ORIGINAL ARTICLE

Antibody responses after two doses of CoronaVac of the participants with or without the diagnosis of COVID-19

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Abstract

Background CoronaVac, an inactivated whole-virion vaccine against COVID-19, has been shown to be safe with acceptable antibody responses by various clinical trials.

Aims The objective was to investigate the post-vaccination antibody levels of both symptomatic and asymptomatic healthcare workers with or without the diagnosis of COVID-19 in an emergency department (ED) of a hospital serving as a pandemic hospital.

Methods This single-centred, prospective study was conducted on 86 participants who were working as nurse or doctor in the ED. The volunteers were older than 18 years and either positive or negative for either computed tomography (CT), real-time reverse transcription polymerase chain reaction (qRT-PCR), or both. Thirty days after the second dose of CoronaVac (3 μg), the antibody levels were chemiluminescent microparticle immunoassay.

Results Mean age of all participants were 33.1 ± 9.1 years. The antibody levels in the qRT-PCR($+$) and CT($+$) groups were significantly higher than the qRT-PCR($-$) and CT($-$) groups, respectively ($p < 0.05$). In the CT($+$)/qRT-PCR($+$) group, the antibody level was significantly higher than the CT($-$)/qRT-PCR($-$) and CT($-$)/qRT-PCR($+$) or CT($+$)/qRT-PCR($-$) group ($p < 0.05$). On the other hand, antibody levels in the hospitalized group were significantly higher than in the non-hospitalized group ($p < 0.05$). A significant positive correlation was observed between the time elapsed after vaccination and antibody levels of the participants ($r = 0.343$; $p = 0.000$).

Conclusion In conclusion, antibody responses of recovered patients COVID-19 diagnosed by both CT and qRT-PCR were much robust than the patients diagnosed by either one of the techniques or undiagnosed/disease-free participants suggesting that severity of the disease likely contributes to the antibody responses after vaccination with CoronaVac.

Keywords Computed tomography · CoronaVac · COVID-19 · qRT-PCR

Introduction

The coronavirus-19 disease (COVID-19) pandemic continues to affect the societies differentially due to the inequality in the healthcare systems and socioeconomical status [1–3]. The literature indicates that the patients who recover from COVID-19 develop cellular immune response and antibodies against the virus for an estimated duration longer than 6 months directing to the development of COVID-19 vaccines [4–6]. There are various methods performed in the development of vaccines including inactivated virus and nucleic acid-based vaccines (DNA and RNA vaccines) [7]. Furthermore, more than 85 vaccines under development are used in clinical trials [8].

Inactivated vaccines have been widely researched and commonly used to provide protection against various

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infectious diseases including respiratory infections [9]. Possible advantages of the inactivated vaccines include their non-replicable in the host and non-transmittable nature [10], inducing both cellular and humoral immunity [11] and easy storage and shipment [12]. The disadvantages of inactivated vaccines, on the other hand, include less immunogenicity, huge amount of virus to be dealt with, and requirement of verification of the antigens/epitopes [13] Although the development and inactivation methods of the inactivated virus vaccines are akin, the isolated virions and adjuvants used in the process differ [7, 9, 14].

In a previous double-blind, randomised, placebo-controlled study conducted in Turkey, efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac) were investigated on subjects aged between 18- and 59-year-old adults who were both seronegative and real-time reverse transcription polymerase chain reaction (qRT-PCR)-negative for the COVID-19 and were administered with two doses of CoronaVac [10]. In this study, we aimed to compare the post-vaccination antibody levels of symptomatic and asymptomatic healthcare workers with or without the diagnosis of COVID-19 in the emergency department (ED) of a tertiary education and research hospital serving as a pandemic hospital.

