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Anti-SARS-CoV-2 Spike Protein RBD Antibody Levels After Receiving a Second Dose of ChAdOx1 nCov-19 (AZD1222) Vaccine in Healthcare Workers: Lack of Association With Age, Sex, Obesity, and Adverse Reactions

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Response to vaccines generally varies according to individual factors of the vaccinated subjects such as demographics and immune status. While there are various reports of factors associated with immunogenicity of mRNA COVID-19 vaccines, little is known about those of adenovirus vector vaccines. We conducted a prospective observational study to assess the relationships of antibody level with age, sex, body mass index (BMI), and adverse reactions (ARs) to an adenovirus vector vaccine, ChAdOx1 nCoV-19. Healthcare workers who planned to receive both the first and second injections of the ChAdOx1 nCoV-19 vaccine at Hanyang University Hospital, Seoul, Korea, were enrolled in the study. Seven days after each injection, participants were asked to complete an online adverse reaction survey. In addition, anti-SARS-CoV-2 spike (S) protein receptor binding domain (RBD) antibody concentration was measured 4 weeks after the second injection. All participants (n = 447, 100%) showed serologic positivity (≥ 0.8 U/mL) 4 weeks after the second injection of ChAdOx1 nCoV-19 vaccine. Furthermore, the anti-SARS-CoV-2 S protein RBD concentration was similar among groups when stratified by age, sex, BMI, or presence and severity of AR; multivariable linear regression found no associations between antibody response to the ChAdOx1 nCoV-19 vaccine and age, BMI, sex, and vaccine-induced ARs. In conclusion, age, sex, obesity, and ARs were not associated with antibody responses after two doses of ChAdOx1 nCoV-19 vaccination.

Keywords: COVID-19, vaccine, antibody, adverse reaction, age, sex, obesity

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has spread worldwide to become the most serious health problem. To protect people from COVID-19 and provide protective immunity, various types of vaccines have been developed and administered to the public (1). While clinical trials and real-world studies showed the immunogenicity and efficacy of these vaccines at the population level (2–5), there is individual variation in immune responses to the vaccination, including antibody responses (6, 7). Experience with other vaccines has demonstrated a wide range of variability in response according to demographics and immune status factors of the vaccinated subjects (8).

While it is difficult to assess the immunogenicity of vaccines, measuring antibody level to SARS-CoV-2 in vaccinated subjects is accepted as a diagnostic test to determine vaccine efficacy despite caveats in interpretation of the results (9). Regarding mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273 COVID-19 vaccines), various factors have been reported to be associated with low antibody responses, including old age (10–22), male sex (11, 13–15, 20, 22), higher body mass index (BMI) (11, 19, 20), medications, and comorbidities (23, 24). Moreover, adverse reactions (ARs) to vaccines are suggested to be related to higher antibody level (14, 15, 17). Contrarily, less is known about factors affecting antibody responses to adenovirus vector vaccines, such as the ChAdOx1 nCoV-19 (AZD1222) vaccine. In this prospective observational study, we measured the serum level of the anti-SARS-CoV-2 spike (S) protein receptor binding domain (RBD) antibody in healthcare workers who were vaccinated twice with the ChAdOx1 nCoV-19 vaccine and assessed the relationships of antibody level with age, sex, BMI, and ARs to the vaccine.

MATERIALS AND METHODS

Study Population and Design

Eligible participants were healthcare workers (HCW) who received both the first (prime) and the second (booster) injections of ChAdOx1 nCoV-19 vaccine at Hanyang University Hospital, Seoul, Korea. The first and second injections were administered between March 8, 2021, and May 28, 2021, approximately 12 weeks apart. In a previous clinical study of ChAdOx1 nCoV-19 vaccine, the severity and intensity of local and systemic reactions was highest one day after vaccination (25). Therefore, seven days after each injection, participants were asked to complete an online AR survey to capture the AR profile within one week of receiving each vaccination. Serum samples were collected 4 weeks after the second injection of ChAdOx1 nCoV-19 vaccine for quantitative measurement of anti-SARS-CoV-2 spike S protein RBD antibody concentration. Written informed consent was obtained from each participant before any study-related procedure was performed.

