이학석사 학위논문

코로나바이러스감염증-19 백신 부스터 샷으로 유도된 중화항체의 오미크론 변이 돌파감염에 대한 면역 상관성

Immune correlation of protection against breakthrough Omicron infection in neutralizing antibodies induced by a booster dose of COVID-19 vaccine

울 산 대 학 교 대 학 원

의 과 학 과

이 정 재

코로나바이러스감염증-19 백신 부스터 샷으로 유도된 중화항체의 오미크론 변이 돌파감염에 대한 면역 상관성

지도교수 김 준 기

공동지도교수 김 성 한

이 논문을 이학석사 학위논문으로 제출함

2024 년 2 월

울 산 대 학 교 대 학 원

의 과 학 과

이 정 재

이정재의 이학석사 학위논문을 인준함

심사위원 신 용 인

심사위원 김 성 한 인

심사위원 김 준 기 인

울 산 대 학 교 대 학 원

2024 년 2 월

영문요약

Although vaccines have been developed as a significant strategy to control the spread of Coronavirus disease 19 (COVID-19), vaccine-induced immunity has waned over time, and breakthrough infections caused by variant strains have been reported. Particularly, with the immune evasion potential of Omicron variant, numerous countries have administered a booster vaccination for individuals who have completed a primary series of the COVID-19 vaccines. Identifying correlation of protection and immunity thresholds is important, nevertheless, there is a paucity of data on the immune correlation of protection from breakthrough Omicron infection in individuals who received a booster dose of COVID-19 vaccines. Therefore, this cohort study conducted to evaluate humoral immune responses including neutralizing antibody against the Omicron variant after a booster vaccination among healthcare workers, and compare those according to subsequent breakthrough Omicron infection.

The study populations were consisted of COVID-19-naïve healthcare workers who agreed with blood sampling 2 weeks and 3 months after a booster dose of mRNA COVID-19 vaccines, at a tertiary hospital, between October and December 2021 (before Omicron-dominant era). Plasma levels of live-virus neutralizing antibodies were measured using a microneutralization assay (ID_{50}) with the SARS-CoV-2 Omicron variant (B.1.1.529). Breakthrough SARS-CoV-2 infection was confirmed by polymerase chain reaction testing of nasopharyngeal specimens, between February and April 2022 (Omicron-dominant era). In addition, we performed anti-SARS-CoV-2 N protein antibody to rule out asymptomatic SARS-CoV-2 infection.

Of a total of enrolled 119 healthcare workers, 56 healthcare workers experienced subsequence breakthrough infection after booster vaccination (breakthrough group). Compared with the remaining healthcare workers who did not experience breakthrough infection (non-breakthrough group), there were no significant differences in the levels of 2-week neutralizing antibodies (ID_{50}) between the breakthrough group (median 1781.9, interquartile range 1499.5.0–4500.0) and non-breakthrough group

(median 2613.9, interquartile range 1770.7–4498.6, p = 0.10). Excluding 8 healthcare workers in the breakthrough group who experienced SARS-CoV-2 infection before the 3-month blood sampling, the levels of 3-month neutralizing antibody titers (ID_{50}) were comparable between the breakthrough group (median 442.2, interquartile range 191.3–807.4) and non-breakthrough group (median 462.4, interquartile range 281.1–592.5, p = 0.39). In addition, no significant difference in the waning of the levels of neutralizing antibody titers over time was observed between the two groups (β = −380.5 [SE, 680.6]; p = 0.58).

Based on our findings, it is suggested that neutralizing antibodies against Omicron variant at 2 weeks and 3 months induced by the booster dose of COVID-19 vaccine were not exhibit immune correlation of protection against subsequent breakthrough Omicron infections.

차례

I. 서론

Since November 2021, the Omicron variant (B.1.1.529) has been categorized as a variant of concern by the World Health Organization and has rapidly spread globally.[1] However, with the immune evasion potential of Omicron and waning vaccine-induced immunity, many countries have administered a booster vaccination for individuals who have received a complete primary series of COVID-19 vaccines.[2-4] While a booster vaccine-induced immunity has shown some protective effects against the Omicron variant, breakthrough infections with SARS-CoV-2 Omicron variant frequently occur in booster-vaccinated individuals.[5,6] However, there is no known threshold of the levels of vaccine-induced immunity for protection against Omicron infection and a paucity of data on the immune correlation of protection against breakthrough Omicron infection in individuals who received booster COVID-19 vaccines. Therefore, this prospective cohort study performed to evaluate humoral immune responses including neutralizing antibody titers against the Omicron variant and S1-specific antibody at 2-week and 3-month after a booster dose of COVID-19 mRNA vaccines among healthcare workers, and compare those according to subsequent breakthrough Omicron infection.

II. 본론

1. 연구방법

Study participants and design

As study populations, healthcare workers without a prior history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, who received a booster dose of COVID-19 vaccines after a primary series were enrolled at Asan Medical Center, a 2,700-bed tertiary hospital in Seoul, South Korea from October to December 2021 (before Omicron-dominant era). Those were received two doses of ChAdOx1 nCoV-19 (ChAdOx1; AstraZeneca), BNT162b2 (Pfizer-BioNTech), or mRNA-1273 (Moderna) as primary series, followed by a booster dose of mRNA COVID-19 vaccines, Pfizer or Moderna, and agreed with peripheral blood sampling at 2 weeks and 3 months after the booster vaccination.

To evaluate immune correlation of protection against breakthrough Omicron infection, we compared humoral immune responses between healthcare workers with and without breakthrough SARS-CoV-2 infection, performing both microneutralization assay to measure neutralizing antibody titer and enzyme-linked immunosorbent assay to measure the SARS-CoV-2 S1-specific IgG antibody titer. Moreover, to evaluate immune correlation of protection against symptomatic breakthrough Omicron infection, we performed subgroup analysis comparing humoral immunity between the symptomatic breakthrough group and non-breakthrough group. 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.

