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Hesitancy for SARS-CoV-2 vaccines and post-vaccination flares in patients with systemic lupus erythematosus

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ABSTRACT

Objectives: To study the rate of SARS-CoV-2 vaccination and post-vaccination disease flares in patients with systemic lupus erythematosus (SLE).
Methods: Patients who fulfilled ≥ 4 of the ACR criteria for SLE were identified and their SARS-CoV-2 vaccination status was traced. Flares of SLE at 6-week post-vaccination were reviewed retrospectively. Clinical characteristics of patients with and without vaccination, and those who did or did not experience post-vaccination flares were compared by statistical analyses.
Results: 914 adult patients with SLE were studied (92.5 % women, age 48.6 ± 14.0 years; SLE duration 14.5 ± 8.6 years). Two doses of the SARS-Cov-2 vaccines (61.5 % BioNTech; 38.5 % CoronaVac) were received by 449 (49.1 %) patients. The vaccination rate in SLE was significantly lower than that of the adult general population (77.8 %; $p < 0.001$) at the time of data analysis. Patients who were hesitant for vaccination were more likely to be hypertensive, have a history of neuromuscular manifestations, and a significantly higher organ damage score (1.10 ± 1.45 vs 0.74 ± 1.15; $p < 0.001$). However, none of these factors were significantly associated with vaccine hesitancy on multivariate analysis. Among 449 vaccinated patients, 37(8.2 %) experienced SLE flares: mild/moderate in 34; severe in 3. In an equal number of unvaccinated SLE controls randomly matched for the post-vaccination observation period, 28(6.2 %) had SLE flares: mild/moderate in 17; severe in 11 (odds ratio [OR] for flare in vaccinated patients 1.40[0.81–2.43]; $p = 0.23$, adjusted for age, sex, active serology, SLE duration and prednisolone use). In vaccinated patients, logistic regression revealed that active lupus serology before vaccination (OR 2.63[1.05–6.62]; $p = 0.04$) and a history of arthritis (OR 2.71[1.05–7.00]; $p = 0.04$) or discoid skin lesion (OR 4.73[1.90–11.8]; $p = 0.001$) were associated with SLE flares following vaccination, adjusted for confounders.
Conclusion: Hesitancy for COVID-19 vaccination is common in SLE patients. Vaccination against SARS-CoV-2 is not significantly associated with increased SLE flares. Patients with active SLE serology or a history of arthritis/discoid lesion are more likely to flare after vaccination.

1. Introduction

Systemic lupus erythematous (SLE) is a multisystem autoimmune disease that predominantly affects the younger population. SLE is more prevalent in Asian countries and the mortality ratio compared to age and gender matched controls was estimated to be 5.25 [1]. Survival of SLE has improved in the past few decades and a recent revisit from our group showed that the 10-year cumulative survival of SLE was significantly better in patients diagnosed between 2005 and 2018 as compared to the period between 1995 and 2004 (94.2 % vs 91.0 %) [2]. However, more than 50 % of the deaths were still related to infective complications and there was no significant improvement over time. Thus, in order to further improve the survival of the disease, reduction of infection risk is of paramount importance. In addition to personal hygiene, physical distancing during viral epidemic and judicious use of immunosuppressive drugs, vaccination is an effective means to reduce infection and mortality risk in SLE [3].

Hesitancy for vaccination is well-recognized in SLE, a prototype systemic autoimmune disease [4]. Concerns of vaccine administration in SLE include reports of de novo development of autoimmune diseases post-vaccination, risk of disease flares, safety of the live attenuated types of vaccines, as well as the doubt about the effectiveness of vaccines in patients receiving immunosuppressive medications. As a result, the vaccination rate for pneumococcus and influenza is relatively low in SLE patients [5]. A large propor-

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tion of patients with rheumatic diseases expressed refusal to the COVID-19 vaccines due to concerns for adverse effects and the lack of research data in these patient subsets [6].

The SARS-CoV-2 epidemic has been haunting the whole world for more than 2.5 years. A total of more than 5.9 billion of the global population has been infection and there are more than 6.4 million deaths [7]. Patients with rheumatic diseases tend to have more serious COVID-19 infection. A study during the very early phase of the epidemic showed that patients with SLE, rheumatoid arthritis and skin psoriasis had slightly increased COVID-related mortality [8]. Another study from Spain reported that patients with connective tissue diseases (but not inflammatory arthritis) were independently associated with severe COVID-19 infection (odd ratio 1.8) [9]. The COVID-19 Global Rheumatology Alliance physician-reported registry showed that among 3729 patients with rheumatic diseases who died of COVID-19 infection, independent factors associated with mortality were general factors (increasing age, male sex and comorbidities), disease specific factors (moderate/high disease activity) and immunosuppressive medications such as glucocorticoids and rituximab [10]. Specifically, in patients with SLE, two registry studies have shown that SLE patients infected with COVID-19 had higher rate of hospitalization and intensive care unit admission, as well as 30–90 day mortality, when compared to matched non-SLE patients [11,12].

