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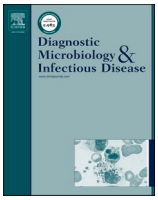

Antibody responses post-booster COVID-19 vaccination: Insights from a single-center prospective cohort study

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ABSTRACT

The study aimed to evaluate the effect of booster dose COVID-19 vaccines on prevention and humoral immune response in individuals with different vaccination schemes during the period BA.4 and BA.5 omicron sub-variants were globally dominant. The study included 146 individuals who preferred different vaccination schemes for booster doses. Anti-spike/RBD-IgG and neutralizing antibody levels were measured 28 days after the booster dose vaccination upon their consent. There is no significant difference between median antibody titers detected according to different vaccination schemes. SARS-CoV-2 neutralizing antibody inhibition percentages were detected significantly higher in serum samples before and after the last booster dose in 2 BNT162b2+1 BNT162b2(99.42 %), 2 BNT162b2 + 2 BNT162b2(99.42 %), and 2 BNT162b2 + 3 BNT162b2(99.42 %) vaccination schemes ($p = 0.004$, $p = 0.044$, $p = 0.002$,respectively). The study indicated that a booster vaccination dose provides a high level of protection against severe COVID-19 and death. We think that the variant-specific pancoronavirus vaccines will be necessary to protect against breakthrough infections.

1. Introduction

Previous studies have shown that the effectiveness of COVID-19 vaccines against SARS-CoV-2 infection decreases several months after the second dose is administered [1]. In particular, the emergence and rapid spread of variants of concern (VoCs) of SARS-CoV-2 suggest that the disease protects the potential of existing vaccines designed against wild-type SARS-CoV-2 may be reduced [2–4]. B.1.1.529 (Omicron), which is one of the major VoCs of the SARS-CoV-2, was first detected in South Africa on November 24, 2021, spread worldwide in a short period and became the dominant variant [5]. The Omicron variant was divided into several subgroups BA.1, BA.2, BA.3, BA.4, BA.5, XE, XD, XF, and known to be responsible for higher binding affinity, increased infectivity, and higher escape rates from the antibody [6,7]. Much as current vaccines are designed specifically for wild-type SARS-CoV-2, memory B cell improvement after infection or booster dose vaccine administration is crucial for protection against various SARS-CoV-2 variants [4]. In the study, we aimed to assess the effect of booster dose COVID-19 vaccines on disease prevention and humoral immune response in individuals with different vaccination schemes during the period BA.4 and BA.5 omicron sub-variants were globally predominant.

2. Materials and methods

2.1. Study design and participants

The study is a prospective, single-center, and observational cohort study. The study cohort comprised 146 individuals who applied to İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine Hospital COVID-19 Vaccination Center for booster dose administration between July 2022 and October 2022. Peripheral blood samples were obtained from the participants 28 days after the booster dose vaccination upon

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their informed consent. The samples were stored in microtubes at -20°C until assayed. On the assay day, serum samples were first brought to +4°C and then to room temperature (+18°C, +25°C) and made ready for use.

Prior history of COVID-19 infection was questioned within three months of the last dose of the participants. The interview was conducted through one-on-one and interrogation of PCR records. During the interview, consent was obtained from all participants, and demographic data (age, gender, symptoms, presence of comorbidities, etc.) were recorded on the follow-up form. Serum samples of the participants included in the study were studied with serology-based tests to determine SARS-CoV-2 IgG titer and neutralizing antibody inhibition percentage after the booster dose.

2.2. Immuno-serological tests

2.2.1. SARS-CoV-2 IgG test

The chemiluminescent microparticle immunoassay (CMIA) method was used to detect SARS-CoV-2 IgG titers (ARCHITECT IgG II Quant test, Abbott, USA), which can quantitatively detect immunoglobulin class G (IgG) antibodies including neutralizing antibodies against the receptor binding domain (RBD) of the spike protein S1 subunit of SARS-CoV-2. The Architect™ and Alinity™ analyzers were used to detect SARS-CoV-2 RBD-specific antibodies in human serum with the SARS-CoV-2 IgG assay.

