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Letter
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Prevalence and Clinical Outcome of Omicron Breakthrough Infection in Patients With Hematologic Disease: A Prospective Observational Cohort Study

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The Omicron variants (OVs) of SARS-CoV-2 are highly transmissible, and the vaccine is less effective against it compared with earlier variants.[1,2] In general cohorts, the symptoms caused by the OVs are reported to be mild.[3] However, the prevalence and severity of OVs in patients with hematologic diseases (HDs) have not been sufficiently reported.[4] Hence, we report a single-center prospective observational cohort study on postvaccination antibody titers, clinical symptoms, and their prognosis to identify risk factors for breakthrough infection by OVs and its severity in patients with HDs.

The anti-SARS-CoV-2 spike antibody (anti-S) titers after the second dose (post-D2) and after the third dose (post-D3) of vaccination were measured between July 2021 and September 2022 in patients with HD and healthcare workers (HCW) for comparison. The incidence of newly confirmed Omicron breakthrough infections among the fully vaccinated (≥D2) participants was investigated from January 1 to September 30, 2022. A flow diagram of patient enrollment is shown in Suppl. Figure S1, and their baseline characteristics according to the infection status are shown in Table 1. Detailed study materials and methods are shown in Suppl. Materials and Methods.

The overall cumulative incidence rates (IR) were compared between the HD and HCW cohorts (Suppl. Figure S2). HCW were significantly younger (median age, 29 years; interquartile range [IQR], 25–46; $P < 0.01$) compared with the patients with HD. Breakthrough infections occurred in 75 (8.1%) of 660 persons per year in HD and 12 (13.6%) of 63 persons per year in HCW cohorts. The cumulative IR was not significantly different between the HD and HCW cohorts (log-rank, $P = 0.08$). The HD patients were divided into D2- and D3-cohorts based on their vaccination status (Suppl. Materials and Methods). The association between the clinical factors and the risk of breakthrough infection in the D2- and D3-cohorts were examined (Suppl. Table S1). Multivariate analysis showed that old age and the recent use of anti-CD20 antibodies were independent and significant, negative and positive predictors for the breakthrough infection in the D2 cohort. In the D3-cohort, none of the clinical variables showed statistical significance.

The anti-S levels at the post-D2 and post-D3 were compared between the HD and HCW cohorts (Suppl. Figure S3A). The median anti-S levels at post-D2 (153 U/mL) and post-D3 (9836 U/mL) in the HD cohort were approximately 6 and 2 times lower than those of the HCW cohort (724 U/mL and 23,523 U/ml), respectively. Furthermore, most of the patients with HD (133/153, 86.9%) and all HCWs (n = 39) showed a decrease in their anti-S levels, with a median decline of 16.8% and 13.2% per month, respectively (Suppl. Figure S3B).

Next, the association between the anti-S levels and infection risk in post-D2 (n = 734) and post-D3 HD patients (n = 525) was analyzed (Figure 1A and 1B). The median time interval between D2 and post-D2, and D3 and post-D3, was 173 days (IQR, 152–191) and 25 days (IQR, 17–37), respectively. Compared with the seronegative patients, there was no significant dose-dependent association between the anti-S levels and the risk of breakthrough infection. Highly variable anti-S levels (median, 112 U/mL; range, 0.4–88,377) before breakthrough infection regardless of subvariants in 42 of 75 (56%) patients, whose anti-S titer were assessable, also support the limited impact of the quantitative role of anti-S levels on protection (Figure 1C).

Longitudinal changes in anti-S, and PCR cycle threshold (Ct) values were available for 9 patients with confirmed OVs (Figure 1D and 1E). Four patients (patients 1–4) achieved a negative PCR result within 21 days, while 5 (patients 5–9) did not. One (patient 3) died on day 14, postinfection, due to the progression of follicular lymphoma.

Five patients with persistent infection were seronegative before infection and 4 remained seronegative until 49 days after infection. All but 1 patient with persistent infection received bendamustine and anti-CD20 antibodies within a year before infection. One patient (patient 8) received bendamustine >2 years prior but had very low T-cell counts (CD4 count: 159/μL and CD8 count: 399/μL). None of the patients with nonpersistent infection received bendamustine treatment within a year.

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Table 1

Demographic and Clinical Characteristics, Treatment, Vaccine Status, and Postvaccination Antibody Titers of the Entire Cohort

