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Reactogenicity and Immunogenicity of the ChAdOx1 nCOV-19 Coronavirus Disease 2019 Vaccine in South Korean Healthcare Workers

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Purpose: The association between reactogenicity and immunogenicity of the ChAdOx1 nCOV-19 is controversial. We aimed to evaluate this association among South Korean healthcare workers (HCWs).

Materials and Methods: Participants received two doses of the ChAdOx1vaccine 12 weeks apart. Blood samples were tested for anti-severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) spike protein receptor binding domain antibodies about 2 months after the first and second doses using the Elecsys Anti-SARS-CoV-2 S assay kits. Adverse events were noted using an online self-reporting questionnaire.

Results: Among the 232 HCWs, pain (85.78% after the first dose vs. 58.62% after the second dose, $p<0.001$) was the most prominent local reaction, and myalgia or fatigue (84.05% vs. 53.02%, $p<0.001$) was the most prominent systemic reaction. The frequency of all adverse events was significantly reduced after the second dose. After the first dose, the anti-SARS-CoV-2 S showed significantly higher titer in the group with swelling, itching, fever, and nausea. Also, the anti-SARS-CoV-2 S titer significantly increased as the grade of fever ($p=0.007$) and duration of fever ($p=0.026$) increased; however, there was no significant correlation between immunogenicity and adverse event after the second dose. The group with pain after the first dose showed a greater increase in the anti-SARS-CoV-2 S difference between the second and first doses compared to the group without pain (542.2 U/mL vs. 363.8 U/mL, $p=0.037$).

Conclusion: The frequency of adverse events occurring after the first dose of the ChAdOx1 was significantly reduced after the second dose. Interestingly, the elevation of anti-SARS-CoV-2 S titer was significantly increased in the group with pain after the first dose.

Key Words: ChAdOx1 nCoV-19, immunogenicity, adverse events

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•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Ever since the first case of coronavirus disease 2019 (COVID-19) was reported in South Korea on January 19, 2020, it has continued to remain a significant threat to the healthcare system, with 1795791 confirmed cases leading to 23079 deaths in the country, as of May 4, 2022.[1] The overall vaccination rate (three doses) in South Korea is 64.4% (89.3% among those aged ≥ 60 years), which is one of the highest worldwide.

Vaccination is an effective medical countermeasure to the ongoing pandemic by providing herd immunity and preventing transmission via close contacts. In addition, vaccination still plays a key role at the time of endemic transition, as it pro-

tects disease progression and mitigates its severity.[2-4] The ChAdOx1 nCoV-19 vaccine (AZD1222) against COVID-19, which was developed at Oxford University, consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1.[5,6] As ChAdOx1 nCoV-19 has shown acceptable efficacy and safety,[7] it has been used in more than 50 countries under emergency use authorization. On February 26, 2021, South Korea launched a national COVID-19 vaccination campaign. According to the prioritization schedule determined by the Korea Disease Control and Prevention Agency, healthcare workers (HCWs) were considered to be at high risk for COVID-19. Therefore, HCWs were assigned in the early phase of the vaccination program and were vaccinated with the ChAdOx1 nCOV-19 vaccine, the fastest available in South Korea.

Reactogenicity is considered a physical manifestation of the expected immune response to vaccination.[8] However, the clinical implication of reactogenicity is unclear, and little is known about the association between reactogenicity and immunogenicity.[9] Therefore, this study aimed to evaluate the association between reactogenicity and immunogenicity of the ChAdOx1 nCOV-19 vaccine among South Korean HCWs.

MATERIALS AND METHODS

Study design and study population

This study included HCWs who voluntarily received two doses of the ChAdOx1 nCoV-19 vaccine against COVID-19 in Gangnam Severance Hospital, a university-affiliated tertiary center, with 879 inpatient admission capacity. Participants received two intra muscular injections 12 weeks apart according to the national vaccination guidelines. The first dose was administered between March 5 and March 26, 2021, and the second was administered between June 3 and June 12, 2021. The ChAdOx1 nCoV-19 vaccine used in South Korea was manufactured by Astra-Zeneca.

Approximately 2 months after the first dose of ChAdOx1 nCoV-19 was administered, a regular health checkup for HCWs was conducted between May 11 and June 14, 2021. At the time of examination, consent about using residual blood samples for research purpose was obtained. Some part of HCWs agreed to participate in the study using residual blood samples. Approximately 2 months after the second dose, a study confirming immunogenicity was announced, and the participants were prospectively enrolled. Additional blood samples were collected between August 16 and August 27, 2021.

The residual blood samples collected at the regular medical checkup after the first dose of ChAdOx1 nCoV-19 were analyzed based on the subjects who agreed to participate in the study after the second dose of vaccination. During this period, a questionnaire on adverse events was conducted. The data were collected comprehensively after a sufficient period of 2 months after the second dose of ChAdOx1 nCoV-19.

Clinical variables

All participants were asked about clinical variables using a self-reporting questionnaire, including 26 questions, through an internet-based platform (Google Surveys). We collected the participants' age, sex, underlying disease and medications, date of vaccination, local and systemic adverse events, duration of adverse events, and use of antipyretic drugs, such as acetaminophen or ibuprofen. Symptoms, signs, or other information related to vaccination were collected only for events within 14 days after each vaccination.

Local reactions included injection site pain/tenderness, redness, and itching. Systemic reactions included fever, nausea/vomiting, diarrhea, and fatigue/myalgia. Adverse events, other than itching, were assessed using the guidelines for toxicity grading scale for healthy adults and adolescent volunteers enrolled in preventive vaccine clinical trials conducted by the U.S. Food and Drug Administration.[10] The researchers established the severity grade for itching. Detailed definitions for the grades are provided in Supplementary Table 1 (only online).