The antibody results of the studied sera were evaluated as Arbitrary Units/mL (AU/mL). The concentrations obtained in AU/mL were multiplied by the correlation coefficient of 0.142 and converted to the "Binding Antibody Unit (BAU/mL)" in the WHO's International Standard for Anti-SARS-CoV-2 immunoglobulins [8]. Accordingly, 50 AU/mL or 7.1 BAU/mL and higher concentrations were considered positive. This test has been reported to be 100 % compatible with the plaque reduction neutralization test (PRNT), and a concentration of 1050 AU/mL was associated with a 1:80 dilution of PRNT [9].

2.2.2. Surrogate neutralization test

In serum samples, neutralizing antibodies that inhibit the binding of the viral SARS-CoV-2 S1-RBD to ACE2 receptors of human cells were detected by surrogate neutralization assay with the competitive ELISA method (SARS-CoV-2 NeutraLISA, Euroimmun, Lübeck, Germany). The EUROIMMUN Analyzer was used to run the SARS-CoV-2 NeutraLISA assay for the detection of RBD-specific neutralizing antibody inhibition percentage in serum. The neutralization capacity was calculated as percent inhibition (IH %) by subtracting the optical density of the patient sample from the ratio of the optical density of the blank. Test results were interpreted following the manufacturer's instructions; IH of <20 % was evaluated as negative, IH of 20 %–35 % as a breakpoint, and IH of ≥35 % as positive. According to the manufacturer's analysis, the EUROIMMUN SARS-CoV-2 NeutraLISA test is 98.6 % compatible with the plaque reduction neutralization test (PRNT) [10].

2.3. Statistical analysis

The Statistical Package for Social Sciences (SPSS) software version 21 (IBM Corp.; Armonk, NY) was used to evaluate the data. Qualitative data are presented as numbers and percentages, and quantitative data are presented as median and IQR25-75. x2 test and Fisher's exact test were used in the evaluation of qualitative data, Student's t-test, Mann Whitney U test, and Kruskal Wallis test were used in the comparison of quantitative data. The correlation analysis evaluated the relationship between SARS-CoV-2 IgG and SARS-CoV-2 RBD-specific neutralizing antibody inhibition percentage results. The normality of the data was assessed using the Shapiro-Wilk test. Since both variables did not follow a normal distribution, the Spearman Rank Correlation test was applied. The $p<0.05$ value was considered significant in all analyses.

3. Results

Of the 146 participants who preferred BNT162b2 as the last booster dose; 15 had were 2 BNT162b2 + 1 BNT162b2, 55 had 2 BNT162b2 + 2 BNT162b2, 11 had 2 CoronaVac + 2 BNT162b2, 37 had 2 CoronaVac + 3 BNT162b2, and 28 had 2 CoronaVac + 4 BNT162b2 vaccination schemes.

Participants (n=146) in the study had a mean age of 45.92 (range between 18-76) of whom 79 (54.1 %) were male, and 67 (45.9 %) were female. No significant difference was detected between SARS-CoV-2 seropositivity in individuals according to gender ($p>0.05$; Table 1). SARS-CoV-2 IgG seropositivity was found to be significantly higher in the group aged 50 years and over who preferred 2 CoronaVac + 3 BNT162b2 and 2 CoronaVac + 4 BNT162b2 vaccination schemes ($p = 0.001$; Table 1). No significant difference was detected between SARS-CoV-2 seropositivity in individuals according to comorbidities.

Of the 59 (40.4 %) participants with a prior history of COVID-19 infection at least 3 months ago. Prior history of COVID-19 infection was found to be significantly higher in the group who preferred 2 BNT162b2 + 1 BNT162b2 vaccination scheme ($p = 0.022$).

One-on-one or cell phone interviews revealed no confirmed case of COVID-19 infection in the three months after the last booster dose. SARS-CoV-2 IgG median antibody titers in blood samples obtained before and after the last dose were compared, SARS-CoV-2 IgG median antibody titers were detected significantly higher after the last dose in all vaccination schemes (Table 2, Fig. 1).

