Safety and Immunogenicity of Inactivated COVID-19 Vaccines Among People Living with HIV in China

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Purpose: Vaccination reduces the incidence of severe COVID-19 and death and effectively limits viral spread. Concerns have been raised about COVID-19 vaccine responses in the large population of HIV-infected patients. This study aims to explore the safety and immunogenicity of the inactivated COVID-19 vaccine in people living with HIV (PLWH).

Patients and Methods: All participants in this study already had their second dose of an inactivated COVID-19 vaccine at least 14 days earlier, without a history of SARS-CoV-2 infection. The primary safety outcomes were the incidence of adverse reactions and changes in CD4⁺ T-cell counts. SARS-CoV-2 IgG and neutralizing antibody responses to the D614G variant and delta variant were measured for immune response assessment.

Results: Forty-seven HIV-infected patients and 18 healthy donors (HDs) were enrolled in this study. Adverse reactions were mild or self-limiting and were reported in 19.1% of HIV-infected patients. Most PLWH developed antibody responses against the inactivated COVID-19 vaccine. The longitudinal analysis of antibody responses in PLWH (median interval between detection and complete vaccination, 59 days) showed that antibodies were maintained for at least three months, though their titers were reduced. However, the antibody-positive rates in PLWH were significantly lower than those in HDs. Additionally, compared to HDs (Geomean titers (GMT) of 165 for D614G and GMT of 72 for delta), the neutralizing antibody titers against the two variants in PLWH (GMT of 43 for D614G and GMT 13 for delta) were decreased significantly (p = 0.018 and p < 0.001, respectively). HIV-infected patients with CD4⁺ T-cell counts ≤350 cells/μL appeared to exhibit a poor antibody response to inactivated vaccination.

Conclusion: Inactivated COVID-19 vaccines appear to be efficacious in PLWH. However, antibody responses in HIV-infected patients are inferior to those in healthy individuals, especially PLWH with lower CD4⁺T-cell counts.

Keywords: human immunodeficiency virus, coronavirus disease 2019, inactivated vaccines, immunogenicity, safety

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has spread to more than 200 countries, with approximately 450 million confirmed cases and 6.0 million deaths as of Mar 12 2022¹. This pandemic is challenging health care systems around the world and has caused tremendous economic losses. To date, there are no specific drugs to treat COVID-19. Therefore, a critical approach to ending the COVID-19 pandemic is preventing the spread of SARS-CoV-2. Vaccination is the most effective and economical approach to controlling COVID-19, and increasing evidence in clinical trials and real-world settings has indicated the vaccines’ encouraging safety and efficacy.²–⁶ However, the studies on vaccine safety and efficacy have
primarily focused on the general population. There is little research on the safety and effectiveness of inactivated vaccines in people living with HIV (PLWH).

PLWH have increased risks of COVID-19 hospitalization and severe outcomes, especially those with immune suppression. Consequently, PLWH should be prioritized to receive SARS-CoV-2 vaccines. The generation of adequate immune responses following COVID-19 vaccination requires a series of cellular interactions between B cells and T cells, in which CD4\(^+\) T cells play a pivotal role. After immunization, virus-specific CD4\(^+\) T cells can differentiate into T follicular helper (Tfh) and Th1 cells. Tfh cells provide “help” signals to B cells, and the interaction of SARS-CoV-2-specific Tfh cells with B cells is critical in developing neutralization antibody responses and long-term humoral immunity. Th1 cells produce interferon γ and related cytokines to exert direct antiviral functions. HIV infection leads to persistent depletion of CD4\(^+\) T cells. Although antiretroviral therapy (ART) can suppress viral replication and rebuild immune function, CD4\(^+\) T-cell recovery is incomplete in some individuals. Thus, there are concerns that the destruction of CD4\(^+\) T cells may affect HIV-infected patients’ immune response to vaccines. Growing evidence on mRNA and adenovirus vector-based vaccines reveals that the vaccines are safe and efficacious and induce a humoral response and cellular immunity to SARS-CoV-2 in PLWH, but whether inactivated vaccines can elicit immune responses among PLWH remains unclear, significantly restricting vaccination progress in China.

