Serum neutralization of SARS-CoV-2 Omicron BA.2, BA.2.75, BA.2.76, BA.5, BF.7, BQ.1.1 and XBB.1.5 in individuals receiving Evusheld

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant is undergoing continuous evolution and convergent mutation, which has led to the rapid emergence of several new variants. These new subvariants carry different mutations in theirreceptor-binding domain (RBD), raising concerns that they may evade neutralizing monoclonal antibodies (mAbs). In this study, we investigated the serum neutralization efficacy of Evusheld (cilgavimab and tixagevimab) antibody cocktails against SARS-CoV-2 Omicron sublineages BA.2, BA.2.75, BA.2.76, BA.5, BF.7, BQ.1.1 and XBB.1.5. Our results show that Evusheld retained neutralizing activity against BA.2, BA.2.75 and BA.5, albeit with somewhat reduced titers. However, the neutralizing activity of Evusheld against BA.2.76, BF.7, BQ.1.1 and XBB.1.5 significantly decreased, with XBB.1.5 showing the greatest escape activity among the subvariants, followed by BQ.1.1, BA.2.76 and BF.7. We also observed that recipients of Evusheld displayed elevated antibody levels in their serum, which efficiently neutralized the original variant, and exhibited different characteristics of infection than those who did not receive Evusheld. These findings provide important guidance for the application of Evusheld in treating SARS-CoV-2 subvariant infections.

Introduction

Since the global outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2020, over 670 million people have been infected worldwide[1], including 6.5 million deaths worldwide[2, 3]. The pandemic has brought about a significant socioeconomic burden and increased global public health risk. While coronavirus disease 2019 (COVID-19) vaccines play an essential role in reducing infections and the number of severe cases, specific populations such as immunocompromised individuals may not mount an adequate immune response to vaccination[4]. Neutralizing monoclonal antibodies (mAbs) against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein have been isolated from convalescent individuals and are effective in preventing or treating COVID-19[5, 6]. Therefore, exploring the efficacy of therapeutic mAbs such as Evusheld can meet the above needs.

Evusheld/AZD7442 is a combination of two fully human long-acting monoclonal antibodies, tixagevimab (AZD8895) and cilgavimab (AZD1061), that bind nonoverlapping epitopes of the SARS-CoV-2 spike protein RBD and sterically block RBD binding to angiotensin-converting enzyme 2 (ACE2)[7]. Evusheld has been approved in many countries or regions worldwide for pre-exposure prophylaxis (PrEP) of SARS-CoV-2 in adults and adolescents over 12 years old. A phase III clinical trial showed that administration of Evusheld reduced the relative risk of symptomatic infection by 82.8% within six months[8]. In addition, serum from individuals receiving Evusheld as PrEP had detectable serum neutralizing activity against BA.5 for up to six months[9].

However, mutations in the RBD portion of the S subunit occur frequently in SARS-CoV-2 sublineages, and these mutations can increase the binding affinity of the RBD to ACE2, resulting in higher infectivity[10, 11]. As of December 2022, the most predominant Omicron sublineages in China are BA.5.2 and BF.7, while BQ.1.1 has become the predominant strain, and XBB.1.5 is outcompeting BQ.1.1 in many other

countries[12, 13]. Given the emergence of new subvariants and the clinical application of Evusheld, we investigated the neutralizing activity against the current prevalent strains worldwide in Evusheld recipients, measured the in vivo anti-RBD antibody titers and analyzed the correlation between Evusheld administration and clinical symptoms of breakthrough COVID-19. This study aims to optimize the utilization of Evusheld and improve our understanding of its efficacy against SARS-CoV-2 subvariants.

Results

Characteristics of blood donors

A total of 90 blood samples were collected from healthy donors, of which 29 had received Evusheld as PrEP, and 61 had not. We classified the donors into two groups: the Evusheld (n = 29; 300 mg) and non-Evusheld groups (n = 61; individuals not receiving Evusheld). A complete description of the donors' characteristics is provided in Table 1. The mean age of the Evusheld group was higher than that of the non-Evusheld group (41.31 ± 6.54 versus 32.43 ± 6.37 years; $P < 0.001$), with a significant difference in sex composition between the two groups ($P < 0.001$). Only three people had asthma or chronic liver disease complications. A majority of individuals (85%) received at least two or three doses of the COVID-19 vaccine before sample collection. Twenty-nine individuals had received a dose of 300 mg of Evusheld by intramuscular injection. The time between the administration of Evusheld and specimen collection was 50.03 ± 28.50 days, and the median observed time to maximum concentration (T_{max}) in vivo at that time had almost reached the peak[14].