During this period, myocarditis and immune thrombotic thrombocytopenia emerged as medical and social issue,[11] and the hospital director informed all HCWs that anyone complaining of atypical adverse events should contact the infectious disease specialists at any time. When these cases were suspected among the HCWs, anti-platelet factor 4 antibody assay or echocardiography was performed.

Antibodies against anti-SARS-CoV-2 spike protein receptor binding domain

Both serum samples after first and second doses of vaccination were tested for anti-SARS-CoV-2 spike (S) protein receptor binding domain (RBD) antibodies [including immunoglobulin (Ig)G]. In addition, Anti-SARS-CoV-2 nucleocapsid (N) was tested using a second serum sample to exclude previous COVID-19 infection. Antibodies against SARS-CoV-2 S protein were quantified using cobas e 801 immunoassay analyzer with Elecsys Anti-SARS-CoV-2 S assay kits (Roche Diagnostics GmbH, Mannheim, Germany). This assay utilizes the electrochemiluminescence immunoassay principle for the quantitative determination of antibodies (including IgG) to the SARS-CoV-2 S protein RBD in human serum. The assay ranges from 0.8 to 250 U/mL. The samples with results below 0.8 U/mL were regarded as negative for anti-SARS-CoV-2 S. When the initial assay result was greater than 250 U/mL, then the sample was diluted 10 times and assayed again. Consequently, anti-SARS-CoV-2 S was quantified in the range of 0.8 to 2500 U/mL. Meanwhile, the antibodies to the N protein of SARS-CoV-2 were qualitatively determined using the Elecsys Anti-SARS-CoV-2 N assay (Roche Diagnostics GmbH). The assay results were interpreted as nonreactive/negative (cutoff index <1) and reactive/positive (cutoff index ≥1). All assays in the present study were performed according to the manufacturer's instructions.

Ethics approval and consent

The protocol for this prospective study was reviewed and approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine in Seoul, Korea (Reg. No. 3-2021-0182 and 3-2021-0245). All procedures were conducted in accordance with the guidelines of the Declaration of Helsinki. The participants provided informed consent to participate in this study.

Statistical analysis

Continuous variables were presented as the mean±standard deviation or median (interquartile range). Categorical variables were presented as the frequency and percentage. The McNemar test was used to compare the proportion of participants who experienced adverse events after the first and second injection. The Jonckheere–Terpstra test was performed for the trend of anti-SARS-CoV-2 S titers according to the severity or duration of adverse events. We compared the differences in serologic titer between the second and first doses in participants with and without adverse events using the Mann–Whitney U test. Multivariable linear regression was conducted to determine whether specific factors among adverse events after the vaccination were associated with differences in serologic titer between the second and first doses. This regression model was adjusted for age, sex, and body mass index (BMI), which are known clinical confounding factors. All *p*-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R package, version 4.1.0 (http://www.R-project.org).

RESULTS

Study participants

There were 2608 HCWs in Gangnam Severance Hospital, a tertiary center in South Korea. Among them, 2562 (98.2%) HCWs received the first dose of the ChAdOx1 nCOV-19 vaccine in March 2021. Regular health checkups are conducted for HCWs in May of every year. In the regular health checkup conducted after the first dose injection, 1209 HCWs agreed to use their residual blood sample for research. The second dose of the ChAdOx1 nCOV-19 vaccine was administered in June 2021, and a total of 2542 (97.4%) HCWs received the second dose at this time. Among the participants, informed consent for prospective blood sample collection was obtained from 381 HCWs. Anti-SARS-CoV-2 S tests were conducted in August 2021.

