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Letter to the Editor

No correlation of neutralizing antibody titers against the Omicron variant after a booster dose of COVID-19 vaccines with subsequent breakthrough Omicron infections among healthcare workers

Edited by: R. Read

Dear editor,

A recent report found that neutralizing antibody titers against Omicron variant induced by booster dose in uninfected individuals were significantly lower than those induced by Omicron variant infection in individuals who received 2-dose or booster dose.[1] Although a booster vaccination has demonstrated some protective effects against the Omicron variant infection, breakthrough infections frequently occur in booster-vaccinated individuals.[2,3] However, data on the immune correlation of protection against breakthrough Omicron infection in individuals who received booster dose are limited. Thus, this prospective cohort study aimed to compare humoral immune responses at 2 weeks and 3 months after a booster dose of COVID-19 mRNA vaccines, respectively, among healthcare workers (HCWs) who experienced Omicron breakthrough infections and those without Omicron infections.

We enrolled HCWs without a history of SARS-CoV-2 infection, who received a COVID-19 booster vaccine after primary series, at Asan Medical Center in Seoul, South Korea from November 2021 to December 2022 (Delta-dominant era). The study was approved by the institutional review board at Asan Medical Center (IRB No 2020–0298) and informed consent was obtained from all the participants.

We measured the serum level of neutralizing antibodies (ID_{50}) and S1-specific IgG antibodies (IU/ml) at 2 weeks and 3 months, respectively, after booster vaccination. The detailed methods about the measurement of immune responses and statistical analysis are described in Supplemental Materials. A breakthrough Omicron infection was defined as the detection of SARS-CoV-2 infection by SARS-CoV-2 polymerase-chain-reaction testing of their nasopharyngeal specimens after 1 February 2022 (Omicron-dominant era). We performed serologic testing for SARS-CoV-2 infection through anti-SARS-CoV-2 nucleocapsid (N) protein antibody at 3 months after the booster vaccination to rule out asymptomatic COVID-19 among HCWs who never had confirmed SARS-CoV-2 infection.

Among 119 HCWs, 60 (51%) received two-dose ChAdOx1 nCoV-19 followed by BNT162b2, 48 (40%) received three-dose BNT162b2, and 11 (9%) received 3-dose mRNA-1273. The median age was 34 years and 89 (75%) were female. Of them, 56 (47%) experienced breakthrough Omicron infection at a median of 124 days (IQR 99.5–150) after booster vaccination (breakthrough group), and the remaining 63 (53%) did not experience Omicron infection (non-breakthrough group). four (3 ChAdOx1-BNT162b2 and 1 mRNA-1273) HCWs who had positive anti-SARS-CoV-2 N protein antibody at 3 months after booster vaccination were excluded from the non-breakthrough infection group (Supplementary Fig. 1). The baseline characteristics between the two groups are presented in Supplementary Table 1.

No significant difference in 2-week neutralizing antibody titers against Omicron was observed between the breakthrough group (median 1781.9, IQR 1499.5.0–4500.0) and non-breakthrough group (median 2613.9, IQR 1770.7–4498.6, $p = 0.10$) (Fig. 1A). In addition, 2-week S1-specific IgG antibody titers were comparable between the breakthrough group (median 4142.2, IQR 2634.6–6099.9) and non-breakthrough group (median 4311.3, IQR 3118.9–5975.3, $p = 0.79$) (Fig. 1B). To measuring the 3-month immune response, 8 HCWs who experienced breakthrough Omicron infection before blood sampling were excluded (Supplementary Fig. 1). No significant difference in neutralizing antibody titers against Omicron 3 months after booster vaccination was observed between the breakthrough group (median 442.2, IQR 191.3–807.4) and non-breakthrough group (median 462.4, IQR 281.1–592.5, $p = 0.39$) (Fig. 1A). In addition, S1-specific IgG antibody titers 3 months after booster vaccination were comparable between breakthrough groups (median 925.7, IQR 602.8–1301.0) and non-breakthrough group (median 1177.3, IQR 651.2–1561.5, $p = 0.18$) (Fig. 1B). We analyzed time interaction by group and compared the slope from the peak antibody titer to the antibody titer at 3 months after booster vaccination. No significant difference in waning slope of neutralizing antibody titers in the time interaction was observed between the two groups ($\beta = -380.5$ [SE, 680.6]; $p = 0.58$) (Fig. 2A). In addition, the waning slope of S1-specific IgG antibody titers in the time interaction was comparable between the two groups ($\beta = 261.8$ [SE, 353.1]; $p = 0.46$) (Fig. 2B).