Characteristics	Total (n = 922)	No Infection (n = 847)	COVID-19 (n = 75)
Age, y; median (IQR)	72 (64–78)	72 (64–78)	68 (57–78)
Age ≥70, n (%)	539 (58.4)	505 (93.7)	34 (6.3)
Female, n (%)	421 (45.7)	389 (92.4)	32 (7.6)
Disease, n (%)			
Lymphoid neoplasms	642 (69.6)	591 (69.8)	51 (68.0)
Malignant lymphoma	431 (46.7)	397 (46.9)	34 (45.3)
Plasma cell dyscrasia	188 (20.4)	173 (20.4)	15 (20.0)
Others	23 (2.5)	21 (2.5)	2 (2.7)
Myeloid neoplasms	219 (23.8)	202 (24.7)	17 (22.7)
Benign hematologic disease	61 (6.6)	54 (5.9)	7 (9.3)
Treatment, n (%)			
Ongoing treatment	377 (40.9)	348 (41.1)	29 (38.7)
CD20 antibody within a year	146 (15.8)	128 (15.1)	18 (24.0)
CD20 antibody+bendamustine within a year	36 (3.9)	30 (3.5)	6 (8.0)
CD38 antibody within a year	82 (8.9)	71 (8.4)	11(14.7)
Allogenic SCT within a year	11 (1.2)	11 (1.3)	0 (0)
Vaccination doses before infection, n (%)			
2	59 (6.4)	30 (3.5)	29 (38.7)
≥3	840 (91.1)	794 (88.4)	46 (61.3)
Missing	23 (2.5)	23 (2.7)	0 (0)
Anti-S level after vaccination, U/mL, median (IQR)			
post-D2 anti-S (n = 820)	157 (22–421)	161 (22–419)	81 (2–556)
post-D3 anti-S (n = 617)	9862 (1439-23,379)	9979 (1536-23,746)	4670 (908-16,805)

ALL = acute lymphoblastic leukemia; AML/MDS = acute myeloid leukemia/myelodysplastic syndrome; anti-S = anti-SARS-CoV-2 antibody titers of spike antigen; CML = chronic myeloid leukemia; IQR = interquartile range; MM = multiple myeloma; MPN = myeloproliferative neoplasms; SCT = stem cell transplantation; sMM/MGUS = smoldering myeloma/monoclonal gammopathy of undetermined significance.

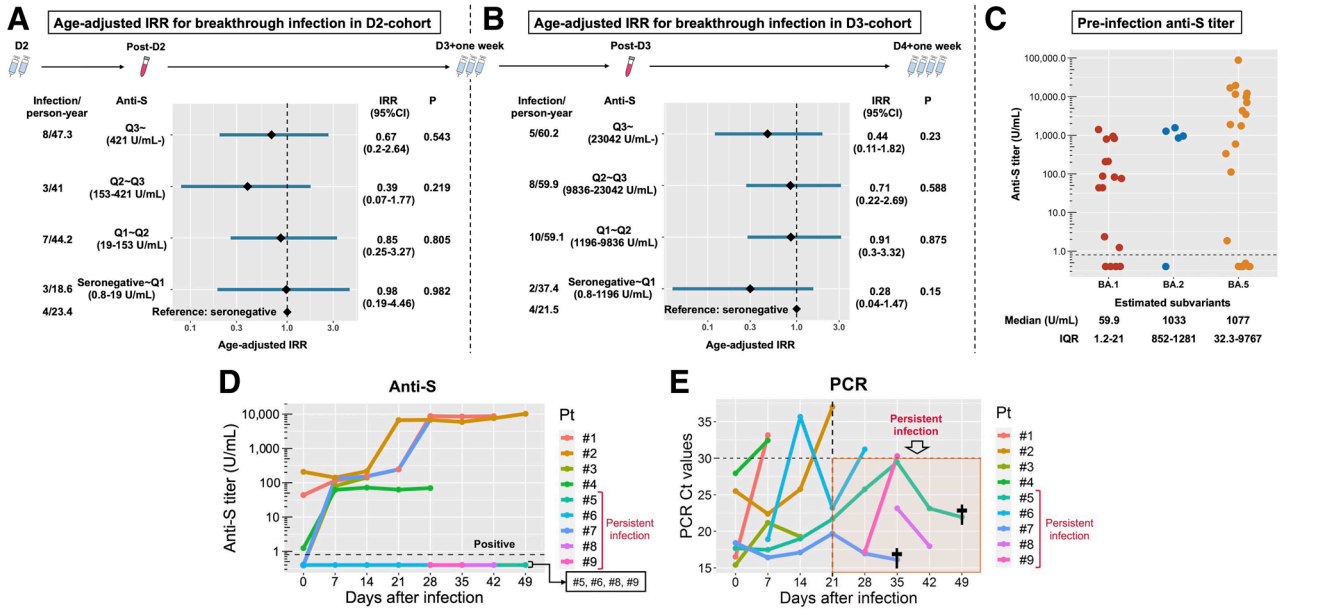

Figure 1. Anti-S levels with breakthrough infection and longitudinal changes of anti-S and cycle threshold of PCR. Forest plot displaying age-adjusted incidence rate ratios of post-D2 anti-S levels in the D2-cohort (A) and post-D3 in the D3-cohort (B) for breakthrough infection. Anti-S values were divided into 4 quartiles, and the IRR of patients with each quartile was compared with those seronegative. The syringe and blood sample icon represent vaccination and anti-S measurement, respectively. (C) Preinfection anti-S levels according to the estimated subvariants (BA.1, BA.2, and BA.5). (D) Longitudinal changes of anti-S and (E) cycle threshold of PCR before and after breakthrough infection in 9 patients. Cross key mark denotes death by COVID-19. Patients 8 and 9 were transferred to our hospital on day 35 and day 28 after the infection. anti-S = anti-spike receptor-binding domain antibody; CI = confidence interval; Ct = cycle threshold; D2 = 2 doses; D3 = 3 doses; D4 = 4 doses; IQR = interquartile range; IRR = incidence rate ratio; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile.

