 0.002 ki-kare test, p= 0.030 Spearman korelasyon katsayısı) ve fark 60 yaşın üzerinde oldukça anlamlıydı (p= 0.017).*

Sonuç: *Bu çalışmada, inaktif bir aşı olan CoronaVac ile sağlık çalışanlarının %91.7'sinde (%9.5'te zayıf ve %82.2'de tam) anti-spike antikorların geliştiği tespitedildi. Antikor gelişimini etkileyen faktörlerin cinsiyet, yaş ve COVID-19 geçirme durumu olduğu belirlendi.*

Anahtar Kelimeler: *COVID-19; CoronaVac; İnaktif COVID-19 aşısı; Antikor*

INTRODUCTION

A novel coronavirus (SARS-CoV-2) that leads to severe acute respiratory syndrome rapidly spread across the whole world, and COVID-19 was declared a pandemic by the World Health Organization in February 2020. By 30 January 2022, 370.572.213 confirmed cases of COVID-19, including 5.649.390 deaths and a total of 10.05 billion administered vaccine doses, were reported to the WHO, and the pandemic continues to peak worldwide[1].

While the personal protection measures, protective equipment usage, hand hygiene and social isolation rules have been recommended since the onset of the pandemic, vaccination studies have also been started because the aforementioned measures alone are not sufficient to stop the pandemic[2]. Vaccines with specific characteristics have been developed by many companies. By the end of 2020, many companies' vaccines had become available with immediate use approval by national authorities, the FDA in the US, and the EMA in Europe, China-India-UK and Russia. There were ten vaccines all over the world, for which WHO gave emergency use approval in December 2021, and efficacy and safety studies of ten other vaccines are still ongoing[3,4].

Coronaviruses are structurally pleomorphic enveloped viruses with characteristic S-protein spikes on their surface. The primary objective of all COVID-19 vaccines is to produce neutralizing antibodies against the S protein of the virus in individuals. The S protein of SARS-CoV-2 is the most suitable antigen for the formation of neutralizing antibodies against this pathogen[5]. Inactivated vaccines, which are among the COVID-19 vaccines, are chemically inactivated vaccines produced in Vero cell culture[6]. Currently, CoronaVac, Sinopharm BBIBP and Covaxin inactive vaccines have been approved by WHO for

emergency use and the clinicaltrials of inactive vaccines such as Valneva VLA2001 (GB-NZ) are ongoing[4,7]. These vaccines are often combined with aluminium or a similar adjuvant aiming to stimulate the immune response. The target of inactivated vaccines includes not only the spike protein but all components of the virus[8]. In Turkey, a Phase III study took place that started on September 14, 2020; regarding the inactivated vaccine CoronaVac. Subsequently, the vaccination of health care workers was started on January 12, 2021, after emergency use approval. The vaccination started gradually for individuals at risk in the community such as age over 65, people with chronic diseases, military personnel, school personnel etc after HCWs and subsequent doses are continued in the community.

Neutralizing antibodies formed after vaccination cannot be routinely examined due to the need for special laboratory infrastructure. The most scientific measurement of antibody response for corona viruses other than neutralizing antibodies is recommended as the measurement of IgM and IgG against S1 protein + N protein[9]. Although it is known that the detected spike antibodies (anti-S IgG) are correlated with the neutralizing antibody level, there is no standard threshold value for significant antibody titre. Therefore, there are difficulties in the interpretation of the results. Additionally, test kits produced by different companies result in different reference ranges.

Antibody testing before vaccination in mass vaccination is not recommended, as it is technically difficult, time-consuming and costly. Antibody screening after vaccination is not also recommended as a routine method but may be done for academic purposes. The main reasons for this are that the detection of neutralizing antibodies showing essential protection after vaccination requires special equipment, experience, time and cost and therefore cannot be applied widely[10].

Our study aimed to measure the anti-spike antibody responses at least 28 days (28-32) after the second dose of CoronaVac, which was administered to health care workers in Turkey at a dose of 3 µg at day 0 and 28 days, and to evaluate the factors associated with antibody response.