Quantification of anti-RBD antibodies against the original SARS-CoV-2 strain

All participants were positive for the anti-RBD antibody tests. The anti-RBD antibody titers in females were significantly lower than those in males ($P = 0.04$) (Fig. 1a). We found that the anti-RBD antibody levels were significantly higher in the Evusheld group than in the non-Evusheld group (2570.7 ± 2568.3 versus 642.1 ± 877.0; $P = 0.006$). The non-Evusheld group showed a significant difference in antibody levels between those with and without previous SARS-CoV-2 infections ($P = 0.048$). Individuals with breakthrough infections and those who were not infected with SARS-CoV-2 after receiving Evusheld had higher anti-RBD antibody titers than those who were infected with SARS-CoV-2 in the non-Evusheld group ($P < 0.001$; $P < 0.001$) (Fig. 1b, 1c). The antibody titers did not differ significantly between those who had received 2 or 3 doses of the COVID-19 vaccine in the Evusheld and non-Evusheld groups ($P = 0.608$ and $P = 0.651$, respectively) (Fig. 1d). A positive interaction was found between vaccinations within 6 months and Evusheld administration, leading to higher anti-RBD antibody levels in the Evusheld group than in those injected more than 6 months prior ($P = 0.003$) (Fig. 1e). However, no significant difference was observed in the non-Evusheld group with SARS-CoV-2 infection ($P = 0.192$). The 50% effective concentrations (EC50) against BA.2, BA.2.75, and BA.5 were positively correlated with the anti-RBD antibody titers ($r = 0.471$, $P = 0.027$; $r = 0.630$, $P = 0.002$; and $r = 0.833$, $P < 0.001$, respectively) (Fig. 1f).

Serum neutralization of Omicron sublineages

We constructed a panel of vesicular stomatitis virus (VSV) pseudovirus-based neutralization assays representing various sublineages of BA.2, BA.2.75, BA.2.76, BA.5, BF.7, BQ.1.1 and XBB.1.5. We did not include BA.4 because its neutralization profile is identical to that of BA.5. The geometric mean titers (GMTs) of antibodies against these sublineages in the Evusheld group increased 30.8-, 26.3-, 2.6-, 18.1-, 3.6-, 3.2-, and 1.9-fold compared with those in the non-Evusheld group, respectively. Evusheld-treated individuals had a significantly higher neutralization activity against BA.2, BA.2.75 and BA.5 than the latter ($P < 0.0001$, $P = 0.0001$, and $P = 0.0004$, respectively). BA.5 remained sensitive to Evusheld, but the decay of the neutralizing activity was accelerated compared with that for BA.2 and BA.2.75. However, the neutralization titers against BA.2.76, BF.7, BQ.1.1 and XBB.1.5 did not show a significant difference from those for the non-Evusheld group (Fig. 2a). The neutralization titers against the different sublineages dropped by varying degrees ranging from 1.9-59.5-fold compared to those for BA.2 in individuals receiving Evusheld (Fig. 2b). EC50 is the effective concentration that inhibits 50% of viral production. In addition, we calculated titers by limiting serum dilutions to determine the EC50. See Supplementary Table 1 for the EC50 values of all testing samples.

Clinical characteristics of SARS-CoV-2 infection

Of the 90 participants, 18 in the Evusheld group and 48 in the non-Evusheld group had been previously infected with SARS-CoV-2, and none of them had repeated infections.

The COVID-19 vaccination rates were 94.4% and 85.4% in individuals receiving Evusheld or not, respectively, and 17 and 40 participants received at least two doses of vaccine among them. Fever was the most common symptom during COVID-19. Gastrointestinal symptoms were relatively rare, with only one individual presenting with these symptoms among all infected participants. The incidence rates of cough, rhinorrhea, dizziness and fatigue were significantly different between the two groups, with less frequent occurrence in the Evusheld group ($P = 0.01$, $P = 0.030$, and $P < 0.001$, respectively). However, the duration of symptoms and proportion of asymptomatic cases were not significantly different between the two groups ($P = 0.303$; $P = 0.226$) (Fig. 3).