Among the cohort of 381 HCWs, one had convalescent CO-

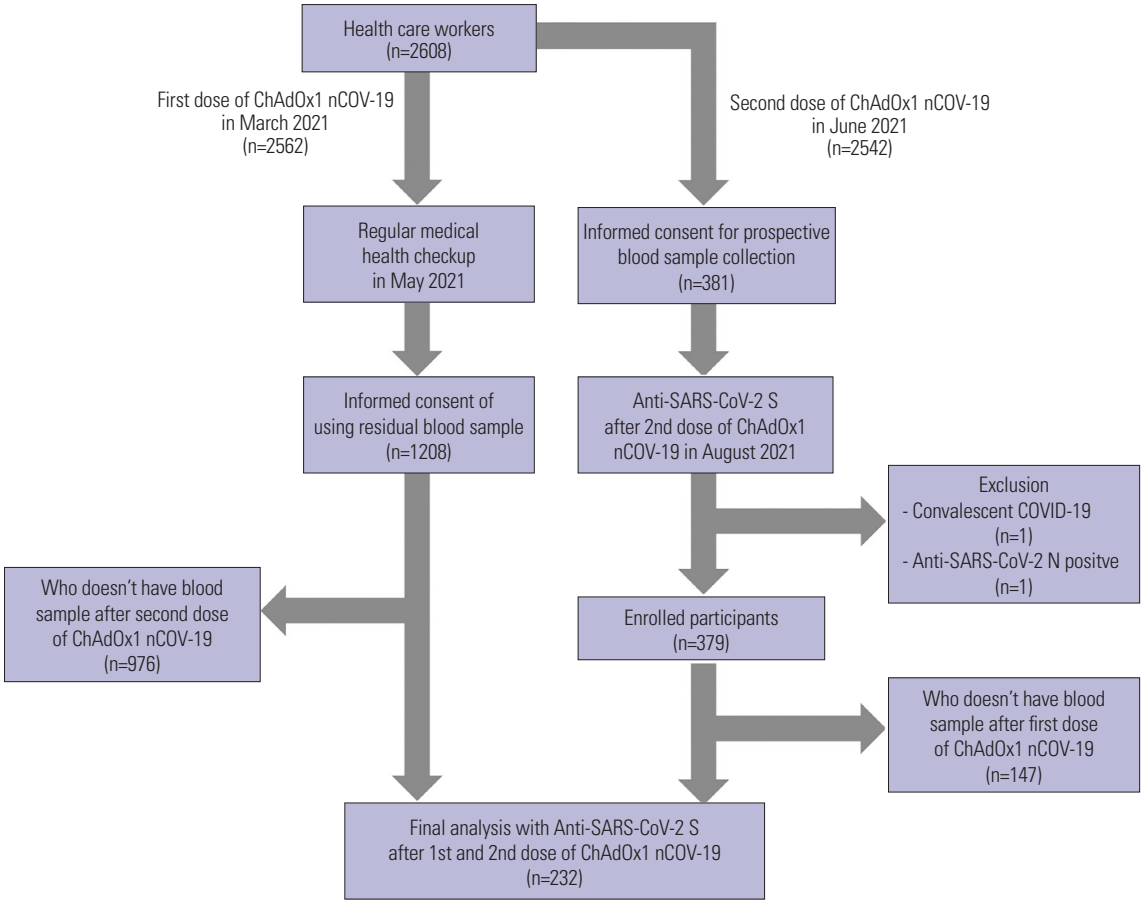

Fig. 1. Flow chart of participants enrolled in this study.

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VID-19, and one was anti-SARS-CoV-2 N-positive. Therefore, these two participants were excluded, and 379 HCWs were enrolled in the study. Among them, 232 HCWs for whom two blood samples were available were finally analyzed (Fig. 1).

Baseline characteristics of HCWs

A total of 232 HCWs were enrolled in the final analysis of this study. The mean age was 39±9.97 years, and 11.21% were male. The mean BMI was 22.14±3.39 kg/m^2 (Table 1). As shown in the gender imbalance, most occupational groups were nurses (53.45%) and ancillary medical providers (22.41%), which included medical assistants, including nursing assistants, physical therapists, occupational therapists, radiographers, emergency medical technicians, hospital porters, and clinical research coordinator. There were 20 physicians (8.62%), four dentists or dental assistants (1.72%), 18 healthcare and administrative staff (7.76%), and three HCWs (1.29%) who were in charge of treating the confirmed COVID-19 patients. Past medical history was investigated for comorbidities, such as hypertension, diabetes, and cardiovascular or cerebrovascular disease. Only the hypertensive underlying disease group accounted for 8.19% of total participants, and the proportion of participants with other medical history was less than 3%. For autoimmune diseases, five patients were taking immunosuppressants, such as oral steroids, and one patient with cancer was undergoing chemotherapy. The mean interval between the first or second vaccination dose and antibody test was 60.20±6.90 days or 74.50±5.30 days, respectively. The average anti-SARS-CoV-2 S titer after the first and second doses of ChAdOx1 nCOV-19 was 81.67±118.60 U/mL and 820.93±715.05 U/mL, respectively.

Table 1. Baseline Characteristics of 232 ChAdOx1 nCOV-19-Vaccinated Healthcare Workers in the Study

Characteristics	Value
Age, yr	39±9.97
Sex, male	26 (11.21)
Height, cm	168.14±88.33
Weight, kg	58.83±10.66
BMI, kg/m^2	22.14±3.39
Occupation, yes	
Physician	20 (8.62)
Nurse	124 (53.45)
Dentist or dental assistant	4 (1.72)
Ancillary medical*	52 (22.41)
Laboratory staff	14 (6.03)
Health care and administrative staff	18 (7.76)
High risk of COVID-19 exposure†, yes	3 (1.29)
Comorbidity, yes	
HTN	19 (8.19)
DM	6 (2.59)
Cardiovascular diseases	5 (2.16)
Cerebrovascular diseases	1 (0.43)
CKD	2 (0.86)
Liver diseases	2 (0.86)
Cancer on going chemotherapy	1 (0.43)
Autoimmune diseases with Immunosuppressive drug use	5 (2.16)
Time interval, days	
1st dose–2nd dose	81.79±5.41
1st dose–1st blood sample	60.20±6.90
2nd dose–2nd blood sample	74.50±5.30
Serologic positivity, U/mL	
After 1st dose	81.67±118.60
After 2nd dose	820.93±715.05

BMI, body mass index; HTN, hypertension; DM, diabetes; CKD, chronic kidney diseases.
All data are shown as mean±standard deviation or n (%).
*Ancillary medical providers are medical assistants, including nursing assistants, physical therapists, occupational therapists, radiographer, emergency medical technicians, hospital porters, and clinical research coordinator. Healthcare and administrative staff includes patient services assistants, clinical dietitians, facility engineers, biomedical researchers, and research assistants; †High risk of coronavirus disease 2019 (COVID-19) exposure means healthcare workers in contact with COVID-19 patients.

Adverse events within 14 days after ChAdOx1 nCOV-19 vaccination

A self-reported questionnaire was conducted to analyze the prevalence, severity, and duration of adverse events after administering two doses of the ChAdOx1 nCOV-19 vaccine. Pain or tenderness was the most prominent local reaction (85.78% after first dose vs. 58.62% after second dose, p<0.001), in addition to redness (16.38% vs. 7.76%, p=0.002), swelling (19.40% vs. 9.91%, p<0.001), and itching sense (17.24% vs. 8.19%, p<0.001) (Fig. 2A). In terms of systemic reactions (Fig. 2B), myalgia or fatigue (84.05% vs. 53.02%, p<0.001), headache (65.95% vs. 38.36%, p<0.001), and fever (37.93% vs.10.78%, p<0.001) were more common than nausea or vomiting (14.66% vs. 7.76%, p=0.002) and diarrhea (6.47% vs. 2.16%, p=0.004). The frequency of the nine adverse events were significantly reduced after the second dose compared to the first dose.

