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Seroprevalence of SARS-CoV-2-specific antibodies and vaccination-related adverse events in systemic lupus erythematosus and rheumatoid arthritis

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ABSTRACT

Background: This study aimed to investigate the seroreactivity of Coronavirus disease 2019 (COVID-19) vaccination and its adverse events among systemic lupus erythematosus (SLE) patients, rheumatoid arthritis (RA) patients, and healthy controls (HCs).

Methods: A total of 60 SLE patients, 70 RA patients and 35 HCs, who received a complete inactivated COVID-19 vaccine (Vero cells) regimen, were recruited in the current study. Serum IgG and IgM antibodies against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) were determined by using chemiluminescent microparticle immunoassay (CMIA).

Results: There were no significant differences regarding the seroprevalences of IgG and IgM antibodies against SARS-CoV-2, and the self-reported vaccination-related adverse events among SLE patients, RA patients and HCs. The inactivated COVID-19 vaccines appeared to be well-tolerated and moderately immunogenic. In addition, case-only analysis indicated that in SLE patients, the disease manifestation of rash and anti-SSA autoantibody were associated with seroprevalence of IgG antibody against SARS-CoV-2, whereas the uses of ciclosporin and leflunomide had influence on the seroprevalence of IgM antibody against SARS-CoV-2. In RA patients, rheumatoid factor (RF) appeared to be associated with the seroprevalence of IgG antibody against SARS-CoV-2.

Conclusion: Our study reveals that the seroprevalences of IgG and IgM antibodies against SARS-CoV-2 and vaccination-related adverse effects are similar among SLE, RA and HCs, suggesting that COVID-19 vaccine is safe and effective for SLE and RA patients to prevent from the pandemic of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel highly contagious respiratory disease [1]. The COVID-19 has spread to most countries and territories across the globe within a few months, resulting in a global outbreak and pandemic [2–4]. The World Health Organization (WHO) has declared that the 2019–2020 outbreak of coronavirus

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constitutes a Public Health Emergency of International Concern (PHEIC) on 30 January 2020, and a pandemic on 11 March 2020 [5,6]. The ongoing pandemic of COVID-19 has posed a big threat to the health and well-being of people worldwide.

A large number of existing studies have suggested that, as compared to general population, patients with systemic lupus erythematosus (SLE) might be at higher risk of hospitalization during their COVID-19 course, and there was also an increased risk of COVID-19 infection and severe outcomes in rheumatoid arthritis (RA) patients, thus the early protection against COVID-19 infection would be of great importance for the management of these patient groups [7–9]. Up to date, several different types of vaccines have been rapidly developed and rollout globally to reduce the morbidity and mortality associated with COVID-19. However, there are still numerous patients with SLE or RA, who did not get COVID-19 vaccine due to concerns about its effectivity and adverse events [10].

Recent study has revealed that, after BNT162b2 vaccination, about 1/3 SLE patients showed lower levels of immunoglobulin G (IgG) antibody against SARS-CoV-2 spike protein receptor binding domain (RBD) than that of healthy controls (HCs), and found that such a low humoral response might be attributed to the immunosuppression [11]. In addition, it has been demonstrated that, after injection with mRNA vaccine BNT162b2, the anti-spike antibody response in SLE patients was influenced by serum baseline total IgG levels, naïve B cell frequencies and SARS-CoV-2-specific T cell response. Of note, the treatments with mycophenolate mofetil (MMF) and methotrexate (MTX) were associated with drastically reduced BNT162b2 antibody response [12]. Nevertheless, considering the different types of vaccines and ethnicities, evidence on the effectiveness and safety of COVID-19 vaccine in Chinese patients with SLE and RA remain scarce. It is therefore relevant and timely to evaluate the tolerability and the occurrence of adverse events following COVID-19 vaccination in SLE and RA patients, in order to improve the optimal management of these patient populations.

In the present study, we aimed to investigate the efficacy of inactivated COVID-19 vaccine in Chinese autoimmune disease (AD) patients (including SLE and RA) and HCs, who has received two doses of inactivated COVID-19 vaccine. This was accomplished by assessment of the seroprevalences of IgG and IgM antibodies against SARS-CoV-2. In addition, the vaccination-related adverse events among SLE, RA and HCs were compared to evaluate the safety of inactivated COVID-19 vaccine. Furthermore, the clinical manifestations and laboratory indicators that might associated with the seroprevalences of IgG and IgM antibodies against SARS-CoV-2 were explored.