Discussion

The findings of this study demonstrate that Evusheld recipients display elevated anti-RBD antibody levels and have different clinical characteristics of COVID-19 compared to the non-Evusheld group individuals. Evusheld has retained neutralizing activity against BA.2, BA.2.75 and BA.5, albeit with gradually reduced titers, but the neutralizing activity against BA.2.76, BF.7, BQ.1.1 and XBB.1.5 decreased significantly, with XBB.1.5 showing the strongest escape activity among the subvariants.

These results may be related to the structure of the spike protein of SARS-CoV-2, which is composed of the S1 and S2 subunits. The RBD on the S1 subunit helps the virus recognize ACE2 on the surface of host cells[15, 16]. Some researchers confirmed that an anti-RBD antibody test and neutralization tests were well

correlated and could effectively identify convalescent COVID-19 individuals[17]. Quantification of anti-RBD antibodies can reflect neutralizing activity against SARS-CoV-2 strains. In our study, we found that individuals receiving Evusheld had significantly higher levels of anti-RBD antibodies than those in the group without Evusheld. Moreover, the antibody titers in individuals without Omicron infection from the Evusheld group were also higher than those of individuals without Evusheld but infected with SARS-CoV-2. Evusheld recipients had relatively strong neutralizing capacity against the original Wuhan SARS-CoV-2 strain compared to those who did not receive Evusheld. Severe mAbs have similar efficacy against the original variant and Omicron variant[18–20]. However, there are limited data available on the anti-RBD antibody titers and the immune response induced by Evusheld against Omicron subvariants.

This study also shows that Evusheld-treated individuals have retained neutralizing activity against BA.2, BA.2.75 and BA.5, which was consistent with observations by others[9, 21, 22]. Studies have revealed that BA.2.75 exhibits reduced evasion of humoral immunity from BA.2 breakthrough-infection convalescent plasma but greater evasion from BA.5 breakthrough-infection plasma than BA.5[23]. Our results showed that individuals receiving Evusheld had the lowest neutralizing activity against BA.5 compared with BA.2 and BA.2.75. However, preliminary research showed that BA.2.75 has significantly reduced susceptibility to therapeutic monoclonal antibodies compared to that of BA.2 and BA.5[24]. This distinction may be caused by different therapeutic mAbs and sample sizes. In addition, in this group, we found that the neutralizing activity against BA.2.76, BF.7, BQ.1.1 and XBB.1.5 decreased significantly, with XBB.1.5 exhibiting the strongest escape activity among the subvariants, followed by BQ.1.1, BA.2.76 and BF.7. More recently, mAbs (Evusheld) failed to neutralize XBB.1/XBB.1.5[25], which is consistent with our results. The FDA update has shown that Evusheld is unlikely to neutralize the XBB.1.5 Omicron variant of SARS-CoV-2[26]. Additionally, we detected low serum neutralizing ability against BQ.1.1 in Evusheld recipients, but a previous study showed that Evusheld lost any antiviral efficacy against BQ.1.1 in individuals with or without BA.1/BA.2 or BA.5 breakthrough infection[27]. The distinct conclusions were likely because mAbs were added in vitro in that study. The varying degrees of neutralization sensitivity observed among different Omicron subvariants may be attributed to the different mutation sites among the variants. The evasion is attributed to several substitions, in particular, S371F, D405N, R408S, F486 and L452R[28, 29]. For example, the absence of the G446S mutation in the RBD is crucial for cilgavimab-neutralizing activity, resulting in elevated activity against BA.2 and BA.5[30, 31]. BQ.1.1 exhibits enhanced fusogenicity and S processing dictated by the N460K mutation[32]. BF.7 has a unique neutralizing antibody escape mechanism, including its signature F486S mutation and a reduction in its fusogenicity and S processing by the D1199N mutation[33, 34]. BA.2.76 has a specific Y248N mutation compared with the other subvariants, which might be the reason for its strong immune evasion ability[35].

