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RESEARCH ARTICLE

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Varicella zoster virus reactivation following COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: A cross-sectional Chinese study of 318 cases

Jiali Chen | Fen Li | Jing Tian | Xi Xie | Qi Tang | Yiyue Chen | Yan Ge

Department of Rheumatology and Immunology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China

Correspondence

Yan Ge, Department of Rheumatology and Immunology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, China.

Email: geyan2003@csu.edu.cn

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Abstract

Recently, varicella-zoster virus (VZV) reactivation has been observed after the administration of coronavirus disease 2019 (COVID-19) vaccines. Autoimmune inflammatory rheumatic diseases (AIIRDs) patients are at a higher risk for VZV reactivation for immunocompromised status. The study aimed to investigate the adverse events (AEs), especially VZV reactivation, following vaccination against severe acute respiratory syndrome coronavirus-2 in a Chinese cohort of AIIRD patients. A cross-sectional survey using an online questionnaire was conducted among AIIRD patients and healthy controls (HCs). Multivariate logistic regression was used to identify potential factors associated with VZV reactivation. 318 AIIRD patients and 318 age and sex-matched HCs who got COVID-19 inactivated vaccines were recruited. The main AIIRDs are rheumatoid arthritis (31.8%) and systemic lupus erythematous (23.9%). Most of patients (85.5%) had stable disease and 13.2% of them had aggravation after vaccination. Compared to HCs, patients had higher rates of rash ($p = 0.001$), arthralgia ($p < 0.001$) and insomnia ($p = 0.007$). In addition, there were 6 (1.9%) AIIRD patients and 5 (1.6%) HCs reported VZV reactivation after the COVID-19 vaccination ($p = 0.761$). Multivariate logistic regression analysis illustrated that diabetes mellitus (odd ratio [OR], 20.69; 95% confidence interval [CI], 1.08–396.79; $p = 0.044$), chronic hepatitis B virus infection (OR, 24.34; 95% CI, 1.27–466.74; $p = 0.034$), and mycophenolate mofetil (OR, 40.61; 95% CI, 3.33–496.15; $p = 0.004$) independently identified patients with VZV reactivation. Our findings showed that the inactivated COVID-19 vaccination was safe for AIIRD patients though some patients could suffer from VZV reactivation.

KEYWORDS

autoimmune inflammatory rheumatic diseases, COVID-19 vaccine, SARS coronavirus, varicella-zoster virus reactivation

1 | INTRODUCTION

The World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) outbreak a pandemic in March 2020.[1] By the end of 14 October, 2022, coronavirus disease-2019 (COVID-19) had infected more than 620 million people across 216 countries or territories, with more than 6.5 million deaths worldwide.[2] COVID-19 has caused dramatic morbidity and mortality worldwide, along with severe disruption to public health and health care systems.[1]

Vaccination is the most important and effective way to prevent COVID-19 infection.[3] To date, there were six types of COVID-19 vaccine available for humans.[3] In China, inactivated COVID-19 vaccine is the most common type approved to be publicly used.[4] By the end of June 2022, roughly 1 billion inactivated vaccine doses have been administered with effectiveness against severe infections ranging from 70% to 95%.[5,6] Although the mechanisms of all vaccines were different, they have several commonly reported adverse events (AEs) including, injection site pain and swelling, fatigue, fever, headache, nausea, and dermatological complications, all of which can develop after the first, second, and/or third dose.[7] More recently, varicella-zoster virus (VZV) reactivation has been reported following vaccination against SARS-CoV-2 in case reports, case series and cross-sectional studies with the prevalence ranging from 0.02% to 10.1%.[8–11] Among these references, the Israel study has revealed that patients with vaccination had higher risk of herpes zoster (HZ) infection (risk ratio, 1.43; 95% CI, 1.20–1.73).[11] VZV reactivation is influenced by the age of the patients and host immune status. It has been considered that aging and immunocompromised state are major risk factors rather than vaccine administration.[12]

Autoimmune inflammatory rheumatic diseases (AIIRDs) patients are immunocompromised and have a higher risk of being infected with COVID-19.[13] Therefore, AIIRD patients should be prioritized for COVID-19 vaccination than the general population.[14] However, the immunocompromised status of AIIRDs patients may lead to a higher risk of VZV reactivation accordingly. To date, there were scant case reports or series studies which reported VZV reactivation emerging after COVID-19 vaccination for AIIRDs patients.[9,15–18] Taken together, this study aims to investigate the AEs, especially VZV reactivation, following vaccination against SARS-CoV-2 in a Chinese cohort of AIIRD patients.

2 | METHODS

2.1 | Study design

This study was a web-based observational survey using an online questionnaire and did not use clinical data extracted retrospectively from clinical archives. The questionnaire was designed using the website http://www.wjx.cn/ and consisted of 32 questions about sociodemographic characteristics, clinical profile of the AIIRD patients, vaccine AEs data and comorbidities (web questionnaire was attached in Supplementary material- Questionnaire). In our study, comorbidities include hypertension, coronary heart disease, diabetes mellitus, chronic pulmonary disease and other non-AIIRDs. This online survey was conducted from April 1, 2022 to April 30, 2022, and disseminated by WeChat, the most popular social media platform in China. Similarly, the survey was conducted on healthy controls (HCs) who received the same vaccines. The study was approved by the Ethics Committee of the Second Xiangya Hospital (K013). All patients gave written informed consent to participate in the study and explicit consent to publish data or images.