2. Methods

2.1. Study subjects

From August 10, 2021 to September 30, 2021, 60 SLE patients and 70 RA patients were recruited from two independent hospitals, the Department of Rheumatology and Immunology at the First Affiliated Hospital of University of Science and Technology of China, and Anqing Hospital Affiliated to Anhui Medical University, respectively. Patients with SLE were diagnosed according to the 1997 revised American College of Rheumatology (ACR) classification criteria [13]. The disease activity of SLE was evaluated by an experienced rheumatologist using the SLE disease activity index (SLEDAI) score [14]. Moreover, the diagnosis of RA was implemented according to the European League Against Rheumatism (EULAR) and ACR 2010 criteria [15]. Thirty-five age and sex-matched healthy volunteers without rheumatic diseases were served as HCs. All patients and HCs had no history of COVID-19 infection, and have established the two doses of inactivated COVID-19 vaccine (Vero Cell) more than two weeks before serum collection. Demographic characteristics (age, gender, body mass index [BMI]), clinical manifestations (duration, comorbidities, type of treatment), routine laboratory results (autoantibody, C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) and vaccination-related information (vaccination date, type of vaccines, adverse events) were obtained from the hospital medical records and self-designed questionnaire, respectively.

2.2. Standard protocol approvals and patient consents

This study was approved by the Ethical Committee of Anhui Medical University (Hefei, Anhui, China). All the study subjects provided informed consent to participate in this study.

2.3. Sample preparation and antibody detection

One tube (5–8 ml) of whole blood was draw in the morning of the day that the subjects underwent memory testing, and the serum was separated and stored at − 80 °C until assayed. The serum IgG and IgM antibodies against SARS-CoV-2 were detected by using SARS-CoV-2 IgG and IgM chemiluminescent immunoassay microparticles (CMIA) (CMU0302/CMU0402, 100 T/kit, AUTOBIO DIAGNOSTICS CO., LTD. Zhengzhou, China) [16,17]. Microparticles were coated by anti-human IgG or IgM antibody, and enzyme conjugate was prepared with HPR-labeled SARS-CoV-2 antigen. The solid phase secondary antibody-IgG or antibody-IgM antibody-enzyme-labelled antigen complex was generated by immunological reactions. The complex catalyzes substrate, resulting in a chemiluminescent reaction, which was proportional to the amount of SARS-CoV-2 IgG or IgM antibody. The serum samples of patients (SLE and RA) and HCs were tested. The sensitivity and specificity of kits were 89% and 100% for IgG, and 90% and 100% for IgM, respectively. The cut-off coefficient was 0.2 for IgG, and 0.1 for IgM. The cut-off value of the kit (cut-off value) was calculated by average relative luminescence unit (RLU) of positive control well × cut-off coefficient. The value of S/CO was used to determine if the sample was positive to IgG or IgM antibodies against SARS-CoV-2, with the use of the equation (RLU of tested samples/cut off), if the value of S/CO $\geq$ 1.00, the result is positive. Otherwise, the result is negative.

2.4. Statistical analysis

For normally distributed data, the mean and standard deviation (SD) were used for statistical descriptions, otherwise, median and interquartile range (IQR) were applied if data with skewed distribution. Comparisons of continuous variables (such as age, BMI, duration) among groups were conducted by using one-way analysis of variance (ANOVA) or Student's *t*-test. Categorical variables (including the seroprevalences of IgG and IgM antibodies against SARS-CoV-2, gender, adverse events) were compared with the use of *Chi*-square test or Fisher's exact test. Statistical analysis was performed in using Statistical Package for the Social Sciences (SPSS) statistical software, version 23.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at 0.05.

3. Results

3.1. Basic characteristics of the study population

The basic characteristics and vaccination-related information were summarized in Table 1. A number of 60 SLE patients, 70 RA patients and 35 HCs were enrolled in the present study, all of study subjects had received two doses of inactivated COVID-19 vaccine (Vero Cell). The three groups were sufficiently matched for age, BMI and gender distribution (all $P > 0.05$) (Table 1). The median duration was 5.0 years in SLE patients (IQR: 2–8 years), and 6.0 years in RA patients (IQR: 2–10 years), respectively (Table 1). Both the days between 1st and 2nd vaccine dose and between 2nd vaccine dose and post-vaccine blood draw showed no significant differences among SLE, RA and HCs groups ($P = 0.452$, $P = 0.324$, respectively) (Table 1). During vaccinations, there were 19 (31.7%) SLE and 61 (87.1%) RA patients who had a continuous

Table 1
Demographic and vaccination-related information of study subjects after COVID-19 vaccines.