In a prospective cohort study from Israel, the risk of breakthrough infections with SARS-CoV-2 was correlated with levels of neutralizing antibodies against ancestral SARS-CoV-2, and the peak titers of neutralizing antibody were more likely associated with the risk of breakthrough infection than the peri–infection titers of neutralizing antibody.[4] However, few data regarding immune correlation of protection against breakthrough Omicron infection after booster vaccination are available. In this study, no significant differences in neutralizing and S1-specific IgG antibody titers at 2 weeks and 3 months after booster vaccination were observed between the breakthrough group and non-breakthrough group. In addition, no significant difference in the waning slope of neutralizing and S1-specific IgG antibody titers in the time interaction was observed between the groups. Similar result was observed in subgroup analysis to compare humoral immune response between the symptomatic breakthrough group and non-breakthrough group (Supplementary Figs. 2 and 3). This finding is not consistent with previous studies supporting the assumption that the presence of the neutralizing antibodies would correlate with the protection from SARS-CoV-2 infection.[5,6] The discrepancy may be due to some pos-

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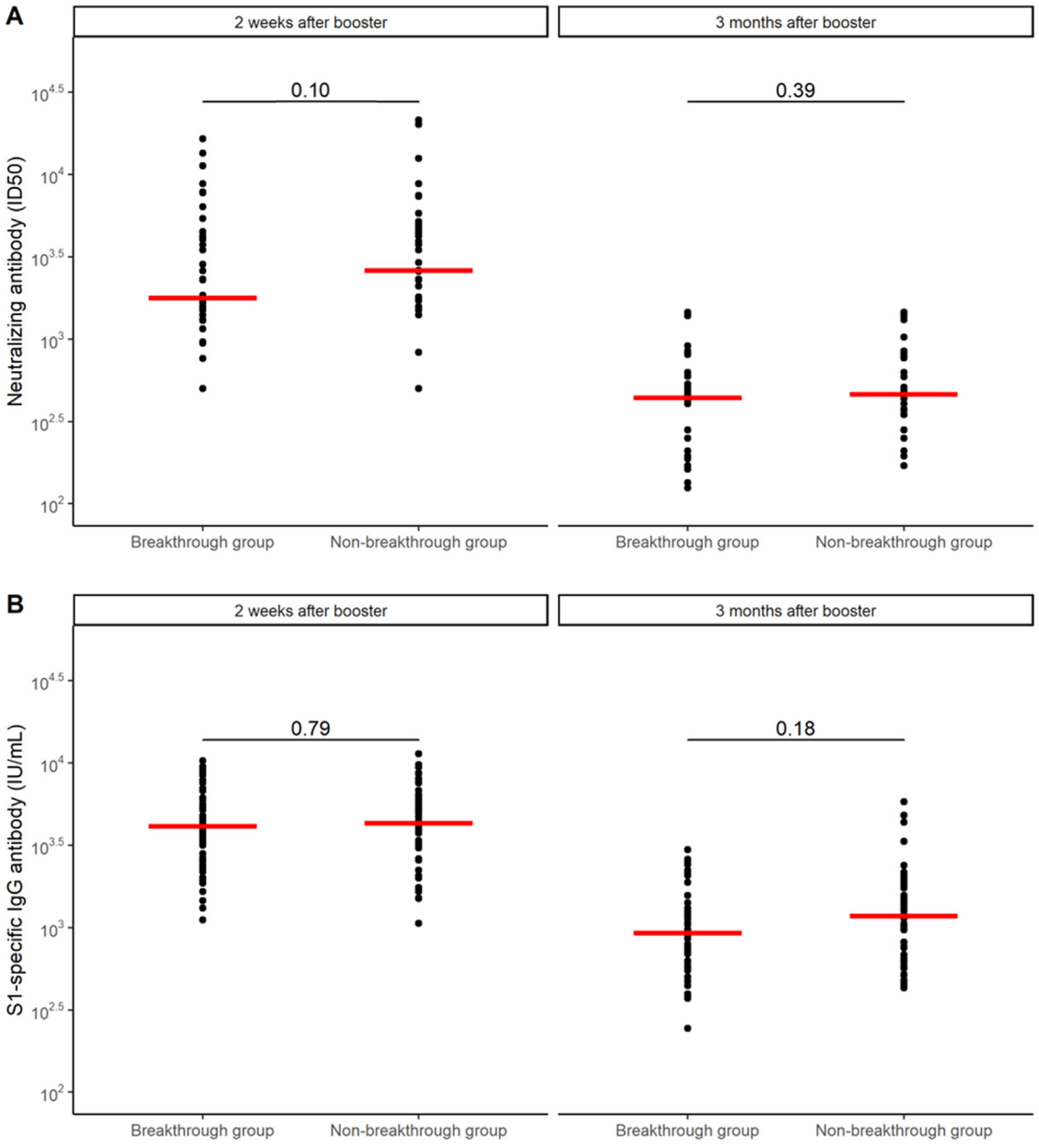