Adverse Event Assessment

The online AR survey was completed by all participants seven days after each injection of ChAdOx1 nCoV-19 vaccine. Demographic and solicited AR data were collected through a series of questionnaires. Demographic data included age, sex, height, weight, occupation, history of allergies, history of COVID-19 infection, comorbidities, and medication history. BMI was categorized into four groups (< 18.5, 18.5-22.9, 23.0-24.9, and ≥25.0 kg/m^2) according to the Asian-Pacific definition of obesity (26). Based on the US Food and Drug Administration guidelines (27), the severity of solicited ARs was graded from 1 to 4 (grade 1, mild; grade 2, moderate; grade 3, severe; grade 4, potentially life threatening). Each AR was classified as systemic or local. The severity of ARs was based on the highest grade of solicited systemic or local AR during either injection.

Quantification of Anti-SARS-CoV-2 Spike Protein Receptor Binding Domain Antibody

Quantification of anti-SARS-CoV-2 S protein RBD antibodies (including IgG) was performed using the Elecsys® Anti-SARS-CoV-2 S immunoassay (Roche Diagnostics International Ltd, Rotkreuz, Switzerland). For each participant, a serum sample was collected 4 weeks after the second dose of ChAdOx1 nCoV-19 vaccine using tubes containing separating gel and was stored at approximately 4°C. The cutoff value for a positive result was defined as ≥ 0.80 U/mL (values < 0.80 U/mL were considered negative results) (28). The lower limit of quantitation was 0.40 U/mL, and samples with a concentration above 250 U/mL were diluted 10-fold for analysis (dilution was considered when calculating sample concentration). The measurement range was 0.40-2,500 U/mL, and values above the range were recorded as 2,500 U/mL.

Statistical Analysis

Demographic characteristics were presented as number of subjects (%). We used Beeswarm Boxplot to show the distribution of the anti-SARS-CoV2 S protein RBD antibody concentration according to age, sex, BMI, and severity of ARs. The antibody titers were natural log (ln)-transformed as an outcome measure to ensure normality. Univariable and multivariable linear regression analyses were performed to verify the associations between immunogenicity and age, sex, BMI, and severity of ARs. To assess the independent relationship between immunogenicity and severity of ARs, we determined standardized beta coefficients (β) before and after adjusting for age, sex, and BMI. All statistical analyses were performed using SAS® 9.4 (SAS Institute, Cary, NC, USA), and a two-sided p-value < 0.05 was considered statistically significant.

RESULTS

Characteristics of the Subjects

A total of 447 HCWs who received both the first and second injections of ChAdOx1 nCoV-19 vaccine was enrolled in the

study, and 388 (86.8%) of them were female (**Table 1**). Age of the subjects ranged from 21 to 63 years, with a mean ± standard deviation (SD) of 40.6 ± 10.9 years. The mean BMI was 22.4 ± 3.1 kg/m^2, and 19.7% (n = 88) of subjects were obese (BMI ≥ 25.0 kg/m^2). The majority of participants was nurses or nursing assistants (n = 282, 63.1%), followed by laboratory staff or physical therapists (n = 48, 10.7%) and physicians (n = 26, 5.8%). Most of the participants did not have comorbidities, though some subjects had hypertension (3.1%), allergy (1.8%), diabetes mellitus (1.8%), asthma (0.7%), chronic liver disease (0.7%), or chronic heart disease (0.5%). In addition, one participant (0.2%) reported previous infection of COVID-19.

Adverse Reactions to Vaccine

Most participants (n = 434, 97.1%) experienced at least one AR (any local or systemic AR) during days 0-7 after either injection (first or second). Overall, the most frequently reported local AR was pain (n = 406, 91.8%), followed by tenderness (n = 386, 86.3%) and induration (n = 138, 30.9%), while the most frequently reported systemic AR was fatigue (n = 391, 87.5%), followed by muscle pain (n = 367, 82.1%), chills (n = 309, 69.1%), and headache (n = 309, 69.1%). In general, both systemic (first injection, n = 389, 87%; second injection, n = 196, 43.8%) and local (first injection, n = 386, 86.4%; second injection, n = 219, 49%) ARs were less frequent after the second injection. In terms of severity of ARs, nearly half of the participants (n = 206, 46.1%) showed at least one grade 3 or 4 AR. At 0-7 days following either (first or second) injection, the most frequently reported grade 3 to grade 4 local AR was tenderness (26.8%), followed by pain (5.8%) and itching (4.4%), while the most frequently reported grade 3 to grade 4 local AR was chills (18.6%), followed by fatigue (18.2%), muscle pain (17%), and fever (6.1%) (**Supplementary Figure 1**).