The B.1.617.2 (delta) variant has rapidly spread and has become the most frequently sequenced lineage worldwide. The delta variant is associated with increased disease severity and hospitalization, and it appears to be more infectious and transmissible. Therefore, it is important to identify whether the current vaccines can elicit the desired levels of antibodies against the delta variant in PLWH.

In this work, we aimed to explore the safety and immunogenicity of inactivated SARS-CoV-2 vaccines in PLWH. Our findings will provide valuable guidance on the vaccination of HIV-infected patients.

**Patients and Methods**

**Study Design and Patients**

This noninterventional study was performed between July 2021 and September 2021 at Beijing Ditan Hospital, and the Ethics Committee of Beijing Ditan Hospital approved it (No. 2021-021-02). Participants included PLWH and healthy donors (HDs) who had gotten their second dose of an inactivated COVID-19 vaccine at least 14 days earlier.

PLWH were recruited in the outpatient clinic of the Department of Infectious Disease, Beijing Ditan Hospital. The critical inclusion criteria for PLWH were as follows: (1) had gotten their second dose of an inactivated COVID-19 vaccine (Sinovac CoronaVac or Sinopharm) at least 14 days earlier; (2) had a positive diagnosis of HIV confirmed by Western blot; (3) had received ART for at least six months; and (4) signed written informed consent. Exclusion criteria: (1) age under 18 years; (2) history of SARS-CoV-2 infection; (3) malignant tumors or severe opportunistic infections; and (4) intellectual or language impairments. After determining the participant’s willingness to enroll, project staff screened the participant for eligibility and obtained their written informed consent. After that, a private room was provided for participants to complete paper-based questionnaires. Blood samples were collected to measure antibodies, CD4\(^+\)/CD8\(^+\) T-cell counts, and HIV viral load testing on the day of inclusion. Additionally, the demographic data, CD4\(^+\)/CD8\(^+\) T-cell counts before vaccination, and data about adverse reactions after vaccination were documented according to the paper-based questionnaires. An experienced clinician determined the causal relationship between vaccination and any adverse reactions reported.

To compare immunogenicity differences between PLWH and the general population, we enrolled HDs whose age and sex were matched with HIV-infected participants at Beijing Ditan Hospital from July 2021 to September 2021. HDs were recruited from the Physical Examination Center, Beijing Ditan Hospital. All of them had completed two doses of inactivated vaccine at least 14 days earlier and had no history of HIV infection. The exclusion criteria were those above. After signing the informed consent form and completing paper-based questionnaires, HDs gave blood samples to evaluate the antibody response after vaccination.
SARS-CoV-2 Antibody Measurement
SARS-CoV-2 IgG antibodies were detected by magnetic particle chemiluminescence immunoassay using a kit (Autobio Diagnostic Co., Ltd.). Concentrations ≥1.2 S/CO were defined as positive.

We used a pseudovirus neutralization assay to evaluate the neutralizing antibody responses to the D614G variant and delta variant of all subjects. Briefly, all subjects’ neutralizing antibody responses to the D614G variant and delta variant were tested using the SARS-CoV-2 pseudotyped virus kit (purchased from Zhongyanguobang Biological Technology Co., Ltd.). After a threefold serial dilution of heated inactivated (56°C, 30 minutes) serum samples, the pseudotyped virus was mixed with serum samples. Vero cells were transferred into the serum/virus mixture and incubated for 24 hours. After incubation, the luciferase substrate (PerkinElmer) was added into each well and incubated in darkness for 2 minutes. We read each well’s relative luminescence units (RLU) after 2-minutes of incubation using a multifunctional enzyme marker (Thermo Fisher Scientific). The half-maximal effective concentration (EC$_{50}$) was determined as the serum dilution that reduced the RLU by 50% compared with the virus control wells (virus and cells only). The EC$_{50}$ values were calculated using nonlinear regression methods as described in the previous studies. The neutralizing antibody titers equaled the reciprocal of EC$_{50}$, and 10 or below was regarded as nonneutralizing.

Statistical Analysis
Statistical analysis was performed using SPSS version 25.0 and R version 4.1.0. Continuous variables are presented as the mean and range or as the median and interquartile range (IQR). Categorical variables are presented as n (%). Geometric mean titers (GMTs) or geometric mean concentrations (GMCs) and 95% confidence intervals (CIs) were calculated after log transformation of antibody titers or concentrations. Differences between groups were assessed using nonparametric tests or the t-test for continuous variables. The difference in categorical variables between the two groups was evaluated using the χ² test. Locally weighted scatterplot smoothing was used to describe the tendency of antibody titers over time. P<0.05 (2-sided) was considered statistically significant.

