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Basic science

Antibody responses following the surge of SARS-CoV-2 Omicron infection among patients with systemic autoimmune rheumatic diseases

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Abstract

Objectives: The surge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant Omicron infections has affected most Chinese residents at the end of 2022, including a number of patients with systemic autoimmune rheumatic diseases (SARDs).

Methods: To investigate the antibody level of the Omicron variant in SARD patients after SARS-CoV-2 Omicron infection, we tested BA.5.2 and BF.7 Omicron variant IgG antibody levels using ELISA on blood samples collected from 102 SARD patients and 19 healthy controls (HCs). The type of SARD, demographics, concurrent treatment, doses of SARS-CoV-2 vaccines and outcomes were also recorded.

Results: A total of 102 SARD patients (mean age: 40.3 years; 89.2% female), including 60 SLE, 32 RA and 10 other SARDs, were identified. Of these, 87 (85.3%) were infected with SARS-CoV-2. We found that the BA.5.2 and BF.7 antibody levels of infected SARD patients were lower than those of HCs ($P < 0.05$). Sixty-five (63.7%) patients had at least one dose of a SARS-CoV-2 vaccine. SARD patients with at least two doses of SARS-CoV-2 vaccine had a higher level of BA.5.2 and BF.7 antibodies than the unvaccinated group ($P < 0.05$). There was no evidence for a significant inhibitory effect of glucocorticoids (GCs) on the BA.5.2 and BF.7 Omicron variant antibody levels in SARD patients. SLE patients using biologic DMARDs had a lower BA.5.2 Omicron variant antibody level than patients using GCs and/or HCQ.

Conclusion: These data suggest that patients with SARDs had a lower antibody response than HCs after Omicron infection.

Lay Summary

What does this mean for patients?

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a type of coronavirus that causes coronavirus disease 2019 (COVID-19). Spread of SARS-CoV-2 led to the COVID-19 pandemic and a global threat to public health. Different variants of SARS-CoV-2 have developed as the virus changes over time. Omicron is one such variant. Patients with systemic autoimmune rheumatic diseases (SARDs), such as rheumatoid arthritis, systemic lupus erythematosus and Sjögren's syndrome, are often treated with drugs called immunosuppressants. Immunosuppressants make the immune system less active, meaning that it is harder to defend against diseases such as COVID-19. As a result, SARD patients are at higher risk of developing severe COVID-19. We performed a study to describe the characteristics and immune responses of SARD patients with COVID-19 Omicron infection in China. We found that SARD patients had fewer antibodies against Omicron than healthy people. We also found that lupus patients who used biologic drugs had a lower antibody level than those using glucocorticoids (steroids) and/or hydroxychloroquine. Importantly, SARD patients who had at least two doses of SARS-CoV-2 vaccine had higher levels of antibodies than unvaccinated patients. These findings suggest that patients with SARDs have a lower antibody response after Omicron infection than healthy people, meaning that their immune systems are less able to defend against future re-infection. Our data therefore support the importance of COVID-19 booster vaccination among patients with SARDs.

Keywords: SARS-CoV-2, Omicron, systemic autoimmune rheumatic diseases, antibody

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Key messages

- BA.5.2 and BF.7 antibody levels of infected SARD patients were lower than those of healthy controls.
- SARD patients with at least two doses of SARS-CoV-2 vaccine had higher levels of Omicron antibodies.
- Combined use of biologic DMARDs might dampen the antibody responses in patients with SLE.

Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Omicron, a variant of SARS-CoV-2, possesses a much higher transmission rate and infectivity than other variants [2], causing a global epidemic and threatening public health [3, 4]. Since December 2022, a significant COVID-19 epidemic has emerged in China following a reduction in prevention and control measures. The self-reported infection rate peaked between 19–21 December 2022; 82.4% of the Chinese population were infected as of 7 February 2023 [5]. The elevated transmission rate of Omicron could be attributable, in part, to its significant ability to evade the immune system. Recent studies have shown that individuals who were previously infected with other SARS-CoV-2 variants or vaccinated could be reinfected with Omicron, implying that Omicron might escape immunity induced by vaccination or previous infection with other SARS-CoV-2 variants [6, 7]. To date, hundreds of Omicron subvariants have been identified, of which the most prevalent variants, both in China and around the world, are BA.5.2 and BF.7 [8]. Several risk factors that have been identified to be associated with increased susceptibility and severe clinical outcomes include immune-mediated inflammatory disease, age, co-infections and co-morbidities [9].

Systemic autoimmune rheumatic diseases (SARDs), including RA, SLE and SS, represent a large group of chronic, multi-organ inflammatory disorders characterized by a breakdown of self-tolerance that lacks self-remission, leading to imbalanced immune responses and tissue damage [10]. Patients with SARDs are usually treated with immunosuppressive drugs, such as glucocorticoids (GCs) and DMARDs, to dampen aberrant immune responses and reduce disease activity, which can also increase the incidence of infections [11]. Some studies have shown that patients with SARDs can be at high risk for SARS-CoV-2 infection and poor outcome after infection [12, 13]. The surge of the SARS-CoV-2 Omicron variant in China poses a serious challenge for the management of patients with SARDs, who are considered to be more susceptible to infections. Correspondingly, concern exists regarding whether SARD patients have a mitigated antibody response to Omicron. However, the clinical characteristics and immune response characteristics of Omicron infection in SARD patients are unclear. Moreover, could the prototype SARS-CoV-2 vaccination help to induce antibodies against Omicron variants? This study was undertaken to describe the clinical and immunological characteristics of Omicron infection in patients with SARDs and to provide evidence for the optimization of management of SARD patients during the Omicron outbreak.

