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Efficacy of antibody response following the vaccination of SARS-CoV-2 infected and noninfected healthcare workers by two-dose inactive vaccine against COVID-19

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Abstract

Sinovac is an inactive vaccine produced against Coronavirus Disease 2019 (COVID-19) for almost a year. No sufficient information is available concerning pro-vaccine immunogenicity. We investigated the efficacy of antibody response following vaccination of SARS-CoV-2-infected and noninfected healthcare workers by a two-dose inactive vaccine against COVID-19. The immunogenicity acquired on the 27th day and 42nd day after the first dose of vaccine (corresponding to Day 14 after the second dose) were compared by the demographics, immunosuppression, comorbidities, postvaccination reaction, and IgG levels of 120 subjects. The overall rate of second postvaccine seropositivity was 97.5% ($n = 117$) of all individuals, and 44 of these were seropositive after the first dose. The percentage of having a previous COVID-19 (59.1%) among seropositive individuals before 2nd vaccination was significantly higher than those of seropositive individuals (10.96%) after second vaccination ($p < 0.0001$). In our study, 35 healthcare workers stated that they had previously had a COVID-19 infection. Anti-SARS-CoV-2 antibody responses in people infected with SARS-CoV-2 follow a classical pattern, with a rapid increase within the first 3 weeks after the appearance of symptoms. Although the titers decreased thereafter, the ability to detect anti-SARS-CoV-2 IgG antibodies supports the view that the majority of subjects previously screened as positive for virus remain intact with confirmed neutralizing activity for up to 6 months.

KEYWORDS

antibody response, COVID-19, infection, Sinovac, vaccination

1 | INTRODUCTION

As an effective treatment of novel Coronavirus Disease 2019 (COVID-19) has not been found yet, the pandemic has continued to affect millions of people for more than 2 years by increasing the mortality rates due to the infection. Vaccination is a well-known and strong weapon of humanity in the fight against severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2). The population immunity induced by fast vaccination is an important global strategy for controlling COVID-19. The vaccination programs should maximize the early effect not to encounter a particularly faster spread of new variants. The healthcare workers battling at the front line are the group who encountered the most damage and the high mortality during the pandemic. The first doses have started to be

administered to the healthcare workers in our country as in many countries.^{1,2}

Several vaccines developed and produced based on the completed vaccine studies have been validated by World Health Organization (WHO) for emergency use considering the public health criteria and administered firstly to the privileged groups.³ The vaccine administered in Turkey since January 2021 is a purified, inactivated, and adsorbed COVID-19 vaccine developed by Sinovac Biotech Corporation.⁴ Sinovac, with a pharmaceutical name CoronaVac and previously known as PiCoVacc, was developed by propagating the SARS-CoV-2 CN2 strain inside Vero Cells and inactivating it with B-propiolactone. In preclinical trials, Sinovac induced SARS-CoV-2-specific neutralizing antibodies (NAbs) in rats, mice, and the rhesus macaque.⁵ The antibodies were found to neutralize 10 representative SARS-CoV-2 strains. As of August 2020, the vaccine has been tested in numerous human clinical trials assessing its safety and immunogenicity and Phase-3 studies have been ongoing.⁶

Many vaccination platforms use a two-dose prime-boost approach for forming an immune response against the virus S1 spike protein, of which titers are related to functional virus neutralization and are increased by augmentation. To provide the first dose of vaccine to more people, the delayed administration of the second dose is asserted in a limited number of studies reflecting the vaccine results.⁷⁻⁹ Also, the number of studies showing the effect of the vaccination in SARS-CoV-2-infected subjects who already had an immunity-enhancing condition is limited.¹⁰⁻¹² In this study, we aimed to assess the new phase of the struggle against COVID-19 by presenting the immunization formed in the healthcare workers after vaccination by two doses of Sinovac. We discussed the efficacy of a second dose since the first vaccine dose would also effectively support the individuals who had already been infected by the SARS-CoV-2. To test the hypothesis, we determined the antibody response developed at the 27th and 42nd days of first vaccination in 120 healthcare workers for whom two doses of Sinovac administration were completed.

2 | MATERIALS AND METHODS

2.1 | Participants

This study was conducted on 120 healthcare workers working in Medicine Hospital of Istanbul Atlas University, who were involved in the vaccination program between January 14 and February 11 of 2021, vaccinated by the inactivated Sinovac vaccine produced by Sinovac, a biopharmaceuticals company headquartered in Beijing, against COVID-19.