Parameters	SLE (n = 60)	RA (n = 70)	HCs (n = 35)	*P*-value
Age (years)	40.08 ± 12.50	40.70 ± 11.73	39.49 ± 10.23	0.868
Sex (male/female)	2/58	6/64	3/32	0.394
BMI (kg/m^2)	21.23 ± 2.34	20.49 ± 1.92	20.83 ± 2.34	0.151
Disease duration (years)	5.0 [2,8]	6 [2,10]	–	–
Days between 1st and 2nd vaccine dose (days)	28 [22,33]	28 [24,31]	32 [23,34]	0.452
Days between 2nd vaccine dose and post-vaccine blood draw (days)	46 [23,82]	47 [19,70]	43 [14,68]	0.324
Regular taking medicine during vaccination (n/ (%))	19 (31.7)	61 (87.1)	–	**0.000**
Self-reported vaccination-related adverse events (n/ (%))	15 (25.0)	16 (22.9)	6 (17.1)	0.671
Rash	2 (3.3)	0 (0)	0 (0)	0.141[a]
Fever	3 (5.0)	4 (5.7)	2 (5.7)	0.981[a]
Swelling	1 (1.7)	2 (2.9)	0 (0)	0.303[a]
Myalgia	4 (6.7)	3 (4.3)	3 (8.6)	0.370[a]
Arthralgia	1 (1.7)	0 (0)	0 (0)	0.575[a]
Diarrhoea	0 (0)	2 (2.9)	0 (0)	0.509[a]
Fatigue	2 (3.3)	2 (2.9)	0 (0)	0.684[a]
Nausea	1 (1.7)	0 (0)	0 (0)	0.575[a]
Tenderness	1 (1.7)	0 (0)	1 (2.9)	0.333[a]
Headache	0 (0)	3 (4.3)	0 (0)	0.236[a]
Prior history of COVID-19 (PCR or IgG) (n/ (%))	0 (0)	0 (0)	0 (0)	–

COVID-19: Coronavirus disease 2019; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HCs: healthy controls;
[a] Fisher's exact test.

use of medicine. In terms of vaccination-related adverse events, we did not observe any significant differences of vaccination-related adverse events among SLE patients, RA patients and HCs ($P = 0.671$), where the most prevalent self-reported vaccination-related adverse events were fever and myalgia among the study subjects. All of study subjects did not have a prior infection of COVID-19. The clinical manifestations, laboratory indexes and the use of medicines among SLE and RA patients were displayed in Table 2.

3.2. Comparisons of serological test for IgG and IgM antibodies against SARS-CoV-2

Sixty SLE patients, 70 RA patients and 35 HCs, who had received two-dose of inactivated COVID-19 vaccine, were measured for IgG and IgM antibodies against SARS-CoV-2. Among the study subjects, about 30 SLE patients (50.0%), 40 RA patients (57.1%) and 23 HCs (65.7%) showed positive test results of IgG antibody against SARS-CoV-2, there were no significant differences of seroprevalence of IgG antibody against SARS-CoV-2 amongst SLE, RA and HCs ($P = 0.325$) (Table 3). In addition, there were 5 SLE patients (8.3%), 6 RA patients (8.6%) and 1 HCs (2.9%) who were tested positive for IgM antibody against SARS-CoV-2, no significant differences regarding the seroprevalence of IgM antibody against SARS-CoV-2 were revealed in SLE patients, RA patients and HCs groups ($P = 0.632$) (Table 3).

3.3. Analysis of the indicators for IgG and IgM antibodies against SARS-CoV-2 in SLE patients

SLE patients who had positive tests for IgG antibody against SARS-CoV-2, showed an increased frequency on the occurrence of rash (20.0% *versus* 0%) and a decreased risk of anti-SSA (positive) (6.7% *versus* 30.0%) than those patients with negative results of IgG antibody against SARS-CoV-2 (Table 4). Moreover, there was a higher frequency

Table 2
Clinical features, laboratory indexes and the use of medicines in SLE and RA patients.