On the 28th day after the last booster dose, the median antibody titer was detected as 6809.6 AU/mL in 2 BNT162b2 + 1 BNT162b2 group, 9119 AU/mL in 2 BNT162b2 + 2 BNT162b2 group, 13045.8 AU/mL in 2 CoronaVac + 2 BNT162b2 group, 7469.6 AU/mL in 2 CoronaVac + 3 BNT162b2 group, 9003.1 AU/mL in 2 CoronaVac + 4 BNT162b2 group. No significant difference was detected between SARS-CoV-2 IgG median antibody titers according to different vaccination schemes ($p = 0.629$; Table 2). SARS-CoV-2 neutralizing antibody inhibition percentages were detected significantly higher in serum samples before and after the last booster dose in 2 BNT162b2 + 1 BNT162b2 (99.42 %), 2 BNT162b2 + 2 BNT162b2 (99.42 %), and 2 BNT162b2 + 3 BNT162b2 (99.42 %) vaccination schemes ($p = 0.004$, $p = 0.044$, $p = 0.002$, respectively) (Table 3). SARS-CoV-2 neutralizing antibody inhibition percentages were detected significantly higher in serum samples before the last booster dose in 2 CoronaVac + 4 BNT162b2 (99.5 %) vaccination scheme ($p = 0.029$). However, no significant difference was detected after the last booster dose between groups ($p = 0.279$; Table 3).

Of the 59 (40.4 %) participants with a prior history of COVID-19 infection at least 3 months ago. No significant difference between the groups with a prior history of COVID-19 and those without a prior history of COVID-19 according to median antibody titers and neutralizing antibody inhibition percentages ($p = 0.239$, $p = 0.840$; Table 4).

The median SARS-CoV-2 IgG antibody titer of those who had post-vaccination COVID-19 infection was 7975 AU/mL, and of those who had not post-vaccination COVID-19 infection was 9081.9 AU/mL. There was no statistically significant difference between the two groups ($p = 0.880$). After the last dose of booster vaccination, SARS-CoV-2 neutralizing antibody inhibition percentages were found to be 99.42 % in both groups ($p = 0.803$).

The Spearman Rank Correlation test was applied to determine the relationship between SARS-CoV-2 IgG antibody titers and SARS-CoV-2 neutralizing antibody inhibition percentages. The correlation coefficient was 0.207, and this relationship was statistically significant ($p = 0.012$). These findings indicate a weak positive correlation between SARS-CoV-2 IgG antibody titers and SARS-CoV-2 neutralizing antibody inhibition percentages results.

4. Discussion

This prospective cohort study was conducted during the period when

Table 1
Demographics data of study group according to vaccination schemes.

Vaccination schemes	2 BNT162b2 + 1 BNT162b2		2 BNT162b2 + 2 BNT162b2		2 CoronaVac + 2 BNT162b2		2 CoronaVac + 3 BNT162b2		2 CoronaVac + 4 BNT162b2		Total		p
Gender	N	%	N	%	N	%	N	%	N	%	N	%	
Male	9	60.0	29	52.7	5	45.5	24	64.9	12	42.9	79	54.1	
Female	6	40.0	26	47.3	6	54.5	13	35.1	16	57.1	67	45.9	0.443
Age													
<50	11	73.3	38	69.1	5	45.5	12	32.4	10	35.7	76	52.1	
≥50	4	26.7	17	30.9	6	54.5	25	67.6	18	64.3	70	47.9	0.001
Comorbidities													
Autoimmunity	0	0.0	1	1.8	0	0.0	1	2.7	2	7.1	4	2.7	-
Malignity	1	6.7	0	0.0	0	0.0	1	2.7	0	0.0	2	1.4	
DM	2	13.3	8	14.5	1	9.1	7	18.9	5	17.9	23	15.8	0.929
Hypertension	2	13.3	5	9.1	1	9.1	9	24.3	9	32.1	26	17.8	0.071
Hypothyroidism	0	0.0	3	5.5	1	9.1	3	8.1	4	14.3	11	7.5	
Cardiac Inf.	0	0.0	3	5.5	0	0.0	3	8.1	3	10.7	9	6.2	
Pulmonary Inf.	2	13.3	1	1.8	1	9.1	2	5.4	0	0.0	6	4.1	
Allergy	1	6.7	0	0.0	0	0.0	1	2.7	1	3.6	3	2.1	
Other	3	20.0	4	7.3	0	0.0	3	8.1	3	10.7	13	8.9	
Prior COVID-19 history	9	60.0	26	47.3	7	63.6	10	27.0	7	25.0	59	40.4	0.022

Table 2
Comparison of median SARS-CoV-2 IgG titers in blood samples taken before and after the booster dose with different vaccination schemes.