Methods

Participants

This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of University of Science and Technology of China (no. 2023-KY-006). Subjects with SARDs (including SLE, RA, SS, AS, vasculitis and UCTD) from the Department of Rheumatology and Immunology, the First Affiliated Hospital of University of Science and Technology of China, were included in the analyses, which covered the Omicron variants pandemic period from December 2022 to January 2023. The following characteristics of SARD patients were recorded: age, sex, disease duration, disease-related characteristics (type of SARD and clinical manifestations), treatment currently received (use of DMARDs), dose of GCs (entered as daily oral prednisone equivalents), vaccination-related characteristics (type of vaccine and number of doses), Omicron infection-related characteristics (presenting symptoms and temperature of fever) and severity after infection, such as mild (no pneumonia), moderate (with pneumonia after imaging examination of lung) and severe (hospitalized, need for oxygen supplementation). Medications taken by patients before COVID-19 were categorized as follows: conventional synthetic (cs) DMARDs, including HCQ, MMF/mycophenolic acid, tacrolimus, CSA, LEF and MTX; biologic (b) DMARDs, including abatacept, belimumab, telitacicept, rituximab, IL-6 inhibitors and TNF inhibitors (anti-TNF); and targeted synthetic (ts) DMARDs, specifically JAK inhibitors and GCs. Nineteen age- and sex-matched healthy controls (HCs) were also recruited from health-care workers who were infected with SARS-CoV-2 Omicron during the same period. Peripheral venous blood samples (5 ml) were obtained from SARD patients and HCs. All participants gave written informed consent, and the study was performed in accordance with the principles of the Declaration of Helsinki.

ELISAs

Nunc MaxiSorp plates were coated with 3 μg/ml recombinant RBD, BA.5 RBD or BF.7 RBD at room temperature for 2 h. After washing four times with PBS (3 min each time), the plates were blocked with 5% non-fat milk in PBS at room temperature for 2 h. Serially diluted serum [5% non-fat milk in PBST (PBS with 0.1% Tween-20)] was added to the plates, which were then incubated at room temperature for 1 h. After washing three times with PBST (3 min each time), horseradish peroxidase-conjugated goat anti-human IgG was added, followed by incubation at room temperature for 1 h. After washing three times with PBST (3 min each time), Tetramethylbenzidine (TMB) substrate was added for 8 min, then stopped by 1 M H_2SO_4. Absorbance at 450 nm was measured with a microplate reader. The antibody titre was calculated as the dilution of the serum that induced an A450 value twice that of the A450 value of the negative control.

Statistical analysis

Continuous variables were expressed as the mean (S.D.) or median (±interquartile range), as appropriate. Categorical variables were expressed as percentages. The Kruskal–Wallis *H* test and Mann–Whitney *U* test were used to compare

continuous characteristics. The statistical package SPSS v.21.0 (IBM) was used. The results were considered statistically significant using a two-sided $P < 0.05$.

Results

Study sample and baseline characteristics

A total of 102 SARD patients were enrolled in this study, including 60 SLE, 32 RA and 10 other SARD patients (3 SS, 3 AS, 2 vasculitis and 1 UCTD). The baseline clinical characteristics are shown in Table 1. The participants were predominantly female (89.2%), and the mean age was 40.3 years (S.D. 15.0 years). Overall, 43 (42.2%) had articular involvement, 29 (28.4%) had renal involvement, and 66 (64.7%) were on combination therapy of two or more categories drugs, with use of GCs, csDMARDs and b/tsDMARDs. Approximately one-third of our patients were receiving ≥10 mg/day prednisone equivalent GC, and 28 (27.5%) were receiving >0–5 mg/day prednisone equivalent. Of all these patients, 65 (63.7%) were vaccinated with the SARS-CoV-2 vaccine, and 60 had received at least two doses of the SARS-CoV-2 vaccine. The vaccination rate in RA patients (90.6%) was higher than that in patients with SLE (60.0%). Eighty-seven (85.3%) were infected with SARS-CoV-2, with the most common symptoms including fever (79.3%), cough (70.1%), malaise (39.1%), expectoration (31.0%), sore throat (28.7%) and ageusia (25.3%). The majority of patients (78.6%) had mild symptoms after SARS-CoV-2 Omicron infection. Four (4.6%) patients had moderate symptoms, with pneumonia after imaging examination of the lung. Only one patient had severe symptoms and was hospitalized, requiring oxygen supplementation.