In addition, dizziness, palpitation, constipation, dyspepsia, paraesthesia, numbness of hands or feet, sweating, menorrhagia, tinnitus, sore throat, insomnia, and anorexia were collected as atypical adverse events within 14 days after vaccination using Google survey. No unusual or serious adverse events were found.

Immune thrombotic thrombocytopenia had been revealed to be a critical adverse event after the ChAdOx1 nCOV-19 vaccination.[11] If clinically suspected, we tested for it using the anti-platelet factor 4 antibody assay among the HCWs at our hospital; however, no such event was reported among the 232 HCWs in this study.

Anti-SARS-CoV-2 S titer after ChAdOx1 nCOV-19 vaccination

Two months after the injection of the first dose, the anti-SARS-CoV-2 S showed significantly higher titer in groups with swell-

ing [median (IQR; Q1–Q3), 72.8 (44.9–128.5) vs. 48.7 (27.4–91.9) U/mL, p=0.002], itching [78.6 (39.1–124.5) vs. 50.1 (30.5–94.4), p=0.032], fever [67.1 (39.1–111.0) vs. 49.9 (26.7–88.8), p=0.024], and nausea or vomiting [78.6 (41.8–129.0), vs. 52.7 (31.7–92.4), p=0.039] (Table 2). However, 2 months after the second dose, the anti-SARS-CoV-2 S did not show a significant correlation with adverse events after the second vaccination (Table 3). Only pain after the first dose of ChAdOx1 nCOV-19 showed a significant difference in anti-SARS-CoV-2 S titer after the second dose [646 (381.0–1070.0) vs. 407.0 (231.0–821.5), p=0.019].

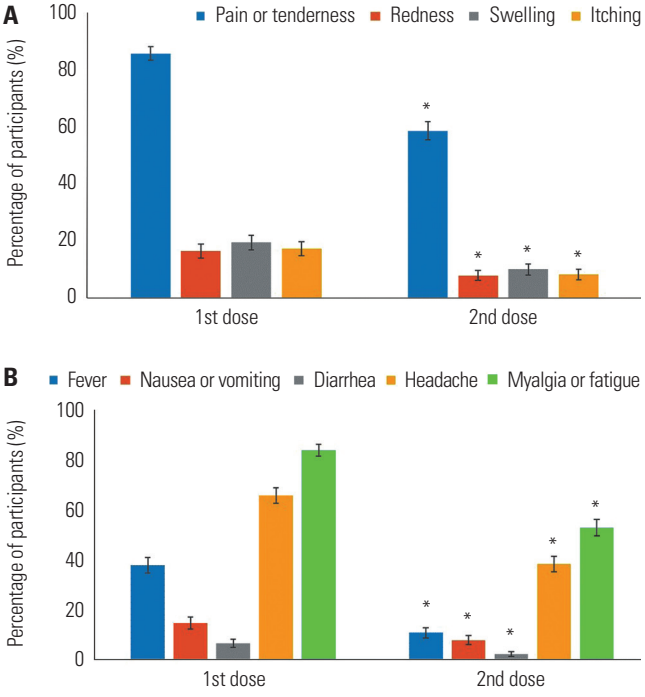

Fig. 2. Adverse events within 14 days after ChAdOx1 nCOV-19 vaccination. (A) Local reaction. (B) Systemic reaction. *All p-values were less than 0.05.

Anti-SARS-CoV-2 S according to adverse event severity

In local adverse events, the anti-SARS-CoV-2 S titer in swelling (p=0.002) and itching (p=0.036) after the first dose showed an increasing trend according to the grade of severity. In systemic adverse events, the anti-SARS-CoV-2 S titer significantly increased according to the fever grade after the first dose (p=0.007). In systemic adverse events with nausea or vomiting, the anti-SARS-CoV-2 S titer increased up to G2, but it was lower in G3 (p=0.039). It showed a similar trend in the analysis of local adverse events with swelling and itching. In the case of headache and myalgia/fatigue, anti-SARS-CoV-2 S titers tended to increase as the severity of adverse events increased after the first dose; however, no statistical significance was noted. Also, there was no correlation between any local and systemic reactions and immunogenicity after the second dose (Fig. 3).

Anti-SARS-CoV-2 S according to adverse event duration

In the local adverse events, the anti-SARS-CoV-2 S titer showed a significant increasing trend as the duration of adverse event

Table 2. Anti-SARS-CoV-2 S Titer after the First Doses of ChAdOx1 nCOV-19 according to Adverse Reactions

Adverse events	After 1st dose		p value
	Yes	No	
Pain or tenderness	56.8 (33.2–103.0)	42.9 (19.3–91.2)	0.063
Redness	60.3 (40.2–106.5)	55.4 (30.3–102.2)	0.226
Swelling	72.8 (44.9–128.5)	48.7 (27.4–91.9)	0.002
Itching	78.6 (39.1–124.5)	50.1 (30.5–94.4)	0.032
Fever	67.1 (39.1–111.0)	49.9 (26.7–88.8)	0.024
Nausea or vomiting	78.6 (41.8–129.0)	52.7 (31.7–92.4)	0.039
Diarrhea	82.5 (36.5–95.3)	55.5 (31.6–104.0)	0.437
Headache	59.8 (33.7–106.5)	49.3 (26.2–82.1)	0.101
Myalgia or fatigue	56.8 (33.2–103.0)	45.7 (26.8–68.1)	0.169

SARS-CoV-2, severe respiratory syndrome-coronavirus-2.
Anti-SARS-CoV-2 S titer (U/mL) are shown as median and interquartile range (Q1–Q3). Anti-SARS-CoV-2 titer was assessed using serum collected 2 months after the first dose of ChAdOx1 nCOV-19.