Furthermore, we also investigated the impact of Evusheld on the clinical characteristics of individuals infected with Omicron subvariants. Previous studies have shown that Evusheld can reduce lung infection caused by certain SARS-CoV-2 subvariants in mice that express human ACE2 despite the decreased neutralization potency in cell culture[36]. Evusheld showed prophylactic efficacy for COVID-19 in lowering

the incidence, hospitalization, and mortality in solid organ transplant recipients, immunocompromised and B cell-depleted patients, and patients with hematological malignancies[37–39]. Our study explored the correlation between Evusheld-based PrEP and the clinical characteristics of recent prevalent Omicron strain infections. Rhinorrhea and dizziness or fatigue occurred less frequently in the Evusheld group than in the non-Evusheld group. However, the duration of symptoms and the proportion of asymptomatic patients in the Evusheld group did not differ significantly between the two groups, which may be because our subjects had received only a single 300 mg dose of Evusheld at the time of sample collection. The recommended single dose of Evusheld for prevention of COVID-19 is 600 mg, and a higher dose of Evusheld is likely to provide greater protection against infection by the Omicron subvariants[26].

It should be noted that our study has several limitations. First, we did not detect the types of infecting SARS-CoV-2 variants and neutralizing antibody levels for all individuals with COVID-19, limiting our ability to analyze the impact of Evusheld on different subtypes of Omicron infection. Second, all individuals receiving Evusheld in our study were injected with only a single 300 mg dose, which may have affected the neutralizing activity and clinical efficacy of the mAbs. Finally, our study relied on VSV-based SARS-CoV-2 pseudoviruses, which can model only viral entry. The contribution of additional mutations other than those in the spike protein to neutralization resistance in these variants cannot be confirmed. Further studies are needed to evaluate long-term immune responses after Omicron subvariant infection and two doses of Evusheld administration.

In conclusion, we evaluated the serum neutralization of Evusheld against BA.2, BA.2.75, BA.2.76, BA.5, BF.7, BQ.1.1, and XBB.1.5 and demonstrated reduced serum neutralizing activity against the recent prevalent Omicron subvariants. The results are essential for guiding Evusheld application and suggest that more mAbs against Omicron subvariants need to be developed to prevent and treat SARS-CoV-2 infection.

Methods

No statistical methods were used to predetermine the sample size. The experiments were not randomized, and the investigators were not blinded to allocation during experiments or outcome assessment.

Sample collection

A total of 90 serum samples from healthy individuals were collected in our hospital from January 9, 2023, to February 3, 2023. Among them, 29 samples were from participants receiving Evusheld as PrEP, and 61 samples were from those who did not receive Evusheld. The demographic characteristics, main infection symptoms, doses and time of vaccination or Evusheld administration were obtained from the participants who answered the questionnaire, and their test results were compared. All participants provided written informed consent before any study procedures were performed. This study was approved by the Ruijin Hospital Ethics Committee in Shanghai.

Construction and production of variant pseudoviruses

The Omicron sublineage spike genes were mammalian codon-optimized and inserted into the pCAGGS vector. HEK293T cells were grown to 90% density before transfection with the indicated spike gene using Lipofectamine 3000 (Invitrogen). After 24 hours of culture at 37°C with 5% CO_2, the supernatants were discarded, and the cells were washed three times with DMEM. The cells were then infected with VSV-G pseudotyped ΔG-luciferase (G*ΔGluciferase, Kerafast) at a multiplicity of infection of 10 for two hours. Next, the cells were washed three times with DMEM, and the culture media were replaced with 3% FBS DMEM containing anti-VSV-G rat serum. The cells were cultured for 24 hours, and then the cell supernatant containing pseudotyped virus was harvested and filtered through a 0.45 μm filter after being centrifuged at 1,250 rpm for 10 minutes. The pseudoviruses were aliquoted and stored at -80°C. Titers of the pseudoviruses were measured before the pseudoviruses were used.

Pseudovirus neutralization assays

Serum was serially diluted and incubated with the pseudoviruses in 96-well plates for 1.5 hours at 37°C. Freshly trypsinized BHK-ACE2 cells were then added to each well and cultured for 20–28 hours in 5% CO_2 incubators at 37°C. One hundred microliters of supernatant was discarded from each well, leaving ~ 100 μl of liquid in each well, and 100 μl of luciferase substrate (Beyotime, RG056S) was added before incubation of the cells in the dark for 2 minutes. The samples were mixed by pipettor action, and 150 μl was transferred to a corresponding 96-well chemiluminescence detection plate (Beyotime, FCP968). Chemiluminescence signals were collected by a luminescence meter (Promega).