Results
Baseline Characteristics
A total of 47 HIV-infected patients and 18 HDs were enrolled in this study. The median age of HIV-infected patients was 34 years (IQR 26–42 years), and 45 (95.7%) were male. The median age of HDs was 37 years (IQR 33–50 years), and all participants were male. The median interval between the completion of full-course vaccination and antibody detection was 59 days (IQR 37–74 days) among HIV-infected patients, which was significantly longer than the interval among HDs (median 28 days, IQR 27–28 days) (p < 0.001) (Table 1). HIV-related parameters are shown in Table 2. The average time from HIV diagnosis to vaccination was 2.5 years (range 0.5–11 years). All patients had been taking antiretroviral treatment (ART) at the time of vaccination, most of them with nucleoside reverse transcriptase inhibitor-based therapy. In addition, 93.6% (44/47) of HIV-infected patients had an undetectable viral load, and the mean CD4+ T-cell count was 474 cells per μL (range 145–926 cells per μL). Six HIV-infected patients had coinfection with syphilis, and three had comorbidities (two diabetes and one cardiovascular disease).

Table 1 The Baseline Characteristics of PLWH and HDs

| Characteristics                  | PLWH (n=47) | HDs (n=18) | Statistic | p-value |
|----------------------------------|-------------|------------|-----------|---------|
| Age, median (IQR), years         | 34 (26–42)  | 37 (33–50) | 1.621     | 0.105   |
| Gender                           |             |            |           |         |
| Male, n (%)                      | 45 (95.70)  | 18 (10.00) | 0.790     | 0.374   |
| Female, n (%)                    | 2 (4.30)    | 0 (0.00)   |           |         |
| Interval time from vaccination to detection, median (IQR) | 59 (37–74) | 28 (27–28) | −4.991   | <0.001  |
Safety of Inactivated COVID-19 Vaccines in PLWH

A total of 19.1% (9/47) of HIV-infected patients had adverse reactions within 28 days after whole-course vaccination, and most occurred within 7 days after whole-course vaccination. The most common local event was injection site pain (6.4%), which generally subsided within 24 hours. Fatigue (6.4%), headache (6.4%), and fever (6.4%) were common systemic adverse events after vaccination (Table 3). All symptoms were mild and self-limiting. None of the HIV-infected patients developed clinical HIV-related events following vaccination, even those patients with CD4+ T-cell counts of ≤350 cells per μL.

After two doses of vaccination, the CD4+ T-cell count and the CD4/CD8 ratio were higher than before (p = 0.06, p = 0.0012, respectively). Nevertheless, the CD8 cell count was significantly lower (p = 0.046) than before (Table 2) (Figure S1).

Immunogenicity of Inactivated COVID-19 Vaccines in PLWH

Most HIV-infected patients developed detectable antibody titers against inactivated COVID-19 vaccines. Neutralizing antibodies to the D614G variant were detected in 74.5% (35/47) of HIV-infected patients, and neutralizing antibodies to the delta variant were detected in 66.0% (31/47) of patients. The GMT for the Delta variant (14, 95% CI 11–19) was 45% that of the D614G variant (31, 95% CI 20–47) (p=0.002). According to the locally weighted scatterplot smoothing, antibody responses in HIV-infected patients declined significantly at 40–60 days after two doses of vaccination and were maintained until at least 101 days, though the titers were reduced (Figure 1).