Confirmation of SARS-CoV-2 infection

During the study period, all healthcare workers who had COVID-19-associated symptoms or

epidemiologic links to confirmed COVID-19 patients were recommended to undergo SARS-CoV-2 polymerase chain reaction (PCR) testing of their nasopharyngeal specimens to identify SARS-CoV-2 infections between February and April 2022 (Omicron-dominant era). A breakthrough Omicron infection was defined as the detection of SARS-CoV-2 infection by PCR testing through respiratory specimen during the Omicron-dominant era. In addition, 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 among healthcare workers who never had confirmed SARS-CoV-2 infection to rule out asymptomatic COVID-19.

Measurement of immune responses

A microneutralization assay with SARS-CoV-2 Omicron variant (B.1.1.529) was used to measure plasma levels of live-virus neutralizing antibodies and was performed in a Bio Safety Level (BSL)-3 laboratory at the Institut Pasteur Korea (Seongnam, South Korea). Briefly, a 100-tissue culture infective dose 50 (100 $TCID_{50}$) of SARS-CoV-2 Omicron variant (hCoV-19/Korea/KDCA447321/2021 NCCP 43408) provided by the Korea Disease Control and Prevention Agency was mixed with an equal volume of diluted plasma specimen, incubated at 37°C for 30 min, and added to Vero cells. After 96 h, the cytopathic effect of SARS-CoV-2 on the infected cells was measured and neutralizing antibody titer calculated as the reciprocal of the highest dilution of test plasma providing 50% neutralization (ID_{50}).

SARS-CoV-2 S1-specific IgG antibody titers were measured using an enzyme-linked immunosorbent assay (ELISA) developed in-house, details of which are described in a previous report.[7] Briefly, 2 mg/mL SARS-CoV-2 S1-His protein (SinoBiological, Beijing, China) was coated onto 96-well plates (MaxiSorp; Thermo Fisher Scientific, Waltham, MA) overnight at 4°C, and then the plates were blocked with 1% bovine serum albumin in phosphate buffered saline (PBS). Plasma

diluted at 1:100 was added and incubated for 2 hours at room temperature. Horseradish peroxidase-conjugated anti-human IgG (Jackson Immunoresearch, West Grove, PA) were used as secondary antibodies. The data are presented as International Units per milliliter (IU/ml), which is standardized with reference pooled sera from International Vaccine Institute (Seoul, South Korea).To determine cut-off values for the ELISA, the mean and standard deviation (SD) of negative control plasma were measured, and cut-off values were defined as mean IU plus three-fold the SD value; the cut-off value was 10 IU/ml for IgG, as reported previously.[8,9]

SARS-CoV-2 N-specific IgG antibody titers were also assessed by ELISA. One mg/mL SARS-CoV-2 N-His protein (SinoBiological, Beijing, China) was coated onto 96-well plates (Thermo Fisher Scientific) overnight at 4°C, and then following procedures are same with S1-specific IgG ELISA. The data are presented as Absorbance Unit per milliliter (AU/mL). The results were considered as negative if the results were under 1.4 AU/ml, positive if the results were over 2.0 AU/ml, and borderline if the results were between 1.4 and 2.0 AU/ml.

Statistical analyses

We used the chi-square or Fisher exact test to analyze categorical variables, as appropriate. Student's t-test or the Mann–Whitney U-test was used for continuous variables according to the normality of the data. We used generalized estimating equations to estimate marginal effects and linear time interaction by group and compare the slope from the peak antibody titer to antibody titer of 3 months after booster vaccination. All tests of significance were two-tailed, and a p-value of <0.05 was considered significant. The R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for the analysis and graphical presentation of the results.

2. 결과

Study population

Among a total 127 fully vaccinated healthcare workers who agreed to blood sampling after a booster vaccination, eight who had a history of COVID-19 were excluded (Figure 1). Among 119 healthcare workers, 60 (51%) received two-dose AstraZeneca followed by Pfizer, 48 (40%) received three-dose Pfizer, and 11 (9%) received three-dose Moderna. The median (range) age was 34 (22-64) years and 89 (75%) were female. Of them, at a median of 124 days (interquartile range [IQR] 99.5–150) after a booster vaccination, 56 (47%) cases of breakthrough Omicron infection were identified (breakthrough group). Among 56 healthcare workers with breakthrough Omicron infection, 37 (66%) experienced symptomatic infection, and all symptomatic infection was mild illness. Of the remaining 63 (53%) healthcare workers who had never been confirmed positive for SARS-CoV-2 by PCR testing, four (3 AstraZeneca-Pfizer and 1 three-dose Moderna) healthcare workers had positive anti-SARS-CoV-2 N protein antibody at 3 months after booster vaccination and were excluded from the non-breakthrough infection group (Figure 1). The baseline characteristics between the two groups are presented in Table 1. No significant difference in the interval from the second dose of primary series of COVID-19 vaccine to the booster vaccination was observed between the breakthrough group and non-breakthrough group (median days 182; IQR, 175–196] vs 182 [IQR, 169.5–197], p = 0.82). The two-dose AstraZeneca followed by Pfizer was more likely administered to healthcare workers in the breakthrough group, and the three-dose Moderna was more likely administered to healthcare workers in the non-breakthrough group (p = 0.01) (Table 1).

Figure 1. Study flowchart.