MATERIALS and METHODS

Design of the Study

Health care workers, between 12th of January till 14th February 2021, which are over the age of 18 who were vaccinated by two doses of CoronaVac at 0 and 28th days and were actively working in the pandemic process were included in this prospective study. Pregnant women and those who had COVID-19 infection in the last 30 days, those who were COVID-19 PCR positive, and HCWs who were not able to receive TWO doses of the vaccine within the 28-32 days period were not included in the study. This study was conducted at the İzmir Bozyaka Education and Training Hospital, Department of Infectious Diseases and Clinical Microbiology (Izmir, Turkey). Approval for our study was obtained from the Ministry of Health Scientific Committee and Health Sciences University İzmir Bozyaka Education and Research Hospital Clinical Research Ethics Committee. In total, 264 people who met the inclusion criteria of our study were identified from their health records, and an appointment was made for the day 28th day after the second dose ofvaccination for sampling.

Informed consent was obtained, and an online questionnaire was administered to all participants on the same day with sampling. In the online form, the following characteristics were assessed: age, sex, weight and height, chronic diseases (e.g., cardiovascular and respiratory diseases, diabetes mellitus or other metabolic diseases, autoimmune diseases, malignancy), other vaccines they had (e.g., influenza, pneumococcal, hepatitis, tetanus and H1N1 vaccines), COVID-19 disease status (symptoms and the results of PCR tests), and post-vaccination adverse effects (PVAE) developing after the COVID-19 vaccine.

Applied Vaccine Information

The CoronaVac vaccine (Sinovac Life Sciences Co.) contains inactivated SARS-CoV-2 virus, aluminium hydroxide, disodium hydrogen phosphate, sodium dihydrogen phosphate and sodium chloride, and a 0.5 mL dose contains 600 SU SARS-CoV-2 virus antigens. CoronaVac was administered to the deltoid muscle as an IM in a hospital setting. The second dose was administered 28 days after the first dose.

Sample Collection and Analysis

Among the people included in the study, 6-7 mL intravenous blood samples were taken into serum separating tubes (SST) between 11th of March and 14th of March and centrifuged at 3500 rpm. The obtained sera were analysedon the same day. Subsequently, anti-receptor binding domain (anti-RBD) anti-SARS-CoV-2 IgG antibodies (Quantivac-Euroimmun/Germany), which apply a recombinant S1 subunit of the SARS-CoV-2 spike protein, thus enabling the detection of IgG antibodies, were measured in serum samples taken by the microplate-based enzyme-linked immune sorbent assay (ELISA) method, in ETI-MAX 3000 (DiaSorin, Italy) automated system.

Anti-SARS-CoV-2 QuantiVac is a specific ELISA for the quantitative detection of anti-SARS-CoV-2 IgG. The specificiyt of the Anti-SARS-CoV-2 QuantiVac ELISA is 99.8%. The diagnostic sensitivity is 56.7%, 90.3%, and 93.2% according to ≤10, >10, ≥21 days after symptom onset or positive COVID-19 PCR test, respectively. The analytical measurement range of the test is 3.2-384.0 Binding Antibody Unit (BAU/ml)[11].

The detected results were classified according to the recommendations of the test kit manufacturer as follows:

BAU/ml: Binding antibody unit

<25.6 BAU/ml Negative (non-response)

25.6-35.1 BAU/ml limit value (weak response)

>35.2 BAU/ml Positive (responsive)

Statistical Analysis

Statistical assessment was performed using IBM SPSS software, version 22.0. Descriptive analyses are presented as the mean, standard deviation and geometric mean for continuous variables and numbers and percentages for categorical variables. Pearson's chi-square test was used in the evaluation of categorical variables, and $p< 0.05$ was accepted as the statistical significance level in all analyses. The relationship between two continuous variables was addressed by correlation analysis. The Spearman coefficient was used since the distribution of the data was not normal. A multivariate logit model was also constructed to examine the impact of multiple variables on the antibody reaction levels.