Finecare™ 2019-nCoV RBD Antibody Test

The 2019-nCoV RBD Antibody Titer Assay Kits were purchased from Guangzhou Wondfo Biotech Co., China. The antibody test is based on fluorescence immunoassay technology, specifically the sandwich immunodetection method. Detection buffer was added to the specimen, and the sample was mixed well. When the specimen was added into the sample well of the Test Cartridge, the fluorescence-labeled detector 2019-nCoV RBD protein bound to anti-RBD antibodies in blood specimens and formed immune complexes. As the complexes migrated on the nitrocellulose membrane by capillary action, the anti-2019-nCoV RBD antibodies were captured by another RBD protein that had been immobilized on the test strip. In brief, 20 μL of plasma was added to the provided buffer tube and mixed for 45 seconds. Then, 75 μL was added to the test cartridge, incubated for 15 minutes at room temperature (RT), and then inserted in the test cartridge holder of Finecare™ FIA Meters holder for measurement on quick mode. The default results unit of this test is displayed as relative fluorescence unit (RFU, AU/mL) or binding antibody units per milliliter (BAU/mL). Readings ≥ 1 AU/mL or ≥ 20 BAU/ml indicate positive results.

Statistical analysis

The statistical analyses for the pseudovirus neutralization assessments were performed using GraphPad Prism for the calculation of the mean value for each data point. Each specimen was analyzed at least twice. The EC50 values were calculated with nonlinear regression in GraphPad Prism. Figures were drawn using GraphPad Software. The statistical significance of differences between different groups was

calculated using the tests indicated in each figure legend. The statistical tests were performed in a two-sided manner, and a p value < 0.05 was considered to indicate statistical significance.

Reporting summary

Further information on the research design is available in the Nature Research Reporting Summary linked to this article.

Declarations

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Competing interests

The authors declare no competing interests.

Data availability

All data supporting the findings of this study are available within the article or from the corresponding authors upon reasonable request, without any restrictions. Source data are provided with this paper.

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Table

Table 1 Characteristics of blood donors

	Evusheld	Non-Evusheld	Total (%)
Donor characteristics			
N	29	61	90 (100)
Age	41 (31-61)	32 (22-51)	36 (22-61)
Female	14	52	66 (73.3)
Male	15	9	24 (26.7)
Obesity	0	1	1 (1.1)
Underlying diseases			
Asthma	0	2	2 (2.2)
Chronic liver disease	1	0	1 (1.1)
Vaccines doses			
0	2	8	10 (11.1)
1	0	3	3 (3.3)
2	6	19	25 (27.8)
3	19	28	47 (52.2)
4	2 (40)	3	5 (5.6)
Anti-RBD antibodies			
Mean ± SD (range)	2570.7±2568.3	642.1±877.0	1263.5±1848.0
Previous COVID-19	18	48	66 (73.3)
Anti-RBD antibodies			
Mean ± SD (range)	2872.6±3125.6	715.8±876.5	1304.0±2011.8
Asymptomatic cases	6	24	30 (33.3)
Duration of symptoms			
Mean days ± SD (range)	7.4 ±5.0	9.0±5.8	8.6±5.6