Absolute lymphocyte counts and lymphocyte subsets were compared between patients with nonpersistent and persistent infections. CD3, CD4, and CD8 counts were significantly lower in patients with persistent infection (Suppl. Figure S4).

Treatment and clinical outcomes of patients with OVs are summarized in Suppl. Table S2. Symptoms at diagnosis in patients without oxygen demand (n = 66, 88.0%) were mild and did not require hospitalization. All asymptomatic patients

were diagnosed with COVID-19 using a screening test because of their close contact with infected patients. Thirteen patients (17.3%) were seronegative before infection, 4 of which (6.4%) required oxygen therapy. Overall, 29 (38.6%) patients received COVID-19-specific therapies and 46 (61.3%) required no treatment.

Nine (12.0%) patients required oxygen therapy for COVID-19 pneumonia. Specifically, patients who received bendamustine within a year were significantly more likely to require oxygen therapy than those who did not (3/6 [50%] versus 6/69 [8.7%]; $P = 0.02$). All 3 patients who died of COVID-19 had a high oxygen demand and poor general condition at the onset. In addition, 3 patients also died due to the worsening of the hematologic malignancies.

The study showed that there was no significant difference in the incidence of breakthrough infections between HD patients and HCWs, despite their potential vulnerabilities including older age, lower antibody titers, and disease-induced and/or treatment-induced immunosuppression. Similar to our results, a disparate COVID-19 prevalence was observed in a previous report that included patients with cancer.[5] In addition, the recent exposure to B-cell depletion therapy was no longer a significant factor for the increased risk of breakthrough infections in the D3-cohort. Altogether, our findings suggest that behavioral factors such as social activity and social distancing measures might be more important than immunological profiles in preventing Omicron infections, at least after booster vaccination.

The OVs have multiple mutations in its spike protein, which is responsible for immune evasion to neutralize antibodies. However, a dose-dependent association between the anti-S levels and the risk of infection was not observed in line with the previous report of the immunocompetent settings.[6] Given the immune escape properties of Omicron, protection may require extremely high antibody titers,[7] or antibodies that are more specific to Omicron than conventional antibodies.[8]

In the present HD cohort, which included 17.3% of seronegative patients after full vaccination, only 3 patients (4.0%) died and only 9 (12.0%) patients required hospitalization. The remaining patients were treated as outpatients or did not require treatment. The mild symptoms of infection and the low mortality rate, even in patients with low antibody titers, suggest that the OV itself causes less frequent and less severe pneumonia than the previous variants. The low hospital admissions and mortality rates were comparable with a larger immunocompetent cohort with OV infections and are reduced from those seen with the Delta variant based on the studies in South Africa and Canada.[9,10]

Prolonged viral shedding of SARS-CoV-2 including OVs was previously described in several case reports and case series with severely immunocompromised patients.[11,12] In our cohort, there was no difference in the frequency of infection with OVs between patients treated with CD20 antibodies plus bendamustine and those treated with drugs other than bendamustine within 1 year. However, in patients with available longitudinal PCR data, delayed viral shedding was observed in 5 patients with Omicron infection who received CD20 antibody therapy plus bendamustine, whereas patients who did not receive the bendamustine did not have delayed viral shedding.

The factors leading to delayed viral shedding include a varying degree of T-lymphocytopenia in persistently infected patients, possibly associated with the use of bendamustine, while CD19 counts did not differ between the 2groups. In our cohort, all 3 patients who died of COVID-19-related pneumonia did not receive a booster dose of vaccination, although booster vaccination does not only dramatically increase the neutralizing antibody titer but also may enhance T-cell reactivity to the OV.[13] In addition, the clinical study, which reported that a booster dose of vaccination reduced the hospitalization and death rates by OV compared with 2 doses of vaccination, was consistent with our observations.

The major strength of this study is its large cohort with detailed clinical information in combination with serological data of patients, including viral kinetic assessment. However, this study also has several limitations. First, we could not directly measure the neutralizing antibody titers against Omicron. The low incidence of breakthrough infections makes it difficult to adjust potential confounding factors. Furthermore, this study was conducted during a limited time window when OVs became predominant with the wide distribution of existing mRNA vaccines. Prophylaxis against OVs has been developed through vaccination with bivalent vaccines[14] and monoclonal antibodies such as tixagevimab-cilgavimab.[15] However, given the antibody response to vaccines and its attenuation in HD patients, there is a possibility that antibody production to these bivalent vaccines may not be sufficient to prevent breakthrough OV infections, rather passive immunization with bivalent vaccines might be more effective, although this should be evaluated in the context of clinical practice.

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AUTHOR CONTRIBUTIONS

KN, DI, and KM contributed to the study design, data collection, data interpretation, provided patient care, and wrote the article. KN and DI performed statistical analysis. MS, AF, RT, YU, DM, and MT collected data and provided patient care. MD, YU, and YO performed serological tests. All authors critically reviewed and approved the article.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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