2.2 | Patients

All AIIRD patients and HCs are Chinese Han population from Hunan province. AIIRD patients were inpatient or outpatient diagnosed in the department of Rheumatology and Immunology in the Second Xiangya Hospital, Central South University, who met the classification of disease. Other inclusion criteria were that the AIIRD patients be Chinese citizens 18 years old or older and be able to read and comprehend Chinese. The types of patients included rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), spondyloarthritis (SpA), systemic sclerosis, inflammatory myopathy, connective tissue disease, mixed connective tissue disease, undifferentiated connective tissue disease, anti-phospholipid syndrome, reactive arthritis, IgG4-related disease, Behçet's disease, anti-neutrophil cytoplasmic antibody-associated vasculitis, Takayasu arteritis, systemic vasculitis, polymyalgia rheumatic, relapsing polychondritis, Adult-onset still's disease, and other rheumatic diseases. HCs who had a history of neoplastic, and autoimmune/autoinflammatory diseases and who were less than 18 years old were excluded. In our study, we recruited AIIRDs patients and HCs at the same time. And, we divided the AIIRDS patients with COVID-19 vaccination and HCs into several groups by age range, including 18–30 years, 31–59 years, and ≥60 years. Then, according to the sex and age in the AIIRDS patients group, we randomly selected related HCs. In that case, the sex- and age were matched between these two groups.

2.3 | Vaccination

All AIIRD patients and HCs were vaccinated with the regimen SARS-CoV-2 inactivated vaccine ranging from first to third dose. The vaccine was produced in China and the brand included Sinopharm (Vero Cell), Sinovac COVID-19 Vaccine (Vero Cell), Sinopharm/WIBP, CanSinoBio, Zhifei Longcom, KCONECAVAC. In addition, some AIIRD patients and HCs were getting foreign brand vaccination. In line with WHO, AEs following immunization were classified as minor reactions (local pain, swelling, or papular erythematous rash without associated systemic symptoms) or

systemic reactions (fever, headache, fatigue, malaise, myalgia) and severe reactions (can be disabling or life-threatening). Notably, the HZ data were recorded, including type of vaccine, dose at the reaction of the HZ, rash duration, rash location, HZ treatment and post-herpetic neuralgia, which is defined as a chronic neuropathic pain condition that persists for 3 months or more following an outbreak of shingles. Photographs and histopathologic findings were also collected, if available.

2.4 | Statistical analyses

We included all AIIRDs patients with COVID-19 vaccination from April 1, 2022 to April 30, 2022, and randomly selected HCs with 1:1 ratio. Quantitative data were presented as the median and the 25th–75th percentile interquartile range (IQR). Qualitative data were described as frequency (percentage). The Mann-Whitney *U* test and Fisher's exact test were used to compare the two groups. Multivariate Logistic regression analyses were used to determine the risk factors for VZV reactivation. Once a univariate statistic was generated, the multivariate model was then built using a forward selection procedure. Variables with a p-value of <0.1 in the univariate analysis were first considered as candidates for the multivariate model, then variables with a p-value of <0.05 were used in the final model, odds ratios (ORs) and 95% confidence intervals (CI) were calculated. We also performed an extensive literature review of VZV reactivation among populations with COVID-19 vaccination and analyzed the clinical characteristics of these patients. Data were analyzed using the SPSS statistical software package (version 24.0; IBM). A two-sided $p < 0.05$ was considered statistically significant in this study.

3 | RESULTS

3.1 | Sociodemographic characteristics of AIIRDs and HCs participants

During the study period, a total of 535 AIIRD participants completed the questionnaire and 318 cases got COVID-19 vaccination. Meanwhile, a total of 318 age and sex statistically matched HCs vaccinated with the COVID-19 vaccine were enrolled in the study. The sociodemographic characteristics of AIIRD patients and HCs are summarized in Table 1. Of AIIRD participants, 241/318 (75.8%) were female and 77/318 (24.2%) were male with a median age of 43 (32 to 52) years, and most of them (223/318, 70.1%) were in the 31–59 age group. Compared to HCs participants, AIIRD participants had higher incidence of comorbidities (60/318, 18.9% vs. 28/318, 8.8%, $p < 0.001$), especially for hypertension (24/318, 7.5% vs. 12/318, 3.8%, $p = 0.039$), chronic liver disease (11/318, 3.5% vs. 1/318, 0.3%, $p = 0.004$) and thyroid disease (10/318, 3.5% vs. 3/318, 0.9%, $p = 0.050$) (Table 1).