Vaccination schemes	N	Blood samples taken before booster dose/ doses SARS-CoV-2 IgG, AU/ mL Median (IQR25-75)	Blood samples taken after booster dose/ doses SARS-CoV-2 IgG, AU/mL Median (IQR25-75)	P*
2 BNT162b2 + 1 BNT162b2	15	2338.30 (602.70-6650.90)	6809.60 (3055.80-17240.10)	0.005
2 BNT162b2 + 2 BNT162b2	55	3264.20 (1448.00-7558.10)	9119.00 (5355-14249.1)	0,000
2 CoronaVac + 2 BNT162b2	11	3908.50 (1817.30-8937.30)	13045.8 (6879.9-25561.4)	0.026
2 CoronaVac + 3 BNT162b2	37	2833.80 (1081.90-7098.40)	7469.6 (5076.4-16336.65)	0.000
2 CoronaVac + 4 BNT162b2	28	2579.60 (1482.30-6074.90)	9003.1 (4730.3-19146.33)	0.000
P**		0.646	0.629	

omicron BA.4 and BA.5 sub-variants were dominant. Regardless of the primary COVID-19 vaccination schemes, booster doses were found to effectively stimulate humoral immune responses. The participants were found to have higher percentages of neutralizing antibody inhibition whose preferred homologous BNT162b2 vaccination scheme. Since there were no confirmed COVID-19 cases in our study group within three months after the last dose of booster vaccination, indicating that booster doses of the COVID-19 vaccines protect against severe COVID-19.

In the study group, those who received 2 CoronaVac + 3 BNT162b2 and 2 CoronaVac + 4 BNT162b2 vaccines was found to be significantly higher at ≥50 group compared to the other groups is related to the our national vaccination policies. In the first period of vaccination, health-care workers and the elderly were declared the priority group and CoronaVac vaccine was administered, and then this group was prioritized again in the booster dose administration with the first mRNA vaccine. In the study group, the high number of those who had previously had a prior history of COVID-19 in the group who received the BNT162b2 vaccine is based on a similar reason. In first period of the national vaccination administrations in the group between the ages of 18-45 without any chronic disease was the latest to receive the vaccine due to national vaccination policy. BNT162b2 mRNA vaccine was the first choice for this group. The high prevalence of COVID-19 in these groups was an expected result, as they are the most mobile population in the public.