SARS-CoV-2 vaccine studies in SLE are limited and generally reported lower immunogenicity to the viral spike protein [13–15]. While serious adverse events were rare, SLE flares were reported to occur in 3.1 % to 27 % of patients after vaccination [13,16,17]. However, most to these SLE flares were self-reported and could not be differentiated from those short-term adverse effects related to the vaccines. This prompts the current study which aims to look at the rate of SARS-CoV-2 vaccination in our Chinese SLE patients and post-vaccination clinical disease flares that required therapeutic intervention.

2. Patients and methods

2.1. Study population

The SARS-CoV-2 vaccination program started in February 2021 in our locality and citizens were strongly advised to have vaccination against the global epidemic. Two vaccines are available: the BNT162b2 RNA (Pfizer-BioNTech) and inactivated vaccine (CoronaVac, China). The RNA vaccine is given in two doses 28 days apart whereas the inactivated vaccine is given in two doses 21 days apart. All citizens of Hong Kong are entitled to have free vaccination in designated centers of the city. Specifically, patients with rheumatic disorders are encouraged by our local Rheumatology Society to receive COVID-19 vaccination in order to reduce the chance of having serious COVID-19 infection [18].

A COVID-19 vaccine registry was established by the Government and information was incorporated into the public hospital computer system. We identified patients who fulfilled $\geq$ 4 of the ACR criteria for the classification of SLE [19] and attended our rheumatology and lupus clinics between April 2021 and March 2022. Their COVID-19 vaccination status and the dates of injection were retrieved, along with their clinical information.

Clinical SLE flares post-vaccination were assessed by a retrospective review of individual medical records. The levels of anti-dsDNA and complements (C3/C4) in the clinic visits before the first dose of vaccination and after the second dose of vaccination were also compared. Data were rounded up in April 2022 when the last patient in this study was followed for 42 days after the second dose of vaccine.

To evaluate whether SLE flares were more common after vaccination, the observation period between first dose and 42 days after second dose of the SARS-CoV-2 vaccines in vaccinated patients were randomly assigned to an equal number of unvaccinated patients (n = 449). SLE flares in this control group were compared with those of the vaccinated patients.

This study was approved by the Research and Ethics Committee of our hospital (protocol number NTWC/REC/22045).

2.2. Definition of SLE flares

Post-vaccination clinical SLE flares were defined as those occurred within 42 days of the second dose or 4 weeks within the first dose (if second dose not received) of COVID-19 vaccination, unless they could be explained by the presence of a definite exacerbating factor. Flares of SLE were defined according to flare instrument used in the safety of estrogens in lupus erythematosus, national assessment (SELENA) trials [20,21], with modifications. Change in treatment was required to define a SLE flare. Essentially, mild/moderate flares were defined as new or worsening manifestations (eg. mucocutaneous lesions, arthritis, serositis, constitutional symptoms, mild renal) that required an increase in prednisone dosage to $\leq$ 0.5 mg/kg/day or initiation of therapy with other drugs such as hydroxychloroquine, non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, coupled with an increase in physicians' global assessment (PGA) by $\geq$ 0.5. Severe flares were defined as new or worsening manifestations (eg. neuropsychiatric, renal, hematological) that required prednisone dosage augmentation to greater than 0.5 mg/kg/day or initiation of therapy with cyclophosphamide, azathioprine, mycophenolate mofetil, calcineurin inhibitors or methotrexate, coupled with an increase in PGA to $\geq$ 2.0.

2.3. Outcomes of interest

The primary outcomes of interest were the rate of SARS-CoV-2 vaccination in our SLE patients and the incidence of disease flares 42-days post-vaccination. Secondary outcomes of interest included factors associated with vaccine hesitancy, change in SLE serology before and after vaccination and factors associated with post-vaccination SLE flares.