SARD patients had lower antibody levels of BA.5.2 and BF.7

In ELISAs of BA.5.2 and BF.7 variant antibodies, we found that the BA.5.2 antibody level of infected SARD patients was lower than that of HCs ($P < 0.05$), and a similar alteration was also observed in the antibody level of the BF.7 variant ($P < 0.01$) (Fig. 1A and B). Subgroup analysis was performed according to the type of rheumatic disease. The SLE group had lower antibody levels of the BA.5.2 variant than the HCs ($P < 0.05$). Among the SARDs groups, the antibody level of the BA.5.2 variant was comparable between SLE and RA patients (Fig. 1A and B). The antibody levels of the BF.7 variant in the RA group were lower than those in the HC group ($P < 0.01$). However, SLE patients had a higher antibody level of the BF.7 variant than RA patients ($P < 0.05$).

Vaccinated SARD patients had higher antibody levels of BA.5.2 and BF.7

Vaccination is one of the most effective ways to control the spread of SARS-CoV-2. Therefore, we analysed the antibody levels of people vaccinated against SARS-CoV-2. As shown in Fig. 1C and C, the vaccinated SARD group had notably higher levels of BA.5.2 and BF.7 antibodies than the unvaccinated group ($P < 0.01$). The same alterations were also observed in the SLE group ($P < 0.01$). The BA.5.2 antibody level of RA patients vaccinated with SARS-CoV-2 was higher than that of RA patients who were unvaccinated. However, no significant difference was found in BF.7 antibody levels between SARS-CoV-2-vaccinated and -unvaccinated patients with RA. Next, we analysed the antibody levels according to doses of vaccine. Compared with the unvaccinated group, SARD patients who had received two doses or three doses of the SARS-CoV-2 vaccine showed significantly higher BA.5.2 and BF.7 antibody levels (Fig. 1E and F). Patients who had received one dose of SARS-CoV-2 vaccine did not show a significant increase in antibody levels after infection.

Use of GCs does not affect antibody levels of BA.5.2 and BF.7

We evaluated the effect of use of GCs on antibody levels. Patients were divided into four groups according to the dosage of GCs (i.e. no GC use, >0–5, 6–9 and ≥10 mg/day prednisone equivalent). As shown in Fig. 2A and B, the antibody levels of BA.5.2 and BF.7 were not significantly different among the four groups ($P > 0.05$). Likewise, there was no significant difference in the BA.5.2 and BF.7 antibody levels according to varying dosages of GC use in SLE patients ($P > 0.05$; Fig. 2C and D).

SLE patients with bDMARDs use had lower antibody levels of BA.5.2

A blunted SARS-CoV-2 antibody response following COVID-19 vaccination has been observed in users of certain DMARDs. We evaluated the effect of different DMARDs on antibody levels. Patients were divided into three groups (i.e. the GCs and/or HCQ group; other csDMARDs group regardless of whether they also used HCQ or GCs; and biologic or targeted synthetic DMARDs (b/tsDMARDs) group with GCs and use of at least one csDMARD). Patients who used b/tsDMARDs had lower levels of BA.5.2 and BF.7 antibodies than the other two groups, but the differences were not statistically significant (Fig. 3A and B). Moreover, the level of BA.5.2 antibody was significantly decreased in SLE patients treated with bDMARDs compared with those treated with GCs and/or HCQ ($P < 0.05$; Fig. 3C). No significant difference in BF.7 antibody levels was found in SLE patients with the use of different DMARDs (Fig. 3D).

Discussion

Our study shows the antibody responses following the surge of SARS-CoV-2 Omicron infection among patients with SARDs. Our results suggest that the BA.5.2 and BF.7 antibody levels of infected SARD patients were significantly lower than those of HCs. We found that at least two doses of prototype SARS-CoV-2 vaccination helped to induce a high level of antibody against BA.5 and BF.7 variants in SARD patients after Omicron infection. Moreover, the use of GCs did not dampen the antibody responses in SARD patients. It should be noted, however, that SLE patients using bDMARDs had a lower BA.5.2 Omicron variant antibody level than patients using GCs and/or HCQ.

To our knowledge, this is the first report on the clinical and immunological characteristics of Omicron infection among SARD patients in China during the Omicron wave of the epidemic [14]. In this study, our data provide real-world evidence that the immunodefensive function against BA.5.2 and BF.7 subvariants of patients with both SARDs and Omicron infection is impaired. A previous study found that SARD patients had lower median (interquartile range) anti-RBD-IgG

Table 1. Demographics, vaccination details, medication use and coronavirus disease 2019 infection details in systemic autoimmune rheumatic disease patients ($n = 102$)

