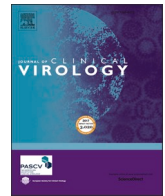




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Comparison of humoral immunogenicity in solid organ transplant recipients after third-dose mRNA vaccine with homologous or heterologous schedules: An observational study

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ABSTRACT

Background: Solid organ transplant recipients (SOTRs) are susceptible to severe coronavirus disease 2019 (COVID-19); however, immunogenicity studies of the Omicron variants per vaccination schedules are still lacking. We examined humoral immunogenicity following third-dose mRNA vaccine administration in Korean SOTRs who received primary COVID-19 vaccine series on homologous or heterologous schedules.

Methods: We recruited SOTRs at Severance Hospital from October 27, 2021, to March 31, 2022. Blood samples were collected between 14 days and 5 months after the second and third mRNA vaccine (BNT162b2 or mRNA-1273) doses. SARS-CoV-2 anti-spike IgG titer was analyzed. The neutralization inhibition rate was analyzed using the surrogate neutralization assay for the wild-type, Delta, and Omicron variants.

Results: No significant differences existed in the SARS-CoV-2 anti-spike IgG positivity rate between the homologous BNT162b2/BNT162b2/BNT162b2 (85%) and other heterologous groups (83% of ChAdOx1/ChAdOx1/BNT162b2, 90% of ChAdOx1/ChAdOx1/mRNA-1273, and 78% of ChAdOx1/BNT162b2/BNT162b2). No significant difference existed in the neutralization inhibition rates between the four groups for wild-type, Delta, and Omicron variants. Median neutralization inhibition rates against the Omicron variant (2–5%) were significantly lower than those against the wild-type (87–97%) and Delta (55–89%) variants ($P < 0.001$).

Conclusions: Regardless of the schedule, the neutralization inhibition rate against the Omicron variant was poor; therefore, additional preventive measures are required in such high-risk populations.

1. Background

Solid organ transplant (SOT) recipients (SOTRs) are immunocompromised individuals representing a high-risk population for severe coronavirus disease 2019 (COVID-19) [1–4]. Despite their vulnerability, a recent meta-analysis reported that the vaccine-induced seroconversion

rate after the primary series of COVID-19 vaccines in SOTRs is as low as 6% compared with that in immunocompetent individuals [5]. Moreover, the vaccine-induced neutralization against the Omicron (B.1.1.529) variant and subvariants, which is currently the dominantly circulating strain worldwide, is remarkably low compared to that against the wild-type variant [6–8]. Therefore, the World Health Organization and

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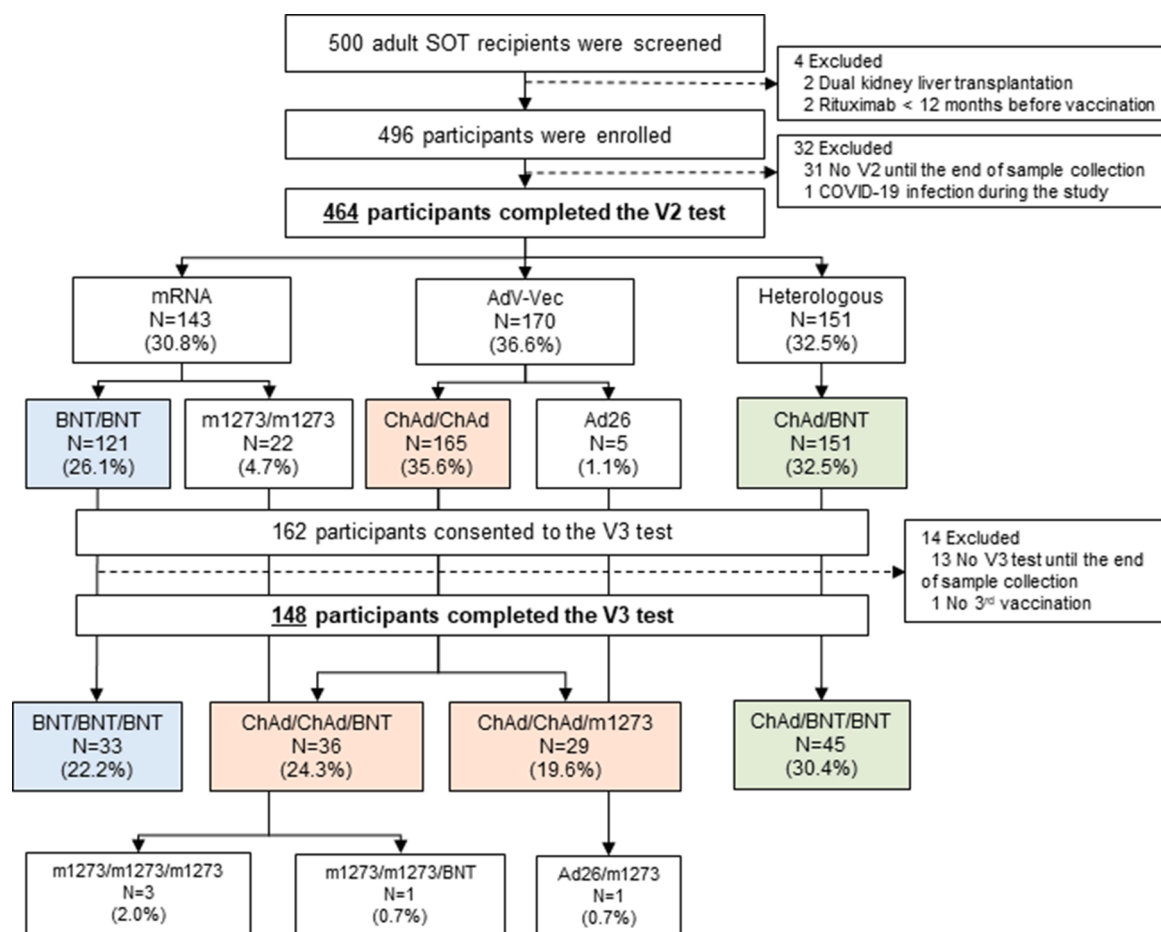