Table 2 Baseline Characteristics of PLWH

| Characteristics                                      | Patients (n=47) |
|------------------------------------------------------|-----------------|
| Time of HIV diagnosis, mean (range), years           | 2.5 (0.5–11)   |
| HIV viral load, median (range), copies/mL            | 20 (20–163,827) |
| CD4+ T cell counts, mean (range), cells/μL          | 474 (145–926)  |
| CD8+T cell counts, median (IQR), cells/μL           | 804 (560–1096) |
| CD4/CD8 ratio, median (IQR)                          | 0.58 (0.43–0.79) |
| CD4+ T cell counts before vaccination, mean (range), cells/μL | 433 (124–801) |
| CD8+ T cell counts before vaccination, median (IQR), cells/μL | 909 (701–1408) |
| CD4/CD8 ratio before vaccination, median (IQR)       | 0.46 (0.30–0.73) |
| ART use, n (%)                                       |                 |
| 2NRTIs+1NNRTIs                                       | 38 (80.9)       |
| 2NRTIs+1INSTIs                                       | 2 (4.3)         |
| 2NRTIs+1PIS                                         | 1 (2.1)         |
| Others                                               | 6 (12.80)       |
| Comorbidities, n (%)                                 |                 |
| Syphilis                                             | 6 (12.80)       |
| Diabetes                                             | 2 (4.30)        |
| Cardiovascular disease                               | 1 (2.10)        |
| Hypertension                                         | 0 (0.00)        |

Abbreviations: NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, nonnucleoside reverse transcriptase inhibitors; INSTIs, integrase inhibitors; PIs, protease inhibitors.
Next, we explored the difference in immunogenicity between PLWH and HDs. Given the difference in the interval time from vaccination to the antibody test between PLWH and HDs, we selected 10 HIV-infected patients who were tested for antibodies at approximately 28 days after the second dose to compare with the 18 HDs. The age, sex, and interval length of the HIV-infected patients were matched with those of the HDs. A baseline comparison between the two groups is shown in Table 4. The samples of the two groups were small, but they still had sufficient power for tests. Neutralizing antibodies to the D614G variant (GMT 43, 95% CI 15–120) and the delta variant (GMT 13, 95% CI 8–22) were generated in 80.0% (8/10) and 70.0% (7/10) of HIV-infected patients, respectively. Comparatively, 100% (18/18) and 94.4% (17/18) of HDs had induced neutralizing antibodies to the D614G and delta variants, respectively. In addition, 70.0% (7/10) of HIV-infected patients and 100% (18/18) of HDs developed SARS-CoV-2 IgG. Positive rates of neutralizing antibodies to the D614G variant and SARS-CoV-2 IgG were significantly lower in PLWH than HDs ($p = \text{ }$

Table 3 Safety of Inactivated COVID-19 Vaccination in PLWH

| Characteristics                        | Patients (n=47) |
|----------------------------------------|-----------------|
| Injection site adverse reactions within 7 days |                 |
| Pain, n (%)                            | 3 (6.4)         |
| Swollen, n (%)                         | 2 (4.2)         |
| Local redness, n (%)                   | 2 (4.2)         |
| Systemic adverse reactions within 7 days |                 |
| Fatigue, n (%)                         | 3 (6.4)         |
| Headache, n (%)                        | 3 (6.4)         |
| Muscle soreness, n (%)                 | 3 (6.4)         |
| Fever, n (%)                           | 2 (4.2)         |
| Diarrhea, n (%)                        | 1 (2.1)         |
| Nausea, n (%)                          | 0 (0.0)         |
| Total adverse reaction within 28 days  |                 |
| Any, n (%)                             | 9 (19.1)        |

Figure 1 Longitudinal changes in antibody response in PLWH since whole-course vaccination. The blue line and strip represent the general trend line and confidence interval, which were calculated using the locally weighted scatterplot smoothing algorithm. Correlation between time since two doses of vaccines and the neutralization antibody titers against the D614G variant (A), Delta variant (B), and IgG (C).
Neutralizing titers against the D614G (p = 0.018) and delta variants (p < 0.001) were significantly lower in PLWH than HDs (GMT of 165 for D614G, GMT of 72 for delta) (Figure 2A). Consistent with those findings, the antibody concentration against SARS-CoV-2 IgG was significantly lower (p = 0.002) in PLWH (GMC 1.15 S/CO, 95% CI 0.26–5.01 S/CO) than HDs (GMC 19S/CO, 95% CI 16–23 S/CO) (Figure 2B). The GMT of the delta variant was 3-fold lower (p = 0.034) than that of the D614G variant in HIV-infected patients and 1.3-fold lower (p = 0.007) in HDs (Figure 2C).