Parameters	SLE (n = 60)	RA (n = 70)
Disease duration (years)	5.0 [2,8]	6.0 [2,10]
ESR (mm/h)	19 [10,24]	20.07 ± 16.68
CRP (g/L)	3.13 (0.86, 6.16)	3.13 (1.04, 5.99)
C3 (g/L)	0.84 ± 0.26	0.67 ± 0.23
C4 (g/L)	0.15 ± 0.79	0.16 ± 0.45
Serum IgA (g/L)	3.03 ± 0.97	2.92 ± 0.67
Serum IgM (g/L)	1.13 ± 0.69	1.06 ± 0.53
Serum IgG (g/L)	14.83 ± 4.70	12.16 ± 2.89
Disease activity score	2.30 ± 3.68 (SLEDAI)	3.71 ± 2.09 (DAS28)
Disease manifestations (n/ (%))		
Renal disease	18 (30.0)	–
Vasculitis	4 (6.7)	–
Arthritis	6 (10.0)	–
Myositis	5 (8.3)	–
Rash	6 (10.0)	–
Alopecia	5 (8.3)	–
Oral ulcer	4 (6.7)	–
Pericarditis	5 (8.3)	–
Pleuritis	0 (0)	–
Leukopenia	7 (11.7)	–
Thrombocytopenia	6 (10.0)	–
Nervous system disorder	1 (1.7)	–
Low complement	1 (1.7)	–
Comorbidities (n/ (%))		
Morning stiffness	–	4 (5.7)
Diabetes	4 (6.7)	2 (2.9)
Hypertension	13 (21.7)	3 (4.3)
Interstitial pneumonia	5 (8.3)	3 (4.3)
Autoantibodies		
Anti-CCP (+/-)	–	30/40
AKA (+/-)	–	14/56
RF (+/-)	–	37/33
Anti-dsDNA (+/-)	5/55	–
Anti-Sm 18 (+/-)	6/54	–
Anti-SSA (+/-)	11/49	–
Anti-SSB (+/-)	9/51	–
Anti-RNP (+/-)	3/57	–
Anti-Ribosomal P (+/-)	3/57	–
Medical therapy		
Prednisone (n/ (%))	55 (91.7)	27 (38.6)
Dose (mg)	8.62 ± 8.82	6.41 ± 2.92
Hydroxychloroquine (n/ (%))	56 (93.3)	26 (37.1)
Dose (mg)	226.78 ± 48.58	230.77 ± 47.07
Methotrexate (n/ (%))	8 (13.3)	40 (57.1)
Dose (mg)	10.25 ± 0.71	15.38 ± 4.92
Ciclosporin (n/ (%))	11 (18.3)	–
Dose (mg)	114.28 ± 62.68	–
Leflunomide (n/ (%))	4 (6.7)	39 (55.7)
Dose (mg)	8.75 ± 2.50	10.28 ± 2.32
Other Medications		
Alfacalcidol (n/ (%))	4 (6.7)	11 (15.7)
Dose (ug)	0.38 ± 0.14	0.43 ± 0.12
Rabeprazole (n/ (%))	3 (5.0)	–
Dose (mg)	17.50 ± 5.00	–
Aspirin (n/ (%))	4 (6.7)	–
Dose (mg)	100	–
Iguratimod (n/ (%))	–	4 (5.7)
Dose (mg)	–	25
Total glucosides of paeony (n/ (%))	–	5 (7.1)
Dose (g)	–	0.78 ± 0.18

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SLEDAI: SLE disease activity index; DAS28: the disease activity score using 28 joint counts

of self-reported vaccination-related adverse events (40.0% *versus* 25.5%), treatments with ciclosporin (60.0% *versus* 10.9%) and leflunomide (40.0% *versus* 3.6%) in SLE patients with positive tests than those with negative results for IgM antibody against SARS-CoV-2 (Supplementary Table 1).

Table 3
Comparisons of serological test for IgG and IgM antibodies against SARS-CoV-2 among SLE, RA and HCs.

Serological indicators	SLE (n = 60)	RA (n = 70)	HCs (n = 35)	Chi-square	*P*-value
IgG antibody against SARS-CoV-2 (+/-)	30/30	40/30	23/12	2.249	0.325
IgM antibody against SARS-CoV-2 (+/-)	5/55	6/64	1/34	1.154	0.632[a]

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HCs: healthy controls;
[a] Fisher's exact test.

Table 4
Bivariate analysis of the indicators for the test of IgG antibody against SARS-CoV-2 in SLE.