Fig. 1. Study flow of participants.

V2 denotes the visits between 14 and 150 days (5 months) after the second shot of the primary series of COVID-19 vaccination. V3 represents the visits between 14 and 150 days (5 months) after the third shot. Ad26 = Ad26.COVS vaccine (Johnson & Johnson/Janssen, Belgium); AdV-Vec = adenoviral vector vaccine; BNT = BNT162b2 vaccine (BioNTech-Pfizer, Germany/US); ChAd = ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca, UK); m1273 = mRNA-1273 vaccine (Moderna, US); mRNA = mRNA vaccine; COVID-19, coronavirus disease 2019; SOT = solid organ transplant.

health authorities of several countries are recommending additional COVID-19 vaccinations for immunocompromised individuals [9,10]. For example, as of July 1, 2022, the Centers for Disease Control and Prevention in the United States recommended three doses of the primary series of vaccination and two doses of booster shots in immunocompromised individuals, and the Korea Disease Control and Prevention Agency recommended three doses of the primary series of vaccination and one dose of a booster shot [11,12].

Additionally, various heterogeneous COVID-19 vaccination schedules are being widely implemented. The immunogenicity of heterologous vaccination (mRNA vaccine as a second or booster shot) is generally regarded to be similar to that of mRNA-based homologous vaccination in immunocompetent individuals [13–15]. However, most studies on the immunogenicity of the COVID-19 vaccination in SOTs have been conducted on homologous mRNA vaccine schedules. In addition, comparisons between homologous and heterologous vaccination schedules in SOTs, particularly for the Omicron variant, are limited.

Previously, we compared the humoral immunogenicity of the primary series of COVID-19 vaccination (homologous/heterologous schedules, two shots) against the wild-type variant in Korean adult SOTs [16]. As a follow-up study, we examined the humoral immunogenicity after the third dose of an mRNA vaccination in Korean adult SOTs who received a homologous or heterologous schedule of the primary series of COVID-19 vaccination. In addition to the wild-type variant, we evaluated the immunogenicity against the Delta

(B.1.617.2) and Omicron variants, which have been prevalent worldwide since July 2021 [17]. We also explored the correlations between immunoassay tests according to SARS-CoV-2 strains.

2. Materials and methods

2.1. Study design

This non-matched observational study was conducted at Severance Hospital, Seoul, Korea. Participant recruitment was conducted from October 27, 2021, to March 31, 2022, and serum samples were collected from December 2021 to March 2022. Serum samples were collected with additional blood draws during blood collection for clinical purposes when the participant visited the outpatient clinic between 14 and 150 days after receiving the third dose (V3) of the COVID-19 vaccine. Written consent was obtained again from participants, and the study protocol was approved by the Institutional Review Board of Severance Hospital (4–2021–0985). Sampling procedures and data collection methods are described in a previous study [16]. A detailed COVID-19 vaccination program in Korea was described in Supplemental Method 1.

2.2. Participants

Adult SOTs (aged ≥ 18 years at the time of the first vaccination) who had participated in the previous study were eligible [16]. Of these participants, those who had received or were willing to receive the third

Table 1
Characteristics of the study participants.