Parameter	All SARDs ($n = 102$)	SLE ($n = 60$)	RA ($n = 32$)	Others ($n = 10$)
Demographics				
Female, *n* (%)	91 (89.2)	57 (95.0)	27 (84.4)	7 (70.0)
Age, mean (s.d.), years	40.3 (15.0)	34.2 (11.4)	53.2 (12.6)	35.4 (16.3)
Organ involvement, *n* (%)				
Articular	43 (42.2)	11 (18.3)	26 (81.3)	6 (60.0)
Pulmonary	7 (6.9)	4 (6.7)	1 (3.1)	2 (20.0)
Haematological	14 (13.7)	9 (15.0)	3 (9.4)	2 (20.0)
Renal	29 (28.4)	27 (45.0)	1 (3.1)	1 (10.0)
Cutaneous	15 (14.7)	15 (25.0)	0 (0.0)	0 (0.0)
Concurrent treatment, *n* (%)				
GC only	9 (8.8)	2 (3.3)	6 (18.8)	1 (10.0)
csDMARDs only	10 (9.8)	2 (3.3)	6 (18.8)	2 (20.0)
b/tsDMARDs only	1 (1.0)	0 (0.0)	0 (0.0)	1 (10.0)
Combination therapy	66 (64.7)	53 (88.3)	9 (28.1)	4 (40.0)
GC use/dose, *n* (%)				
No GC use	30 (29.4)	5 (8.3)	19 (59.4)	6 (60.0)
GC >0–5 mg/day prednisone equivalent	28 (27.5)	22 (36.7)	4 (12.5)	2 (20.0)
GC 6–9 mg/day prednisone equivalent	4 (3.9)	4 (6.7)	0 (0.0)	0 (0.0)
GC ≥10 mg/day prednisone equivalent	34 (33.3)	25 (41.7)	7 (21.9)	2 (20.0)
Vaccination details, *n* (%)				
Vaccinated	65 (63.7)	36 (60.0)	29 (90.6)	0 (0.0)
Vaccine type, *n* (%)				
Inactivated vaccine	48 (47.1)	25 (41.7)	23 (71.9)	0 (0.0)
Recombinant protein vaccine	13 (12.7)	8 (13.3)	5 (15.6)	0 (0.0)
Adenovirus vaccine	1 (1.0)	1 (1.7)	0 (0.0)	0 (0.0)
Vaccine doses, *n* (%)				
1	4 (3.9)	3 (5.0)	1 (3.1)	0 (0.0)
2	23 (22.5)	12 (20.0)	11 (34.4)	0 (0.0)
3	36 (35.3)	21 (35.0)	15 (46.9)	0 (0.0)
4	1 (1.0)	0 (0.0)	1 (3.1)	0 (0.0)
COVID-19 infection, *n* (%)				
Infected	87 (85.3)	52 (86.7)	26 (81.3)	9 (100%)
Symptoms, *n* (%)				
Fever	69 (79.3)	41 (78.8)	21 (80.8)	7 (77.8)
Cough	61 (70.1)	36 (69.2)	22 (84.6)	3 (33.3)
Expectoration	27 (31.0)	15 (28.8)	11 (42.3)	1 (11.1)
Malaise	34 (39.1)	20 (38.5)	10 (38.5)	4 (44.4)
Myalgia	15 (17.2)	9 (17.3)	4 (15.4)	2 (22.2)
Headache	18 (20.7)	8 (15.4)	7 (26.9)	3 (33.3)
Shortness of breath	5 (5.7)	2 (3.8)	2 (7.7)	1 (11.1)
Sore throat	25 (28.7)	21 (40.4)	4 (15.4)	0 (0.0)
Abdominal pain and/or diarrhoea	3 (3.4)	1 (1.9)	1 (3.8)	1 (11.1)
Vomiting	4 (4.6)	2 (3.8)	1 (3.8)	1 (11.1)
Anosmia	15 (17.2)	10 (19.2)	3 (11.5)	2 (22.2)
Ageusia	22 (25.3)	13 (25.0)	7 (26.9)	2 (22.2)
Appetite changes	9 (10.3)	4 (7.7)	5 (19.2)	0 (0.0)
Temperature of fever, *n* (%)				
37.3–38°C	32 (36.8)	23 (44.2)	6 (23.1)	3 (33.3)
38.1–39°C	27 (31.0)	16 (30.8)	8 (30.8)	3 (33.3)
39.1–41°C	8 (9.2)	2 (3.8)	5(19.2)	1 (11.1)
COVID-19 infection symptoms, *n* (%)				
Mild	82 (94.3)	49 (94.2)	25 (96.2)	8 (88.9)
Moderate	4 (4.6)	3 (5.8)	1 (3.8)	0 (0.0)
Severe	1 (1.1)	0 (0.0)	1 (3.8)	0 (0.0)
Aggravation of SARD after COVID-19 infection, *n* (%)				
Yes	24 (27.6)	10 (19.2)	13 (50.0)	1 (11.1)

bDMARDs: biological DMARDs; COVID-19: coronavirus disease 2019; csDMARDs: conventional synthetic DMARDs; GC, glucocorticoid; SARD: systemic autoimmune rheumatic disease; tsDMARDs: targeted synthetic DMARDs.

levels and neutralizing function against the Omicron BA.2 variant than the healthy group, which was consistent with our results [15]. Yamaguchi *et al.* also reported that the levels of anti-Omicron RBD/spike IgG were significantly lower in patients with RA and SLE than in HCs [16]. Among SARD patients, the levels of antibodies against BA.5.2 and BF.7 in vaccinated individuals were higher than those in unvaccinated individuals. Furthermore, our study found that the number of vaccinations was positively associated with the level of antibodies in SARD patients, highlighting the beneficial role of booster vaccination in protecting SARD patients from Omicron infection.