2.4. Statistical analyses

Unless otherwise stated, values in this study were expressed as mean ± standard deviation (SD). Comparison of data between two groups was performed by the independent Student's *t*-test for continuous variables and Chi-square test for categorical variables (Fisher's exact test was used when the frequency of any cell of the contingency table was $\leq$ 5). Paired Students' *t*-test was used to compare the change in continuous variables before and after vaccination. Factors associated with vaccine hesitancy and SLE flares were studied by separate logistic regression models, with inclusion of essential clinical variables and other covariates with P values of < 0.10 on univariate analyses. Statistical significance was defined as a p value of<0.05, two-tailed. All statistical analyses were performed using the SPSS program (version 18.0 for Windows 10).

3. Results

3.1. Clinical characteristics of patients and vaccination rate

Up to the time of data analysis, 5,239,707 of our local adult population (77.8 %) had received 2 doses of SARS-CoV-2 vaccines [22].

A total of 914 patients with SLE who attended our clinics were studied (92.5 % women, age 48.6 ± 14.0 years; SLE duration 14.5 ± 8.6 years). All were ethnic Chinese. Four hundred and forty-nine (49.1 %) patients had received two doses of the SARS-Cov-2 vaccines (61.5 % BioNTech; 38.5 % CoronaVac). The vaccination rate of SLE patients was significantly lower than that of the general population (p < 0.001).

Table 1 shows the clinical and demographic features of the patients who did and did not receive SARS-CoV-2 vaccination. No significant differences in age, sex and the prevalence of SLE manifestations were observed between the two groups except for a history of myositis or severe neuropsychiatric manifestations that required immunosuppressive therapies. Moreover, patients who were hesitant for vaccination were more likely to be hypertensive (23.4 % vs 17.8 %; p = 0.04) and have a significantly higher cumulative organ damage score (SDI) (1.10 ± 1.45 vs 0.74 ± 1.15; p < 0.001). Patients who did not have vaccination had a higher prevalence of stroke, coronary artery disease or peripheral vascular disease in the past but the difference from the vaccination group was not statistically significant. Unvaccinated patients were more likely to have ever received cyclophosphamide (22.8 % vs 17.4 %; p = 0.04) or calcineurin inhibitors (26.0 % vs 20.0 %; p = 0.03) treatment during the course of the disease. However, logistic regression of clinical variables (P < 0.10 on univariate analysis) did not reveal any factors significantly associated with vaccine hesitancy (data not shown).

Table 1
Clinical characteristics of SLE patients who did or did not receive COVID-19 vaccination.

	Vaccinated (N = 449)	Unvaccinated (N = 465)	P
	Mean ± SD; Number (%)		
Age, years	48.3 ± 13.4	48.8 ± 14.6	0.53
SLE duration, years	14.7 ± 8.6	14.3 ± 8.6	0.51
Women	410 (91.3)	435 (93.5)	0.20
Clinical manifestations (prevalence)			
Arthritis	295 (65.7)	293 (63.0)	0.40
Facial rash	213 (47.4)	221 (47.5)	0.98
Discoid rash	46 (10.2)	54 (11.6)	0.51
Mucosal ulceration	61 (13.6)	68 (14.6)	0.65
Photosensitivity	103 (22.9)	107 (23.0)	0.98
Raynaud's phenomenon	80 (17.8)	90 (19.4)	0.55
Hemolytic anemia	95 (21.2)	111 (23.9)	0.33
Leukopenia (<4,000/mm^3)	151 (33.6)	165 (35.5)	0.56
Thrombocytopenia (<100,000/mm^3)	106 (23.6)	115 (24.7)	0.69
Lymphopenia (<1500/mm^3)	266 (59.2)	300 (64.5)	0.10
Lymphadenopathy	77 (17.1)	81 (17.4)	0.91
*Neuropsychiatric	32 (7.1)	57 (12.3)	0.009
**Renal	227 (50.6)	249 (53.5)	0.36
Serositis	77 (17.1)	97 (20.9)	0.15
Myositis	6 (1.3)	23 (4.9)	0.002
Cutaneous vasculitis	60 (13.4)	63 (13.5)	0.94
Gastrointestinal	34 (7.6)	51 (11.0)	0.08
Secondary thromboembolic APS	27 (6.0)	30 (6.5)	0.78
SLE damage index (SDI)	0.74 ± 1.15	1.10 ± 1.45	<0.001
History of stroke	21 (4.7)	33 (7.1)	0.12
History of coronary heart disease	13 (2.9)	24 (5.2)	0.08
History of peripheral vascular disease	3 (0.7)	8 (1.7)	0.23
History of hypertension	80 (17.8)	109 (23.4)	0.04
History of diabetes mellitus	32 (7.1)	26 (5.6)	0.34
Immunosuppressive medications, ever			
Prednisolone	363 (80.8)	397 (85.3)	0.07
Hydroxychloroquine	326 (72.6)	329 (70.8)	0.53
Azathioprine	219 (48.8)	229 (49.2)	0.89
Mycophenolate mofetil	166 (37.0)	174 (37.4)	0.89
Calcineurin inhibitors	90 (20.0)	121 (26.0)	0.03
Cyclophosphamide	78 (17.4)	106 (22.8)	0.04