Table 3. Anti-SARS-CoV-2 S Titer after the Second Doses of ChAdOx1 nCOV-19 according to Adverse Reactions

Adverse events	After 1st dose		p-value	After 2nd dose		p value
	Yes	No		Yes	No	
Pain or tenderness	646.0 (381.0–1070.0)	407.0 (231.0–821.5)	0.019	642.0 (375.0–1117.7)	597.5 (355.0–925.2)	0.165
Redness	793.0 (415.7–1083.2)	609.0 (357.0–1000.0)	0.151	800.0 (516.7–1094.5)	616.0 (359.7–1000.0)	0.290
Swelling	619.0 (409.5–889.5)	630.0 (359.0–1050.0)	0.768	773.0 (519.0–1123.0)	616.0 (358.5–983.0)	0.177
Itching	628.5 (379.7–983.2)	623.0 (360.2–1037.5)	0.831	534.0 (367.0–832.0)	630.0 (363.5–1025.0)	0.337
Fever	575.5 (354.0–953.5)	656.5 (377.2–1043.0)	0.251	569.0 (269.0–826.5)	648.0 (370.0–1022.0)	0.421
Nausea or vomiting	623.0 (478.0–976.0)	624.5 (358.7–1005.5)	0.755	556.0 (422.2–782.2)	647.0 (364.7–1029.0)	0.512
Diarrhea	582.0 (299.0–907.0)	630.0 (366.5–1060.0)	0.575	299.0 (243.0–589.5)	630.0 (371.0–1022.0)	0.065
Headache	638.0 (371.5–1011.0)	606.0 (354.0–964.0)	0.586	616.0 (368.5–978.5)	630.0 (361.0–1011.0)	0.910
Myalgia or fatigue	619.0 (367.0–966.0)	630.0 (360.5–1221.5)	0.687	1050.0 (646.0–1770.2)	960.5 (606.0–1534.0)	0.543

SARS-CoV-2, severe respiratory syndrome-coronavirus-2.
Anti-SARS-CoV-2 S titer (U/mL) are shown as median and interquartile range (Q1–Q3). Anti-SARS-CoV-2 titer was assessed using serum collected 2 months after the second dose of ChAdOx1 nCOV-19.

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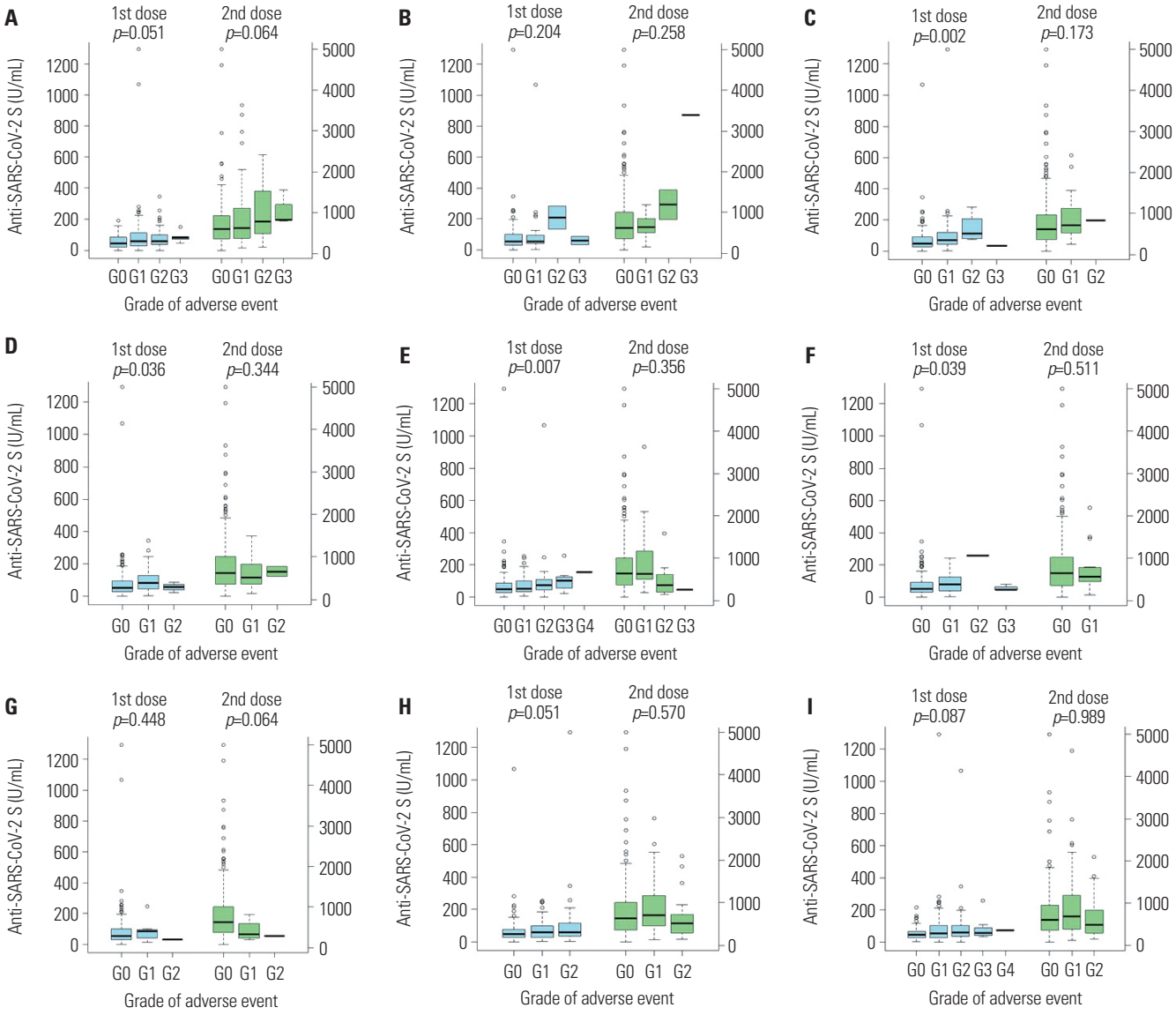