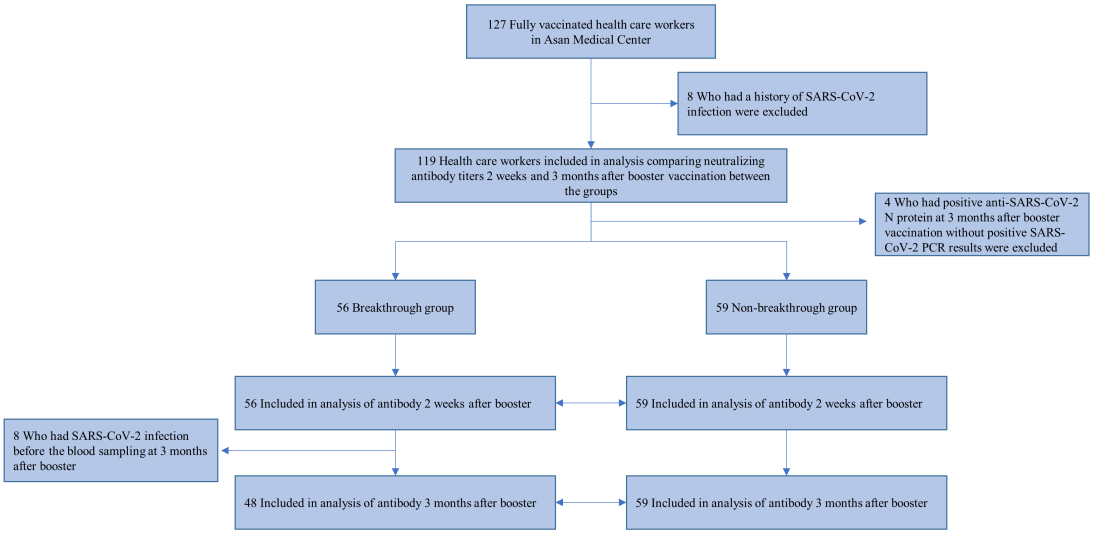


Table 1. Characteristics between the breakthrough group and non-breakthrough group.

Characteristics	Breakthrough group (n = 56)	Non- breakthrough group (n = 59)	p value
Age, median (range), years	35 (22–59)	33 (24–64)	0.22
Sex			
Female	41 (73)	45 (76)	0.87
Male	15 (27)	14 (24)	
Type of vaccination,			
AZ-AZ-PF	34 (61)	23 (39)	0.01
PF-PF-PF	21 (37)	27 (46)	
MO-MO-MO	1 (2)	9 (15)	
Interval from second dose to booster dose, median (IQR), days	182 (175–196)	182 (169.5–197)	0.82
Interval from booster dose to infection, median (IQR), days	124 (99.5–150)	Not applicable	
COVID-19 severity			
Asymptomatic	19 (34)	Not applicable	
Mild	37 (66)	Not applicable	

Data are presented as no. (%) of individuals unless otherwise indicated. Abbreviations: IQR, interquartile range; AZ, AstraZeneca (ChAdOx1 nCoV-19); PF, Pfizer (BNT162b2); MO, Moderna (mRNA-1273).

Immune correlation of protection against Omicron infection

Blood samples were obtained 2 weeks after booster vaccination, and we measured the serum level of neutralizing antibodies and S1-specific IgG antibodies at 2 weeks and 3 months, respectively, after booster vaccination. We compared both neutralizing and S1-specific antibody titer at 2 weeks after booster dose between the breakthrough group and non-breakthrough group. No significant difference in 2-week neutralizing antibody titers (ID_{50}) 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) (Figure 2-A). 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) (Figure 2-B).

Blood samples were obtained 3 months after booster vaccination, and we performed both microneutralization assay with SARS-CoV-2 Omicron variant and in-house developed ELISA. To measuring the 3-month immune response, 8 healthcare workers who experienced breakthrough Omicron infection before blood sampling were excluded in the analysis comparing neutralizing and S1-specific antibody titers 3 months after booster vaccination between the groups (Figure 1). No significant difference in neutralizing antibody titers (ID_{50}) 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) (Figure 2-A). 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) (Figure 2-B).

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) (Figure 3-A). In addition, the waning slope of S1-specific IgG antibody titers in the time interaction was comparable between the two groups (β = 261.8 [SE, 353.1]; p = 0.46) (Figure 3-B).

Figure 2. Comparison of neutralizing antibody and S1-specific IgG antibody titers between the breakthrough group and non-breakthrough group.