RESULTS

A total of 264 HCWs [166 females (63%), 98 males (37%)] whose ages were between 23-69 (mean 44.2 ± 11.58) were included in the study. The mean age of men was 46.9 ± 12.4, and that for women was 42.6 ± 10.7. There were 117 doctors, 79 nurses, 47 laboratory workers and health officers, and 21 office workers and security guards in our sample HCW. The education level of 231 (87.5%) participants was university and college graduates. Of 103 people who had chronic diseases, hypertension was the most common (n= 58), followed by chronic obstructive pulmonary diseases (n= 5) and asthma (n= 11). After vaccination, 22 (8.3%) were unresponsive, 25 (9.5%) had a weak response, and 217 (82.2%) had a response.

Of the participants, 73 had COVID-19 infection at any time before they were vaccinated. The antibody response was higher in HCWs who had COVID-19 infection before vaccination (p= 0.015). The results are given in Table 1.

Only one individual who had COVID-19 before was found to have a negative antibody, and this individual was a 61-year-old male who

Table 1. COVID-19 disease history and antibody responses

History of COVID-19 infection	COVID-19 PCR	Symptom	Nonresponse n (%)	Weak response n (%)	Response n (%)
No (n= 182)	Neg	Neg	21 (11.5%)	20 (11%)	141 (77.5%)
Yes (n= 73)			1 (1.3%)	5 (7%)	67 (91.7%)
Do not know (n= 9)	Not analysed**	Neg			9 (100%)
Total (n= 264)			22 (8.3%)	25 (9.5%)	217 (82.2%)

*No history of contact or complaints.

Table 2. GMT of antibody titres (BAU/mL)* according to age, sex and COVID-19 infection history

	n	Mean	SD**	GMT***
Gender				
Female	166	99.342	64.1510	80.146
Male	98	95.477	73.4558	68.641
Age				
<60	234	102.198	68.3707	80.233
≥60	30	64.440	51.2807	47.903
COVID-19 inf.				
No	182	82.758	59.0344	64.109
Yes	73	129.896	73.3005	107.854

*BAU/ml: Binding antibody unit.
**SD: Standard Deviation.
***GMT: Geometric Mean Titer.

had COVID-19 in November 2020. No clinical symptoms and a history of contact were present, but the individuals recorded a positive COVID-19 PCR test. This individual had no history of chronic disease or medication. In our study, antibody response was found to be significantly lower in males (p= 0.022), there was a significant decrease in antibody response with advancing age (p= 0.002 Chi-square test, p= 0.030 Spearman coefficient), and the difference was highly significant (p= 0.0005) among individuals above the age of 60. Chi-square test revealed a statistically significant difference between antibody response and gender, age, COVID-19 infection history, previous H1N1 pandemic vaccine and PVAE. However, no relationship was found between the presence of chronic diseases or an immunosuppressive condition, regular medication use, having another vaccine in the last year, such as influenza (except H1N1 pandemic vaccine), pneumococcus, tetanus, and hepatitis and the body mass index (BMI) of the individuals.

A multivariate logit model was used to examine the impact of age, sex, COVID-19 infection and the presence of any other chronic disease on the antibody reaction, which also confirmed our results. H1N1 pandemic vaccine and PVAE, which were significant in univariate analysis, were not significant in multivariate analysis. Age (above 60 years of age), sex, and COVID-19 infection are important determinants of antibody reaction levels. The geometric mean titres (GMT) of individuals with the age ≥60 and <60 were 47.903 and 80.223: the GMT's of male vs. female individuals were 68.641 and 80.146 and the GMT's with and without the history COVID-19 infection were 107.854 and 64.109, respectively. The results are given on Table 2.

All of the analysed factors affecting the antibody response to the COVID-19 vaccine are summarized in Table 3.

DISCUSSION

The CoronaVac vaccine, which is currently applied in Turkey, is an inactive vaccine containing aluminium hydroxide adjuvant produced by Sinovac Company in China. The Phase I/II study was conducted in a single-centre, double-blinded, randomized placebo-controlled study in China with 743 individuals aged between 18-59, and the vaccine was found to be immunogen and safe as a result of a study[12].