TABLE 1 | Characteristics of the study population.

	Subjects (n = 447)
Age (years)	
21-30	120 (26.9)
31-40	80 (17.9)
41-50	152 (34.0)
51-63	95 (21.2)
Sex	
Female	388 (86.8)
Male	59 (13.2)
Body mass index (kg/m^2)	
< 18.5	32 (7.2)
18.5-22.9	251 (56.1)
23.0-24.9	76 (17.0)
≥25.0	88 (19.7)
Occupation	
Nurse/nursing assistant	282 (63.1)
Physician	26 (5.8)
Laboratory staff or physical therapist	48 (10.7)
Other	91 (20.4)
Comorbidities	
Hypertension	14 (3.1)
Any allergy other than asthma	8 (1.8)
Diabetes mellitus	8 (1.8)
Asthma	3 (0.7)
Chronic liver disease	3 (0.7)
Chronic heart disease	2 (0.5)
Adverse reactions to any vaccination*	
None	13 (2.9)
Grade 1	46 (10.3)
Grade 2	182 (40.7)
Grade 3 or 4	206 (46.1)

Values are presented as number (%) of subjects.
**Severity of adverse reactions was determined as the highest grade of local or systemic adverse reaction to any ChAdOx1 nCoV-19 vaccination.*

Associations Between Immunogenicity and Age, Sex, BMI, and Severity of AR

All participants (n = 447, 100%) showed serologic positivity (≥ 0.8 U/mL) 4 weeks after the second injection of ChAdOx1 nCoV-19 vaccine. Among them, the median (IQR) anti-SARS-CoV-2 S protein RBD concentration was 747.0 (455.0-1324.0) U/mL. The anti-SARS-CoV-2 S protein RBD concentrations were similar among groups when stratified by age (median for 21-30 years old = 787.0 U/mL; median for 31-40 years old = 678.0 U/mL; median for 41-50 years old = 852.0 U/mL; median for 51-63 years old = 720.0 U/mL), sex (median for female = 753.0 U/mL; median for male = 744.0 U/mL), or BMI (median for <18.5 kg/m^2 = 707.5 U/mL; median for 18.5-22.9 kg/m^2 = 747.0 U/mL; median for 23.0-24.9 kg/m^2 = 832.5 U/mL; median for ≥25.0 kg/m^2 = 748.5 U/mL) (**Figure 1**). The concentration also was similar when stratified by presence and severity of both local and systemic ARs (median for no local AR = 877.5 U/mL; median for Grade 1 local AR = 781.5 U/mL; median for Grade 2 local AR = 734.0 U/mL; median for Grade 3 or 4 local AR = 709.0 U/mL; median for no systemic ARs = 828.0 U/mL; median for Grade 1 systemic ARs = 830.0 U/mL; median for Grade 2 systemic AR = 748.5 U/mL; median for Grade 3 or 4 systemic AR = 693.0 U/mL) (**Figure 2**). Furthermore, a multivariable linear regression analysis of anti-SARS-CoV-2 S protein RBD concentration found no significant association of antibody concentration with age, sex, BMI, or severity of AR (**Table 2**).

DISCUSSION

The efficacy and immunogenicity of COVID-19 vaccines vary among recipients. In this prospective observational study, we determined antibody levels 4 weeks after the second dose of the ChAdOx1 nCoV-19 vaccine (AZD1222) in HCWs and explored the relationships with host factors including age, sex, obesity, and vaccine-induced adverse reactions. We found a lack of association between antibody response to the ChAdOx1 nCoV-19 vaccine and age, sex, obesity, and vaccine-induced ARs.