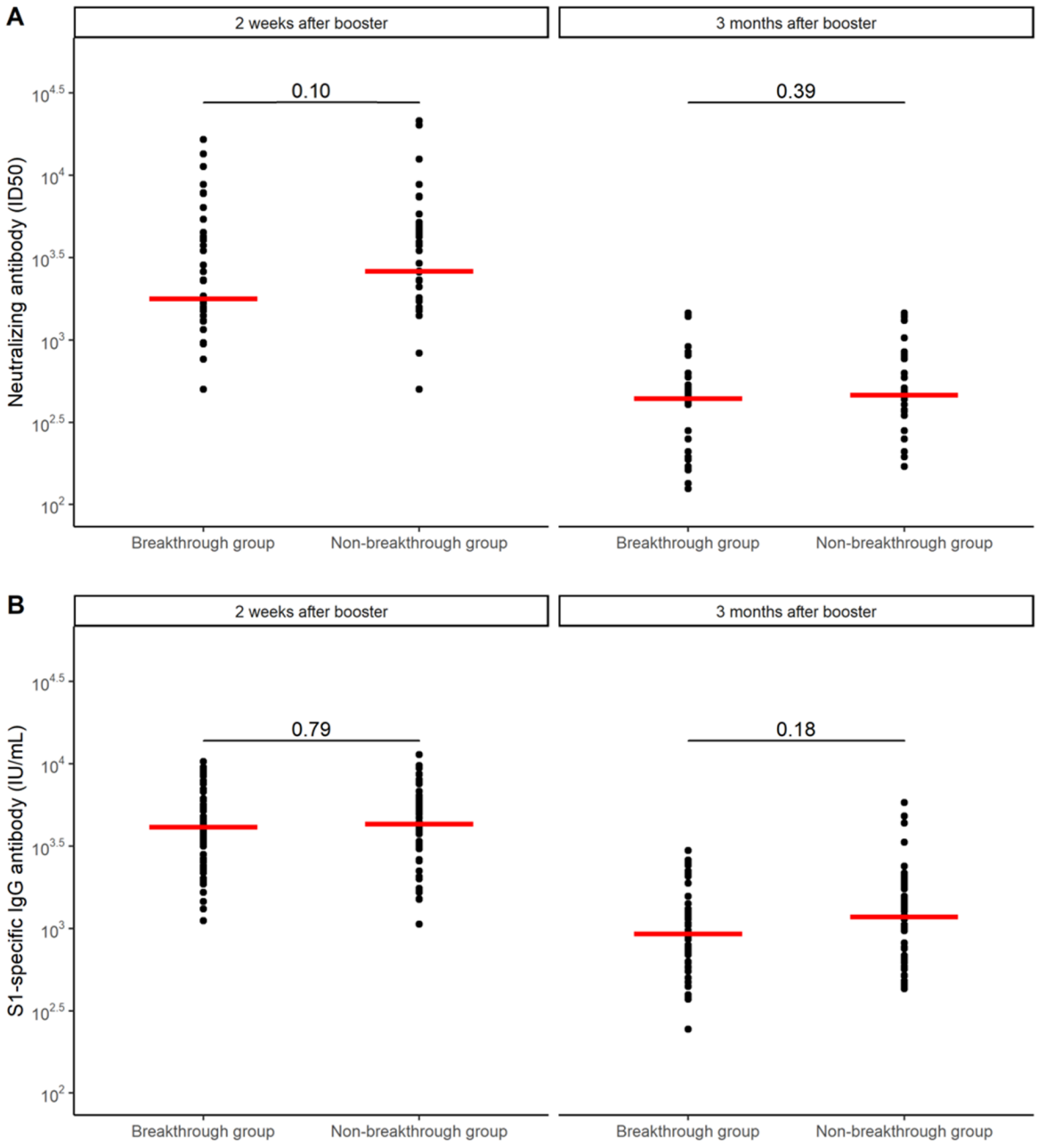
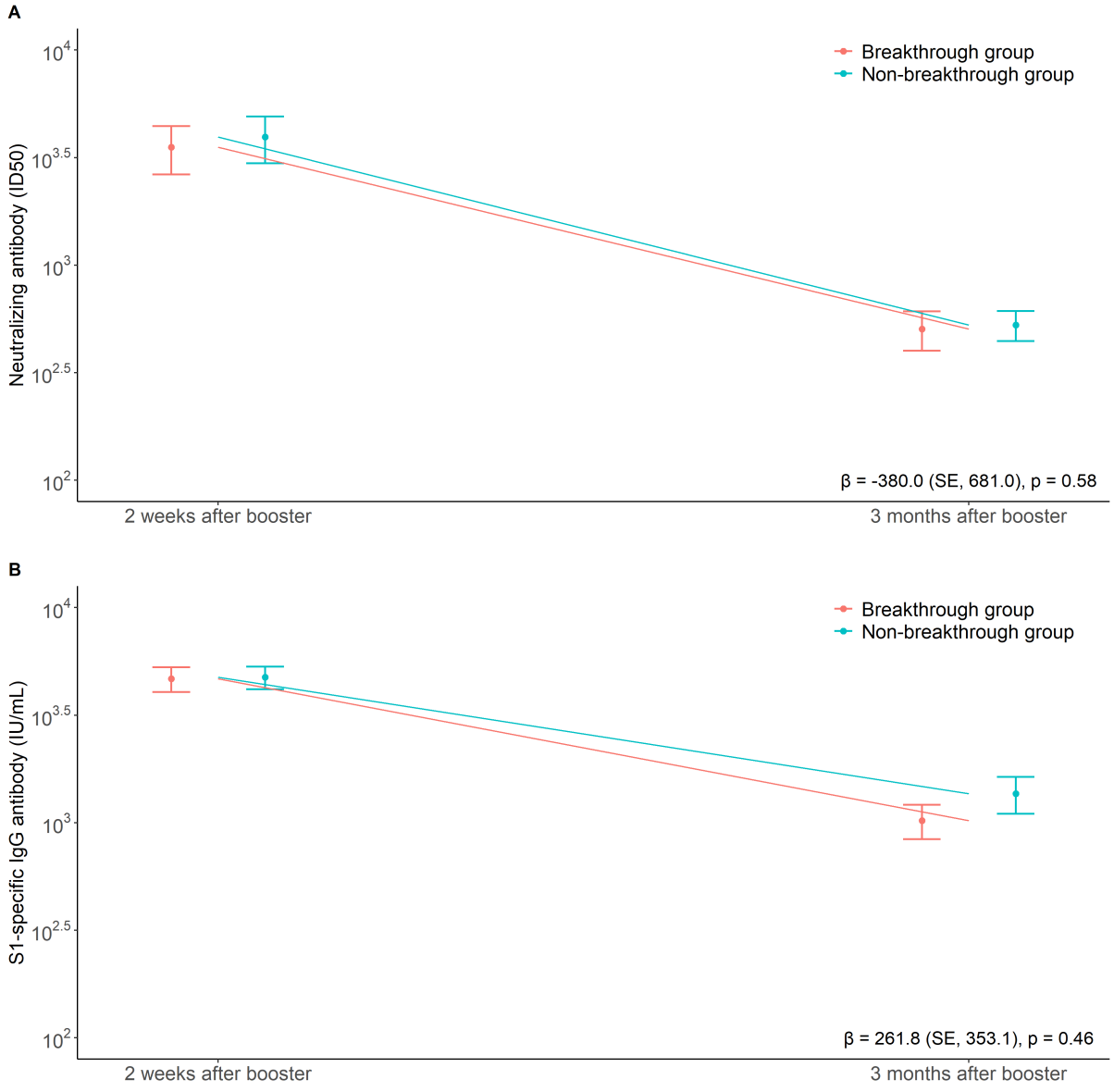