Fig. 1. Comparison of neutralizing antibody and S1-specific IgG antibody titers between the breakthrough group and non-breakthrough group. Horizontal lines indicate the median.

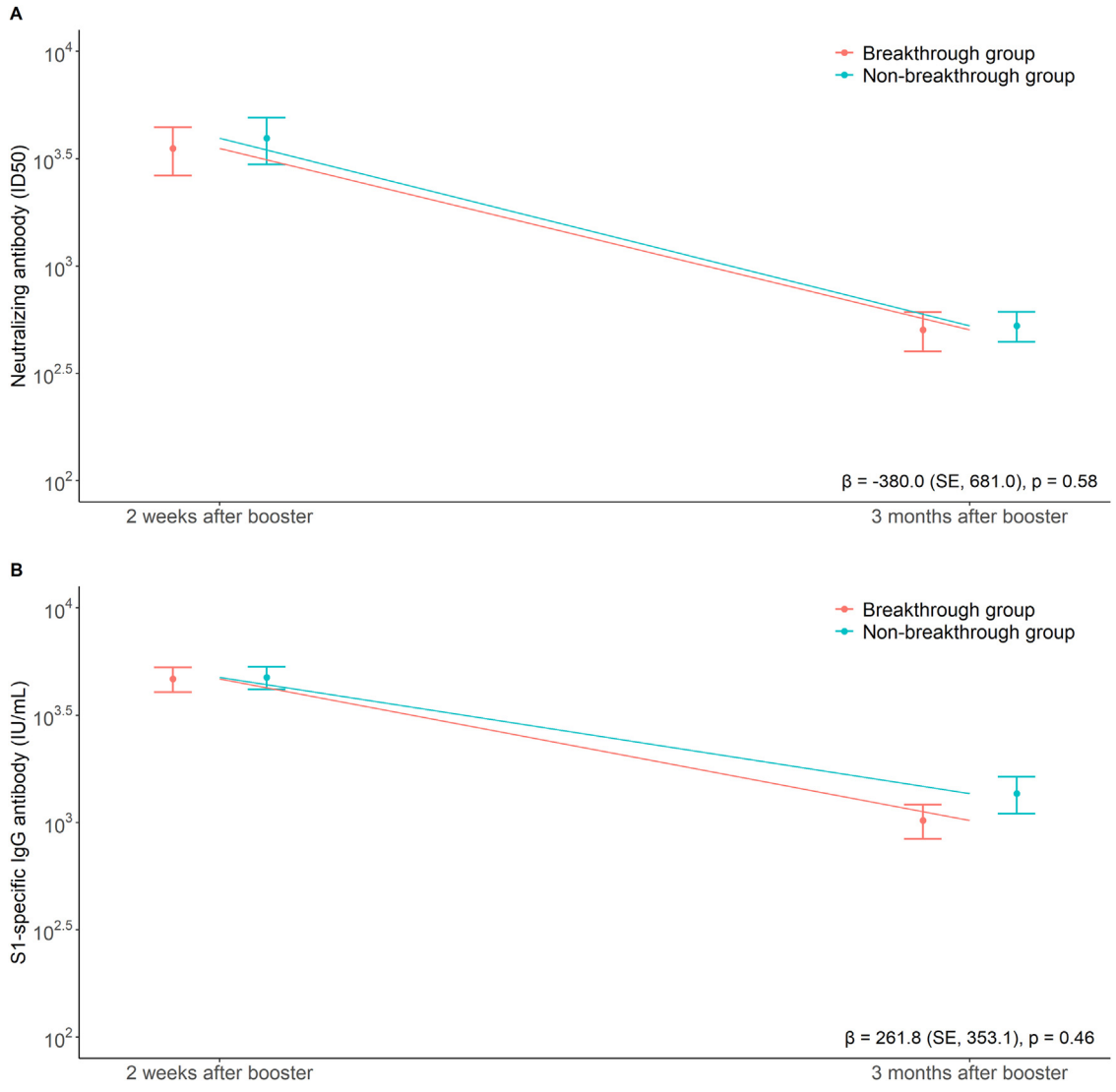

Fig. 2. Time interaction of neutralizing antibody and S1-specific IgG antibody titers according to Omicron (B.1.1.529) breakthrough infections.

sibilities. First, due to the relatively small sample size, we could not find any statistically significant differences. However, this possibility might not be high, considering that not only there was no difference in neutralizing antibody titers measured during outbreak of Omicron, but also there was no difference in the decreasing slope of neutralizing antibody titers over time between the groups. Second, unlike the ancestral strain or the Delta variant (B.1.617.2), Omicron infection is more likely to be confined to the upper respiratory tract,[7] and maintaining a steep concentration gradient with much higher plasma neutralizing antibody titer is required to prevent the cases of such mild infection.[5] Since all the breakthrough Omicron infection cases in our study was asymptomatic or mild illness, the result could be explained by the possibility that the level of neutralizing antibody induced after booster dose is not sufficiently high to prevent mild disease.

In conclusion, neutralizing antibody titers against Omicron at 2 weeks and 3 months after the booster dose of COVID-19 vaccines was not correlated with subsequent breakthrough Omicron infections.