In a Phase III study of the same vaccine conducted in Brazil in which 5879 individuals were included, authors reported an overall efficacy of 50.7% (95% CI: 36.0-62.0) 14 days or more after the second dose for CoronaVac against symptomatic COVID-19; however, the efficacy in preventing the need for assistance (defined as a score ≥3 on the WHO Clinical Progression Scale) was 83.7% (58.0-93.7) and efficacy against moderate and severe cases was 100% (56.4-100.0) [13]. There are other inactivated vaccine studies in China and different countries, and new studies are still ongoing[14,15].

The CoronaVac Phase III study was conducted in Turkey in September 2020 with the participa-

Table 3. Factors affecting/parameters antibody response to the COVID-19 vaccine

	Total= 264 n (%)	p*	p**	AOR*** (95% CI)
Male sex	98 (37)	**0.022**	**0.043**	**2.711 (1.031-7.124)**
>60 age	30 (11.4)	**0.0005**	**0.017**	**3.768 (1.264-11.229)**
No history of COVID	182 (69)	**0.015**	**0.046**	**8.035 (1.033-62.472)**
Having H1N1 pandemic vaccine	54 (20.5)	**0.044**	0.061	2.587 (0.958-6.987)
No PVAE	113 (42.8)	**0.011**	0.905	1.066 (0.372-3.056
Presence of chronic diseases	103 (39)	0.484	0.431	0.671 (0.249-1.812)
Presence of an immunosuppressive status	10 (3.8)	0.138	-	
Regular medication use	98 (37)	0.311	-	
Having had influenza vaccination in the last year	86 (32.6)	0.751	-	
Having had pneumococcal vaccine in the last year	37 (14)	0.587	-	
Having had hepatitis or tetanus vaccine in the last six months	14 (5.3)	0.535	-	
BMI< 25 kg/m^2	137 (51.9)	0.281	-	

* Chi-square test.
** Multivariate analysis (logistic regression).
***Adjusted odds ratio.

tion of 3675 HCWs and 6539 individuals from the public (10214 people in total), and the efficacy rate of the vaccine administered at a dose of 3 µg with a 0-14 day scheme was reported to be 83.5%for the prevention of PCR-confirmed symptomatic COVID-19[16]. In another study involving 1072 HCWs from Turkey, SARS-CoV-2 anti-spike antibodies were examined 28 days after the first dose and 21 days after the second dose after CoronaVac. It was reported that anti-spike antibodies were detected at a protective level in 77.8% after the first dose and in 99.6% after the second dose. In their study, the antibody levels between HCWs with and without COVID-19 was statistically significant[17].

In our study, for HCWs with and without a COVID-19 infection history, the full antibody response rates were 91.7% and 77.5%, respectively. The antibody titres tended to be lower in HCWs with no prior COVID-19 infection. These results showed that people who had COVID-19 can generate high antibody levels, thus they should undergo a different vaccination programme.

In our study, we found that the antibody response weakened with advancing age, and this difference was more prominent over the age of 60. Although a CoronaVac study in Chile reported a seroconversion rate of 18.1% for the age group ≥60 years after day 14, which was a lower percentage than that among individuals younger than 60 years old (47.8%), the response was 100% 28 days after the second dose[18]. Although higher rates of antibodies in individuals over 60 years old were reported in the phase I/II studies conducted by Wu et al., this difference could be occurring because our analysis was performed with the ELISA method and the study by Wu et al was performed with the plaque reduction neutralization test (PRNT), and our number of people over 60 years old was comparably lower[19]. In a meta-analysis comparing the efficacy of nine different vaccines used worldwide, it was reported that there was no statistically significant difference in the ability of vaccines to prevent symptomatic disease in the elderly population[20]. However, we still think that more realistic data can be obtained, and the issue of age should be considered by following up the larger number of vaccinated individuals over the age of 60. The concept of immune ageing is rather complex, and there is no validated method for measuring its degree. With advancing age, the numerical value of T cells capable of responding to a vaccine and the survival rate of T cells, especially CD8 T cells, decrease significantly. B

cells; on the other hand, although their number does not decrease much with age, fewer functional antibodies are produced due to the decreased expression of certain proteins. Therefore, lower antibody responses can be expected among elderly individuals[21,22].