TABLE 1 Baseline characteristics of patients with AIIRDs and healthy controls

Characteristics	COVID-19 vaccination		
	AIIRDs patients	Healthy controls	*p* Value
No. of cases	318	318	NA
Gender, *n* (%)			
Male	77 (24.2)	98 (30.8)	0.062
Female	241 (75.8)	220 (69.2)	0.062
Age, years, median (IQR)	43 (32–52)	41 (32–52)	0.072
Age group in years, *n* (%)			
18–30	63 (19.8)	67 (21.1)	0.694
31–59	223 (70.1)	227 (71.4)	0.727
≥60	32 (10.1)	24 (7.5)	0.263
BMI (Kg/m^2), median (IQR)	21.9 (19.9–24.0)	22.0 (20.2–23.9)	0.407
Medical history, *n* (%)	60 (18.9)	28 (8.8)	<0.001
Hypertension	24 (7.5)	12 (3.8)	0.039
Coronary heart disease	4 (1.3)	4 (1.3)	1.000
Cerebrovascular disease	2 (0.6)	1 (0.3)	1.000
Diabetes mellitus	10 (3.1)	5 (1.6)	0.191
Chronic pulmonary disease	3 (0.9)	2 (0.6)	1.000
Chronic renal disease	3 (0.9)	1 (0.3)	0.624
Chronic liver disease	11 (3.5)	1 (0.3)	0.004
Thyroid disease	10 (3.1)	3 (0.9)	0.050
Chronic infection	11 (3.5)	1 (0.3)	0.004

Note: Statistical significance was determined by Mann–Whitney *U* test and Chi-square (χ^2) test.

Abbreviations: AIIRDs, autoimmune inflammatory rheumatic diseases; BMI, body mass index; IQR, interquartile range; NA, not available.

3.2 | Clinical characteristics of AIIRDs patients

The clinical characteristics of AIIRD patients are summarized in Table 2. The most common AIIRDs reported were RA (101/318, 31.8%), SLE (76/318, 23.9%), SpA (50/318, 15.7%) and SS (36/318, 11.3%). All patients with median disease duration of 6 (2 to 10) years. Regarding treatments, 32.7% (104/318) of patients took oral corticosteroids and the main dose was ≤5 mg/day (76.9%, 80/318), and 40.6% (129/318) of patients had taken hydroxychloroquine (HCQ). In addition, 47.8% (152/318) of patients took immunosuppressive agents or disease-modifying anti-rheumatic drugs, and the major agents were methotrexate (11.9%, 38/318), Cyclosporin A

TABLE 2 Clinical characteristics of AIIRDs patients who get vaccinated

Variables	Overall (*n* = 318)
Autoimmune inflammatory rheumatic diseases, *n* (%)	
Rheumatoid arthritis	101 (31.8)
Systemic lupus erythematosus	76 (23.9)
Spondyloarthritis	50 (15.7)
Sjögren's Syndrome	36 (11.3)
Vasculitis	9 (2.8)
Systemic sclerosis	8 (2.5)
Connective tissue disease	8 (2.5)
Inflammatory myopathy	7 (2.2)
Mixed connective tissue disease	6 (1.9)
Gout	6 (1.9)
Positive antibodies	6 (1.9)
Adult still disease	4 (1.3)
IgG4 related disease	1 (0.3)
Disease duration, years, median (IQR)	6 (2–10)
Medications, *n* (%)	
Corticosteroid (mg/day)	104 (32.7)
≤5	80 (76.9)
5–10	12 (11.5)
10–30	12 (11.5)
Hydroxychloroquine	129 (40.6)
Immunosuppressive agents *OR* DMARDs	152 (47.8)
Methotrexate	38 (11.9)
Leflunomide	22 (6.9)
Sulfasalazine	7 (2.2)
Iguratimod	24 (7.5)
Mycophenolate mofetil	33 (10.4)
Cyclosporin A	36 (11.3)
Tacrolimus	6 (1.9)
Cyclophosphamide	7 (2.2)
Azathioprine	3 (0.9)
Biological agents	82 (25.8)
TNF inhibitor	61 (19.2)
JAK inhibitor	8 (2.5)
Abatacept	6 (1.9)
Secukinumab	3 (0.9)
Belimumab	1 (0.3)
Telitacicept	3 (0.9)

Abbreviations: AIIRDs, autoimmune inflammatory rheumatic diseases; DMARD, disease modifying anti-rheumatic drugs; IQR, interquartile range.

(11.3%, 36/318), mycophenolate mofetil (MMF, 10.4%, 33/318), Iguratimod (7.5%, 24/318) and leflunomide (6.9%, 22/318). Furthermore, 25.8% (82/318) of patients took biological agents, and the main agent was tumor necrosis factor-α inhibitor (19.2%, 61/318) and JAK inhibitor (2.5%, 8/318) (Table 2).