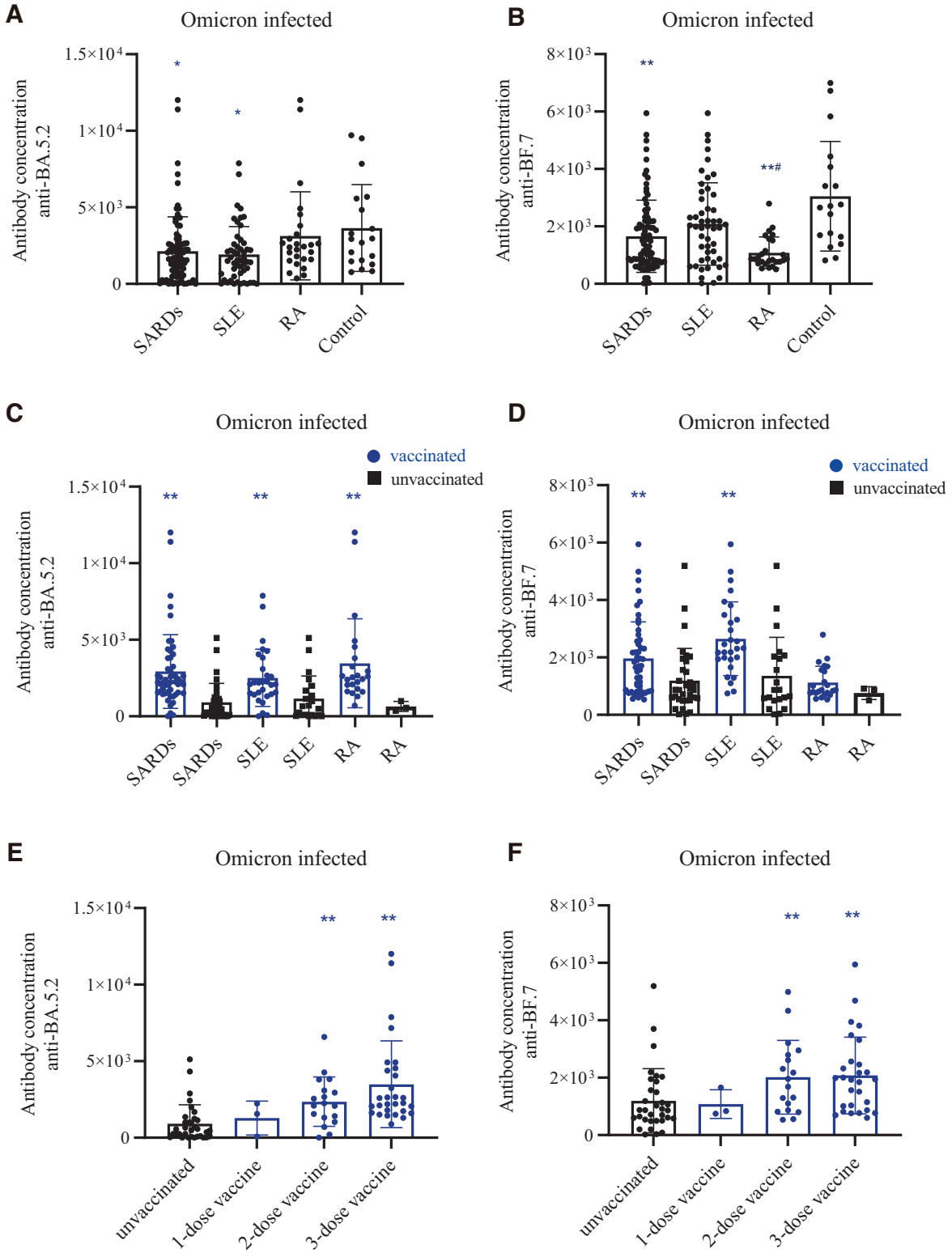

Figure 1. The antibody concentrations in systemic autoimmune rheumatic disease patients and controls infected with severe acute respiratory syndrome coronavirus 2 Omicron. (**A**) Quantitative analysis of RBD antibody titres against the Omicron BA.5.2 variant calculated by ELISA. Compared with control, $^{*}P < 0.05$. (**B**) Quantitative analysis of RBD antibody titres against the Omicron BF.7 variant calculated by ELISA. Compared with control, $^{**}P < 0.01$; compared with SLE group, $^{\#}P < 0.05$. (**C** and **D**) Quantitative analysis of RBD antibody titres against the Omicron BA.5.2 (C) and BF.7 (D) variants calculated by ELISA between the vaccinated group and unvaccinated group, $^{**}P < 0.01$. (**E** and **F**) Quantitative analysis of RBD antibody titres against the Omicron BA.5.2 (E) and BF.7 (F) variants calculated by ELISA in SARD patients with different vaccine doses, $^{**}P < 0.01$. SARD: systemic autoimmune rheumatic disease