Fig. 3. Anti-SARS-CoV-2 S titer according to the adverse event severity within 14 days after ChAdOx1 nCOV-19 vaccination. (A) Pain or tenderness. (B) Redness. (C) Swelling. (D) Itching. (E) Fever. (F) Nausea or vomiting. (G) Diarrhea. (H) Headache. (I) Myalgia or fatigue. Each anti-SARS-CoV-2 titer was assessed using serum collected 2 months after each dose of ChAdOx1 nCOV-19. SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

was longer, especially in terms of pain/tenderness (p=0.013), swelling (p<0.001), and itching (p=0.006) after the first dose. In the systemic adverse events, the anti-SARS-CoV-2 S titer significantly increased as the duration of fever increased after the first dose (p=0.026). In nausea/vomiting (p=0.013) and headache (p=0.040) systemic reactions, the anti-SARS-CoV-2 S titer increased up to 7 days, but was lower in 14 days. In other systemic reactions, diarrhea and myalgia/fatigue showed no correlation between symptom duration and immunogenicity of vaccination. However, after the second dose, the anti-SARS-CoV-2 S titer and duration of adverse events showed no significant correlation (Fig. 4).

Differences in the anti-SARS-CoV-2 S titer between the second and first doses of ChAdOx1 nCOV-19

The differences in anti-SARS-CoV-2 S titer between the second and first doses of ChAdOx1 nCOV-19 were analyzed based on adverse events. Only pain or tenderness reactions after the first dose showed clinical significance (Supplementary Table 2, only online). The group with pain or tenderness after the first dose showed a greater increase of anti-SARS-CoV-2 S titer compared to the group without pain or tenderness (542.2 vs. 363.8 U/mL, p=0.037). The visual presentation is shown in Fig. 5. This showed the same trend even after adjusting for age, gender, and BMI using multivariable linear regression analysis (Table 4). The age and BMI were not significantly associated with anti-SARS-CoV-2 S titer increase. Among the adverse events groups, pain or tenderness after the first dose showed a positive