3.3 | AEs of COVID-19 vaccination for all participants

All participants got at least one-dose regimen of SARS-CoV-2 inactivated vaccine, and the most common brand was Sinopharm [Vero Cell] and Sinovac COVID-19 Vaccine (Vero Cell). There were 41.5% (132/318) and 56.0% (178/318) AIIRDs patients get the second and third dose of COVID-19 vaccination, respectively. Accordingly, for HCs, 25.5% (81/318) and 73.0% (232/318) get the second and third dose of COVID-19 vaccine. Among those participants, 33.3% (106/318) of AIIRD patients and 30.2% (96/318) of HCs had reported some types of side effects. The most common types were injection reactions, followed by fatigue, myalgia, rash, arthralgia, headache, insomnia, abdominal symptom, fever, and chills. Compared to HCs, AIIRD patients had higher incidences of rash (19/318, 6.0% vs. 3/318, 0.9%, $p = 0.001$), arthralgia (15/318, 4.7% vs. 0/318, 0.0%, $p < 0.001$) and insomnia (8/318, 2.5% vs. 0/318, 0.0%, $p = 0.007$) (Table 3). After vaccination, most of the patients (85.5%, 272/318) had stable disease activity, but 13.2% (42/318) of patients reported disease aggravation (Table 3). Among these patients, 57.2% (182/318) of AIIRD patients consulted rheumatologists and 25.5% (81) patients had medication adjustments before getting a vaccination. To avoid the bias of medication adjustment, we compared the rate of aggravation between patients with drug adjustment (11.1%, 9/81) and patients without (9.9%, 10/101) with an insignificant difference ($p = 0.791$, Supporting Information: Table 1).

3.4 | Characteristics of VZV reactivation after COVID-19 vaccination

There were 6/318 (1.9%) AIIRD patients and 5/318 (1.6%) HCs reported VZV reactivation after COVID-19 vaccination ($p = 0.761$). The specific characteristics of each patient were presented in the Table 4. All AIIRD patients were female (6/6, 100%) with a median age of 54 (30 to 69) years. The disease type included SLE (50.0%, 3/6), RA (16.7%, 1/6) and SpA (33.3%, 2/6), and main medications included corticosteroid (50.0%, 3/6) with dose ranging from 2.5 to 5 mg/day, HCQ (33.3%, 2/6), MMF (50.0%, 3/6) and JAK inhibitor (16.7%, 1/6). The median time to VZV onset was 20 (8–98) days after vaccination, and most of them were involved with the third dose (66.7%, 4/6) and the second dose (33.3%, 2/6). In addition, diabetes mellitus (DM) (33.3%, 2/6) and hepatitis B virus (HBV) (33.3%, 2/6) were the main comorbidities (Supporting Information: Table 2).

TABLE 3 Adverse events of AIIRDs patients and healthy controls who get vaccinated

Variables	AIIRDs patients	healthy controls	*p* Value
No. of cases	318	318	NA
Infection of COVID-19, *n* (%)	1 (0.3)	1 (0.3)	1.000
Vaccination dose, *n* (%)			
First	8 (2.5)	5 (1.6)	0.401
Second	132 (41.5)	81 (25.5)	<0.001
Third	178 (56.0)	232 (73.0)	<0.001
Vaccine, *n* (%)			
Sinopharm [Vero Cell]-Inactivated COVID-19 vaccination	148 (46.5)	126 (39.6)	0.078
Sinovac COVID-19 Vaccine (Vero Cell), Inactivated	123 (38.7)	157 (49.4)	0.007
Sinopharm/WIBP	70 (22.0)	56 (17.6)	0.164
CanSinoBio	2 (0.6)	1 (0.3)	1.000
Zhifei Longcom	46 (14.5)	42 (13.2)	0.646
KCONECAVAC	17 (5.3)	10 (3.1)	0.169
Foreign vaccine	3 (0.9)	2 (0.6)	0.499
Adverse events, *n* (%)			
None	212 (66.7)	222 (69.8)	0.443
Injection reaction	34 (10.7)	47 (14.8)	0.122
Fatigue	26 (8.2)	27 (8.5)	0.886
Myalgia	24 (7.5)	36 (11.3)	0.104
Rash	19 (6.0)	3 (0.9)	0.001
Arthralgia	15 (4.7)	0 (0.0)	<0.001
Headache	12 (3.8)	6 (1.9)	0.151
Insomnia	8 (2.5)	0 (0.0)	0.007
Abdominal pain/Nausea/Vomiting	4 (1.3)	1 (0.3)	0.373
Low fever	3 (0.9)	3 (0.9)	1.000
Chills	2 (0.6)	2 (0.6)	1.000
Rheumatologist consulting before vaccination, *n* (%)	182 (57.2)		
Medication adjustment before vaccination, *n* (%)	81 (25.5)		
Disease activity of AIIRDs, *n* (%)			
Aggravation	42 (13.2)		
Alleviation	4 (1.3)		
Stable	272 (85.5)		

Note: Statistical significance was determined by Chi-square (χ^2) test.

Abbreviations: AIIRDs, autoimmune inflammatory rheumatic diseases; NA, not available.

Regarding all participants, most of them were diagnosed at the Dermatology department, followed by the community hospital, the Rheumatology department, the clinic and another department. The main rash location included the vaccinated arm, abdomen, face, back, and buttocks. In addition, all participants were treated with Acyclovir/Valaciclovir. More patients in the AIIRD group took Pregabalin and Gabapentin because of the post-herpetic neuralgia with an insignificant difference (83.3%, 5/6 vs. 40.0%, 2/5, $p = 0.242$). Similarly, there was no statistical difference for the rash duration (18 [12–30] vs. 7 [7–20], $p = 0.157$) and vaccine brand ($p = 0.567$) between the AIIRD and HCs group. In addition, there was no significant difference in gender, age, comorbidities, time to onset of VZV reactivation and dose of COVID-19 vaccine between AIIRD patients and HCs cohort ($p = 0.182$, $p = 0.314$, $p = 0.455$, $p = 0.462$, $p = 1.000$, respectively) (Supporting Information: Table 2).