The study protocol was approved by the Non-Interventional Scientific Research Ethical Committee of Istanbul Atlas University (Date: February 15, 2021; No: 06) and in accordance with the ethical standards of the Declaration of Helsinki. The patients filled out a case consent form including the information of name and surname, occupation, age, gender, height/weight at the time of sampling,

previous SARS-CoV-2 infection, use of immunosuppressants if available, the presence of chronic diseases, date of the first vaccination, date of the second vaccination, any postvaccination reaction. All data were compared according to the previous SARS-CoV-2 infection and seroconversion after the first dose and second dose of vaccination.

2.2 | Blood collection

Whole blood was drawn from the participants by using the vacuum blood collection method on the 27th day after the first vaccination and on the 14th day after the second vaccination (corresponding to Day 42 of the first dose). The samples were taken to silicon tubes including micronized silica particles and serum separator to accelerate blood coagulation. The blood samples were left for 30 min at room temperature before centrifugation. They were centrifuged at 20–25°C at 1300–2000g for 10 min. In the serum samples obtained, IgG antibody levels produced against receptor-binding domain (RBD) protein of SARS-CoV-2 S1 was measured by the method given below.

2.3 | Indirect chemiluminescence assay method

The levels of SARS-CoV-2 IgG (COV2G) formed against RBD domain of S1 protein in the serum samples collected were measured by a reactive indirect chemiluminescent method using SIEMENS ADVIA Centaur Kit XP device. The cut-off index of a positive result was ≥ 1.0 and the indexes ≥ 1.0 were accepted as SARS-CoV-2 IgG positive and as seroconversion was achieved. The measurement range of the test was between 0.50 and 20.00 Index. For the cases with an index ≥ 20.00 , the quantitative results were obtained using the serum of individuals with a negative result in the SARS-CoV-2 IgG test as a diluent.

The absolute change was calculated as the difference between antibody level after the 42nd day of the first dose and antibody level after the 27th day of the first dose. The percent change is the ratio of the absolute change to the antibody level measured on the 27th day of the first dose, which is calculated by a formula: (absolute change \times 100/antibody level after the 27th day of the first dose).

2.4 | Statistical analysis

All statistical analyses were performed by using GraphPad InStat Version 3.06. The categorical variables of the two groups were analyzed using the χ^2 test. Continuous data were analyzed using the parametric unpaired t test for means (body mass index [BMI]) or nonparametric Mann-Whitney test for medians (age, IgG levels after first and second vaccination, absolute, and percent change). Mean values were expressed along with standard deviation, and median values were expressed with the range. Spearman's rank correlation

coefficient (r) was calculated to examine the correlation between the percent change in antibody levels and all demographical and serological findings of vaccinated individuals. The significance level was $p < 0.05$.

3 | RESULTS

The mean age of the participants was 37.19 ± 11.33 and most of them were female (63.3%). In total, 16.7% of participants were immunosuppressed and 22.5% had at least one comorbidity, including hypertension, diabetes asthma, allergy, and malignancy (Table 1).

Thirty-six individuals (30%) had a previous COVID-19 before vaccination. One patient was excluded from the negative patient group because it was not known whether she had COVID-19 (Table 2). Comparison of the demographic and serological data between individuals with or without COVID-19 before vaccination showed that the mean age, distribution of gender, mean BMI, the frequency of immunosuppression and comorbidities, and occurrence of postvaccination reaction did not differ among the two groups. However, the mean IgG levels of the positive COVID-19 group after the first dose of vaccination were significantly higher than those of the negative group ($p < 0.0001$), while the mean IgG levels after the second dose were comparable between groups. The absolute change and the percent change were significantly higher in the negative COVID-19 group compared to those in the positive group ($p < 0.0001$) (Table 2).