Figure 3. Time interaction of neutralizing antibody and S1-specific IgG antibody titers according to Omicron (B.1.1.529) breakthrough infections.



Immune correlation of protection against symptomatic Omicron infection

No significant difference in the 2-week neutralizing antibody titers (ID_{50}) against Omicron infection was observed between the symptomatic breakthrough group (median 1670.0, IQR 1500.0–4500.0) and the non-breakthrough group (median 2613.9, IQR 1770.7–4498.6, p = 0.09) (Figure 4-A). Additionally, the 2-week S1-specific IgG antibody titers were comparable between the symptomatic breakthrough group (median 3984.9, IQR 2395.1–6098.5) and non-breakthrough group (median 4311.3, IQR 3118.9–5975.3, p = 0.66) (Figure 4-B).

No significant difference in the neutralizing antibody titers (ID_{50}) against Omicron 3 months after booster vaccination was observed between the symptomatic breakthrough group (median 486.0, IQR 209.7–807.4) and non-breakthrough group (median 462.4, IQR 281.1–592.5, p = 0.76) (Figure 4-A). The S1-specific IgG antibody titers 3 month after booster vaccination were also comparable between the symptomatic breakthrough group (median 855.5, IQR 622.0–1206.3) and non-breakthrough group (median 1177.3, IQR 651.2–1561.5, p = 0.24) (Figure 4-B).

No significant difference in the waning slope of neutralizing antibody titers in the time interaction between the symptomatic breakthrough group and non-breakthrough group ($\beta = -387.0$ [SE, 790.0]; p = 0.62) (Figure 5-A). Moreover, the waning slope of the S1-specific IgG antibody titers in the time interaction was comparable between the two groups ($\beta = 272.0$ [SE, 430.0]; p = 0.53) (Figure 5-B).

Figure 4. Comparison of neutralizing antibody and S1-specific IgG antibody titers between the breakthrough group (symptomatic) and non-breakthrough group.