Parameters	IgG antibody against SARS-CoV-2 positive (n = 30)	IgG antibody against SARS-CoV-2 negative (n = 30)	*P*-value
Regular taking medicine during vaccination (n/ (%))	9 (30.0)	10 (33.3)	0.781
Self-reported vaccination-related adverse events (n/ (%))	7 (23.3)	8 (26.7)	0.561
Disease manifestations (n/ (%))			
Renal disease	8 (26.7)	10 (33.3)	0.573
Vasculitis	3 (10.0)	1 (3.3)	0.612[a]
Arthritis	4 (13.3)	2 (6.7)	0.671[a]
Myositis	3 (10.0)	2 (6.7)	1.000[a]
Rash	6 (20.0)	0 (0)	**0.024**[a]
Alopecia	5 (16.7)	0 (0)	0.052[a]
Oral ulcer	3 (10.0)	1 (3.3)	0.612[a]
Pericarditis	0 (0)	0 (0)	–
Pleuritis	1 (3.3)	0 (0)	1.000[a]
Leukopenia	3 (10.0)	4 (13.3)	1.000[a]
Thrombocytopenia	4 (13.3)	2 (6.7)	0.671[a]
Nervous system disorder	1 (3.3)	0 (0)	1.000[a]
Low complement	2 (6.7)	0 (0)	0.492[a]
Diabetes	0 (0)	4 (13.3)	1.000[a]
Hypertension	5 (16.7)	8 (26.7)	0.532
Interstitial pneumonia	1 (3.3)	4 (13.3)	0.353[a]
Autoantibodies (n/ (%))			
Anti-dsDNA	1 (3.3)	4 (13.3)	0.353[a]
Anti-Sm 18	5 (16.7)	1 (3.3)	0.195[a]
Anti-SSA	2 (6.7)	9 (30.0)	**0.020**
Anti-SSB	2 (6.7)	7 (23.3)	0.071
Anti-RNP	1 (3.3)	2 (6.7)	1.000[a]
Anti-Ribosomal P	1 (3.3)	2 (6.7)	1.000[a]
Medical therapy (n/ (%))			
Prednisone	28 (93.3)	27 (90.0)	1.000[a]
Hydroxychloroquine	27 (90.0)	29 (96.7)	0.612[a]
Methotrexate	2 (6.7)	6 (20.0)	0.254[a]
Ciclosporin	6 (20.0)	5 (16.7)	0.739
Leflunomide	3 (10.0)	1 (3.3)	0.612[a]

Anti-dsDNA: anti-double stranded DNA; Anti-Sm: anti-Smith antibody; Anti-SSA: anti-Sjögren's-syndrome-related antigen A; Anti-SSB: anti-Sjögren's-syndrome-related antigen B; Anti-RNP: anti-nuclear ribonucleoprotein; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SLE: systemic lupus erythematosus
[a] Fisher's exact test.

3.4. Analysis of the indicators for IgG and IgM antibodies against SARS-CoV-2 in RA

RA patients with positive tests for IgG antibody against SARS-CoV-2, showed a lower frequency of positivity to rheumatoid factor (RF) (42.5% *versus* 66.7%) than those patients with negative results of IgG antibody against SARS-CoV-2 (Table 5). Nevertheless, we did not observe any association of clinical features and medications use with the seroprevalence of IgM antibody against SARS-CoV-2 in RA patients (Supplementary Table 2).

Table 5
Bivariate analysis of the indicators for the test of IgG antibody against SARS-CoV-2 in RA.

Parameters	IgG antibody against SARS-CoV-2 positive (n = 40)	IgG antibody against SARS-CoV-2 negative (n = 30)	*P*-value
Regular taking medicine during vaccination (n/ (%))	33 (82.5)	28 (93.3)	0.283[a]
Self-reported vaccination-related adverse events (n/ (%))	6 (15.0)	7 (23.3)	0.375
Disease manifestations (n/ (%))			
Morning stiffness	4 (10.0)	0 (0)	0.130[a]
Diabetes	2 (5.0)	0 (0)	0.054[a]
Hypertension	2 (5.0)	1 (3.3)	1.000[a]
Interstitial pneumonia	2 (5.0)	1 (3.3)	1.000[a]
Autoantibodies (n/ (%))			
Anti-CCP	17 (42.5)	13 (43.4)	0.944
AKA	9 (22.5)	5 (16.7)	0.546
RF	17 (42.5)	20 (66.7)	**0.045**
Medical therapy (n/ (%))			
Prednisone	12 (30.0)	15 (50.0)	0.089
Hydroxychloroquine	14 (35.0)	12 (40.0)	0.668
Methotrexate	25 (62.5)	15 (50.0)	0.296
Leflunomide	19 (47.5)	20 (66.7)	0.110

Anti-CCP: anti-cyclic citrullinated peptide; AKA: anti-keratin antibody; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; RA: rheumatoid arthritis; RF: rheumatoid factor
[a] Fisher's exact test.