Variable		BNT/BNT /BNT N = 33		ChAd/ChAd /BNT N = 36		ChAd/ChAd m1273 N = 29		ChAd/BNT /BNT N = 45	
		N or median	% or (Q1, Q3)	N or median	% or (Q1, Q3)	N or median	% or (Q1, Q3)	N or median	% or (Q1, Q3)
Sex	Male	17	51.5	21	58.3	20	69.0	28	62.2
	Female	16	48.5	15	41.7	9	31.0	17	37.8
Age at SOT	Years	46	31–53	55	49–59	55	50–57	45	38–54
	<60	29	87.9	29	80.6	23	79.3	42	93.3
	≥60	4	12.1	7	19.4	6	20.7	3	6.7
SOT type	KT	13	39.4	16	44.4	8	27.6	43	95.6
	LT	20	60.6	20	55.6	21	72.4	2	4.4
BMI (kg/m ²)	<25	22	66.7	25	69.4	26	89.7	37	82.2
	≥25	11	33.3	11	30.6	3	10.3	8	17.8
Underlying conditions	None	14	42.4	8	22.2	9	31.0	11	24.4
	Diabetes	8	24.2	14	38.9	11	37.9	14	31.1
	Hypertension	15	45.5	21	58.3	16	55.2	29	64.4
	Cardiovascular disease ^a	4	12.1	6	16.7	2	6.9	2	4.4
Cigarette smoker	No	18	54.5	19	52.8	11	37.9	24	53.3
	Ex-/Current smoker	15	45.5	17	47.2	18	62.1	21	46.7
SARS-CoV vaccine-related information									
Age at the first dose of vaccination	Years	54	45–60	64	60–67	64	62–68	55	46–62
	<60	25	75.8	9	25.0	1	3.4	32	71.1
	≥60	8	24.2	27	75.0	28	96.6	13	28.9
Intervals between SOT and the first dose of vaccination	Months	121	63–159	113	60–160	131	99–167	85	51–138
	≤60 months								
	>60 months								
Intervals between first and second shots	Days	38	22–43	78	78–78	78	78–78	78	78–78
Intervals between second and third shots	Days	86	71–113	89	79–110	106	94–114	120	113–138
Intervals between the third (second for Ad26) shot and V3	Days	37	27–51	51	40–69	45	36–61	56	36–75
	14–60 days	27	81.8	20	55.6	21	72.4	27	60.0
	61–150 days	6	18.2	16	44.4	8	27.6	18	40.0
Use of IS drugs									
Number of IS drugs	≤2	17	51.5	17	47.2	16	55.2	10	22.2
	>2	16	48.5	19	52.8	13	44.8	35	77.8
Main IS drug	No	0	0.0	0	0.0	0	0.0	1	2.2
	Tacrolimus	31	93.9	33	91.7	27	93.1	40	88.9
	≤5	14	45.2	14	42.4	11	40.7	12	30.0
	>5	17	54.8	19	57.6	16	59.3	28	70.0
	Cyclosporine	2	6.1	3	8.3	2	6.9	4	8.9
mTOR inhibitor ^b	No	30	90.9	33	91.7	28	96.6	44	97.8
	Yes								

Data shown as medians (Q1–Q3) or n (%). Q1 = lower interquartile; Q3 = upper interquartile; BNT = BNT162b2 vaccine (BioNTech-Pfizer, Germany/US); m1273 = mRNA-1273 vaccine (Moderna, US); ChAd = ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca, UK); IQR = interquartile range; SOT = solid organ transplant; KT = kidney transplantation; LT = liver transplantation; BMI = body mass index; IS = immunosuppressive; mTOR = mammalian target of rapamycin. Calculated as the sum of the main IS drug, antimetabolite, the mTOR inhibitor, and other IS drugs and steroids at the time of initiation of COVID-19 vaccination.

^a Indicates angina/acute myocardial infarction, arrhythmia, and/or heart failure.

^b Indicates sirolimus or everolimus.

shot were recruited in this study. The exclusion criteria were as follows: (1) recipients within 90 days of SOT at the time of the first shot of the SARS-CoV-2 vaccine, (2) recipients of rituximab within the year prior to receiving the first shot of the SARS-CoV-2 vaccine, (3) recipients with medical conditions in which vaccination is difficult because of modulation of immunosuppressive agents due to graft rejection or acute illness, and/or (4) recipients with SARS-CoV-2 infection history during the study period or serologic evidence of SARS-CoV-2 infection that was checked during the visit during V2 (between 14 and 150 days after the second dose) and V3. Qualitative detection of the IgG antibody against the N protein (Abbott Diagnostics, Abbott Park, IL, USA; detection cut-off < 1.4) was performed for serologic exclusion of past SARS-CoV-2 infection.

2.3. Outcomes

As a primary outcome, we compared the humoral immunogenicity between the COVID-19 vaccination groups by measuring positivity rate,

SARS-CoV-2 anti-S IgG titer, and neutralization inhibition rate (%) at V3. Enzyme-linked immunosorbent assay (ELISA) using the SARS-CoV-2 IgG II Quant assay (Abbott Diagnostics, Abbott Park, IL, USA; detection cut-off < 7.1 BAU/mL) and surrogate neutralizing antibody assay (sNAA) using the cPass SARS-CoV-2 Neutralization Antibody Detection kit (GenScript Inc., Piscataway, NJ, USA; protection cut-off < 30%) were performed according to the manufacturer's instructions. The neutralization inhibition rate was evaluated against the wild-type, Delta, and Omicron variants. As secondary outcomes, predicting factors affecting humoral immunogenicity were explored.