In a cohort study conducted in Singapore during the period when the

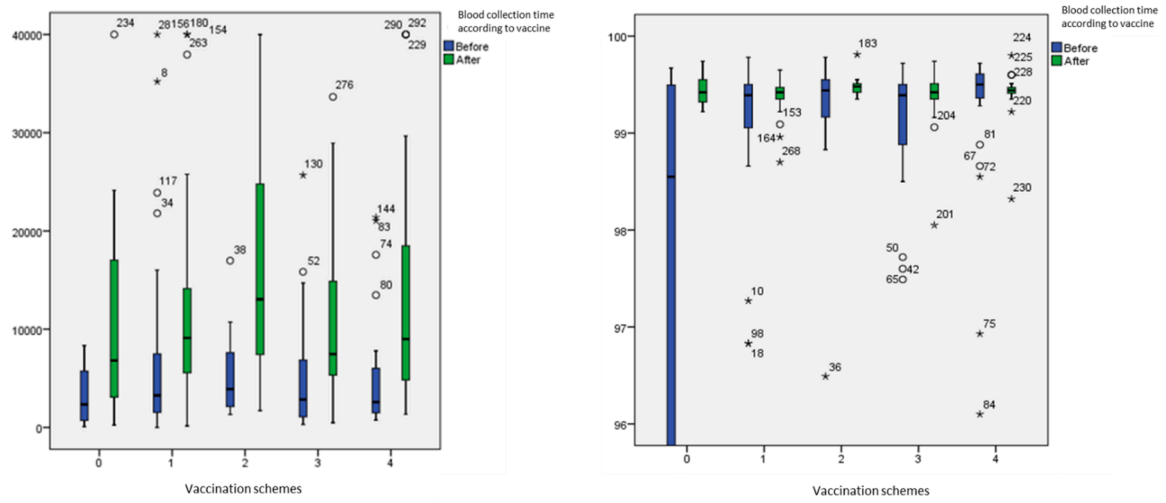

Fig. 1. Median SARS-CoV-2 IgG titers and median percentages of SARS-CoV-2 neutralizing antibody inhibition in blood samples taken before and after vaccination, according to vaccination schedules.

Table 3
Comparison of median percentages of SARS-CoV-2 neutralizing antibody inhibition in blood samples taken before and after the booster dose with different vaccination schemes.

Vaccination schemes	N	Blood samples taken before booster dose/doses nAb, IH% Median (IQR 25-75)	Blood samples taken after booster dose/doses nAb, IH% Median (IQR 25-75)	p
2 BNT162b2+ 1 BNT162b2	15	98.55 (84.3-99.55)	99.42 (99.29-99.55)	0.004
2 BNT162b2 + 2 BNT162b2	55	99.39 (98.89-99.50)	99.42 (99.35-99.48)	0.044
2 CoronaVac + 2 BNT162b2	11	99.44 (99.11-99.55)	99.48 (99.42-99.51)	0.120
2 CoronaVac + 3 BNT162b2	37	99.39 (98.75-99.5)	99.42 (99.35-99.53)	0.002
2 CoronaVac + 4 BNT162b2	28	99.50 (99.35-99.61)	99.44 (99.41-99.48)	0.991
p	0.029	0.276		

omicron variant was dominant, the effectiveness of the booster mRNA vaccine against severe COVID-19 infection was reported at 87.4 % in 2,441,581 adults aged 30 years and older. They also reported that the booster mRNA vaccine was effective against severe COVID-19 for 6 months, regardless of the vaccination scheme. In addition to this, they reported that the three doses of inactivated SARS-CoV-2 vaccines provided more protection than two doses of inactivated SARS-CoV-2 vaccines [11]. In another study reported from Chile, a homologous or heterologous booster dose provided a high protection against both severe COVID-19 infection and mortality. Heterologous booster dose vaccinations have been reported to have higher efficacy compared to homologous booster vaccinations [12]. In a retrospective cohort study conducted with 3,009 healthcare workers from Türkiye, it was reported that booster dose vaccination with inactivated CoronaVac vaccine or mRNA BNT162b2 vaccine significantly increased the efficacy against COVID-19. However, a higher efficacy rate was found against COVID-19 in healthcare workers who preferred one or two doses of BNT162b2 vaccine as a booster dose [13]. In the SARS-CoV-2-specific immune response, the levels and neutralization properties of anti-S IgG antibodies together with the Th1 response are important for protection. However, with these protective immune responses decreasing over time after COVID-19 vaccination, "breakthrough infections" emerged due to decreasing vaccine efficacy and the spread of new variants [14,15]. It has been suggested that reduced neutralization activity against SARS-CoV-2 variants in individuals with low levels of neutralizing antibodies may be associated with breakthrough infections [16]. Many studies reported that the protective effects of neutralizing antibodies after vaccination or infection against new variants, especially omicron sub-variants, decrease over time and that these variants have mechanisms of escape from the immune response [17–20]. Therefore, booster dose vaccination was strongly recommended in many countries particularly Israel, during the delta variant was dominant [21,22]. Studies have shown that booster dose COVID-19 vaccination increases serum anti-spike antibody levels and neutralization antibody titers against omicron [23–26]. CoronaVac and mRNA vaccines administered as boosters have been reported to increase RBD-specific memory B cells and rapidly produce antibodies targeting various variants such as omicron [27–31]. In the study conducted in our center, it was reported that antibody titers increased 8-fold after the booster dose, and administration of mRNA vaccine as a booster dose may provide more effective protection against severe COVID-19, especially in individuals with risk factors [32]. Although the heterologous vaccination scheme is generally more immunogenic than the homologous vaccination scheme, individuals vaccinated with any booster dose are observed to have milder symptoms even if they are infected with SARS-CoV-2 [17,33,34,31,35].