TABLE 1 Demographic features of vaccinated individuals

Parameters	Total (n = 120)
Age (years)	
Mean \pm SD	37.19 \pm 11.33
Median [min–max]	40 [20–58]
Gender, N (%)	
Male	44 (36.7)
Female	76 (63.3)
Occupation, N (%)	
Physician	34 (28.3)
Nurse/midwife	19 (15.8)
Administrative officer	8 (6.7)
Cleaning staff	23 (19.2)
Others	36 (30)
BMI (kg/cm ²)	
Mean \pm SD	24.57 \pm 3.78
Median [min–max]	24.33 [16.61–38.97]
Immunosuppression, N (%)	20 (16.7)
Comorbidities, N (%)	27 (22.5)

Abbreviation: BMI, body mass index.

Comparison of the demographic and serological data according to the seroconversion results are shown in Table S1. The antibody positivity rate after two doses of vaccine was detected as 97.5%. One hundred and seventeen individuals achieved a seroconversion after two doses of vaccination, while three individuals were IgG negative on the 42nd day after two doses of vaccine, although they were not immunosuppressive and did not have any comorbidity. Two of these individuals whose absolute change and percent change in IgG levels were lower than those of immunized individuals had a previous COVID-19 before vaccination, but did not show any difference in the demographics compared to immunized individuals. In other words, seroconversion did not occur in 5.6% of 36 individuals who had a previous COVID-19 before the vaccination (Table S1).

Comparison of the demographic and serological data between individuals before and after the second vaccination is listed in Table S2. A total of 36.7% of all participants had the antibody positivity before the second vaccination, while 60.8% turned seropositive after the second dose. The individuals who were seropositive before the second vaccine were significantly younger than those who were seropositive after the second dose ($p = 0.0001$). There was no significant difference in gender, BMI, comorbidity, immunosuppression, and postvaccination reactions between the two groups. The most common postvaccination reaction was pain. The percentage of having a previous COVID-19 (59.1%) among seropositive individuals before the second vaccination was significantly higher than those of seropositive individuals (10.96%) after the second vaccination ($p < 0.0001$). The median IgG level increased from 6.23 to 7.91 index in the seropositive patients before the second vaccine, while the median level increased from 0.28 to 6.11 index in the seronegative people. The absolute and percentage change in antibody levels of seropositive individuals after the second vaccination were significantly higher than those of seropositive individuals before the second vaccination ($p < 0.0001$) (Table S2).

The correlation analysis between the percent change in antibody levels and the demographical and serological findings of all vaccinated individuals are shown in Table S3. There was no significant correlation in terms of gender, BMI, immunosuppression, comorbidities, and postvaccination reaction. However, age had a significant positive correlation with the percent change in antibody levels ($p = 0.0133$). The presence of the previous COVID-19 and IgG levels after the first vaccination showed a significant negative correlation with the percent change in antibody levels ($p < 0.0001$) (Table S3).

The levels of IgG antibody compared by the day of vaccination and seropositivity in the seropositive healthcare workers and the percentage change of IgG levels in seropositive individuals before and after the second dose of vaccination were pictured in Figure 1. As the median percentage change of individuals who became seropositive before the second vaccination was far lower than those of individuals who became seropositive after the second vaccination (Table S2), the second dose of vaccine contributed to the percent change in IgG levels of naïve vaccinated individuals (Figure 1).

TABLE 2 Comparison of the demographic and serological data between individuals with or without Covid-19 infection before vaccination

Parameters	Covid-19 infection before vaccination		p value
	Positive (n = 36)	Negative (n = 83)	
Age (years)			
Mean ± SD	36.58 ± 10.42	37.2 ± 11.59	0.6706
Median [min-max]	40 [21-54]	39 [20-58]	
Gender, N (%)			
Male	15 (41.67)	29 (34.9)	0.623
Female	21 (58.33)	54 (65.1)	
BMI (kg/m ²)			
Mean ± SD	24.66 ± 4.12	24.52 ± 3.66	0.8576
Median [min-max]	24.41 [16.61-38.97]	24.22 [17.3-33.66]	
Immunosuppression, N (%)	9 (25)	11 (13.3)	0.1911
Comorbidities, N (%)	9 (25)	18 (21.7)	0.8743
Postvaccination reaction, N (%)			
Pain	6 (16.7)	20 (24.1)	0.8673
Rash/redness	0 (0)	3 (3.6)	
Fever	2 (5.6)	3 (3.6)	
Headache	3 (8.3)	11 (13.3)	
Myalgia	1 (2.8)	2 (2.4)	
Others	7 (19.4)	22 (26.5)	
IgG levels			
After 1st vaccination			
Mean ± SD	10.23 ± 19.21	1.35 ± 2.88	<0.0001
Median [min-max]	4.67 [0-83.9]	0.31 [0-13.24]	
After 2nd vaccination			
Mean ± SD	10.12 ± 14.56	9.35 ± 7.48	0.5189
Median [min-max]	6.81 [0.01-69.6]	7.55 [0.84-40.9]	
Absolute change ^a			
Median [min-max]	1.25 [-26.09 to 11.1]	5.78 [-5.47 to 40.5]	<0.0001
Percent change ^b			
Median [min-max]	23.29 [-64.24 to 55 500]	2499.91 [-41.31 to 27 828.57]	<0.0001