2.4. Statistical analyses

The sample sizes for analysis were not based on statistical hypothesis, and we attempted to enroll as many participants as possible from among those enrolled in the previous study. The positive rates between vaccination groups [BNT162b2 vaccine (BioNTech-Pfizer, Germany/US; hereafter referred to as BNT)/BNT/BNT as a reference group] were

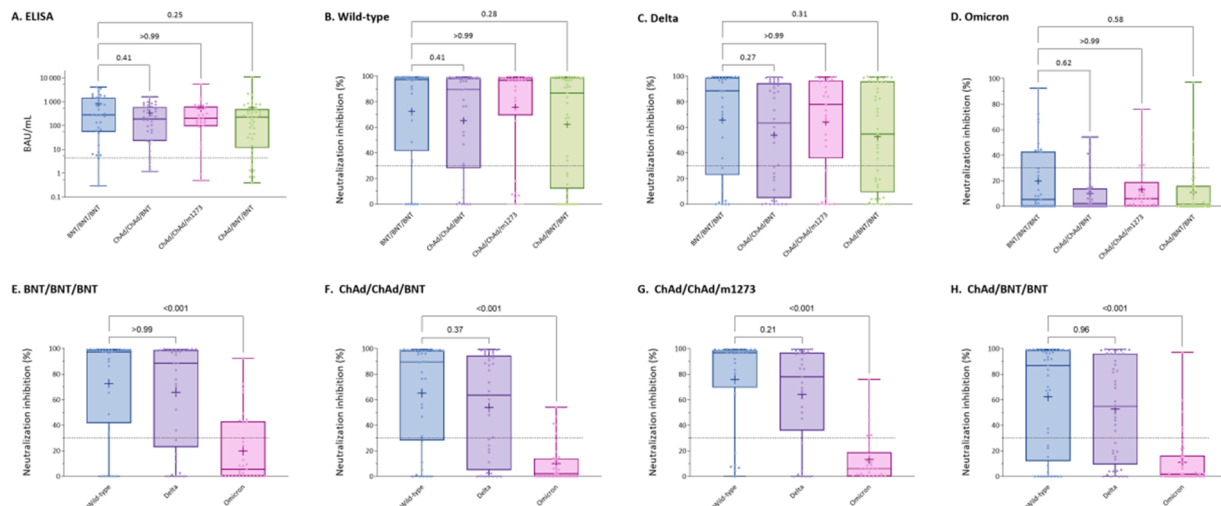


Fig. 2. Humoral immunogenicity after the third shot of the COVID-19 vaccine in SOT recipients.

Neutralization inhibition rates according to SARS-CoV-2 strain. Box-and-whisker plots display the SARS-CoV-2 anti-S IgG titer after the third shot by (A) ELISA and the neutralization inhibition rates for the (B) wild-type, (C) Delta, and (D) Omicron variants. The neutralization inhibition rates according to vaccine schedule: Box-and-whisker plots display the SARS-CoV-2 anti-S IgG titer after the third shot by (E) BNT/BNT/BNT, (F) ChAd/ChAd/BNT, (G) ChAd/ChAd/m1273, and (H) ChAd/BNT/BNT. Crosses denote the mean value. Dashed lines indicate the detection cut-off (< 7.1 BAU/mL by ELISA, < 30% by neutralization assay). Crosses represent the mean value. BNT = BNT162b2 vaccine (BioNTech-Pfizer, Germany/US); ChAd = ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca, UK); m1273 = mRNA-1273 vaccine (Moderna, US); ELISA = enzyme-linked immunosorbent assay; SOT = solid organ transplant; BAU = binding antibody units.

compared using relative risk (RR). Comparisons of the SARS-CoV-2 anti-S IgG titer and neutralization inhibition rate between the vaccination groups or for different strains were analyzed using the Kruskal–Wallis test with Dunn’s multiple comparisons. Correlations between ELISA and neutralization assays were analyzed using Spearman’s correlation coefficients after transforming the SARS-CoV-2 anti-S IgG antibody titer to a \log_{10} value. A simple linear regression was used to evaluate the immunogenicity according to the time interval between the second and third vaccinations. A two-sided P -value < 0.05 was considered statistically significant. All statistical analyses were performed on GraphPad Prism version 9.2.0 (GraphPad Software, La Jolla, CA, USA) and the SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Participant characteristics