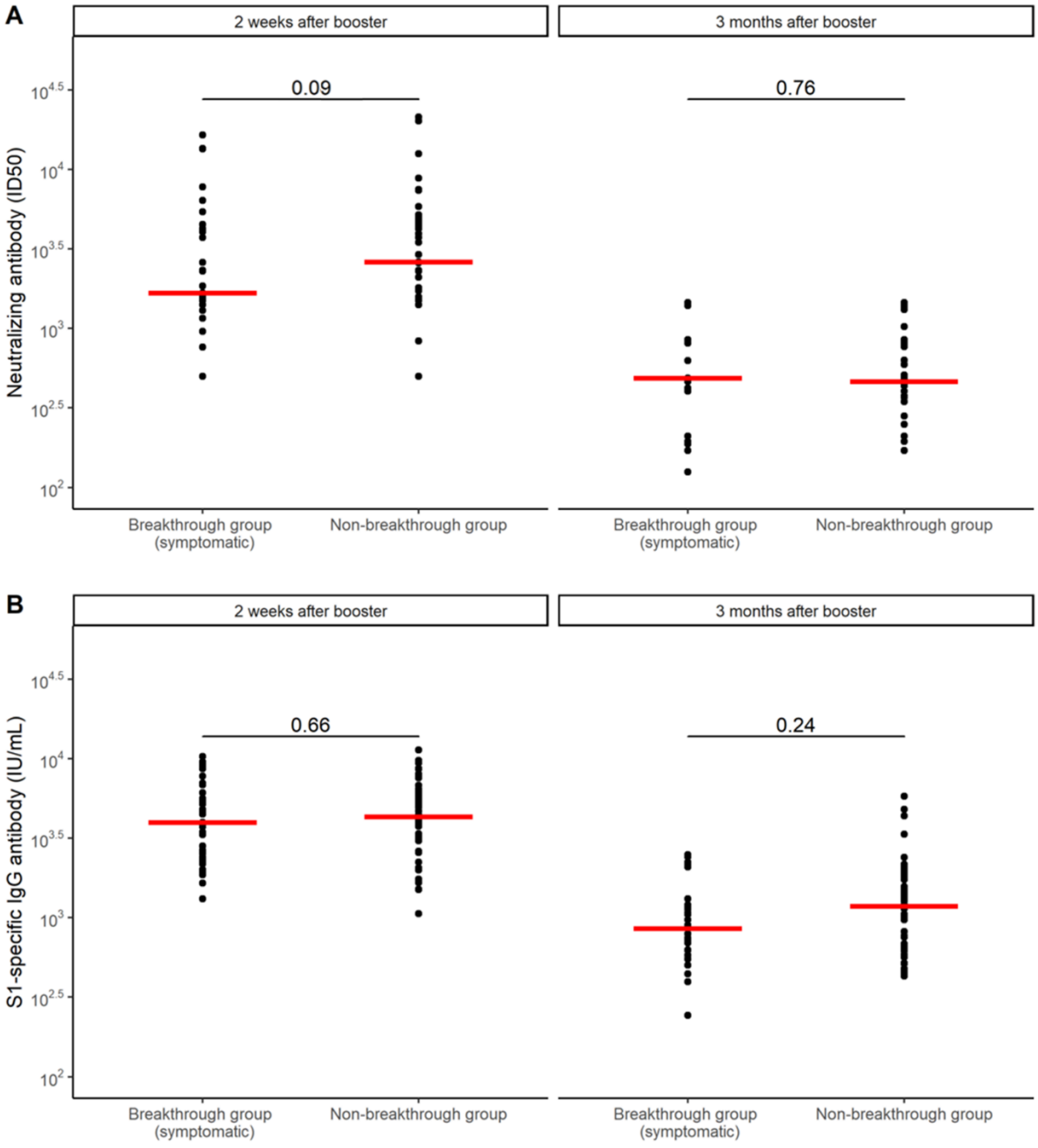
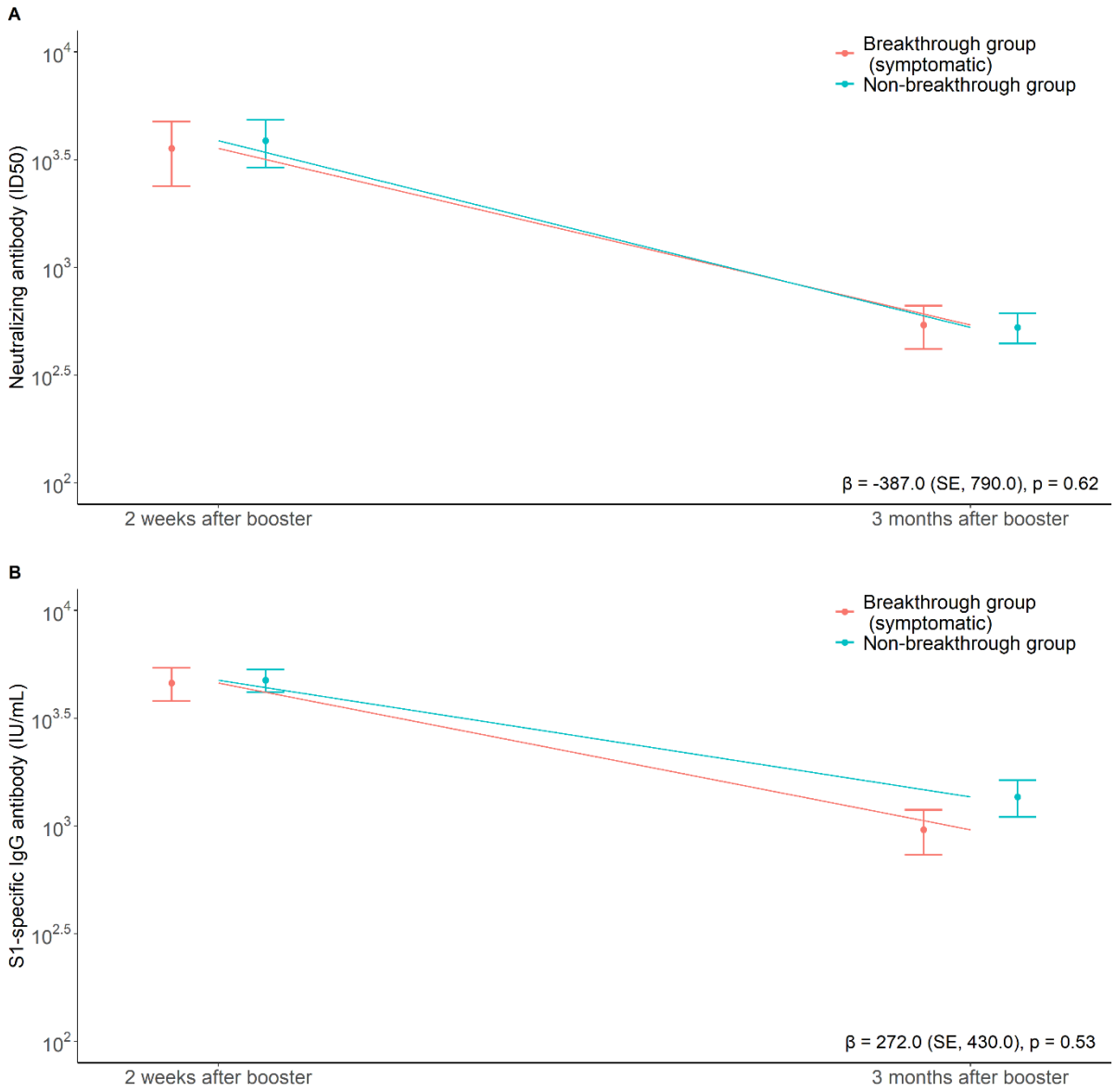


Figure 5. Time interaction of neutralizing antibody and S1-specific IgG antibody titers between the breakthrough group (symptomatic) and non-breakthrough group.



III. 결론

In this study involving healthcare workers who received booster COVID-19 mRNA vaccines after the primary series, we compared the humoral immune response between healthcare workers who experienced Omicron breakthrough infections and healthcare workers without Omicron infections. No significant differences in the level of neutralizing and S1-specific IgG antibody 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. Therefore, no immune correlation of protection against breakthrough Omicron infection was identified in individuals who received booster COVID-19 vaccines.