Forty-seven HIV-infected patients were divided into two groups to investigate the effect of CD4+ T-cell count on the development of SARS-CoV-2 antibodies: suboptimal immune recovery (CD4+ T cells ≤350 cells/μL) and good immune recovery (CD4+ T cells > 350 cells/μL), according to CD4+ T-cell recovery after ART.17 Next, we compared the antibodies between the two groups. The output of the equilibrium test on the baseline characteristics between the two groups is shown in Table 5. Neutralizing antibodies to the D614G variant and levels of SARS-CoV-2 IgG in the group with CD4+ T cell counts ≤350 cells/μL were reduced significantly lower (p= 0.015 and p = 0.036, respectively) than in the other group (Figure 3).

**Discussion**

This study suggests that inactivated COVID-19 vaccines appear to be efficacious in PLWH. However, the antibody responses to inactivated SARS-CoV-2 vaccines in PLWH are inferior to those in healthy individuals. Although this study was too small to conclude that inactivated COVID-19 vaccines are safe in PLWH, the incidence and severity of adverse reactions were consistent with those previously described in the HIV-negative population,4,6 for whom inactivated COVID-19 vaccines are safe.

In this work, the rate of adverse events was similar to that reported in the CoronaVac Phase 1/2 trial,6 and all adverse reactions of HIV-infected patients were mild or self-limiting. None of the participants developed clinical HIV-related
events, even in those with low CD4⁺ T-cell counts. Vaccination may lead to the activation of cellular immunity and the transcription of HIV from the latent reservoir, which may result in a further decline in CD4⁺ T-cell counts.³ Our study showed no adverse effects on CD4⁺ T-cell counts in PLWH after full-course vaccination, consistent with Ibarz-Pavon’s study, which reported no changes in CD4⁺ T-cell counts after PLWH received the heptavalent pneumococcal conjugate vaccine.¹⁸ Additionally, we found an increase in the CD4/CD8 cell ratio, which may have resulted from a post-ART recovery of immune function. However, the results of safety should be interpreted with caution because our study sample size was small, and some common adverse reactions could have been missed. Further studies should be conducted in larger PLWH cohorts.

It is crucial for us to collect data on the immunogenicity of vaccination in HIV-infected individuals because impaired immunity may reduce the magnitude of the response and the persistence of protection.¹² Previous studies have reported that the immune responses to vaccines (such as H1N1 2009 and Hepatitis B) of HIV-infected individuals are inferior to those of the general population.¹⁹,²⁰ Thus, in the present study, we assessed the immunogenicity of inactivated COVID-19 vaccination in PLWH. We found that inactivated SARS-CoV-2 vaccines elicited antibody responses in PLWH. After two doses of inactivated COVID-19 vaccines, the antibody level peaked at approximately 40 days. After that, the antibody responses decreased significantly at 40~60 days and were maintained for at least three months at a lower level. Consistent with our results, Frater et al reported that after the ChAdOx1 nCoV-19 vaccine was administered, antibodies against SARS-CoV-2 spike protein in PLWH gradually decreased after reaching a peak at 42 days but were maintained at least until approximately 56 days.³ However, compared to HDs, PLWH had significantly weaker antibody responses to

| Characteristics                          | CD4≤350 Cells/µL (n=13) | CD4>350 Cells/µL (n=34) | Statistic | p-value |
|------------------------------------------|-------------------------|-------------------------|-----------|---------|
| Age, median (IQR), years                 | 36 (31–48)              | 32 (25–40)              | −1.416    | 0.157   |
| Gender                                   |                         |                         |           |         |
| Males, n (%)                             | 13 (100%)               | 32 (94.1%)              | 0.799     | 0.371   |
| Females, n (%)                           | 0 (0%)                  | 2 (5.9%)                |           |         |
| Interval time between vaccination and antibody test, mean, (range), days | 52 (24–98) | 60 (23–101) | −1.111 | 0.272   |

Figure 3 The difference in antibody responses between patients with different CD4⁺ T cell counts. PLWH were divided into patients with CD4⁺ T cell counts≤350 µL and CD4⁺ T cell counts>350 µL. The difference in NAb titers against the D614G variant (A), the delta variant (B), and the concentration of SARS-CoV-2 IgG (C) between the two groups was shown. The short black lines indicate mean and 95% CI.
inactivated vaccines. The positive rates of neutralizing antibodies against the D614G virus and SARS-CoV-2 IgG in PLWH were markedly lower than those in HDs. SARS-CoV-2 IgG concentrations and neutralizing antibody titers against the D614G and delta variants also declined significantly in PLWH compared to HDs. Similar to our research, a study from Chile showed that immune responses to inactivated COVID-19 vaccines in immunocompromised patients were markedly weaker than those of healthy controls. Further analysis revealed a markedly lower antibody level in patients with CD4+ T-cell counts ≤350 cells per μL, consistent with the finding that CD4+ T-cell count is positively correlated with neutralizing antibody responses to inactivated SARS-CoV-2. Therefore, a booster dose or dose adjustment might be needed in HIV-infected individuals, especially those with lower CD4+ T-cell counts.