Protective immunity of the COVID-19 vaccines has been observed in T cell and B cell responses (7, 29). Following immunization, the dendritic cells detect vaccine antigens and activate T cells in draining lymph nodes, leading to B cell proliferation and production of antibodies specific for the vaccine proteins (30). Heterogeneity in immune responses among vaccine recipients can explain the variation in COVID-19 vaccine efficacy. It is well known that host-related factors such as age, sex, and obesity can impact vaccine efficacy (31). Recent studies on the immune responses of mRNA COVID-19 vaccines

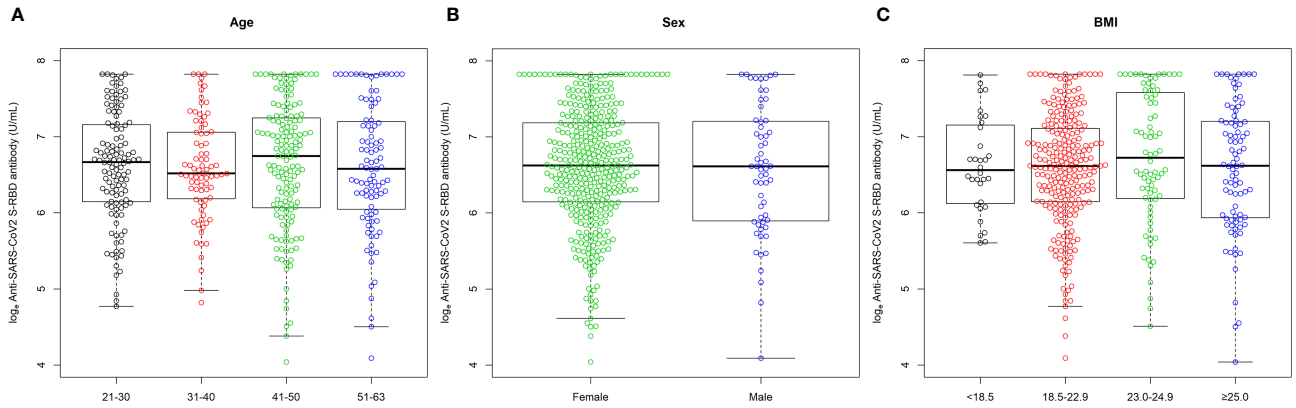

FIGURE 1 | Distribution of log-transformed (ln) antibody concentration at 4 weeks after the second injection of ChAdOx1 nCoV-19 vaccine according to **(A)** age (years) group, **(B)** sex, and **(C)** body mass index (kg/m^2) group. Antibody was expressed as the natural logarithm of concentration of anti-SARS-CoV-2 S protein RBD. Upper and lower whiskers represent the highest and lowest data points, respectively, excluding any outliers. The horizontal lines in the middle, top, and bottom of the box represent the median, 75th percentile, and 25th percentile, respectively.

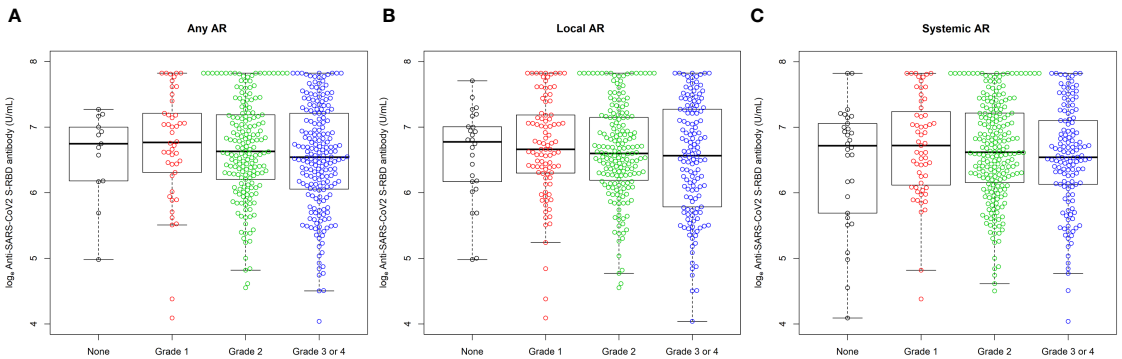

FIGURE 2 | Distribution of log-transformed (ln) antibody concentration at 4 weeks after the second injection of ChAdOx1 nCoV-19 vaccine according to severity of **(A)** any adverse reactions, **(B)** local adverse reactions, and **(C)** systemic adverse reactions to any ChAdOx1 nCoV-19 vaccination. Antibody was expressed as the natural logarithm of concentrations of anti-SARS-CoV-2 S protein RBD. Upper and lower whiskers represent the highest and lowest data points, respectively, excluding any outliers. The horizontal lines in the middle, top, and bottom of the box represent the median, 75th percentile, and 25th percentile, respectively.

reported lower antibody responses in subjects who are of older age, male, and obese (32). Contrary to the large body of evidence regarding this relationship in mRNA COVID-19 vaccines, such as the BNT162b2 COVID-19 vaccine, little is known about the impact of host factors on antibody responses to viral vector vaccines.

