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LETTER

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Antibody levels and the risk of SARS-CoV-2 infection during the Omicron surge

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Abstract: We examined the association between antibody titer levels and risk of coronavirus disease 2019 (COVID-19) infection in the general Japanese population, including a total of 1,972 participants between June and September 2022. Specifically, we ascertained participants' IgG antibody titers targeting the spike protein and infection status, and subsequently examined the association between antibody titer categories (< 2,500, 2,500–5,000, 5,000–10,000 and > 10,000 AU/mL) and COVID-19 infection to estimate risk ratios (RR) and their 95% confidence intervals (CI). Compared to the lowest category, the adjusted RR for participants with antibody titers ≥ 10,000 AU/mL was 0.38 (95% CI: 0.20–0.71). The observed non-linear relationship between the titers and the risk of infection showed that the risk decreased as the participant's antibody titer increased, but the slope became milder when the antibody titer reached approximately 10,000 AU/mL. These findings may contribute to the use of an individual's antibody titer to consider appropriate timing of vaccination.

***Keywords*:** antibody titer category, COVID-19, general population, spike protein, vaccination

Vaccinations increase the levels of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Lower antibody titers were associated with the increased risk of infection during the Alpha and Delta surge (*1,2*), although few studies have examined this during the Omicron surge (*3,4*). A cohort study that included healthcare workers revealed that a lower antibody category divided by a specific value was associated with the increased risk during the Omicron surge (*4*). However, a more detailed assessment of the association between the levels of antibody titers and the risk is warranted in the general population, especially in the elderly.

The Bizen Coronavirus Disease 2019 (COVID-19) Antibody Test project (BCAT) is a community-based prospective cohort study that began on June 3, 2022, where antibody titers were measured every two months among residents of Bizen City, Okayama, Japan, or people working in the city. The study was approved by the Ethics Committee of Okayama University Hospital (No. 2205-061). We recruited a total of 1,972 participants over the age of 18. For this analysis, we included up to the second titer measurement from participants who had provided at least one measurement between June 3 and September 23, 2022. We excluded titer measurements if the vaccination was administered within two months of the measurement, yielding a total of 2,345 measurements from 1,649 participants. BA.5 subvariants of the Omicron variant were dominant during the period.

We collected fingertip whole blood samples (30 μL) and used the Mokobio SARS-CoV-2 immunoglobulin M (IgM) & immunoglobulin G (IgG) Quantum Dot immunoassay test kit (Mokobio Biotechnology R&D Center Inc., Rockville, MD, USA) to measure IgG antibody titers targeting the spike protein receptor-binding domain (*5,6*). We also confirmed whether the participants had tested positive for COVID-19 infection during the period between June 1 and September 25 and linked the infection status (*i.e.*, positive or negative) with the most recent antibody measurement information within two months. Since all positive cases that occurred in Okayama Prefecture were registered until September 25, we obtained the infection history from the Okayama Prefecture Registry and supplemented this with the self-reported questionnaire for those who did not live in the prefecture.

We examined the association between antibody titer category (< 2,500, 2,500–5,000, 5,000–10,000, and ≥ 10,000 AU/mL) and COVID-19 infection using a generalized estimating equation model accounting for a correlation within a participant, assuming a Poisson distribution with robust error variance. We then estimated risk ratios (RRs) and their 95% confidence intervals (CIs) adjusting for sex and age categories (18–39, 40–59, 60–79, and ≥ 80 years). We also evaluated the non-linear relationship between antibody titers

Table 1. A antibody titers and COVID-19 infection in Bizen city, Japan (n = 1,649)[a]

IgG (AU/mL)	COVID-19 infection case / Total measurement (%)	Adjusted RR (95% CI)[b]
< 2,500	105 / 1418 (7.4)	1.0 (ref)
2,500–5,000	14 / 340 (4.1)	0.57 (0.33–0.99)
5,000–10,000	8 / 266 (3.0)	0.42 (0.21–0.85)
≥ 10,000	9 / 328 (2.7)	0.36 (0.18– 0.71)

[a] We analyzed 2345 measurements from 1649 participants with no missing variables. [b] Adjusted for sex and age categories. CI, confidence interval; COVID-19, coronavirus disease 2019; IgG, Immunoglobulin G; arbitrary unit AU; RR, risk ratio.

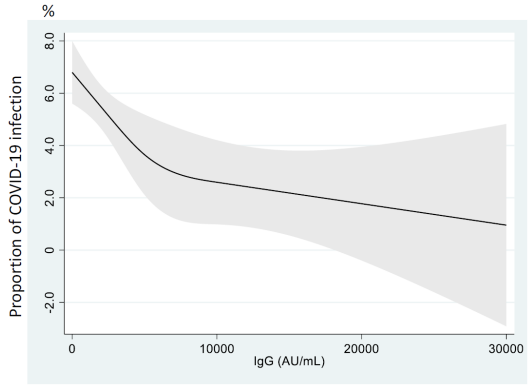

Figure 1. Association between immunoglobulin G (IgG) values (AU/mL) and the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (%). The natural cubic spline that had three knots (2,500, 5,000, and 10,000 AU/mL) is shown as a black line and the 95% confidence intervals (CIs) are shown as a gray range. The upper limit of antibody titers was set at 30,000 AU/mL, as instructed by manufacturer's instructions; any value exceeding this limit was replaced into the upper limit. The shape of the spline curves did not change when we used different number of knots (*e.g.*, from 3 to 7).

(continuous) and the risk using natural cubic spline curves. All analyses were conducted with Stata SE version 17 (StataCorp LP, College Station, TX, USA).

A total of 136 of the 1,649 participants were infected during the study period. Higher antibody titers were associated with a lower risk. Compared with the lowest antibody category, the adjusted RR was 0.38 (95% CI: 0.20–0.71) for the participants with antibody titers ≥ 10,000 AU/mL (Table 1). The risk decreased as the antibody titer of the participant increased, although the slope became mild at antibody titers of approximately 10,000 AU/mL (Figure 1).

Despite several limitations, such as residual confounding due to underlying diseases or the assumption of the same antibody titer during the two months after the measurement, this study showed that higher antibody titers were associated with lower risk of infection in a dose-response manner during the Omicron surge. Moreover, the risk declined sharply at antibody titers of approximately 10,000 AU/mL. These findings could contribute to the use of an individual's antibody titer to consider appropriate timing of vaccination.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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