4. Discussion

In view of the serious pandemic of COVID-19, there are several different types of vaccines that have been developed. Mass vaccination is a crucial public health measure for limiting the spread of COVID-19 and providing an early protection against SARS-CoV-2, especially in fragile populations [18–21]. Nevertheless, the current evidence about the efficacy and safety of COVID-19 vaccination in patients with AD is scarce, only a handful of small studies have investigated the humoral immune response to COVID-19 vaccine (mostly mRNA vaccine) in white AD patients, there is still a lack of evidence regarding the effectiveness and safety of inactivated COVID-19 vaccine in Chinese patients with AD. Here, we enrolled a number of 165 participates with fully vaccinated against inactivated COVID-19 vaccine, including 60 SLE patients, 70 RA patients and 35 HCs. After testing for the serum IgG and IgM antibodies against SARS-CoV-2, the results indicated that the seroprevalences of both IgG and IgM antibodies against SARS-CoV-2 showed no significant differences among SLE patients, RA patients and HCs groups. Moreover, the prevalence of mild adverse events was similar between AD patients (SLE and RA) and HCs. These findings indicated that inactivated COVID-19 vaccination might exert the similar protective effects in AD patients and HCs, supporting that there were the considerable efficacy and safety of the inactivated COVID-19 vaccination in SLE and RA.

Several previous literatures have been conducted to assess the immune response in patients with SLE after COVID-19 vaccination [11,12]. Moyon Q et al. performed a prospective study with the recruitment of 126 patients with SLE, and investigated the humoral and cellular responses induced by BNT162b2 mRNA vaccine against COVID-19. They observed that BNT162b2 vaccine was well-tolerated and not associated with the baseline disease activity of SLE. Interestingly, it showed that the uses of MMF and MTX were reversely correlated to the antibody response of BNT162b2, whereas the anti-spike antibody response was positively associated with baseline total IgG serum levels, naïve B cell

frequencies and SARS-CoV-2-specific T cell response [12]. Additional study has evaluated the seroreactivity and disease flares after COVID-19 vaccination in SLE, it demonstrated that, after fully vaccinated, there were significantly lower levels of IgG antibody against SARS-CoV-2 spike RBD in SLE patients than that of controls [11]. This is inconsistent with our findings, where we found that there were no differences of IgG antibody against SARS-CoV-2 between SLE patients and HCs. Moreover, the history of immunosuppressant or prednisone treatments and the level of anti-dsDNA prior to vaccination showed the correlations with the lower vaccine responses, and the seroreactivity of IgG antibody against SARS-CoV-2 was strongly associated with the higher titers of SARS-CoV-2 microneutralization and productions of antigen-specific interferon (IFN)-γ [11]. In our study, the results of case-only analysis indicated that the disease manifestation of rash and anti-SSA autoantibody were correlated with the seroreactivity of IgG antibody against SARS-CoV-2, while the self-reported vaccination-related adverse events and the uses of ciclosporin and leflunomide were associated with the seroreactivity of IgM antibody against SARS-CoV-2. These findings suggested that the disease manifestation, serum autoantibody, self-reported vaccination-related adverse events and the uses of ciclosporin and leflunomide might be associated with the humoral immune response to COVID-19 vaccine in SLE.