Material and methods

Study design and participants

Our study was designed as a single-centred, prospective study. The study was approved by the clinical research ethics committee of our hospital (Date: 02/03/2021, Number: 1811). A total of 86 healthcare workers (doctors and nurses) working in the ED of a pandemic hospital who volunteered to participate in the study and had a positive or negative COVID-19 qRT-PCR test before March 2021 and received two doses of CoronaVac (3 µg) during the vaccination period were included. The exclusion criteria of the study were to be under the age of 18, to be healthcare worker working in different clinics, not to be health personnel (nurse or doctor), and to be unvaccinated personnel. Moreover, healthcare workers who received other medications such as antibiotics, corticosteroids, or antipyretics after second dose of vaccination were not included in the study.

After 30 days of second dose of vaccination, volunteers were invited to the hospital. Medical records (blood type, comorbidity, length of hospital stay, computed tomography (CT) of the chest results, qRT-PCR results) and demographical characteristics (age and gender) of the participants were investigated. Moreover, serum samples were collected from the volunteers in order to determine the antibody responses of the participants.

Serological chemiluminescence immunoassay for SARS-CoV-2

Quantitative detection of immunoglobulin class G (IgG) antibodies, including neutralizing antibodies against the receptor-binding region (RBD) of the spike protein S1 subunit of SARS-CoV-2 were determined by performing the chemiluminescent microparticle immunoassay (CMIA) method in the serum samples obtained in this study. The serum samples were analysed using the SARS-CoV-2 IgG test (ARCHITECT IgG II Quant test, Abbott, USA) on an ARCHITECT immunoassay analyser.

The results obtained from all serum samples analysed were evaluated as arbitrary unit/mL (AU/mL). The cutoff value was set at 50.0 AU/mL, and values lower than 50.0 AU/mL were evaluated as negative while values equal to or higher than 50.0 AU/mL were evaluated as positive. In addition, the concentrations obtained in AU/mL can be 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 immunoglobulin [15]. Accordingly, concentrations of 50 AU/mL or 7.1 BAU/mL and above can be considered positive. It was also reported that this test was 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 [16].

Statistical analysis

All statistical analyses were conducted by using Statistical Package for the Social Sciences version 27.0 (SPSS 27.0; IBM). In the descriptive statistics of the data, mean, standard deviation (SD), median, lowest, highest, frequency, and ratio values were used. The distribution of variables was analysed by Kolmogorov–Smirnov test. Kruskal–Wallis and Mann–Whitney U tests were used in the analysis of quantitative independent data. Wilcoxon signed rank test was used in the analysis of quantitative dependent data. Spearman correlation test was used in the correlation analysis.

Results

The mean age of all participants were 33.1 ± 9.1 years (min–max $= 21.0$–58.0 and median $= 29.0$) and most of the participants were 20–29 years old (Table 1). Of all participants, 45 of them (52.3%) were female, and 41 of them (47.7%) were male. Most of the participants ($n = 73$; 84.9%) did not have any comorbid diseases including hypertension, diabetes mellitus, chronic obstructive pulmonary

Table 1 Participants' characteristics. (Note: Data are expressed as numbers (*n*), percentages (%), or minimum–maximum (min–max) and mean ± standard deviation (SD))

		Min–max	Median	Mean ± SD/*n* (%)
Age	20–29			44 (51.2)
	30–39			20 (23.3)
	≥ 40			22 (25.6)
Blood type	0 (+)			30 (34.9)
	0 (−)			1 (1.2)
	A (+)			41 (47.7)
	A (−)			1 (1.2)
	B (+)			8 (9.3)
	B (−)			3 (3.5)
	AB (+)			2 (2.3)
Antibody levels (AU/mL)	Pre-vaccination	0.1–10.0	3.1	4.1 ± 4.0
	Post-vaccination	0.9–3004.7	448.0	649.7 ± 652.8
Days to vaccination		0.0–398.0	0.0	98.6 ± 140.1
qRT-PCR result	(−)			50 (58.1)
	(+)			36 (41.9)
CT result	(−)			66 (76.7)
	(+)			20 (23.3)
CT(−)/qRT-PCR (−)				47 (54.7)
CT (+)/qRT-PCR(+)				17 (19.8)
CT(−)/qRT-PCR(+) or CT(+)/qRT-PCR(−)				22 (25.6)
Hospitalization	(−)			77 (89.5)
	(+)			9 (10.5)