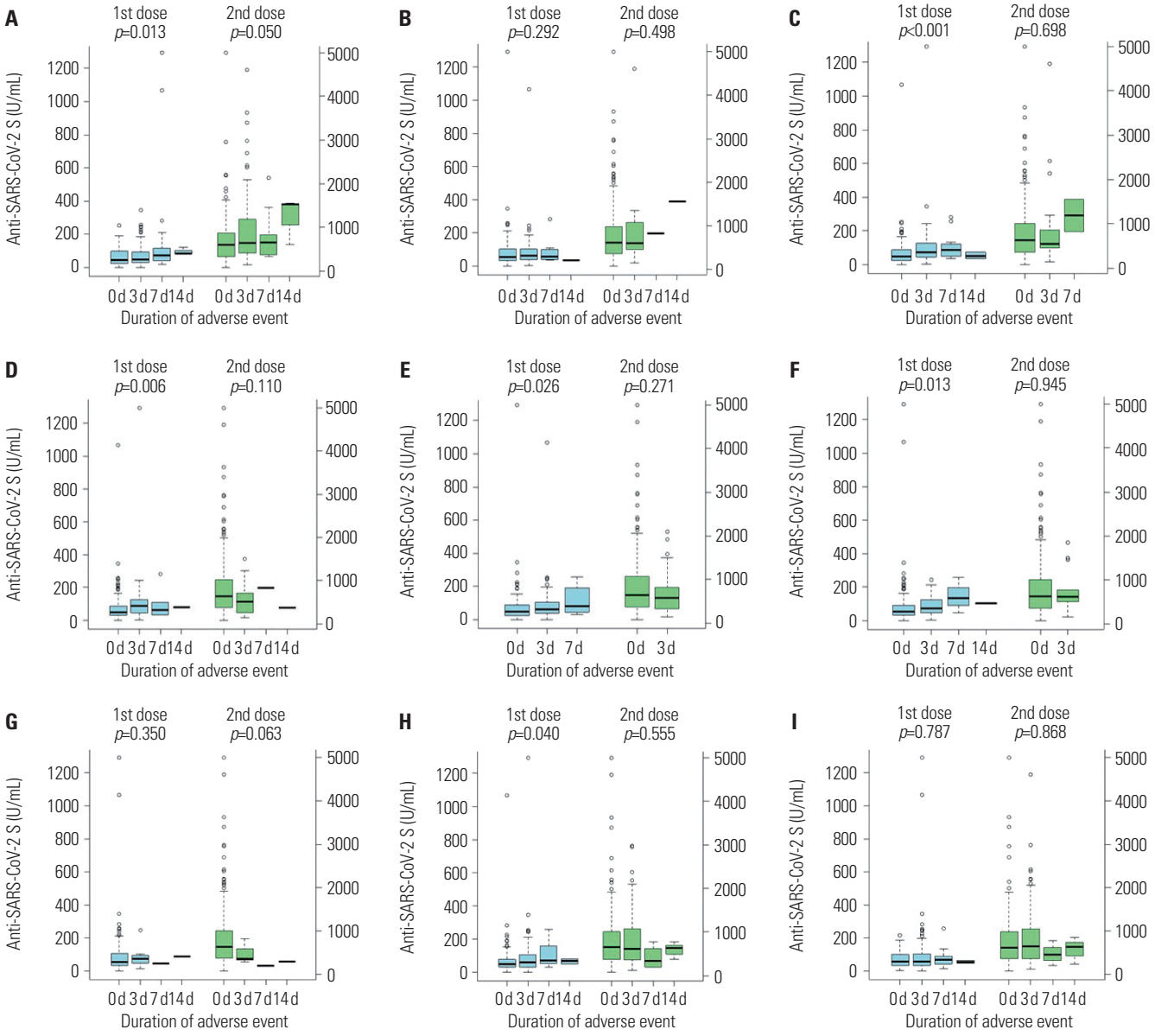

Fig. 4. Anti-SARS-CoV-2 S titer according to the adverse event duration within 14 days after ChAdOx1 nCOV-19 vaccination (A) Pain or tenderness. (B) Redness. (C) Swelling. (D) Itching. (E) Fever. (F) Nausea or vomiting. (G) Diarrhea. (H) Headache. (I) Myalgia or fatigue. Each anti-SARS-CoV-2 titer was assessed using serum collected 2 months after each dose of ChAdOx1 nCOV-19. SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

correlation with the differences of anti-SARS-CoV-2 S titer between the second and first doses (p=0.046), and this trend was also observed in the male sex subgroup (p=0.017).

DISCUSSION

The results of this study provide preliminary idea about the frequency of localized and systemic adverse events after two doses of ChAdOx1 nCOV-19 vaccinations among South Korean HCWs. The frequency of all local and systemic adverse events after the second dose was significantly reduced compared to that after the first dose (Fig. 2). In other studies about the reactogenicity of COVID-19 vaccines, the common local adverse event was pain at the injection site, and common systemic adverse events were headache or fatigue, in line with our results.[7,9,12,13] Other reports have also shown that the frequency of adverse events after receiving the ChAdOx1 nCOV-19 vaccine decreased after the second dose compared to the first dose.[7,14,15]

The reason for not including the analysis after the booster shot in this study was that heterologous booster vaccination was performed among South Korean HCWs. The mRNA-based vaccination was performed for booster shots,[16] and we analyzed the comparison of homogenous platform vaccine responses.

In addition, when the degree of adverse events was stratified according to the severity, adverse events such as swelling,

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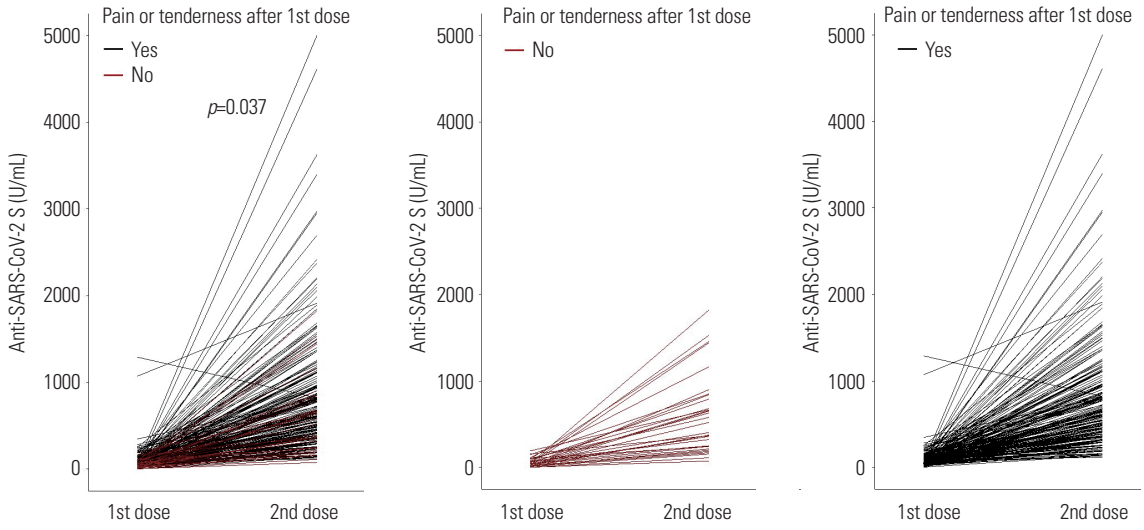

Fig. 5. Differences of anti-SARS-CoV-2 S titer between the second and first doses of ChAdOx1 nCOV-19 according to pain or tenderness localized reaction. SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2.

Table 4. Multivariable Linear Regression Model Associated with Differences in the Anti-SARS-CoV-2 S Titer between the Second and First Doses of ChAdOx1 nCOV-19

Variables	β (SE)	*p* value
Pain or tenderness after first dose of ChAdOx1 nCOV-19	271.537 (135.69)	0.046
Age	0.017 (4.94)	0.997
Sex, male	380.984 (159.51)	0.017
BMI	-0.585 (14.96)	0.968

BMI, body mass index; SE, standard error; SARS-CoV-2, severe respiratory syndrome-coronavirus-2.

itching, fever, and nausea or vomiting after the first dose were significantly related to the anti-SARS-CoV-2 S titer. As the severity of adverse events increased, the anti-SARS-CoV-2 S titer also tended to increase. This trend was the same in the analysis related to the adverse event duration, as well as headache duration. However, all values were not significant after the second dose, unlike the results after the first dose.