Notably, for those participants who had VZV reactivation, there were 2/6 (33.3%) AIIRD patients and 1/5 (20.0%) HCs had a prior history of VZV reactivation before getting COVID-19 vaccine. Besides, there was 1 AIIRD patient who had got Varicella-zoster vaccine in the last 5 years. However, there was no participant who had got the HZ vaccine (Supporting Information: Table 2).

To compare the relationship between numbers of treatment and patients with HZ reactivation or rash duration, as well as the relationship between rash duration or comorbidities and postherpetic neuralgia, it is difficult to analyze statistical difference for the small sample size. According to the figure, there seem to be positive relationship between rash duration and medication number or post-herpetic neuralgia (Supporting Information: Figure 1). However, the result still needs further large-sample and multi-center study to clarify.

3.5 | Factors associated with VZV reactivation after COVID-19 vaccination

AIIRD patients were divided into two groups according to VZV reactivation: patients with VZV reactivation (VZV+, $n = 6$) and patients without VZV reactivation (VZV−, $n = 312$). Univariable analysis showed that DM ($p = 0.013$), chronic HBV infection ($p = 0.010$) and medication of MMF ($p = 0.016$) were risk factors in predicting VZV reactivation. To further assess the independent predictors for developing VZV reactivation, a multivariate logistic regression analysis was performed. Of note, DM (OR, 20.69; 95% CI, 1.08–396.79; $p = 0.044$), chronic HBV infection (OR, 24.34; 95% CI, 1.27–466.74; $p = 0.034$), and MMF (OR, 40.61; 95% CI, 3.33–496.15; $p = 0.004$) persisted as independent risk factors for predicting VZV reactivation after COVID-19 vaccination (Table 5).

3.6 | Reported studies about VZV reactivation following vaccination against SARS-CoV-2

There are 18 studies that have reported the VZV reactivation following vaccination against SARS-CoV-2 worldwide, including

TABLE 4 Characteristics of each patient with HZ reactivation after getting COVID-19 vaccine

Variables	AIIRDs patients					
	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Female	Female	Female	Female	Female	Female
Age	69	60	47	32	70	25
BMI (Kg/m^2)	22.2	26.3	22.5	22.0	20.0	30.7
AIIRDs disease	SpA	RA	SLE	SLE	SpA	SLE
Comorbidities	DM	Hyperlipidemia	None	None	DM	None
Medications	/	JAK inhibitor	Steroid, 5 mg/d; HCQ, MMF	Steroid, 2.5 mg/d, MMF	/	Steroid, 2.5 mg/d; HCQ; MMF
Rheumatologist consulting before vaccination	No	No	Yes	Yes	No	No
Medication adjustment before vaccination	No	No	No	No	No	No
Disease activity	Stable	Aggravation	Stable	Aggravation	Stable	Stable
Time to VZV onset after vaccination, days	10	90	30	3	10	120
Vaccination dose associated with rash	Third	Third	Third	Second	Third	Second
Diagnosis department	Community hospital	Other departments	Dermatology	Clinic	Community hospital	Rheumatology
Rash location	Abdomen	Back	Buttocks	Face	Abdomen	Vaccinated arm
Treatments	Acyclovir; Pregabalin	Acyclovir; Gabapentin	Valaciclovi	Acyclovir	Valaciclovi; Pregabalin	Valaciclovi; Gabapentin
Rash durations, days	13	30	20	7	15	30
Postherpetic neuralgia	Yes	Yes	Yes	No	Yes	Yes
Vaccine type	Sinopharm [Vero Cell]-Inactivated COVID-19 vaccination	Sinovac COVID-19 Vaccine (Vero Cell), Inactivated	Sinopharm/WIBP	Sinopharm/WIBP	Sinopharm [Vero Cell]-Inactivated COVID-19 vaccination	Zhifei Longcom
Prior history of Herpes Zoster	No	Yes	No	Yes	No	No
Get vaccination of Varicella zoster vaccine	Yes	No	No	No	No	No
Get vaccination of Herpes zoster vaccine	No	No	No	No	No	No

Abbreviations: AIIRDs, Autoimmune inflammatory rheumatic diseases; BMI, Body Mass Index; DM, Diabetes mellitus; HCQ, Hydroxychloroquine; MMF, Mycophenolate mofetil; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; SPA, Spondyloarthritis.