Of the 464 SOTs who participated in the previous study, 162 consented to participate in this study. Among them, 14 were excluded; 13 did not meet V3 until the end date of sample collection, and 1 did not receive the third dose of vaccination. Finally, 148 participants were included. The median age at the first dose of vaccination was 60 years [Inter quartile range (IQR), 52 to 65 years], and the male-to-female ratio was 1.6. Among the participants, 56% ($n = 83$) underwent kidney transplantation, and 44% ($n = 65$) underwent liver transplantation. Seventy-three percent ($n = 108$) of participants received a vaccination at least 60 months from SOT, and 68% ($n = 101$) had received three or more immunosuppressants at the time of the initiation of the COVID-19 vaccination. The median time interval between the second and third vaccinations was 110 days (IQR, 86–121 days), and that between the third vaccination and sample collection was 49 days (IQR, 35–67 days). The four vaccination groups accounted for 97% of the total participants ($n = 143$): ChAdOx1 nCoV-19 (Oxford-AstraZeneca, UK; hereafter referred to as ChAd)/BNT/BNT: 30% ($n = 45$); ChAd/ChAd/BNT: 24%, $n = 36$; BNT/BNT/BNT: 22%, $n = 33$; ChAd/ChAd/mRNA-1273 vaccine (Moderna, US; hereafter referred to as m1273): 20%, $n = 29$; and others: 3%, $n = 5$ (Fig. 1). The characteristics of the four vaccination groups are detailed in Table 1.

3.2. Primary outcomes

The SARS-CoV-2-anti-S IgG titers and the neutralization inhibition rates according to testing methods are shown in Fig. 2A–D. No significant differences were observed in the positivity rate between the homologous BNT/BNT/BNT group (85%) and the other heterologous vaccination groups (83% of ChAd/ChAd/BNT, 90% of ChAd/ChAd/m1273, and 78% of ChAd/BNT/BNT, respectively) when analyzed using ELISA (Table 2). Similarly, no significant differences were observed in the positivity rate of neutralization inhibition ($\geq 30\%$ of threshold) between the four vaccination groups for both the wild-type (69–82%) or Delta variants (61–73%) (Table 2). In contrast, the neutralization inhibition rate against the Omicron variant was significantly decreased compared with those against the wild-type or Delta variants, regardless of the vaccination schedule (Fig. 2E–H). In the four vaccination groups, the median neutralization inhibition rate against the Omicron variant was 2–5%, which was 2–10% of the rates against the wild-type (87–97%) and Delta (55–89%) variants ($P < 0.001$ for all). The same trend was observed when the sensitivity analysis was performed using ELISA (≥ 7.1 BAU/mL) and the neutralization assay ($\geq 30\%$ of inhibition) by including only positive cases; the results are shown in Table 2.

3.3. Predicting factors for humoral immunogenicity

We analyzed the factors that were associated with positivity after the third dose of vaccination. The results revealed that initiation of vaccination after 5 years or more following SOT, less than three immunosuppressants, and positive humoral responses after the second dose of vaccination were predictors of positive humoral immunogenicity in all SARS-CoV-2 strains (Supplemental Tables 1–3; Supplemental Figs. 1A–D, 2A–D). In particular, for the Omicron variant, 17 out of 24 responders (71%) at V3 showed positive neutralization against the wild-type variant at V2. Their neutralization inhibition rate at V2 was 72%, which was 2.9 times higher than that (25%) of non-responders (Supplemental Figs. 1D, 2D).

We then evaluated the humoral immunogenicity according to the interval between the second and third doses for each vaccination group. In BNT/BNT/BNT and ChAd/BNT/BNT groups, which received mRNA

Table 2
Humoral immunogenicity based on the COVID-19 vaccine groups.

	ELISA				Neutralization assay (Wild-type)				Neutralization assay (Delta)				Neutralization assay (Omicron)			
	Positivity rate (%)	RR	95%CI	P	Positivity rate (%)	RR	95%CI	P	Positivity rate (%)	RR	95%CI	P	Positivity rate (%)	RR	95%CI	P
BNT/BNT/BNT	84.9				81.8				72.7				27.3			
ChAd/ChAd/BNT	83.3	0.98	0.80–1.21	0.86	72.2	0.88	0.68–1.14	0.35	61.1	0.84	0.60–1.17	0.31	13.9	0.51	0.19–1.37	0.17
ChAd/ChAd/m1273	89.7	1.06	0.87–1.28	0.58	79.3	0.97	0.76–1.24	0.80	75.9	1.04	0.78–1.40	0.78	17.2	0.63	0.24–1.67	0.35
ChAd/BNT/BNT	77.8	0.92	0.74–1.13	0.44	68.9	0.84	0.65–1.09	0.20	62.2	0.86	0.63–1.17	0.33	11.1	0.41	0.15–1.10	0.07
SARS-CoV-2 IgG antibody titer, BAU/mL/Neutralization inhibition above positivity ^a	Median	Q1	Q3	P ^b	Median	Q1	Q3	P ^b	Median	Q1	Q3	P ^b	Median	Q1	Q3	P ^b
BNT/BNT/BNT	587.5	136.5	1578.3	reference	98.9	89.9	99.2	reference	97.6	77.8	99.3	reference	49.2	43.5	70.4	reference
ChAd/ChAd/BNT	255.0	94.9	712.4	0.25	97.9	80.3	98.9	0.44	92.1	71.9	97.8	0.35	41.3	37.1	50.5	0.39
ChAd/ChAd/m1273	244.1	131.6	717.7	0.37	97.4	91.9	99.1	>0.99	89.6	68.8	98.2	0.43	44.5	32.2	65.1	0.78
ChAd/BNT/BNT	327.6	104.1	730.2	0.49	97.2	83.6	99.1	0.73	89	61.4	98.8	0.27	50.6	37.1	78.3	>0.99