Figures

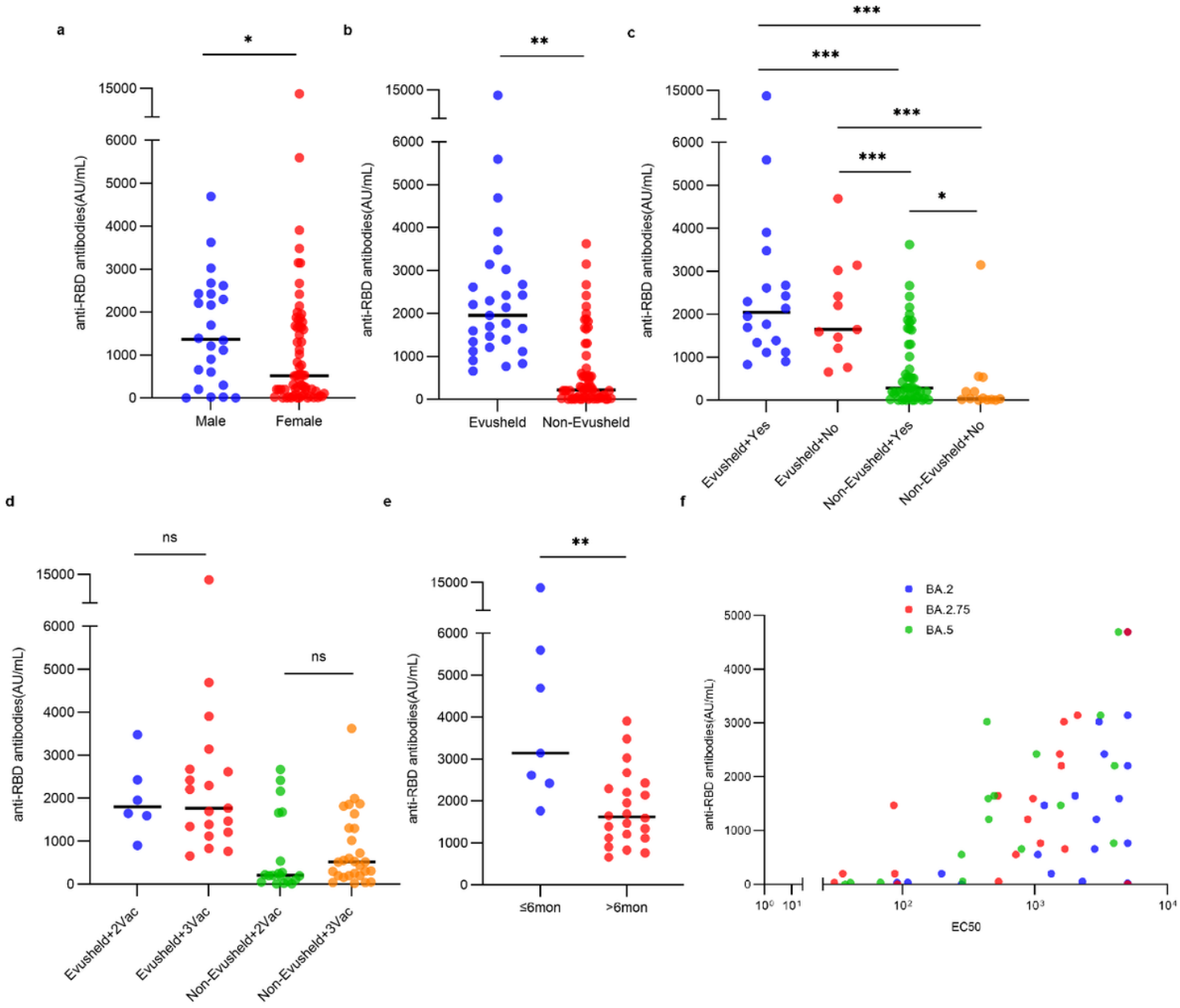

Figure 1

Serum levels of anti-RBD antibody against the original SARS-CoV-2 strain in different groups. a, Anti-RBD antibody levels in the serum of males and females (P =0.04). **b,** Anti-RBD antibody levels in individuals receiving Evusheld (n=29) or not (n=61) (*P*=0.006). **c,** Anti-RBD antibody levels in the Evusheld group and non-Evusheld group individuals with or without SARS-CoV-2 infection (n=90). Evusheld+SARS-CoV-2 infection versus non-Evusheld+SARS-CoV-2 infection (p<0.001), Evusheld+without SARS-CoV-2 infection versus non-Evusheld+SARS-CoV-2 infection (p<0.001), Evusheld+without SARS-CoV-2 infection versus non-Evusheld+without SARS-CoV-2 infection (p<0.001), Evusheld+ SARS-CoV-2 infection versus non-Evusheld+ without SARS-CoV-2 infection (p<0.001). **d,** Anti-RBD antibody levels in individuals who had received 2 or 3 doses of COVID-19 vaccine in the Evusheld or non-Evusheld groups. **e,** Anti-RBD antibody levels in the Evusheld group individuals vaccinated with the COVID-19 vaccine within 6 months (n=7) or beyond 6 months (n=22) (*P*=0.003). **f,** The relationship between neutralizing activity and anti-RBD

antibody levels (n=22). Anti-RBD antibody levels were measured based on fluorescence immunoassay technology using the Finecare^{TM} 2019-nCoV RBD Antibody Test. The dotted line represents the median. Statistical analysis was performed using unpaired two-tailed Mann—Whitney tests. *P < 0.05; **P < 0.01; ***P < 0.001; ns, not significant. RBD, receptor-binding domain; EC50, 50% effective concentration; Yes, SARS-CoV-2 infection; No, without SARS-CoV-2 infection; 2Vac, 2 doses of COVID-19 vaccination; 3Vac, 3 doses of COVID-19 vaccination.