TABLE 5 Univariate and multivariate analyses for risk factors of VZV reactivation following COVID-19 vaccination

Variables	Univariate analysis			Multivariate analysis		
	VZV + (*n* = 6)	VZV−(*n* = 312)	*p* Value	ORs	95%CI	*p* Value
Gender, female, *n* (%)	6 (100.0)	215 (68.9)	0.183			
Age, year, median (IQR)	33 (31–41)	41 (32–52)	0.228			
AIIRDs type, *n* (%)						
SLE	3 (50.0)	73 (23.4)	0.150			
RA	1 (16.7)	100 (32.1)	0.669			
SpA	2 (33.3)	48 (15.4)	0.240			
Disease duration, year, median (IQR)	12 (2, 14)	6 (2, 10)	0.336			
Medical history, *n* (%)						
Diabetes mellitus	2 (33.3)	8 (2.6)	0.013	20.69	1.08–396.79	0.044
Chronic liver disease	1 (16.7)	10 (3.2)	0.192			
Chronic HBV infection	2 (33.3)	7 (2.2)	0.010	24.34	1.27–466.74	0.034
Medications, *n* (%)						
Corticosteroid	3 (50.0)	101 (32.4)	0.397			
Hydroxychloroquine	2 (33.3)	127 (40.7)	1.000			
Immunosuppressive agents	3 (50.0)	149 (47.8)	1.000			
Mycophenolate mofetil	3 (50.0)	30 (9.6)	0.016	40.61	3.33–496.15	0.004
Biological agents	1 (16.7)	85 (27.2)	1.000			
JAK inhibitor	1 (16.7)	7 (2.2)	0.159			
Prior history of Herpes Zoster, *n* (%)	2 (3)	110 (35.3)	1.000			
Get vaccination of Varicella zoster vaccine, *n* (%)	0 (0.0)	2 (0.6)	1.000			
Get vaccination of Herpes zoster vaccine, *n* (%)	0 (0.0)	4 (1.3)	1.000			

Abbreviations: AIIRDs, Autoimmune inflammatory rheumatic diseases; HBV, Hepatitis B virus; IQR, Interquartile Range; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; SpA, Spondyloarthritis.

6 case reports, 7 case series and 5 cross-sectional studies. The detailed characteristics were presented in Supporting Information: Table 3. Most patients were injected with messenger RNA (mRNA) vaccine and came from western countries, such as the USA, Spain and Turkey. For the cross-sectional studies, the prevalence of VZV reactivation was significantly different, ranging from 0.2% to 10.1%. Notably, Pedro et al. have reported VZV reactivation in rheumatic patients with a prevalence of 0.2%,[9] which was significantly lower than our patients (0.2% vs. 1.9%, $p < 0.001$). For participants with demographic and vaccination information, most of them were female (67.8%, 9336/13773) with a median age of 61 (45, 71) years, and the common vaccine dose was the first dose (63.6%, 1196/1881), followed by the second dose (36.4%, 685/1881). In addition, the time to VZV reactivation was 6 (2–20) days (Table 6).

To compare the difference between our study and other reported studies, we included 20 reported AIIRDs patients and 8 of them had detailed clinical characteristics from 6 studies in a total of 13773 population. Compared to our patients, reported AIIRDs patients had lower rate of SLE patients (5.0%, 1/20 vs. 50.0%, 3/6, $p = 0.028$), shorter time to VZV onset (6 [2–12] vs. 20 [3–160], $p = 0.024$). Moreover, reported AIIRDs patients were mostly suffered from VZV reactivation after the first dose (87.5%, 7/8 vs. 0.0%, 0/6, $p = 0.028$). However, the second (33.3%, 2/6) and third injection (66.7%, 4/6) were the usual risk dose for our patients. In addition, compared to other studies, our patients were younger and had a higher incidence of corticosteroids and MMF. The small sample size may contribute to the insignificant statistical differences ($p = 0.0378$, $p = 0.621$, $p = 0.089$, Table 6).

4 | DISCUSSION

COVID-19 is a global public health crisis with severe disruption to health care and socioeconomical systems.[19] Vaccination is an important tool to prevent COVID-19 infection and was approved emergently to tackle this crisis.[3] Patients with AIIRDs are immunocompromised and have a higher risk of experiencing worse outcomes from COVID-19.[13] However, there is no direct evidence of the safety and efficacy of the COVID-19 vaccine in these patients, which may cause these patients to be unwilling or hesitant to be vaccinated.[5]

TABLE 6 Characteristic differences between our study and reported studies about VZV reactivation.

	Reported studies		Our study	
	All participants (*n* = 13773)	AIIRDs (*n* = 20)	AIIRDs (*n* = 6)	*p* Value[a]
Sex	*n* = 13773	*n* = 8	*n* = 6	
Female, *n* (%)	9336 (67.8)	7/8 (87.5)	6 (100.0)	1.000
Age, years, median (IQR)	61 (45, 71)	65 (36, 73)	54 (30, 69)	0.378
AIIRDs, *n* (%)		*n* = 20	*n* = 6	
SLE		1 (5.0)	3 (50.0)	0.028
RA		10 (50.0)	1 (16.7)	0.197
SpA		1 (5.0)	2 (33.3)	0.123
SS		2 (10.0)	0 (0.0)	1.000
AAV		1 (5.0)	0 (0.0)	1.000
PMR		1 (5.0)	0 (0.0)	1.000
UNK		4 (20.0)	0 (0.0)	1.000
Vaccination dose, *n* (%)	*n* = 1881	*n* = 8	*n* = 6	
First	1196 (63.6)	7 (87.5)	0 (0.0)	0.005
Second	685 (36.4)	1 (12.5)	2 (33.3)	0.538
Third	0 (0.0)	0 (0.0)	4 (66.7)	0.429
Time to VZV onset, days, median (IQR)	7 (3–14)	6 (3–7)	20 (8–98)	0.024
Medications, *n* (%)		*n* = 17	*n* = 6	
Corticosteroid		5 (29.4)	3 (50.0)	0.621
Hydroxychloroquine		4 (23.5)	2 (33.3)	0.632
Mycophenolate mofetil		2 (11.8)	3 (50.0)	0.089
Methotrexate		2 (11.8)	0 (0.0)	1.000
Biological agents				
JAK inhibitor		2 (11.8)	1 (16.7)	1.000
Others[b]		6 (35.3)	0 (0.0)	1.000