ELISA = enzyme-linked immunosorbent assay; IQR = interquartile range; BNT = BNT162b2 vaccine (BioNTech-Pfizer, Germany/US); m1273 = mRNA-1273 vaccine (Moderna, US); ChAd = ChAdOx1 nCoV-19 vaccine (Oxford-AstraZeneca, UK); Q1 = lower interquartile; Q3 = upper interquartile; BAU = binding antibody units.

^a Only positive cases on ELISA (≥ 7.1 BAU/mL) and neutralization assay ($\geq 30\%$ of inhibition threshold) were included.

^b Kruskal–Wallis test with Dunn's multiple comparison test was performed.

vaccines for both the second and third doses, although it was not statistically significant, the immune responses increased as the interval prolonged, except for the change in the neutralization inhibition rate in the BNT/BNT/BNT group for the Delta variant (Fig. 3A–D).

3.4. Correlation between ELISA and neutralization assay results

The correlation between the SARS-CoV-2 anti-S IgG antibody titer of ELISA and the neutralization inhibition rate of the neutralization assay was high for the wild-type ($r = 0.95$, 95% confidence interval (CI) = 0.93–0.96, $P < 0.001$) and Delta ($r = 0.96$, 95% CI = 0.94–0.97, $P < 0.001$) variants. However, for the Omicron variant, the correlation was lower ($r = 0.47$, 95% CI = 0.32–0.59, $P < 0.001$) than that in the wild-type or Delta variants. The ELISA-positive, sNAA-negative rate determined for the Omicron variant was 80% (95% CI = 73–87%), which was significantly higher than that for the wild-type (33%; 95% CI = 18–49%) or Delta (49%; 95% CI = 35–63%) variants (Supplemental Table 4; Supplemental Fig. 3).

3.5. Humoral immunogenicity in cases with other vaccination schedules

Of the five participants not belonging to the four vaccination groups, three were vaccinated with m1273/m1273/m1273, and one was vaccinated with m1273/m1273/BNT or Ad26.COV2.S (Johnson & Johnson/Janssen, Belgium; hereafter referred to as Ad26)/m1273. All five participants showed positivity not only in ELISA but also in the neutralization assay for the wild-type and Delta variants (both 100%), and four patients (80%) showed positive neutralization inhibition for the Omicron variants (one case of m1273/m1273/m1273) (Supplemental Table 5).

4. Discussion

Based on our findings, the humoral immunogenicity in SOTRs after the third dose of mRNA vaccine was comparable between the heterologous (ChAd/ChAd/BNT, ChAd/ChAd/mRNA, and ChAd/BNT/BNT) and homologous (BNT/BNT/BNT) vaccination schedules. The findings revealed that the humoral immunogenicity against the Omicron variant was significantly low regardless of the vaccination schedule, highlighting the need for further protection of immunocompromised individuals. Moreover, it also demonstrated that a positive result obtained from ELISA in SOTRs might not be a neutralizing positivity against the Omicron variant and this result are more likely to be "false positives" when used currently for the purpose of evidence of immunity to Omicron; therefore, careful interpretation is warranted.

Comparable humoral immunogenicity after a third mRNA COVID-19 vaccine dose between homologous and heterologous schedules in SOTRs was one of the notable findings of our study. Previously, we reported that the ChAd/ChAd group of SOTRs has inferior humoral immunogenicity compared with the BNT/BNT or ChAd/BNT groups [16]. In this follow-up study, however, we found that this inferiority could be overcome with the third mRNA vaccine shot. Similar results have been reported in studies on the general population [15,18]. For example, in a recent phase II randomized clinical trial (COV-BOOST), the differences in humoral immunogenicity between the primary series of BNT/BNT and ChAd/ChAd vaccination have been reported to become similar after a booster BNT dose [19]. However, because our findings did not directly compare the mRNA vaccine as the third dose with other vaccines, such as ChAd or Ad26, we cannot imply that the mRNA vaccine as a third dose is superior to other vaccines in SOTRs. Chiang et al. reported better humoral immunogenicity in the heterologous vaccine group using Ad26 when comparing mRNA and Ad26 as a third-dose vaccine after two doses of mRNA in kidney transplant recipients [20]. In contrast, Reindl-Schwaighofer et al. reported no significant difference in the humoral immunogenicity when mRNA and Ad26 were compared as the third vaccination in kidney transplant recipients [21]. Therefore, a