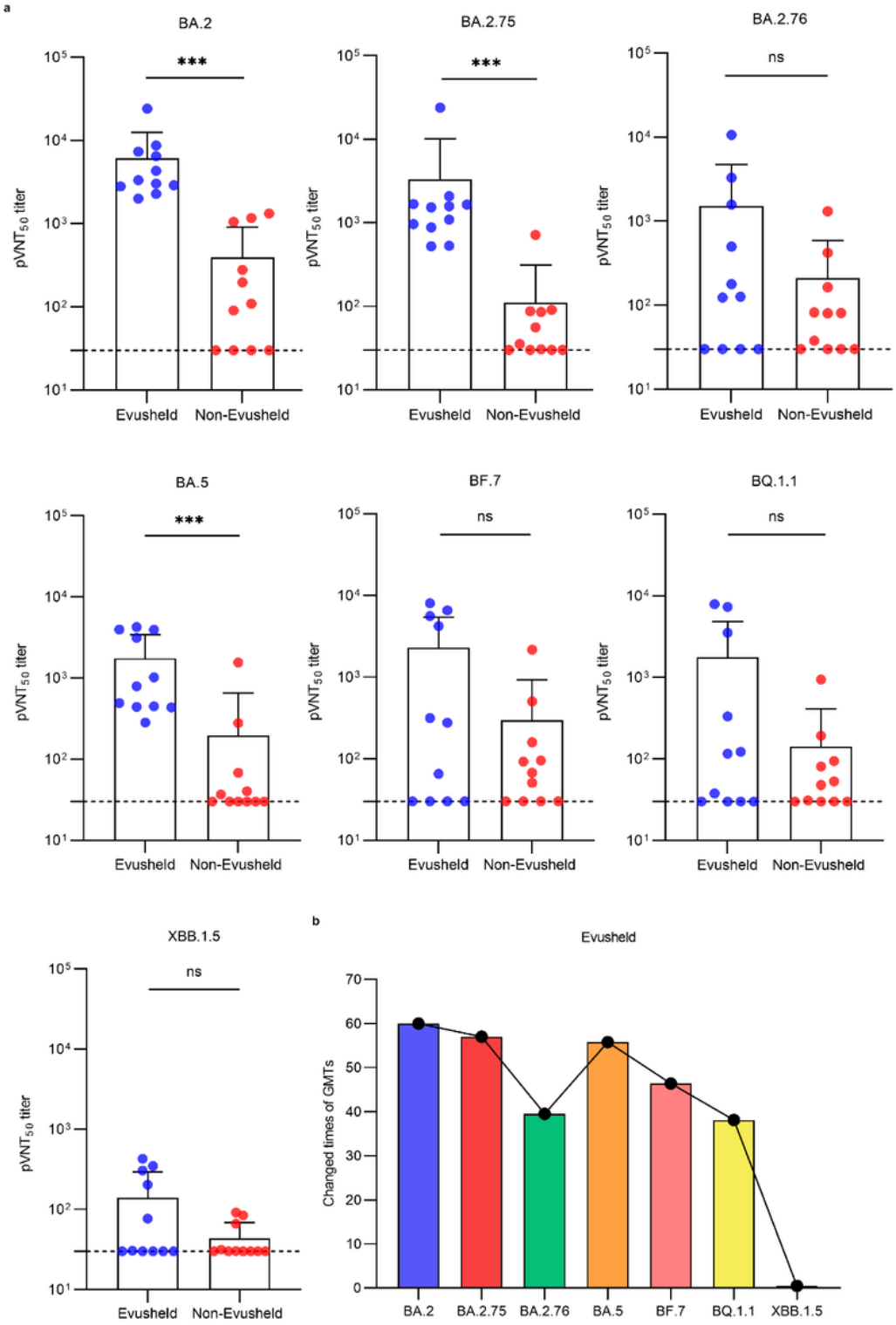

Figure 2

Pseudovirus-neutralizing antibody activity against variants of concern (VOCs) of SARS-CoV-2 in individuals receiving Evusheld or not. a, The scatterdot plot showsthe pVNT50 values of the samples. Each dot represents a sample. Box plots indicate the mean and standard deviation (SD). The blackdotted line represents the detection threshold.Statistical analysis was performed using unpaired two-tailed Mann–Whitney tests. ***P < 0.001; ns, not significant. **b,** The changed times of geometric mean titers (GMTs) in Evusheld group.