Abbreviations: AAV, ANCA-associated vasculitis; AIIRDs, Autoimmune inflammatory rheumatic diseases; IQR, Interquartile Range; PMR, Polymyalgia rheumatic; RA, Rheumatoid arthritis; SLE, Systemic lupus erythematosus; SpA, spondyloarthritis; SS, Sjogren's syndrome; UNK, Unknown/Missing; VZV, Varicella zoster virus.

[a]Statistical significance was compared between AIIRDs groups, and determined by Mann–Whitney *U* test and Chi-square (χ^2) test.

[b]Others biological.

Therefore, evaluating the safety of the COVID-19 vaccines in AIIRDs patients could help governments and rheumatologists to take reasonable measures to increase vaccine coverage and meet the requirements for community immunity. In our study, the incidence of AEs corresponded to 33.3% in patients with AIIRD compared to 30.2% in HCs. Notably, the AEs were minor and there were no serious or major AEs in both groups. Compared to the HCs group, AIIRD patients had higher incidences of rash (6.0%) and arthralgia (4.7%) ($p = 0.001$, $p < 0.001$), and this phenomenon may relate to disease aggravation which is up to 13.2% in our study. In addition, AIIRDs patients had a higher rate of insomnia owing to anxiety ($p = 0.007$). In our previous study, the results demonstrated that 32.9% of AIIRD patients were willing to receive the COVID-19 vaccine, and the others (67.1%) were uncertain or unwilling, and the main hesitation was that the vaccine may aggravate AIIRD disease (63.0%) and may cause vaccine-related AEs (19.9%).[7] Overall, although there was some mild AEs after getting the SARS-CoV-2 vaccines, the inactivated vaccination is safe, and disease aggravation is needed to pay attention in AIIRDs patients.

Recently, VZV reactivation has been reported after COVID-19 vaccines administration, 6 of the studies were case reports, 7 were case series and 5 were cross-sectional studies (Supporting Information: Table 1). Among these cross-sectional studies, the prevalence of VZV reactivation was ranging from 0.2% to 10.1%. In addition, most patients were injected with mRNA vaccine and came from western countries. However, inactivated COVID-19 vaccine is the most

common type approved to be publicly used in China. Therefore, the correlation between VZV reactivation and the inactivated vaccines was still unclear especially in AIIRD patients. In that case, we conducted a web-based, cross-sectional study of AEs and VZV reactivation following the COVID-19 vaccine in 318 AIIRDs patients and 318 HCs from provinces of Hunan, China. Of these participants, 33.3% of AIIRDs patients and 30.2% of HCs reported AEs, and there was no significant difference in the VZV reactivation between these two groups (6, 1.9% vs. 5, 1.6%, $p = 0.761$). In addition, we showed that DM, chronic HBV infection and MMF were independent factors for identifying patients with VZV reactivation, which could help rheumatologists take reasonable measures to avoid this potential risk. To the best of our knowledge, our study represents the first study investigating the prevalence of VZV reactivation after the inactivated vaccine in the AIIRDs patients of China.

VZV, a pathogenic and neurotropic human alpha-herpes virus, can cause varicella (chickenpox) which usually occurs in children primarily.[20] Following primary infection, this virus becomes latent in neurons of cranial nerve ganglia, dorsal root ganglia, and autonomic ganglia.[20] Then, viral can reactivated and cause HZ spontaneously or triggered by some potential factors, which characterizes as painful or pruritic cutaneous vesicular eruptions following typical dermatomal distributions.[20] Notably, owing to diminished cell-mediated immunity (CMI), the older population suffers from a higher risk of VZV reactivation.[21] However, AIIRDs and HCs in our study seem to have younger age than that of reported studies, though the statistical difference is insignificant (Table 4 and Table 6). Given only 6 patients and 5 HCs have reported VZV reactivation, selection and reporting biases may lead to the difference, then, multi-center and large sample size studies were needed to conduct in the future.