Abbreviations: BMI, body mass index; Covid-19, Coronavirus Disease 2019.

^aAbsolute change = antibody level_{42nd} - antibody level_{27th}.

^bPercent change = [(antibody level_{42nd} - antibody level_{27th})/antibody level_{27th}] × 100.

4 | DISCUSSION

The general regime in the vaccination against COVID-19 is administering the vaccines in two doses. It was understood that the vaccination after the first dose had a weak immune response when the vaccines started to be tested for the first time. This situation formed the necessity of administering the second dose for the formation of a strong antibody response. All tests at the Phase-1 step of

development of Moderna and Pfizer vaccines showed that both doses of the vaccine had a very high effect of preventing the infection upon administration.¹¹ Comparing the effectiveness of the vaccines, Pfizer-BioNTech mRNA vaccine (BNT162b2) was found to be highly effective against symptomatic COVID-19, with an efficacy of 94% in a randomized clinical trial and an effectiveness of 94%–95% in Israel.¹³ Tanriover et al. reported that the efficacy of the vaccine was 83.5% in the Phase-3 clinical trial of the CoronaVac vaccine conducted in

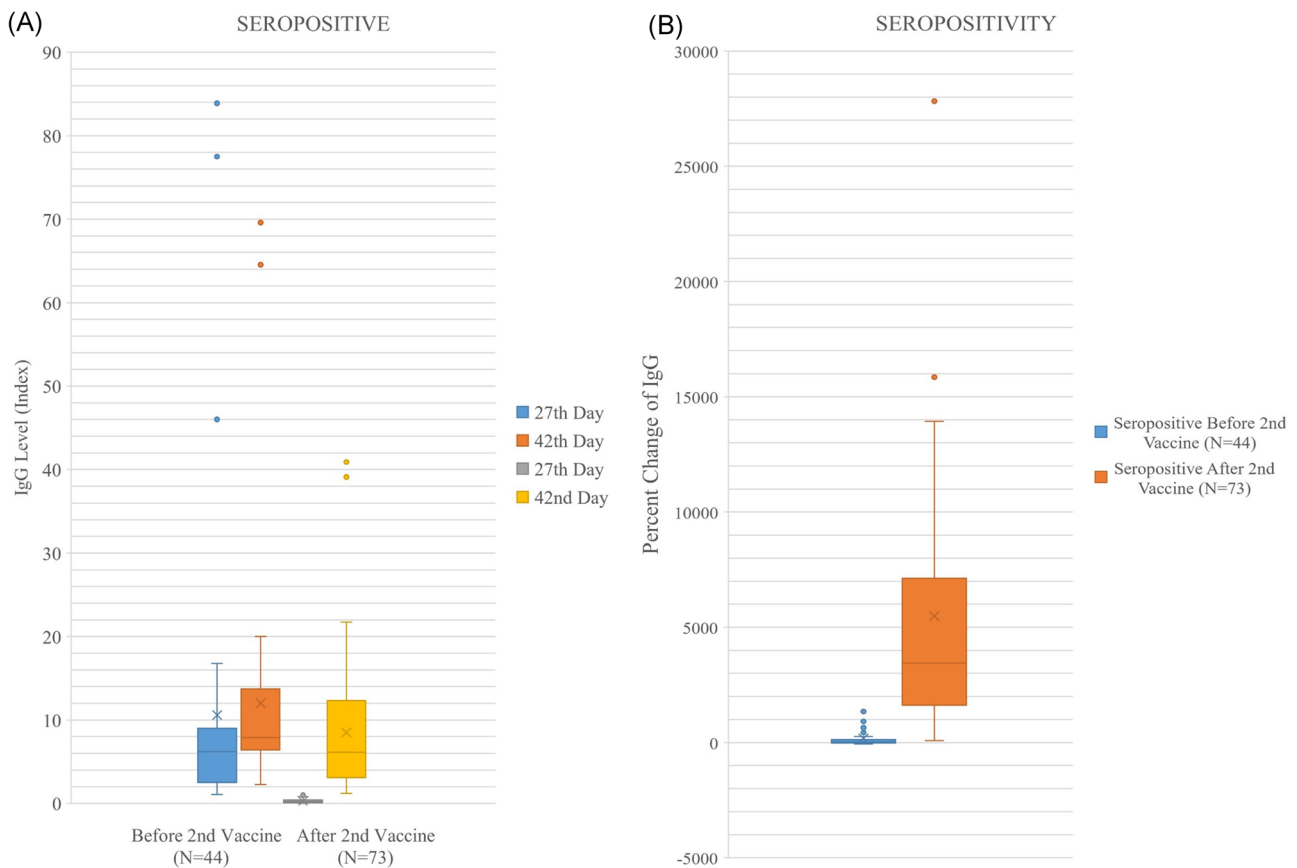


FIGURE 1 (A) The graphical representation of levels of IgG antibody formed against receptor-binding domain of Coronavirus Disease 2019 S1 protein compared by the day of vaccination and seropositivity in the healthcare workers. (B) The graphical representation of the percentage change of IgG levels in seropositive individuals before and after the second dose of vaccination (1 index = 21.8 binding antibody unit/ml)

Turkey. Although the vaccine showed a lower efficacy compared to the Pfizer-BioNTech vaccine, it can be accepted as an acceptable protection rate.¹⁴ Another study indicated that Oxford–AstraZeneca chimpanzee adenovirus-vectored vaccine ChAdOx1 nCoV-19 (AZD1222) had 70.4% efficacy, providing lower protection against infection than those of CoronaVac and Pfizer-BioNTech vaccines.¹⁴ In this study, in which the postvaccination antibody responses of 120 healthcare worker following two doses of vaccination by Sinovac was tested, the efficacy of the vaccine was found to be 97.5%.