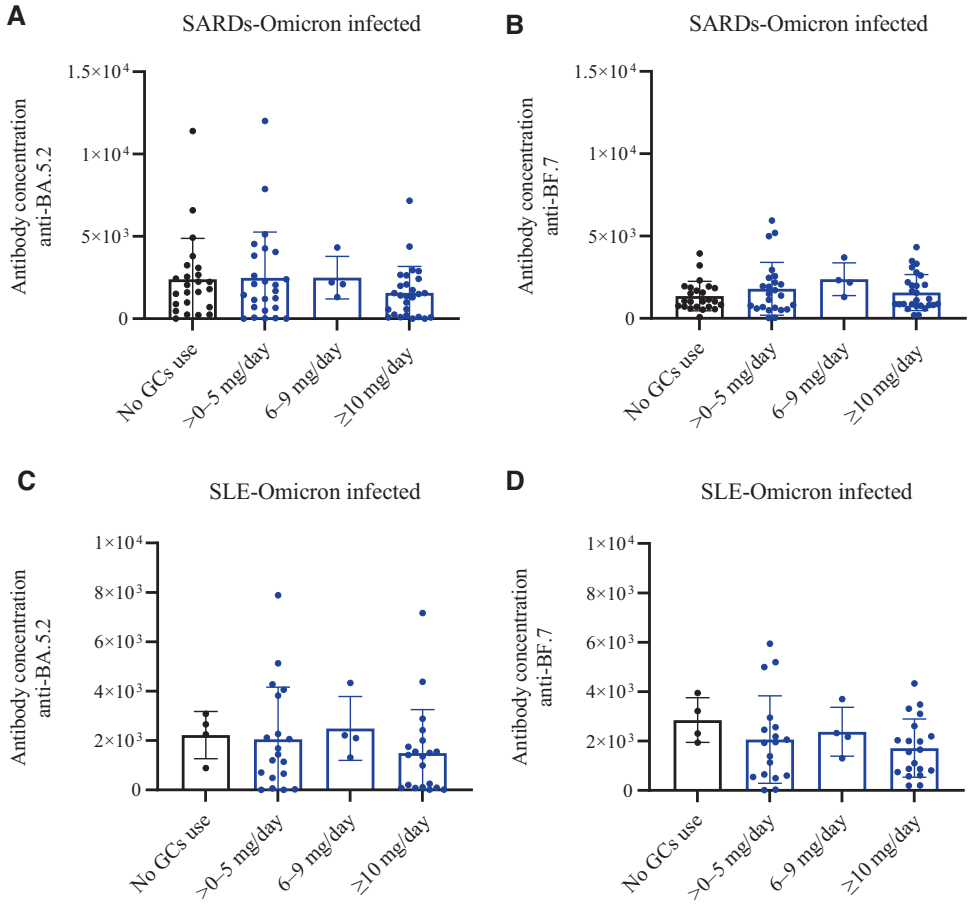

Figure 2. The association between glucocorticoid use and antibody concentration in systemic autoimmune rheumatic disease patients infected with severe acute respiratory syndrome coronavirus 2 Omicron. (**A** and **B**) Quantitative analysis of RBD antibody titre against Omicron BA.5.2 (A) and BF.7 (B) variants calculated by ELISA in SARD patients with different dosages of glucocorticoid use. (**C** and **D**) Quantitative analysis of RBD antibody titre against Omicron BA.5.2 and BF.7 variants calculated by ELISA in SLE patients with different dosages of glucocorticoid use. GCs: glucocorticoids; SARD: systemic autoimmune rheumatic disease

Patients with SARDs who are treated with immunosuppressive csDMARDs, bDMARDs (e.g. rituximab) or under GC exposure of ≥10 mg/day are at a higher risk of COVID-19, with poor clinical outcomes [17–19]. Moreover, several immunosuppressants (e.g. rituximab, MTX, MMF, abatacept and GCs) are associated with an impaired humoral response despite booster immunization [20]. Prior investigations on earlier vaccines (before Omicron) found that GCs, MMF, TNF inhibitors, tocilizumab, abatacept and rituximab were all associated with non-response after proper vaccination [21]. In our study, no significant difference in the BA.5.2 and BF.7 antibody levels was found among SARD patients with varying doses of GCs. The high proportion (64.7%) of combination therapy in SARD patients and the medication of other immunosuppressants (MTX, HCQ or MMF) might conceal the real effect of GCs on the antibody response. A previous study found reduced SARS-CoV-2 neutralizing capacity in chronic inflammatory disease patients under TNF-α blockade [22]. Treatment with bDMARDs or a combination of bDMARDs and csDMARDs was associated with reduced antibody levels in patients with immune-mediated inflammatory diseases [23]. In our study, we found that SLE patients with GCs, csDMARDs and bDMARDs (including rituximab, belimumab and Telitacicept) combination therapy had reduced antibody levels compared with patients using GCs and/or HCQ. Subgroup analysis of RA patients was not conducted owing to the sample size for some drug groups.