As Delta (B.1.617.2) became the dominant variant in some countries, breakthrough infections after mRNA and adenovirus-vectored vaccinations have been widely reported.[5,10-13] However, few studies related to the immune correlation of protection for neutralizing antibody against the circulating SARS-CoV-2 strains are available. In a prospective cohort study from Israel, levels of neutralizing antibodies against ancestral SARS-CoV-2 were correlated with the risk of breakthrough infections with SARS-CoV-2. In addition, the risk of breakthrough infection was more likely associated with the peak titers of neutralizing antibody than the peri-infection titers of neutralizing antibody.[11] However, limited data deal with immune correlation of protection against breakthrough Omicron infection after booster vaccination. In this study, since we could not observe significant difference in humoral immunity including neutralizing after booster vaccination between the breakthrough group and non-breakthrough group, we were unable to determine the cut-off value of neutralizing antibody titers for protection against Omicron variant. This result is not consistent with previous studies supporting the assumption that the levels of the neutralizing antibodies would correlate with the protection from SARS-CoV-2 infection.[14,15]

The discrepancy could arise from several potential factors. Firstly, due to the relatively small sample size of our study population, we were unable to detect any statistically significant distinctions. However, this is not a highly likely scenario, supported by the fact that not only no distinction was observed in neutralizing antibody titers measured during outbreak of Omicron, where most infections occurred, but also no distinction was observed in the waning slope of neutralizing antibody titers over time between the two groups. Secondly, in contrast to the original strain or the Delta variant (B.1.617.2), Omicron variant is more prone to being confined to the upper respiratory tract.[16,17] and this necessitates the maintenance of a steep concentration gradient with much higher plasma levels of neutralizing antibody to avert the cases of such mild infection.[15] Given all cases of the breakthrough Omicron infection in our study were asymptomatic or mild illness, the outcomes could be explained by the assumption that the levels of neutralizing antibody titers induced by booster vaccination is not sufficiently high to prevent mild disease. However, since the preventive effect on severe COVID-19 caused by lower respiratory tract infection could be obtained by a relatively lower neutralizing antibody titer,[15] further studies regarding immune correlation of protection against severe Omicron infection are needed. In addition, since T-cell immune response and humoral immunity may likely play an important role in preventing severe COVID-19,[18,19] additional studies exploring cellular immune response against breakthrough Omicron infection or progression to severe diseases are needed.

It is worth noting that the healthcare workers in the breakthrough group more likely received the two-dose AstraZeneca followed by Pfizer and the healthcare workers in non-breakthrough group more likely received the three-dose Moderna. This suggests that the preventive effect against breakthrough Omicron infection may differ depending on the type of vaccines. This result is consistent with that in reported previous studies, revealing higher vaccine efficacy of the Moderna vaccine than the Pfizer vaccine before the emergence of the Omicron variant.[20] Further studies are

needed to establish different vaccine effectiveness of booster dose against breakthrough Omicron infection according to the type of vaccines.

This study had some limitations. First, although we measured the neutralizing antibody titers using a microneutralization assay with SARS-CoV-2 Omicron variant (B.1.1.529), which was initially the prevalent sublineage of the Omicron variant, sublineage BA.2 has surpassed sublineage BA.1 in South Korea after April 2022. Therefore, measuring neutralizing antibody titers against SARS-CoV-2 Omicron variant (B.1.1.529) could be limited in evaluating immune responses among healthcare workers infected with Omicron variant (BA.2). Second, since the breakthrough group and non-breakthrough group were not randomized, the level of exposure to the SARS-CoV-2 Omicron variant between the groups may not have been the same. Thus, the healthcare workers living more carefully may not experience breakthrough Omicron infection even if the neutralizing antibody titers were relatively low, and these behavioral factors were not measured in this study. Last, healthcare workers have a higher level of exposure to SARS-CoV-2 than the general population as those attend to patients who are undiagnosed as having COVID-19 until proper isolation. This different level of exposure to SARS-CoV-2 Omicron variant could introduce some bias toward the null and some caution is needed for generalizing our findings into general population.

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

참고문헌 목록

1. Centers for Disease Control and Prevention. New SARS-CoV-2 Variant of Concern Identified: Omicron (B.1.1.529) Variant. https://emergency.cdc.gov/han/2021/han00459.asp?ACSTrackingID=USCDC_511-DM71221&ACSTrackingLabel=HAN%20459%20-%20General%20Public&deliveryName=USCDC_511-DM71221%20(Accessed%20on%20December%2003,%202021). Accessed July 10, 2022.

2. Andrews N, Stowe J, Kirsebom F, et al. Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant. *N Engl J Med.* 2022;386(16):1532-1546.

3. Garcia-Beltran WF, St Denis KJ, Hoelzemer A, et al. mRNA-based COVID-19 vaccine boosters induce neutralizing immunity against SARS-CoV-2 Omicron variant. *Cell.* 2022;185(3):457-466 e454.

4. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Effect of mRNA Vaccine Boosters against SARS-CoV-2 Omicron Infection in Qatar. *N Engl J Med.* 2022;386(19):1804-1816.

5. 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):792-793.

6. Kuhlmann C, Mayer CK, Claassen M, et al. Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *The Lancet.* 2022;399(10325):625-626.

7. Kim JY, Kwon J-S, Bae S, et al. SARS-CoV-2-specific antibody and T cell response kinetics according to symptom severity. *The American Journal of Tropical Medicine and Hygiene.* 2021;105(2):395.

8. Lardeux F, Torrico G, Aliaga C. Calculation of the ELISA's cut-off based on the change-point analysis method for detection of Trypanosoma cruzi infection in Bolivian dogs in the absence of controls. *Memórias do Instituto Oswaldo Cruz.* 2016;111:501-504.

9. Classen DC, Morningstar JM, Shanley JD. Detection of antibody to murine cytomegalovirus by enzyme-linked immunosorbent and indirect immunofluorescence assays. *Journal of Clinical Microbiology.* 1987;25(4):600-604.