The emergence of SARS-CoV-2 variants (such as delta and omicron) has raised concerns about increased virus transmissibility and reduced vaccine effectiveness. We evaluated the differences in neutralizing antibodies to D614G and the delta variant in PLWH. The results suggest that most HIV-infected individuals showed detectable neutralizing antibody titers against the two variants. However, the GMT for the delta variant was significantly lower than the GMT for the D614G variant in PLWH, which is consistent with Chang Liu’s finding that mRNA vaccines induced an antibody response to some variants, but the neutralization of the delta variant was reduced. A weaker neutralizing antibody titer against the delta variant may affect inactivated vaccine efficacy. Real-world data from HIV-negative individuals in China have shown that the protection rate of inactivated vaccines against COVID-19 caused by delta variant infection was 59%, and efficacy exceeded the minimum threshold of 50% set by the World Health Organization. However, data about vaccine effectiveness against delta variant infection in PLWH are sparse. Further study is needed to determine the protection rate provided by inactivated COVID-19 vaccines against delta and other variants in PLWH. Contrary to the findings of Liu, who reported that PLWH have spike receptor binding domain-protein specific IgG (S-RBD-IgG) antibody titers comparable to those of healthy controls following inactivated COVID-19 vaccination, our study revealed a poor immune response in PLWH compared with HDs. This discrepancy may be due to differences in detection indicators. The D614G and delta variants harbor mutations in the RBD, so neutralizing titers to the pseudotyped virus may better show the immune response to the two variants elicited by vaccination than titers of S-RBD-IgG. New variants can lead to immune evasion and thus a decrease in the antibody response elicited by vaccination. HIV can attenuate immunity to other infections, so that PLWH may show a poor antibody response to SARS-CoV-2 variants.

Our study has several limitations. First, the influence of sex on immune responses was not investigated because most HIV patients were male. Second, our groups were relatively small and came from a single institution, which may have biased the results. Therefore, our conclusions can only be generalized after further validation among a sizeable HIV-infected cohort. Third, the interval time from vaccination to detection was too long in some participants, which may have led us to underestimate the antibody-positive rates. Fourth, the pseudovirus neutralization assay has some limitations. Pseudoviruses cannot complete the same life cycle as live viruses, and its conformation, density, and distribution pattern of the spike protein may not be the same as in live viruses. Furthermore, we did not examine the cellular immune response due to the limitations of experimental conditions, but further research on the T-cell response will be carried out in the future. Last but not least, there was a significant difference in the length of time from vaccination to detection between PLWH and HDs. Thus we selected 10 HIV-infected patients whose age, sex, and detection time were matched with those of HDs to compare their antibody responses. Although the sample size was small, sufficient power for tests was still achieved due to the significant difference between the two groups.

All together, our results suggest that inactivated vaccines are efficacious in HIV-infected patients. Humoral immunity responses in PLWH are inferior to those in healthy individuals, especially those with lower CD4+ T-cell counts.

**Abbreviations**

PLWH, people living with HIV; HDs, healthy donors; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ART, antiretroviral therapy; HCs, healthy controls; IQR, interquartile range; GMTs, geometric mean titers; GMCs, geometric mean concentrations; CIs, confidence intervals; S-RBD-IgG, spike receptor binding domain-protein specific IgG.
Institutional Review Board Statement
This study was performed in accordance with the declaration of Helsinki, and approved by the Institutional Ethics Committee of Beijing Ditan Hospital, Capital Medical University (No. 2021-021-02, date of approval: Jul 5 2021).

Data Sharing Statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Informed Consent Statement
Informed consent was obtained from all subjects involved in the study.

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Disclosure
The authors declare that they have no competing interests.

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