Older patients with COVID-19 showed decreased adaptive immune responses (33), which might contribute to higher mortality and worse outcomes than those in younger patients. In elderly people, decreased immune responses to other vaccines have been observed and explained by immunosenescence (34, 35). For immunogenicity of the BNT162b2 COVID-19 vaccine, a lower antibody response in older adults (65-85 years) than in younger adults (18–55) was observed in the clinical trial (36). These findings were confirmed from global real-world studies regardless of race (10–22). Interestingly, antibody responses to the mRNA-1273 COVID-19 vaccine in older adults were similar to those of younger adults in a clinical trial (37). While immune responses, including antibody responses, to the ChAdOx1 nCoV-19 vaccine were similar between young and old subjects in clinical trials (7, 38), real-world evidence is needed to evaluate the possible relationship between age and antibody responses of the ChAdOx1 nCoV-19 vaccine. Consistent with the observations from clinical trials, we found that age is not associated with antibody responses to the ChAdOx1 nCoV-19 vaccine.

In addition to age, associations of sex with vaccine responses have been acknowledged (39, 40). With the exception of a few vaccines, males are more likely to have lower antibody responses than females. Given the higher mortality and poorer outcomes of COVID-19 in males (41), it is very important to assess the impact of sex on the immunogenicity of COVID-19 vaccines. Previous studies on the association between sex and antibody responses to the BNT162b2 COVID-19 vaccine have not yielded

TABLE 2 | Linear regression models for natural log-transformed anti-SARS-CoV2 S-RBD antibody at 4 weeks after the second injection of ChAdOx1 nCoV-19 vaccine.

	Univariable analyses		Multivariable analyses					
	Standardized β	p-value	Standardized β[a]	p-value	Standardized β[b]	p-value	Standardized β[c]	p-value
Age (years)	-0.037	0.4327	-0.071	0.1721	-0.059	0.2465	-0.056	0.2899
Female	0.021	0.6613	0.039	0.4271	0.038	0.4442	0.029	0.5550
BMI (kg/m^2)	0.010	0.8375	0.038	0.4649	0.037	0.4716	0.032	0.5370
Severity of any AR	-0.072	0.1266	-0.095	0.0563	–		–	
Severity of local AR	-0.063	0.1817	–		-0.079	0.1079	–	
Severity of systemic AR	-0.017	0.7132	–		–		-0.035	0.4861

AR, adverse reaction; BMI, body mass index.

Multivariable models adjusted for age, sex, BMI, and [a] any AR; [b] local AR; [c] systemic AR.

consistent results. While some studies reported lower antibody concentration in males than in females (11, 13–15, 20, 22), this association was not observed in other studies (10, 12, 18, 42). In the present study, we found no significant difference in antibody response to the ChAdOx1 nCoV-19 vaccine between males and females. Our findings confirm previous observations from clinical trials that sex is not associated with cellular or antibody responses to the ChAdOx1 nCoV-19 vaccine (7).

Obesity, or high BMI, is a risk factor for morbidity and mortality of COVID-19 (43). Since obesity is known to interfere with the immune response to some vaccines, such as the hepatitis B and A vaccines and the influenza vaccine (44), concerns arose regarding possibly low efficacy and immunogenicity to COVID-19 vaccines in obese people (45). Clinical trials of mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273 COVID-19 vaccines) showed similar efficacy between people with or without obesity (2, 3). However, Pellini and colleagues reported decreased antibody responses to the first dose of BNT162b2 COVID-19 vaccine in a obesity or pre-obesity group among HCWs in Italy (19). In their analysis after the booster dose of the BNT162b2 COVID-19 vaccine, BMI was not significantly associated with antibody response (20). In the present study, we observed no difference in the concentration of anti-SARS-CoV-2 S protein RBD antibody between BMI groups in HCWs vaccinated with prime and booster doses of the ChAdOx1 nCoV-19 vaccine. These findings suggest that obesity is not related with antibody responses to the ChAdOx1 nCoV-19 vaccine.