In our study, male sex was associated with a low antibody response. In another study reported from Turkey, post-CoronaVac seropositivity was found to be higher in women than in men ($p< 0.001$), which is consistent with the findings of our study[17]. There is evidence that the immunological response to antigen may differ between sexes. In women, the number and activity of innate immune cells such as monocytes, macrophages, and dendritic cells are higher than those in men. Thus, responses to both infections and vaccines can be higher in women than in men. Women have a higher proportion of CD4+ T cells and CD4+/CD8+ T cells; the CD8+ T cell count is also lower than that of men. B cell count, IgG and IgM were similar in adulthood in both sexes. Adult women typically have a high inflammatory cell-mediated immune response to vaccines, which may explain the better effectiveness of vaccines in women than in men[23-25]. There was no emphasis on sex in any of the phase studies conducted on CoronaVac, and we think that the higher vaccine response in women identified in our study should be considered when monitoring larger cohorts.

In our study, no relationship was found between the presence of chronic disease and antibody response ($p= 0.484$). Similarly, antibody unresponsiveness in patients who regularly use drugs due to chronic diseases was slightly higher than that in those who did not use drugs, but the difference was not statistically significant ($p= 0.398$). Additionally, no significant difference was found in the antibody responses of 10 individuals who had immunosuppressive drugs (malignancy or immunosuppressive drug use) for any reason compared with those who had not ($p= 0.138$).

This study showed that individuals who had COVID-19 infection before and then received a vaccine had higher antibody titres, in accordance with our expectations. Certain studies have demonstrated that the antibody response in people is reduced after COVID-19 infection, especially in individual show are asymptomatic[26]. In a study on SARS, it was reported that the antibodies developed decreased over time, and this decrease accelerated after the 16^{th} month and even disappeared in the third year[27]. It is difficult to predict how long the antibodies will continue to be presented in those who have the disease and whether there will be a difference in the duration of antibody persistence in those vaccinated after the disease. We anticipate that this issue will be clarified with long-term follow-up.

As with many infectious diseases that can be prevented by vaccination, it seems important to vaccinate a significant part of the community with available and accessible vaccines, as well as protective measures such as hand washing, mask and safety distance to protect against COVID-19 infection. Since inactivated vaccines are developed with conventional methods and do not carry live virus particles, they are considered safer. However, individuals vaccinated with inactivated vaccines should also be monitored in terms of antibody-dependent enhancement (ADE) and vaccine-associated enhanced respiratory disease (VAERD), as in other COVID-19 vaccines[28,29]. Additionally, it is not yet clear whether the formation of strong antibodies against the inactivated vaccine will protect people from COVID-19 infection or how long this protection will continue. Moreover, it should be kept in mind that the antibody levels measured in serum against the vaccine only show the B lymphocyte response, the T cell activity representing the memory cells is also very important in the response to the vaccine, and the sensitivity of these tests will be lower than the neutralization test results with PRNT.

This study had some limitations, primarily that we did not have information about the previous antibody levels before vaccination. The previous antibody levels would have strengthened our results. Our sample size is limited, which may have affected the results. Another limitation of this study is that it did not involve control groups or adjustment with the baseline characteristics and is a single centre study.

The strength of the study is that all our sample consisted of health professionals; therefo-

re, all COVID-19 PCR records and COVID-19 medical records were well known, thereby making our findings robust.

CONCLUSION

In our study, it was determined that 91.7% of anti-spike antibodies were detected with CoronaVac, and the antibody response was lower in patients with advanced age, male sex, no prior COVID-19 infection, no PVAE, and a history of the H1N1 vaccine.

ETHICS COMMITTEE APPROVAL

This study approval was obtained İzmir Bozyaka Training and Research Hospital Clinical Research Ethical Committee (Decision no: 2021/27, Date: 10.12.2021).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: HÖÖ, ST

Data Collection or Processing: SAC, ST

Analysis/Interpretation: ST

Literature Search: HÖÖ

Writing: ST, HÖÖ

Final Approval: HÖÖ

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