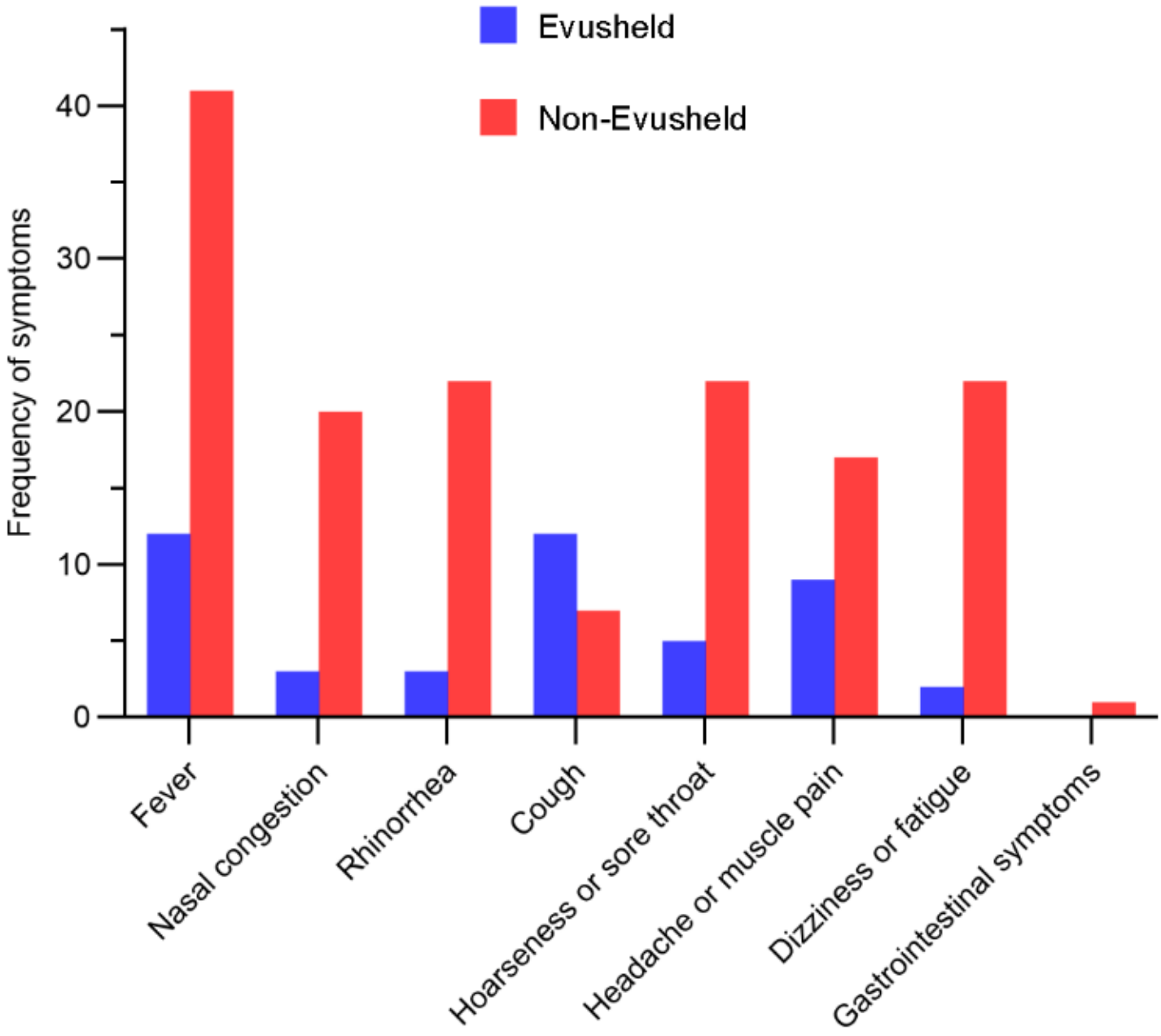

Figure 3

The frequency of symptoms in individuals infected with SARS-CoV-2 between the Evusheld group and non-Evusheld group. Statistical analysis was performed using unpaired two-tailed Mann–Whitney tests.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.xlsx