Two months after the second vaccination, the final anti-SARS-CoV-2 S titer using serum showed no correlation between adverse events after the second dose and immunogenicity. However, only the group with pain or tenderness after the first dose of ChAdOx1 nCOV-19 showed significantly high titer in the second serum. The difference in anti-SARS-CoV-2 S titer between the first and second doses according to the presence of each adverse event showed a significant increase in the group with pain after the first dose compared to the group without pain. Even after adjusting for age, sex, and BMI, the pain at the fist dose of vaccination site still affected the change in anti-SARS-CoV-2 S titer, same as in the male subgroup. In this study, gender was adjusted in the multivariate linear regression model, and subgroup analysis was performed to overcome some of these effects. However, as the extent of the effect of gender difference remains unclear, caution is needed in interpreting the results of this study. Moreover, since this study included a small sample size and only a small proportion of male HCWs, further studies with larger sample size are required.

Reactogenicity refers to adverse events that occur after vaccination, and the adverse events can include local symptoms, such as pain, redness, swelling, and itching at the injection site, as well as systemic symptoms, such as fever, nausea, diarrhea, headache, and myalgia. After injection, local cells are stimulated, followed by immune cells' migration to the injection site. As a result, multiple immune factors such as cytokines, vasodilators, and complement factors are produced, developing local symptoms, and their passage into the bloodstream contributes to the development of systemic symptoms.[8] Since this reactogenicity is the result of an innate and adaptive immune response, it is commonly believed that reactogenicity and immunogenicity are closely correlated.[17] For example, HBsAg-adjuvanted vaccines against the hepatitis B virus demonstrated a significant association between systemic reactogenicity and inflammatory markers, such as interleukin-6 or interferon-γ signals.[18]

During the COVID-19 pandemic, many studies investigated the association between reactogenicity and immunogenicity; however, the results were inconsistent. In previous ChAdOx1 nCOV-19 studies, the anti-SARS-CoV-2 S protein RBD concentration was not associated with the presence and severity of adverse events after two doses of the ChAdOx1 nCOV-19 vaccine.[19] For the 135 adults who received a SARS-CoV-2 vaccine (ChAdOx1 nCOV-19 or BNT162b2), the grades of local and systemic adverse events were not significantly associated with anti-S1 IgG levels in the ChAdOx1 nCOV-19 or BNT162b2 vaccines.[9]

In other vaccine platform studies, severity scores of adverse events following the BNT162b2 vaccination (Pfizer-BioNTech)

also showed no correlation with antibody titers at 1 month after the vaccination.[20] In addition, reactogenicity after the second dose of the BNT162b2 vaccine was not associated with serum antibodies against spike IgG.[21]

However, other studies have proposed that the severity of adverse events were surrogate markers of antibody response.[22,23] For example, the degrees of the local adverse events after the two doses of ChAdOx1 nCov-19 were significantly associated with the S1-specific IgG Ab titers.[24] A fever of over 38°C after the second dose of the BNT162b2 vaccine was associated with a higher concentration of circulating spike IgG titers.[25] In other studies, participants with systemic reactions tended to have higher antibody titers from 3 to 6 months after the second dose of the BNT162b2 vaccine.[26] In another study, the total score of vaccination side effects was positively correlated with antibody response after the BNT162b2 vaccination.[27] Therefore, the results of this study can serve as additional medical support and evidence for future studies on vaccination against COVID-19.

This study has several limitations. First, it was impossible to confirm immunogenicity, such as T-cell response, by measuring only the binding antibody. In addition, anti-SARS-CoV-2 S titers were measured using serum collected at 60.2 days after the first dose and 74.5 days after the second dose. Since the antibody titers were compared after an average of 2 months after the vaccination, the waning of immunity must be considered. Also, there may be a recall bias in collecting questionnaires about adverse events and duration after ChAdOx1 nCov-19. Second, since HCWs were the participants of this study, only active age populations were included; therefore, the effect on the immune response of elderly individuals cannot be known. Third, it is difficult to compare the results for mRNA-based vaccines, as only two doses of the adenovirus-based vaccine platform were studied. Lastly, the gender ratio of HCWs in our hospital is 29%:71% (male:female). Since many nursing women participated in the study, it seems that the proportion of male participants has decreased in particular, indicating a gender distribution bias.

This study also has its strengths. It has a novelty in that it compares not only the frequency of adverse events, but also the duration of adverse events and antibody titers. In addition, the study demonstrated that pain after the first dose of the ChAdOx1 nCOV-19 vaccine was significantly related an increase in antibody titer differences between the second and first doses of vaccination. Fig. 5 presents an excellent visualization of the conclusion. Therefore, the results of this study can be used as evidence for the correlation between adverse events and antibody titers after vaccinations.

In conclusion, the frequency of adverse events occurring after the first dose of the ChAdOx1 nCOV-19 vaccine was significantly reduced after the second dose. The severity and duration of fever after the first dose of vaccination showed a correlation with the anti-SARS-CoV-2 S titer after the first dose. However, no significant correlation was observed after the second dose. Interestingly, the elevation of anti-SARS-CoV-2 S titer between the second and first doses was significantly increased in the group with pain or tenderness after the first dose compared to the group without pain.

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