The reasons are uncertain for why age and sex did not show association with antibody response after ChAdOx1 nCoV-19 vaccine in this study while old age and male sex are reported to be associated with low antibody response after mRNA COVID-19 vaccines. However, neutralizing antibody levels were shown to be relatively higher in mRNA COVID-19 vaccines, while ChAdOx1 nCoV-19 vaccine was shown to induce polyfunctional antibodies, which are capable of mediating neutralization and other antibody-dependent effector mechanisms (46). Therefore, the differences regarding the association of age and sex with antibody response may be caused by the fact that mRNA COVID-19 and ChAdOx1 nCoV-19 vaccines induce different kinds of antibodies.

Adverse reactions to vaccines can indicate a strong immune response (47). There are conflicting results on the associations between reactogenicity to the COVID-19 vaccine and antibody responses. Kontou et al. found that HCWs with any AR to the first or second injection of the BNT162b2 COVID-19 vaccine had higher antibody titers than those without any AR (14). Contrarily, other studies reported that the severity of local or systemic adverse reactions to the BNT162b2 COVID-19 vaccine is not related to antibody reactions (48, 49). Regarding the ChAdOx1 nCoV-19 vaccine, a previous study showed an association between antibody response and systemic AR, but not local reactions, after the first dose (50). In our study, we examined whether ARs to the first and second doses of the ChAdOx1 nCoV-19 vaccine were associated with anti-SARS-CoV-2 S protein RBD antibody titers 4 weeks after the second dose. Contrary to previous reports, we did not find significant difference in antibody concentration according to presence or severity of local or systemic adverse reactions. Furthermore, in the analysis of the ARs after the first and second vaccinations, there were no significant associations (**Supplementary Figures 2**, **3**). The inconsistent results can be explained by the difference in time points of the antibody measurements (after a single dose versus after two doses) and statistical analysis methods (univariable versus multivariable) among studies. Given that ARs occur more frequently in females and younger people (51), the associations between adverse reactions and antibody reactions should be analyzed after adjusting for these possible confounding factors.

The major strength of this study is that we demonstrated that subjects who were vaccinated with two doses of the ChAdOx1 nCoV-19 vaccine had acceptable antibody responses, and host factors of age, sex, BMI, and ARs were not associated with antibody reactions in a prospective observational real-world study. However, this study has limitations that should be acknowledged. First, while we measured anti-SARS-CoV-2 antibody, not the neutralizing antibody or cellular immune response, it cannot project overall immune response and neutralizing activity. Given the strong correlation between anti-SARS-CoV-2 antibody and neutralizing antibody concentrations (29), we assume that anti-SARS-CoV-2 antibody reflects protective immunity. Second, because antibody level can vary over time, a single measurement does not reflect overall antibody response and immunogenicity of the recipients. Therefore, we selected the day of antibody measurement based on knowledge that maximum antibody titer was observed 28 days after vaccination according to a previous clinical trial (7). Third, since this was a single-center study and the subjects were HCWs, the study population may not properly represent the general population. Older adults were not enrolled and majority

of the enrolled subjects (86.8%) were females. Thus, we could not determine the impact of older age (over 65 years) on antibody responses, and our claim that sex has little impact on antibody response is somewhat limited. While previous clinical trials in a small number of subjects showed similar immunogenicity among age groups (38) and sexes (49), further studies are warranted in a real-world setting with a large number of subjects. Fourth, there is a possibility that other host factors such as comorbidities or medications affected antibody responses to COVID vaccines. Since the subjects of this study were HCWs who had relatively fewer comorbidities than the normal population, we could not address this issue in this study.

In conclusion, subjects showed fair antibody responses after two doses of the ChAdOx1 nCoV-19 vaccine. Age, sex, and obesity were not associated with antibody responses after vaccinations. In addition, ARs to the vaccines did not predict the antibody responses to the ChAdOx1 nCoV-19 vaccine. These findings help assure the public and vaccine recipients of vaccine efficacy and immunogenicity.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Hanyang University Seoul Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SL and J-YM contributed equally to data analysis, data interpretation, and writing of the manuscript. S-KL, HL, and SL contributed to statistical analyses. S-HK and SL designed the study. YY, TP, DP, and T-HK contributed to data acquisition and clearing. JS, HY, and S-HK oversaw data analysis, data interpretation, and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.779212/full#supplementary-material

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