CT computed tomography, *qRT-PCR* real-time reverse transcription polymerase chain reaction

disease, and hyperthyroidism. Most of the participants had the blood type of 0 (+) and A (+) (Table 1). Mean antibody levels before and after vaccination were 4.1 ± 4.0 and 863.1 ± 1381.5 AU/mL, respectively (Table 1). Most of the participants were qRT-, qRT-PCR-, and CT-negative (qRT-PCR(−)/CT(−); Table 1). Most of the participants did not require hospitalization.

There were no significant differences between the age groups and genders with respect to serum antibody levels ($p = 0.984$ and $p = 0.357$, respectively; Table 2). Moreover, no significant differences were observed in serum antibody levels between the participants according to the presence of the comorbid diseases ($p = 0.226$ and Table 2). The antibody levels in the qRT-PCR(+) group were significantly higher than the qRT-PCR(−) group ($p < 0.05$; Table 2). Also, in the CT(+) group, antibody levels were significantly higher than in the CT(−) group ($p < 0.05$; Table 2). In the CT(+)/qRT-PCR(+) group, the antibody level was significantly higher than the CT(−)/qRT-PCR(−) and CT(−)/qRT-PCR(+) or CT(+)/qRT-PCR(−) group ($p < 0.05$). On the other hand, CT(−)/qRT-PCR(+) or CT(+)/qRT-PCR(−) group exhibited significantly higher levels of antibody than the CT(−)/qRT-PCR(−) group ($p < 0.05$; Table 2). Moreover, antibody levels in the hospitalized group were significantly higher than in the non-hospitalized group ($p < 0.05$; Table 2).

Post-vaccination antibody levels increased significantly compared to pre-vaccination levels ($p < 0.05$; Table 3). Moreover, a significant positive correlation was observed between the time elapsed after vaccination and the antibody levels of the participants ($r = 0.343$; $p = 0.000$).

Discussion

In this study, we found that COVID-19 infection and two doses of vaccination with CoronaVac significantly increases antibody levels compared to only vaccination. Moreover, participants showing both CT and qRT-PCR positivity had significantly higher amount of antibody levels compared to participants with positivity of either CT, qRT-PCR, or none of them. Moreover, vaccination robustly increases the antibody levels against SARS-CoV-2, and this increase positively correlates with the time elapsed after vaccination.

The data of preclinical studies conducted on rodents, rabbits, and nonhuman primates regarding the efficacy and safety of the inactivated vaccines showed promising results [17–20]. Moreover, efficacy and safety of CoronaVac were investigated in phase 1 and 2 trials, and these trials showed similar efficacy at both 3 μg and 6 μg doses [21, 22]. Various interim results, on the other hand, showed varying efficacies

Table 2 Antibody levels of the participants. (Note: Data are expressed as minimum–maximum (min–max), median and mean ± standard deviation (SD))