10. Chemaitelly H, Tang P, Hasan MR, et al. Waning of BNT162b2 Vaccine Protection against SARS-CoV-2 Infection in Qatar. *N Engl J Med.* 2021;385(24):e83.

11. Bergwerk M, Gonen T, Lustig Y, et al. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. *N Engl J Med.* 2021;385(16):1474-1484.

12. Lim SY, Jung J, Kim JY, et al. Breakthrough infections and waning immune responses with ChAdOx1 nCoV-19 or mRNA vaccine in healthcare workers. *Clin Transl Med.* 2022;12(4):e804.

13. Abu-Raddad LJ, Chemaitelly H, Bertollini R. Waning mRNA-1273 Vaccine Effectiveness against SARS-CoV-2 Infection in Qatar. *N Engl J Med.* 2022;386(11):1091-1093.

14. Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nat Med.* 2021;27(11):2032-2040.

15. Khoury DS, Cromer D, Reynaldi A, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med.* 2021;27(7):1205-1211.

16. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *The Lancet.* 2022;399(10332):1303-1312.

17. Hui KPY, Ho JCW, Cheung MC, et al. SARS-CoV-2 Omicron variant replication in human bronchus and lung ex vivo. *Nature.* 2022;603(7902):715-720.

18. Rydyznski Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity. *Cell.* 2020;183(4):996-1012.e1019.

19. Peng Y, Mentzer AJ, Liu G, et al. Broad and strong memory CD4(+) and CD8(+) T cells induced

by SARS-CoV-2 in UK convalescent individuals following COVID-19. *Nat Immunol.* 2020;21(11):1336-1345.

20. Steensels D, Pierlet N, Penders J, Mesotten D, Heylen L. Comparison of SARS-CoV-2 Antibody Response Following Vaccination With BNT162b2 and mRNA-1273. *JAMA.* 2021;326(15):1533-1535.

국문요약

백신은 코로나바이러스감염증-19 를 예방하고 전파를 통제하기 위한 중요한 전략으로 개발되었으나, 백신 유도 면역은 시간이 지나면서 약해지고, 변이주에 의한 돌파감염 사례들이 보고되었습니다. 특히, 오미크론 변이주가 기존의 면역을 회피할 능력이 있는 것으로 알려져, 많은 국가에서는 코로나바이러스감염증-19 백신의 초기 접종을 완료한 사람들에게 부스터 백신을 투여하고 있습니다. 돌파감염을 예방할 수 있는 면역 상관성을 보이는 적절한 중화항체 역가를 규명하는 것이 중요함에도 불구하고, 코로나바이러스감염증-19 백신 접종자를 대상으로 한 오미크론 변이 돌파감염에 대한 면역 상관성에 관련된 데이터는 부족합니다. 따라서 이 코호트 연구는 의료계 종사자들을 대상으로 오미크론 변이 돌파감염에 따른 코로나바이러스감염증-19 mRNA 백신 부스터 접종으로 유도된 체액성 면역반응을 측정하고 오미크론 변이 돌파감염에 따른 항체 역가를 비교하고자 합니다.

이전에 코로나바이러스감염증-19 과거력이 없는 서울아산병원 의료계 종사자들로 연구대상자를 선정하였고 이들은 코로나바이러스감염증-19 mRNA 백신 부스터 샷을 투여 받은 후 2 주 그리고 3 개월 채혈에 동의하였습니다. 미세중화분석법을 사용하여 SARS-CoV-2 오미크론 변이주(B.1.1.529)에 대한 중화항체의 혈장 역가를 측정하였고, 국내에 오미크론 변이주이 유행하던 기간동안 코로나바이러스감염증-19 관련 증상이 있거나 역학적 연관성이 있는 연구대상자에게 비인두 중합효소연쇄반응 검사를 시행하여 코로나바이러스감염증-19 돌파감염을 확인하였습니다. 또한 무증상 코로나바이러스감염증-19 를 배제하기 위해 SARS-CoV-2 N 단백에 대한 항체검사를 시행하였습니다.

총 119 명의 의료계 종사자들 중 56 명이 부스터 백신 접종 이후 오미크론 돌파감염을 경험하여 돌파감염군으로 분류하였고, 돌파감염을 경험하지 않은 나머지 의료계 종사자들을 비돌파감염군으로 분류하였습니다. 두 그룹을 비교하였을 때, 부스터 백신 접종 후 2 주가 지난 시점에 오미크론 변이주에 대한 중화항체 역가(ID_{50})는 돌파감염군 중앙값 1781.9(사분범위 1499.5–4500.0)와 비돌파감염군 중앙값 2613.9(사분범위 1770.7–4498.6)으로 두 군 사이에 유의미한 차이가 없었습니다(p = 0.10). 부스터 샷 투여 3 개월째 채혈 전에 SARS-CoV-2 감염이 확인된 8 명을 제외하고, 부스터 백신 접종 후 3 개월 시점에 오미크론 변이주에 대한 중화항체 역가(ID_{50})는 돌파감염군 중앙값 442.2(사분범위 191.3–807.4)와 비돌파감염군 중앙값 462.4(사분범위 281.1–592.5)으로 두 군 사이에 유의미한 차이가 없었습니다(p = 0.39). 또한 두 군 사이에 시간에 따른 중화항체 역가의 감소 정도에서 통계적으로 유의미한 차이가 관찰되지 않았습니다(β =-380.5 [SE, 680.6]; p = 0.58).

이러한 연구 결과를 바탕으로 코로나바이러스감염증-19 백신의 부스터 샷으로 유도된 2 주 그리고 3 개월 시점의 오미크론 변이주에 대한 중화항체가 이후에 발생한 오미크론 변이주 돌파감염에 대한 면역 상관성을 나타내지 않았음을 확인할 수 있었습니다.