CMI plays a critical role in the protection of VZV reactivation.[22] Studies have reported COVID-19 infection can damage the function of CD4+ T cells, natural killer cells, and CD8+ T cells, which may potentially lead to HZ reactivation.[23] However, VZV reactivation following COVID-19 vaccination appears contradictory. Studies reported that increased CD8+ T cell and CD4+ T cells immunity has been clearly documented after the mRNA COVID-19 vaccine. A hypothesis for this paradox has emerged and suggests that VZV CMI are not capable of controlling VZV infection for the massive shift of naïve CD8+ cells.[8] In addition, among vaccinated individuals, induction of type I interferon and proinflammatory cytokines may relate to abrogation of toll-like receptors signaling, which negatively modulates antigen expression and VZV CMI. In our study, AIIRDs and HC patients suffered from VZV reactivation after the second and third dose, in contrast, other reported studies mainly occurred after the first dose. In addition, the median time to VZV onset was longer in our study than that of other studies (20 [8–98] vs. 6 [3–7] days, $p = 0.024$). We suppose that the vaccine-induced specific immunity may have clinical relevance to some extent. Recent studies have compared the difference in immune response between different vaccines, and they demonstrated that mRNA induced higher neutralizing antibodies than inactivated vaccine.[24] However, frequencies of CD4 and CD8+ T cells were higher for the inactivated vaccines than the mRNA vaccines.[24] Given the related study is lacking, it still needs further study to investigate the pathogenesis of VZV reactivation after inactivated COVID-19 vaccine in AIIRDs patients.

Patients with AIIRDs are susceptible to infection for abnormalities of immune system, including leukopenia, lymphopenia, low complement, and dysfunction of immune cells for treatments of corticosteroid, immunosuppressive agents and biological agents.[25] In addition, prior studies reported that dysregulated humoral immunity and weaker VZV-specific cellular immune response might lead to VZV reactivation in RA and SLE patients.[26,27] In our study, there were 6 patients who had VZV reactivation, including SLE, RA, and SpA. For SLE patients, it was reported that the rate of VZV reactivation ranges from 6.4 to 91.4 cases/1000 patient-year, and can occur at all ages.[28] Similarly, prior studies suggested that RA is correlated with a 1.5 to 2-fold higher risk for HZ than healthy older control.[29] Furthermore, the prevalence of VZV reactivation was 11.0 per 1000 patient-years in ankylosing spondylitis patients.[30] Given the higher risk of HZ in AIIRDs patients, the incidence of VZV reactivation corresponded to 1.9% in patients with AIIRD compared to 1.6% in HCs of our study. It may pose the question of whether VZV reactivation following the COVID-19 vaccine was a potential causality or just a pure coincidence.[31]

Except for the susceptible factors of AIIRDs patients, regression analysis has demonstrated some independent risk factors that can contribute to VZV reactivation, including MMF, DM and chronic HBV infection. It is well known that MMF is a widely used immunosuppressive agent for AIIRDs patients. The main mechanism was inhibiting guanosine production and diminishing proliferation of T cells, which can lead to T cell immunity disorder and then contribute to VZV reactivation.[32] Besides, DM patients were susceptible to infections more often than individuals without DM. It was reported that DM patients had impaired VZV-specific CMI.[33,34] To our knowledge, there was no reported study about VZV reactivation and HBV infection. We proposed that exhausted CD8+ T cells or other factors may negatively influence the VZV immunity,[35] and further studies are needed to define the potential pathogenesis of VZV reactivation.

This study had some limitations. First, it was a single-center study from Hunan province with small sample size, as well as a web-based study. All of these could lead to biases in the patients who responded to the survey, and further multi-center studies with a larger cohort will be needed to corroborate our findings. Second, AIIRD patients voluntarily vaccinated have milder disease conditions. Factors that can influence the virus immunity were not included and analyzed, including disease activity of AIIRDs, physiological or psychological stressors and comorbidities. Third, the data collection period of 1 month was short, which might limit comprehensive evolution, especially after the third dose of COVID-19 vaccine. Fourth, we did not concentrate on immunological changes about VZV infection, which could be helpful to understand the immune responses after COVID-19 vaccination and VZV reactivation in AIIRD patients. Therefore, clinical research about AIIRDs disease, stressors and

comorbidities, and pathogenesis research about COVID-19 vaccination and VZV reactivation should be conducted in the future.

5 | CONCLUSION

In conclusion, the inactivated COVID-19 vaccines are safe for AIIRD patients although there was some mild AEs, however there was no significant difference between AIIRD patients and HCs. AIIRD patients could suffer from VZV reactivation after the COVID-19 vaccination. Comorbidities of DM, chronic HBV infection, and medicine of MMF were independent risk factors for VZV reactivation. This information could help rheumatologists recognize risky patients and take reasonable measures. In addition, further clinical trial and pathogenesis research of COVID19 vaccination and VZV reactivation among AIIRD patients is warranted.

AUTHOR CONTRIBUTIONS

Jiali Chen, designed the questionnaire, analyzed the results and wrote the manuscript. Fen Li, Jing Tian, Xi Xie and Yiyue Chen conducted and supervised the survey. Yan Ge designed, supervised and edited the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, Yan Ge (geyan2003@csu.edu.cn), upon reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the Second Xiangya Hospital (K013). All patients gave written informed consent to participate in the study and explicit consent to publish data or images.

ORCID

Yan Ge http://orcid.org/0000-0003-4378-6990

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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