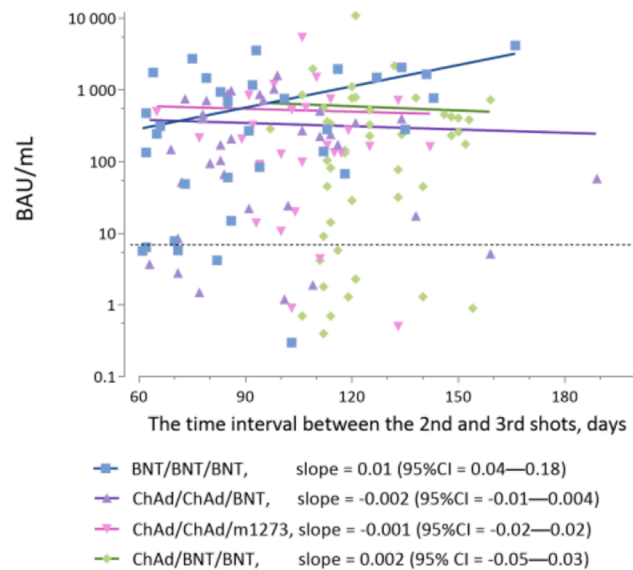
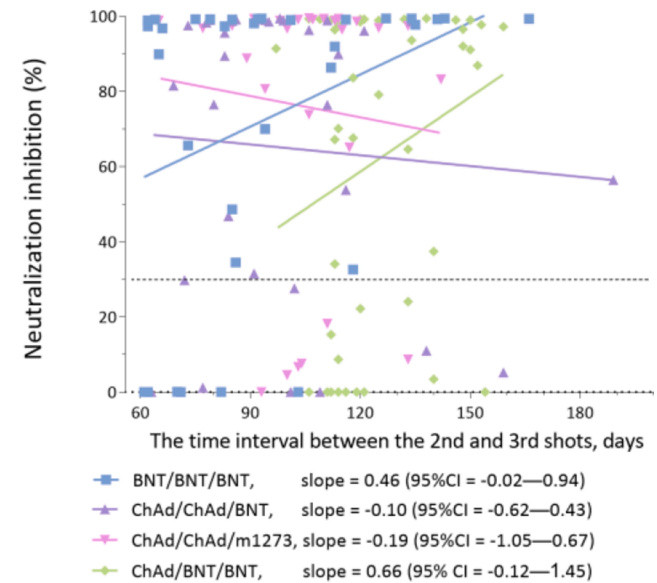
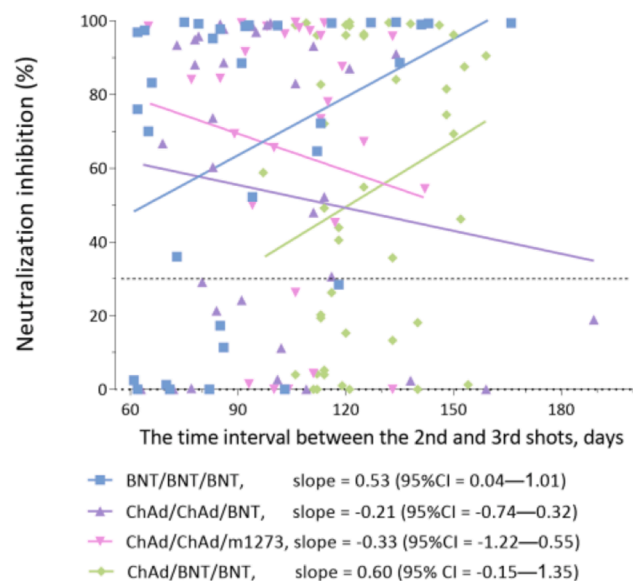
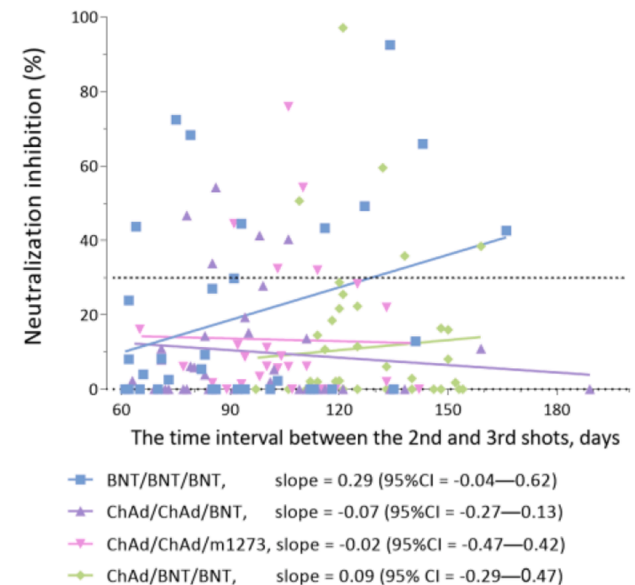
A. ELISA**B. Wild-type****C. Delta****D. Omicron**

Fig. 3. Humoral immunogenicity according to the interval between the second and third shots of the COVID-19 vaccine of each vaccine group. (A) ELISA results and neutralization inhibition rates for the (B) wild-type, (C) Delta, and (D) Omicron variants.