Supplement materials

Supplementary material associated with this article can be found, in the online version.

Declaration of Competing Interest

There is no conflict of interest for all authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.10.007.

References

1. Dimeglio C, Migueres M, Chapuy-Regaud S, et al. Comparative effects of mRNA vaccine booster and natural Omicron infection on the neutralizing antibody response. *J Infect* 2022;**85**(1):e4–6.
2. Kuhlmann C, Mayer CK, Claassen M, Maponga T, Burgers WA, Keeton R, et al. Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *Lancet* 2022;**399**(10325):625–6.
3. CDC COVID-19 Vaccine Breakthrough Case Investigations Team COVID-19 vaccine breakthrough infections reported to CDC - United States, January 1-April 30, 2021. *MMWR Morb Mortal Wkly Rep.* 2021;**70**(21):792–3.
4. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. COVID-19 breakthrough infections in vaccinated health care workers. *N Engl J Med* 2021;**385**(16):1474–84.
5. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med* 2021;**27**(7):1205–11.
6. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med* 2021;**27**(11):2032–40.
7. Hui KPY, Ho JCW, Cheung MC, Ng KC, Ching RHH, Lai KL, et al. SARS–CoV-2 Omicron variant replication in human bronchus and lung *ex vivo*. *Nature* 2022;**603**(7902):715–20.

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