Recently, there were emerging evidence that have evaluated the immunogenicity and safety of COVID-19 vaccine in RA patients [22,23]. Li et al. have explored and assessed the influences of COVID-19 vaccination on the disease flare in patients with RA, they found that the flare of arthritis was not correlated with the COVID-19 vaccination despite the different types of vaccines, the adjusted incidence rate ratio (IRR) was 0.86 (95%CI: 0.73–1.01) for two doses of BNT162b2, and 0.87 (95% CI: 0.74–1.02) for CoronaVac [23]. Another study attempted to investigate the SARS-CoV-2-specific humoral response in RA patients with fully BNT162b2-mRNA vaccination, and it observed that the serum IgG antibody against SARS-CoV-2 spike RBD was detectable in the majority of RA patients (97%) and in all HCs (100%). Furthermore, no significant differences on the levels of IgG antibody against SARS-CoV-2 spike RBD were revealed among RA patients who undergone tumor necrosis factor (TNF)-α-inhibitors treatment with or without disease-modifying antirheumatic drugs (DMARDs), or taking DMARDs with or without corticosteroids [22]. Our study found that the seroprevalences of serum IgG and IgM antibodies against SARS-CoV-2 did not differ between RA patients and HCs who received a fully two doses of inactivated COVID-19 vaccine. However, we unveiled that RF was negatively associated with the seroreactivity of IgG antibody against SARS-CoV-2 in RA patients. These evidences, together with our findings, demonstrated that the COVID-19 vaccination might not trigger an arthritis flare, and it could induce the similar humoral response as healthy people, suggesting that COVID-19 vaccination is effective and safe for RA patients.

There are several limitations that should be acknowledged in the present study. First, the sample size of study subjects was relatively small, only 165 subjects (60 SLE, 70 RA and 35 HCs) were included, which may weaken the robustness of the study. Second, the detection of humoral immune responses against to SARS-CoV-2 were conducted at a single time point after fully vaccination, thus the better understanding about the dynamic changes of seroreactivity of IgG and IgM antibodies against SARS-CoV-2 between 1st and 2nd vaccination is not available. Furthermore, it should be noticed that the majority of patients with SLE did not have a continuous medication activity, so the relations of the medication use with the seroreactivity of COVID-19 vaccine in SLE are still not clear.

Despite the limitations, our study also has its advantages. In contrast to previous studies, where the evaluation of humoral immune response was implemented in Caucasian patients with SLE or RA after getting the mRNA vaccine (BNT162b2). To the best of our knowledge, this is the first study that investigates and assesses the seroprevalences of IgG and IgM antibodies against SARS-CoV-2 in Chinese patients with SLE and RA, who received a fully inactivated COVID-19 vaccination. The findings of our study provide the evidence about the effectiveness and safety of inactive virus vaccine in patients with SLE and RA, it would be helpful for the physicians in guiding their patients towards accepting such vaccines.

5. Conclusions

Overall, the current study revealed that there are considerable seroprevalences of IgG and IgM antibodies against SARS-CoV-2 and the occurrence of adverse events between patients and HCs, supporting that inactivated COVID-19 vaccine are well-tolerated in SLE and RA patients. Our findings might reassure patients who remain hesitant about COVID-19 vaccinations, and help physicians in guiding their patients towards accepting such vaccines.

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Ethics approval and consent to participate

This study was approved by the Ethical Committee of Anhui Medical University (Hefei, Anhui, China). All the study subjects provided informed consent to participate in this study.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Peng Wang: Conceptualization, Formal analysis, Methodology, Writing – Original Draft. **Jing Ni:** Data curation, Methodology, Writing – original draft preparation. **Ya-Ya Chu:** Formal analysis, Validation. **Qing-Qing Chen:** Methodology, Validation. **Guo-Cui Wu:** Software, Validation. **Yang Fang:** Resources, Investigation. **Cong Chen:** Resources. **Ruo-Di Zhang:** Resources. **Ling-Qiong Jiang:** Visualization. **Yan Zhao:** Investigation. **Xi Fang:** Investigation. **Jun He:** Supervision, Investigation. **De-Guang Wang:** Conceptualization, Supervision. **Gui-Hong Wang:** Conceptualization, Resources, Writing – Review & Editing. **Hai-Feng Pan:** Conceptualization, Writing – Review & Editing, Project administration.

Conflict of interest statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Data Availability

No data was used for the research described in the article. Data available on request from the authors.

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None.

Author contributions

Hai-Feng Pan, De-Guang Wang and Gui-Hong Wang conceived of the presented idea. Peng Wang and Jing Ni were responsible for data interpretation, and writing of the manuscript. developed the theory and performed the computations. Yang Fang, Cong Chen, Ruo-Di Zhang, and Ling-Qiong Jiang were responsible for the clinical management, patient recruitment, and data collection. Ya-Ya Chu, Guo-Cui Wu and Qing-Qing Chen verified the analytical methods. Yan Zhao, Xi Fang and Jun He performed the serological testing. All authors discussed the results and contributed to the final manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2022.112997.

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