In the article published by Tartof et al.,¹⁵ the efficacy of the mRNA BNT162b2 (Pfizer-BioNTech) vaccine was investigated for up to 6 months and the efficacy against COVID-19 was found as 73% for fully vaccinated individuals. It has been reported that the rate of vaccine effectiveness against COVID-19-related hospital admissions was 90% in the first 5 months and decreased to 47% after 5 months. It has been stated that an additional dose may be required up to 6 months after two doses of vaccine for boosting the efficacy.¹⁵ Another study evaluated the tolerability and immunogenicity of recombinant adenovirus type 5 (Ad5-vectored vaccine against COVID-19) expressing the spike protein of SARS-CoV-2 strain and determined that the antibodies increased significantly on the 14th day and peaked 28 days after the vaccination.¹⁶ Therefore, we

investigated the antibody response on the 27th day after the first vaccination and on the 14th day after the second vaccination (corresponding to Day 42 of the first dose) and the mean IgG index on the 27th day after the first vaccination was found to be higher among previously infected individuals than noninfected ones. However, the IgG index on the 14th day after the second vaccination did not differ according to the previous infection history. Unfortunately, we did not examine the long-term antibody response and immunogenicity rates of the healthcare workers.

Limited data on immune responses to single-dose vaccination with BNT162b2 are available, and vaccine responses following previous natural infections have not been assessed in clinical trials.¹¹ In the study conducted by Saadat et al.,⁸ the first dose of Pfizer-BioNTech or Moderna vaccines effectively formed the high antibody response in subjects who were recovered from the infection among the individuals randomly vaccinated.⁸ Although we have limitations on the individual immunities that were not measured before the first doses of the Sinovac vaccination, it is valuable that a stronger humoral response was reported in individuals with prior COVID-19 after vaccination by the first dose of Sinovac, and we are of the opinion that this first dose may support a previous immunization as observed by other researchers.^{8,17} In our study, 35 healthcare

workers stated that they had previously had a COVID-19. Anti-SARS-CoV-2 antibody responses in subjects infected with SARS-CoV-2 follow a classical pattern, with a rapid boost within the first 3 weeks after the appearance of symptoms. Although the titers decreased thereafter, the ability to detect anti-SARS-CoV-2 IgG antibodies remained intact in the majority of subjects who were previously screened positive for virus with confirmed neutralizing activity for up to 6 months.¹⁸ More advanced studies are needed to conclude that giving priority to the first doses of vaccines administrations in developing countries where there is a shortage of vaccines will be effective in gaining the acceleration of community immunity.