There are some limitations to our study. The gold standard in the evaluation of humoral immune response after vaccination is to detect neutralizing antibodies using the PRNT method. However, PRNT is a difficult and laborious method to perform due to special requirements such as biosafety level 3 (BSL3) laboratory conditions and the need for qualified personnel. Therefore, the tests included in the WHO SARS-CoV-2 Immunoglobulin Standardization study and compatible with the PRNT method were used in our study. Although the humoral immune response was assessed with serologic tests, parameters associated with specific cellular immunity could not be assessed. The second limitation is PCR or SARS-CoV-2 nucleocapsid tests could not be performed for screening COVID-19 infection in the follow-up period. And, we have no information about the participants' history of asymptomatic infection.We were also able to collect peripheral blood samples 28 days after vaccination; It would be better to collect samples for follow-up purposes after a longer period of time (e.g. after 90 days).

In conclusion, our study indicated that a homologous or heterologous booster vaccination dose provides a high level of protection against severe COVID-19, including against severe infection and death. Although COVID-19 pandemic severity is relent nowadays, we believe that COVID-19 to become endemic in the future and continue to circulate in the population. Therefore, we think that the variant-specific pancoronavirus vaccines will be necessary to protect against reduced immunity and breakthrough infections. In addition, this study demonstrates that while there is a relationship between SARS-CoV-2 IgG antibody titers and neutralizing antibody inhibition percentages, it is not a strong one. We think that studies with larger sample sizes and different methodological approaches be conducted to investigate this relationship in more detail.

Ethics approval

This study was approved by Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Clinical Research Ethics Committee (Date: Nov 4, 2022, and Decision No: 528284).

Informed consent and data privacy

Written informed consent was obtained from the participated in this study. Personal data privacy has been protected.

Table 4
Comparison of median SARS-CoV-2 IgG titers and median percentages of SARS-CoV-2 neutralizing antibody inhibition in blood samples taken before and after the booster dose according to COVID-19 infection.

COVID-19 history	Blood samples taken before booster dose/doses SARS-CoV-2 IgG, AU/mL Median (IQR25-75)	Blood samples taken after booster dose/doses SARS-CoV-2 IgG, AU/mL Median (IQR25-75)	p	Blood samples taken before booster dose/doses nAb, IH% Median (IQR 25-75)	Blood samples taken after booster dose/doses nAb, IH% Median (IQR 25-75)	p
Without prior history of COVID-19	2521.10 (1080.3-7418.50)	9081.90 (4935.7-16810.2)	0.000	99.39 (98.55-99.55)	99.42 (99.35-99.51)	0.000
With prior history of COVID-19	3468.40 (1966.8-6286.1)	7975.00 (5342.4-17240.1)	0.000	99.39 (99.22-99.5)	99.42 (99.35-99.48)	0.012
P	0.239	0.880		0.840	0.803	

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CRediT authorship contribution statement

Harika-Öykü Dinç: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Günay Can:** Writing – review & editing, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Beyhan Budak:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Ferhat-Osman Daşdemir:** Writing – review & editing, Validation, Software, Resources, Methodology, Investigation, Data curation. **Elif Keskin:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Data curation. **Hayriye Kirkoyun-Uysal:** Writing – review & editing, Validation, Resources, Methodology, Investigation, Formal analysis, Data curation. **Okan Aydoğan:** Writing – review & editing, Validation, Software, Resources, Investigation, Formal analysis, Data curation. **Ilker-Inanç Balkan:** Writing – review & editing, Visualization, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization. **Rıdvan Karaali:** Writing – review & editing, Visualization, Software, Resources, Methodology, Investigation, Data curation. **Sevgi Ergin:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Neşe Saltoğlu:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Bekir Kocazeybek:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Bekir KOCAZEYBEK reports financial support was provided by Istanbul University Cerrahpasa. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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