Our investigation has several limitations. First, this study was conducted in a single health-care system in Hefei, China. Consequently, owing to different demographics, our findings cannot be representative of other areas of China or the world. Second, risk factors associated with worse outcomes in SARD patients after SARS-CoV-2 Omicron infection were not analysed because fewer admissions of SARD patients with severe symptoms were included in our study. Last, this research was administered by questionnaires, and some patients might not have provided accurate information about their treatment of diseases.

In conclusion, in this study, we have outlined the clinical and immunological characteristics of SARD patients infected with Omicron. During the SARS-CoV-2 wave in China, in which the Omicron sublineages BA.5.2 and BF.7 were dominant, unvaccinated SARD patients had lower antibody production, suggesting the need for valuable prevention and management strategies, especially SARS-CoV-2 booster vaccination. Moreover, SLE patients receiving bDMARD combination therapy seem to present a lower antibody level, and it remains important to continue to reappraise vaccination strategies, including the implementation of personalized approaches for these patients.

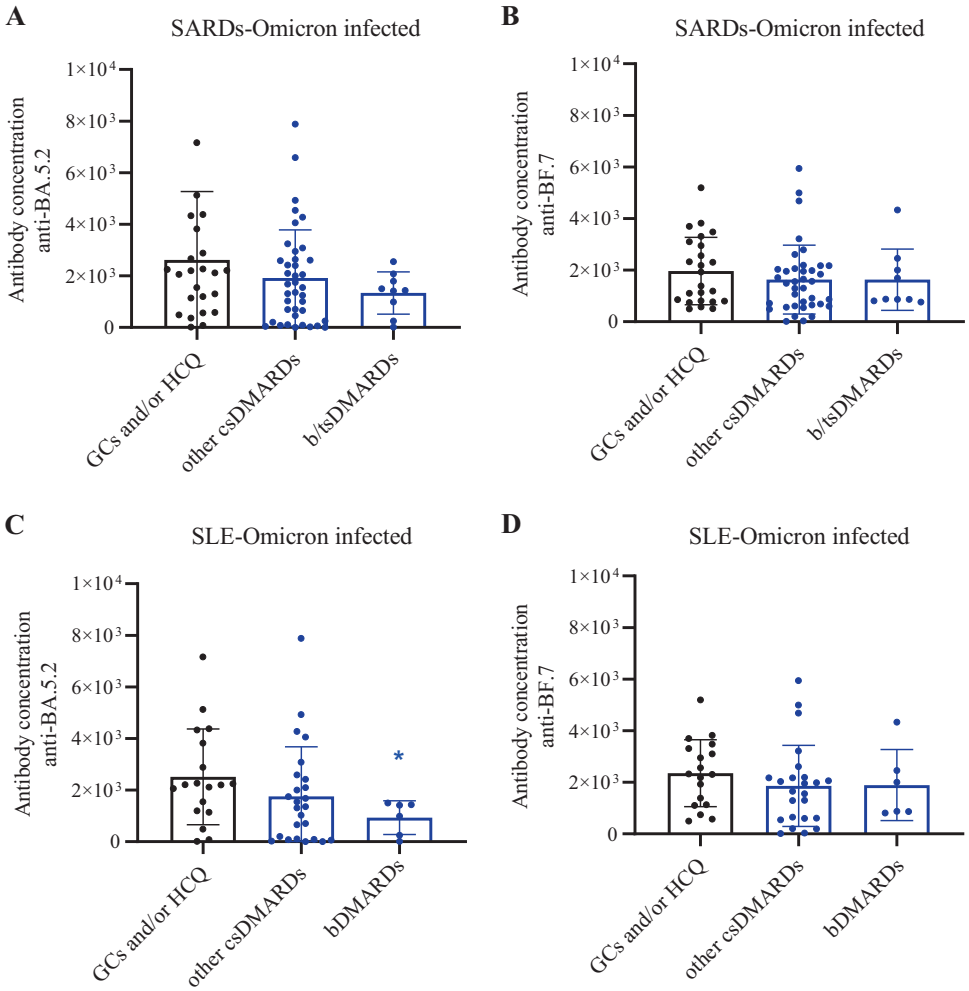

Figure 3. The association between the use of different DMARDs and the antibody concentration in systemic autoimmune rheumatic disease patients infected with severe acute respiratory syndrome coronavirus 2 Omicron. (**A** and **B**) Quantitative analysis of RBD antibody titres against the Omicron BA.5.2 (A) and BF.7 (B) variants calculated by ELISA in SARD patients treated with different DMARDs. (**C** and **D**) Quantitative analysis of RBD antibody titre against Omicron BA.5.2 (C) and BF.7 (D) variants calculated by ELISA in SLE patients with use of different DMARDs. Compared with the GCs and/or HCQ group, $*P < 0.05$. b/tsDMARDs: biological/targeted synthetic DMARDs; csDMARDs: conventional synthetic DMARDs; GCs: glucocorticoids; SARD: systemic autoimmune rheumatic disease

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Author contributions

Z.C., W.B., T.-C.J., T.X. and D.-L.T. conceived the project and designed the experiments. Y.-W.L., Q.W. and H.-Z.J. collected blood samples from the people and designed the questionnaire. N.X. and W.B. worked on data collection and analysis. Y.-J.L., M.-Y.L., Q.-Q.W. and Y.-X.Z. tested antibody titres. N.X., Y.-J.L. and Z.C. wrote the manuscript. All authors edited and proofread the manuscript.