Many vaccine researchers have claimed that NABs induced by vaccination are protective against SARS-CoV-2 infection.¹⁹ NABs generally bind to S-protein in some domains within or near the RBD, preventing the virus from binding to the ACE2 receptor of human cells. In the IgG immunoassay method that we use, the increase in IgG antibody levels formed against the RBD domain of SARS-CoV-2 S1 protein in the vaccinated individuals supports this opinion. Moreover, we measured the seropositivity rate after two doses of vaccine as 97.5% among all individuals; 36.7% of all were seropositive before the second vaccination, while 60.8% were seropositive after the second dose. A Phase-3 trial conducted in Turkey reported similar seropositivity results with our rates; 89.7% of vaccine recipients were seropositive for CoronaVac vaccination and 92% of those who were seropositive also produced protective levels of NABs at least 14 days after the second dose of vaccine.¹⁴ Seropositivity decreased with increasing age in both genders,¹⁴ as we observed that the seropositive individuals immunized after the first dose of vaccination were younger than those immunized after the second dose.

One of the biggest discussions concerning the efficacy of the vaccine is surely developing the antibody response against new variants. It is known that the new variants discovered until now increase the speed of the spread of SARS-CoV-2. However, those variants do not impact the ratio of an individual's affection rate. The vaccines are designed in a manner to include antibodies towards various parts of a virus. Therefore, antibodies recognize other parts, although a part of the virus is mutated. The presence of a variant decreasing the vaccine's efficacy should be considered, and advanced vaccination studies should be conducted for the new variants of SARS-CoV-2 to develop new effective vaccines against COVID-19.²⁰

The biggest limitation of the present study is the small sample size, which may be considered as not enough to conclude that previous infection may post the seroconversion. Another limitation is the lack of measurement of the level of antibodies in both infected and not infected groups before vaccination. The general challenge of studies related to COVID-19 diseases is that it is not confirmed that COVID-negative patients were not infected before; however, individuals who did not show any symptoms in the general course of the disease were considered COVID-negative, but there is still a possibility that these people had the disease without showing any symptoms (asymptomatic). However, the findings of this study

suggest that the second dose of Sinovac posts the immune response in naïve vaccinated individuals. The last limitation is that an evaluation was not performed for the patients who had the disease as the healthcare workers with a history of disease might be infected at different times and the results of prevaccination antibody levels were not available.

One of the major challenges for the commercially available serology assays is that their binding antibody results are provided in arbitrary units per milliliters (ARU/ml). Thus, the results between assays are highly variable, although they target the same SARS-CoV-2 antigen. In our study, the antibody levels were presented as index units and it corresponds to 21.8 binding antibody unit/ml (BAU/ml) according to the standards determined by the kit manufacturer. However, there are reports stating that the BAU can be correlated with the level of NABs.^{21,22}

As a result, this study demonstrated that a previous COVID-19 in healthcare workers may boost the seroconversion even at the first dose of vaccination by Sinovac if they were infected previously. Anti-S protein levels may contribute to the percent change in IgG levels of naïve vaccinated individuals and may be considered as a determinant in vaccination. Future studies are required to determine the amount of anti-S protein of the subjects to be vaccinated; therefore, the number of booster shots can be determined.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

The study protocol was approved by the Non-Interventional Scientific Research Ethical Committee of Istanbul Atlas University (Date: February 15, 2021; No: 06) and in accordance with the ethical standards of the Declaration of Helsinki. Informed consent was obtained from all participants for the study.

AUTHOR CONTRIBUTIONS

Bagnu Dundar and Hatice Nur Halipci Topsakal contributed to the design and implementation of the study. Kadriye Karahangil and Hatice Nur Halipci Topsakal collected the data and performed the analysis and interpretation of data. All authors discussed the results and commented on the manuscript. All the authors reviewed and approved the final manuscript to be published.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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