Dashed lines denote the detection cut-off (< 7.1 BAU/mL by ELISA, < 30% by neutralization assay); ELISA = enzyme-linked immunosorbent assay; BAU = binding antibody units.

large-scale prospective comparative study should be conducted on SOTRs to clarify these controversial findings.

Al Jurdi et al. reported that the Omicron variant exhibited insufficient immunogenicity in kidney transplant recipients, with only a 12% positivity rate of neutralization inhibition after the third-dose mRNA vaccination [22]. Similarly, Kumar et al. reported decreased neutralization inhibition against the Omicron variant with a 15–18% positivity rate after the third-dose mRNA vaccination in SOTRs; the study showed that the neutralizing antibody titer against the Omicron variant decreased by up to 19-fold compared to that in the wild-type variant [23]. These results highlight the need for additional booster vaccinations in SOTRs and imply the need for other preventive measures. As a non-vaccine preventive measure, monoclonal antibodies such as

bebtelovimab and AZD7442 (tixagevimab and cilgavimab) can be considered [24–27]. However, since the in vitro efficacy and effectiveness in the real world of these monoclonal antibodies also vary depending on the variants; therefore, careful attention and monitoring are required, particularly for the BA.5 or BQ.1/BQ.1.1 Omicron sub-variants, which are currently prevalent [24,26–28]. Based on effectiveness against prevalent strains, this monoclonal antibody prophylaxis must be prioritized, especially in SOTRs with factors predicting poor vaccine-induced humoral immunogenicity, such as less than 5 years after transplantation, use of three or more immunosuppressants, and no/poor humoral immunogenicity after the third-dose vaccination. Additionally, non-pharmacological interventions such as reducing exposure to crowds, wearing masks in indoor settings, and washing

hands can be effective preventive measures, for this vulnerable population.

Although there was no statistical significance, it is noteworthy that the longer the interval between the second and third BNT doses, the higher the immunogenicity tendency. Concordantly, our previous study also reported similar results when comparing neutralization inhibition according to the interval between first BNT and second BNT doses; the 42-day group (65%) showed higher rates than the 21-day group (45%) without a statistical significance ($P = 0.13$) [16]. These findings are consistent with previous studies by other researchers. For instance, it has been reported that the 7–8-week schedule led to higher immunogenicity and lower incidence of rare adverse reactions such as myocarditis compared to the 3–4-week schedule between mRNA vaccines in the general population [29,30]. Therefore, follow-up studies must be conducted to determine the optimal mRNA vaccination interval for better vaccine efficacy in immunocompromised SOTRs who are expected to have reduced vaccine-induced immunogenicity.

Our study also has several limitations. First, this study was a non-randomized study conducted according to Korea's changing COVID-19 vaccination policy; therefore, the variables for each vaccine group, such as vaccination interval and visit schedule, could not be controlled in advance. Second, the number of participants may not be sufficient to demonstrate the statistical significance of the immunogenicity and predictor variables between each vaccine group. Third, cell-mediated immunogenicity was not evaluated. Lastly, there is a possibility of underpowering due to an insufficient number of participants in each vaccination schedule group to detect the difference.

To our knowledge, this study used the largest cohort to date to evaluate the immunogenicity of homologous and heterologous vaccinations for different SARS-CoV-2 strains, including the Omicron variant in SOTRs. Additionally, it is the first study to assess the immunogenicity of the third-dose vaccination in an Asian SOT population.

In conclusion, third-dose mRNA vaccine-based heterologous vaccinations with ChAd/ChAd/BNT, ChAd/ChAd/mRNA, and ChAd/BNT/BNT in SOTRs showed comparable humoral immunogenicity with homologous BNT/BNT/BNT vaccination. However, because of the very low humoral immunogenicity of the Omicron variant, additional or combinational prophylaxis should be considered in these high-risk individuals.

Authors' contributions

JM Kang, JH Lee, Y Park, and MS Kim had full access to the study data and take full responsibility for the integrity and accuracy of this analysis. JM Kang and JH Lee contributed equally to this study. Y Park and MS Kim contributed equally as co-corresponding authors.

Concept and design: JM Kang, JH Lee, Y Park, and MS Kim; Data acquisition, analysis, and interpretation: KH Huh, MS Kim, JH Lee, DJ Joo, JG Lee, MY Kim, M Lee, I Jung, and JM Kang; Laboratory analysis: Y Park and S Kim; Drafting of the manuscript: JM Kang, JH Lee, HY Kim, Y Park, and MS Kim; Statistical analysis: JM Kang, HY Kim, MJ Lee, and MY Kim.

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Declaration Competing of Interest

The authors of this manuscript have no conflicts of interest to disclose, as described by the American Journal of Transplantation.

Data availability statement

These data are licensed for this analysis only and will be made available upon reasonable request to the corresponding author.

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Supplementary materials

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