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References

1. Lvov DK, Alkhovsky SV. [Source of the COVID-19 pandemic: ecology and genetics of coronaviruses (Betacoronavirus: Coronaviridae) SARS-CoV, SARS-CoV-2 (subgenus Sarbecovirus), and MERS-CoV (subgenus Merbecovirus).]. Vopr Virusol 2020; 65:62–70.
2. Chatterjee S, Bhattacharya M, Nag S, Dhama K, Chakraborty C. A detailed overview of SARS-CoV-2 Omicron: its sub-variants, mutations and pathophysiology, clinical characteristics, immunological landscape, immune escape, and therapies. Viruses 2023;15: 167.
3. Cao Y, Wang J, Jian F *et al.* Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature 2022;602:657–63.
4. Dhama K, Nainu F, Frediansyah A *et al.* Global emerging Omicron variant of SARS-CoV-2: Impacts, challenges and strategies. J Infect Public Health 2023;16:4–14.

5. Fu D, He G, Li H *et al.* Effectiveness of COVID-19 vaccination against SARS-CoV-2 Omicron variant infection and symptoms - China, December 2022-February 2023. China CDC Wkly 2023;5:369–73.
6. Pulliam JRC, van Schalkwyk C, Govender N *et al.* Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. Science 2022;376:eabn4947.
7. Mahase E. Omicron sub-lineage BA.2 may have "substantial growth advantage," UKHSA reports. BMJ 2022;376:o263.
8. Pan Y, Wang L, Feng Z *et al.* Characterisation of SARS-CoV-2 variants in Beijing during 2022: an epidemiological and phylogenetic analysis. Lancet 2023;401:664–72.
9. Zsichla L, Müller V. Risk factors of severe COVID-19: a review of host, viral and environmental factors. Viruses 2023;15:175.
10. Goldblatt F, O'Neill SG. Clinical aspects of autoimmune rheumatic diseases. Lancet 2013;382:797–808.
11. Atzeni F, Bendtzen K, Bobbio-Pallavicini F *et al.* Infections and treatment of patients with rheumatic diseases. Clin Exp Rheumatol 2008;26:S67–73.
12. Conway R, Grimshaw AA, Konig MF *et al.*; COVID-19 Global Rheumatology Alliance. SARS-CoV-2 infection and COVID-19 outcomes in rheumatic diseases: a systematic literature review and meta-analysis. Arthritis Rheumatol 2022;74:766–75.
13. Ehrenfeld M, Tincani A, Andreoli L *et al.* Covid-19 and autoimmunity. Autoimmun Rev 2020;19:102597.
14. Kawano Y, Patel NJ, Wang X *et al.* Temporal trends in COVID-19 outcomes among patients with systemic autoimmune rheumatic diseases: from the first wave through the initial Omicron wave. Ann Rheum Dis 2022;81:1742–9.
15. Intapiboon P, Uae-Areewongsa P, Ongarj J *et al.* Impaired neutralizing antibodies and preserved cellular immunogenicity against SARS-CoV-2 in systemic autoimmune rheumatic diseases. NPJ Vaccines 2022;7:149.
16. Yamaguchi Y, Nameki S, Kato Y *et al.* Persistence of SARS-CoV-2 neutralizing antibodies and anti-Omicron IgG induced by BNT162b2 mRNA vaccine in patients with autoimmune inflammatory rheumatic disease: an explanatory study in Japan. Lancet Reg Health West Pac 2023;32:100661.
17. Akiyama S, Hamdeh S, Micic D, Sakuraba A. Prevalence and clinical outcomes of COVID-19 in patients with autoimmune diseases: a systematic review and meta-analysis. Ann Rheum Dis 2021;80:384–91.
18. Gianfrancesco M, Hyrich KL, Al-Adely S *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.
19. Avouac J, Drumez E, Hachulla E *et al.*; FAIR/SFR/SNFMI/SOFREMIP/CRI/IMIDIATE Consortium and Contributors. COVID-19 outcomes in patients with inflammatory rheumatic and musculoskeletal diseases treated with rituximab: a cohort study. Lancet Rheumatol 2021;3:e419–26.
20. Furer V, Eviatar T, Zisman D *et al.* Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. Ann Rheum Dis 2021;80:1330–8.
21. Krasselt M, Wagner U, Nguyen P *et al.* Humoral and cellular response to COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases under real-life conditions. Rheumatology (Oxford) 2022;61:SI180–8.
22. Geisen UM, Rose R, Neumann F *et al.* The long term vaccine-induced anti-SARS-CoV-2 immune response is impaired in quantity and quality under TNFα blockade. J Med Virol 2022;94:5780–9.
23. Kartnig F, Mrak D, Simader E *et al.* Safety and immunogenicity of a third COVID-19 vaccination in patients with immune-mediated inflammatory diseases compared with healthy controls. Ann Rheum Dis 2023;82:292–300.