		Antibody levels (AU/mL)			p
		Min–Max	Median	Mean ± SD	
Age	20–29	62.6–1947.7	552.9	618.2 ± 423.3	0.984 [K]
	30–39	0.9–1994.6	453.7	662.8 ± 545.0	
	≥ 40	52.6–9481.0	464.4	1535.1 ± 2540.1	
Gender	Male	0.9–7978.8	549.4	970.8 ± 1376.8	0.357 [K]
	Female	52.6–9481.0	488.6	765.0 ± 1393.9	
Comorbid disease	(−)	0.9–9481.0	470.7	745.9 ± 1167.0	0.226 [m]
	(+)	52.6–7978.8	632.3	1521.6 ± 2189.4	
CT(−)/qRT-PCR(−)		0.9–1732.8	403.9	464.4 ± 358.1	**0.000 [K]**
CT(+)/qRT-PCR(+)		62.6–9481.0	1682.0	2212.6 ± 2675.4	
CT(−)/qRT-PCR(+) or CT(+)/qRT-PCR(−)		83.0–1554.4	735.4	672.3 ± 349.4	
qRT-PCR result	(−)	0.9–1732.8	440.2	501.5 ± 387.1	**0.002 [m]**
	(+)	62.6–9481.0	770.4	1365.4 ± 1994.7	
CT result	(−)	0.9–1732.8	448.7	505.5 ± 346.2	**0.000 [m]**
	(+)	62.6–9481.0	1262.9	2043.1 ± 2493.6	
Hospitalization	(−)	0.9–9481.0	458.0	671.8 ± 1117.7	**0.000 [m]**
	(+)	488.6–7978.8	1947.7	2500.3 ± 2245.2	

CT computed tomography, *qRT-PCR* real-time reverse transcription polymerase chain reaction, *K* Kruskal–Wallis test, *m* Mann–Whitney *U* test

of various vaccines between 62.1 and 95% [10, 23–28]. This difference is probably due to the different effectiveness of different vaccines produced on different platforms, and higher efficacies were detected after vaccination with the mRNA vaccines [24, 25]. In addition, it has been shown that BNT162b2 vaccination resulted in higher levels of neutralizing antibodies compared to CoronaVac after the second dose [29]. Also, an interim study investigated the immunogenicity and safety of third dose of CoronaVac showed that a third dose six or more months later significantly increased the antibody levels and suggested that optimization of timing of the third dose should be carefully planned [30].

The neutralizing antibody levels against COVID-19 were suggested to correlate the protection against the disease [31–33]. In our study, higher antibody levels were observed in the groups that were infected with COVID-19 confirmed with CT and qRT-PCR compared to the diagnosis with single method and undiagnosed volunteers. This result suggests that immune system of the COVID-19-infected participants

has already been activated by SARS-CoV-2 infection, and additional two doses of CoronaVac remarkably boost the antibody levels and generate a significant immune response.

Our study had some limitations. First of all, T-cell responses were not evaluated after the two doses of Corona-Vac vaccine. A previous study reported low T-cell responses in the participants who were neither infected with SARS-CoV-2 nor contacted with someone with COVID-19 [21]. On the other hand, virus-specific CD8+ and CD4+ T cells were detected in the patients recovered from COVID-19 [34, 35]. Therefore, it might be important to observe the T-cell responses after two doses of CoronaVac vaccination in the patients who recovered from COVID-19. Second, we did not check the individuals regarding the variant of the virus that COVID-19-infected participants had and how their immune response and antibody levels were upon Corona-Vac vaccination.

Conclusion

In conclusion, two doses of CoronaVac significantly induced the antibody levels that were more prominent in the recovered COVID-19 patients. Moreover, antibody responses were significantly higher in the participants who had been diagnosed with COVID-19 by both CT and qRT-PCR. In order to provide sustainable immunity, the antibody levels should be followed throughout the pandemic. More studies are needed to observe the protection of two doses of

Table 3 Pre-vaccination and post-vaccination antibody levels of the participants. (Note: Data are expressed as minimum–maximum (min–max), median and mean ± standard deviation (SD))

	Min–Max	Median	Mean ± SD	p
Pre-vaccination	0.1–10.0	3.1	4.1 ± 4.0	**0.000 [W]**
Post-vaccination	0.9–3004.7	448.0	649.7 ± 652.8	

W Wilcoxon signed rank test

vaccination against different virus variants should be investigated, and either additional doses or mixing up with other vaccines produced by using different platforms should be considered carefully.

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Declarations

Ethical statements The study was approved by the clinical research ethics committee of our hospital (Date: 02/03/2021, Number: 1811).

Conflict of interest The authors declare no competing interests.

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