SLE = systemic lupus erythematosus; SD = standard deviation; APS = antiphospholipid syndrome; SDI = SLE international collaborative clinic organ damage index.
* those requiring immunosuppressive therapies (eg. psychosis, acute confusional state, neuropathy, mononeuritis multiplex, myelitis, myasthenia gravis).
** according to American College of Rheumatology criteria for renal involvement.

3.2. SLE flares post SARS-CoV-2 vaccination

All patients who received SARS-CoV-2 vaccination had apparent disease quiescence during the first dose of vaccine. Among the 449 vaccinated patients, SLE flares occurred in 37 (8.2 %) patients: mild/moderate in 34 (renal [n = 16], mucocutaneous lesions [n = 13], arthritis [n = 8], serositis [n = 3] and thrombocytopenia [n = 2]) and severe in 3 (renal [n = 2], gastrointestinal [n = 1]) patients. In patients with renal flare post-vaccination, all except one had a history of lupus nephritis and 12 (67 %) had renal biopsy before. Fourteen (78 %) of these patients had active SLE serology before vaccination. Renal biopsy was only repeated in three patients because of patients' reluctance and the service cut-down during the COVID-19 outbreak. All SLE flares responded to the usual treatment regimens.

In the unvaccinated SLE controls (n = 449) randomly matched for the post-vaccination observation period, SLE flares occurred in 28 (6.2 %) patients: mild/moderate in 17 (renal [n = 8], mucocutaneous lesions [n = 11], arthritis [n = 4], serositis [n = 1], hematological [n = 6], neuropsychiatric [n = 2] and ocular [n = 2]) and severe in 11 (renal [n = 6], neuropsychiatric [n = 1], hematological [n = 3] and cutaneous vascular [n = 1]) patients. The rate of SLE flares was not significantly higher in vaccinated than unvaccinated patients (odds ratio [OR] 1.40[0.81–2.43]; p = 0.23; adjusted for age, sex, SLE duration, active serology before vaccination and the use of prednisolone).

3.3. Factors associated with SLE flares after SARS-CoV-2 vaccination

Table 2 and Table 3 show the clinical characteristics, autoantibody profile, lupus serology and immunosuppressive medications

Table 2
Clinical characteristics of SLE patients who did or did not have flares after COVID-19 vaccination.

	SLE flares (N = 37)	No SLE flares (N = 412)	P
	Mean ± SD; Number (%)		
Age, years	42.4 ± 13.4	48.8 ± 13.2	0.008
SLE duration, years	13.2 ± 9.6	14.8 ± 8.5	0.33
Women	34 (91.9)	376 (91.3)	0.90
BioNTech vaccine	23 (62.2)	253 (61.4)	0.93
Clinical manifestations (prevalence)			
Arthritis	31 (83.8)	264 (64.1)	0.02
Facial rash	14 (37.8)	199 (48.3)	0.22
Discoid rash	10 (27.0)	36 (8.7)	<0.001
Mucosal ulceration	8 (21.6)	53 (12.9)	0.14
Photosensitivity	10 (27.0)	93 (22.6)	0.54
Raynaud's phenomenon	10 (27.0)	70 (17.0)	0.13
Hemolytic anemia	7 (18.9)	88 (21.4)	0.73
Leukopenia (<4,000/mm^3)	13 (35.1)	138 (33.5)	0.84
Thrombocytopenia (<100,000/mm^3)	4 (10.8)	102 (24.8)	0.07
Lymphopenia (<1500/mm^3)	24 (64.9)	242 (58.7)	0.47
Lymphadenopathy	7 (18.9)	70 (17.0)	0.77
*Neuropsychiatric	1 (2.7)	31 (7.5)	0.50
**Renal	23 (62.2)	204 (49.5)	0.14
Serositis	10 (27.0)	67 (16.3)	0.10
Myositis	0 (0.0)	6 (1.5)	0.46
Cutaneous vasculitis	4 (10.8)	56 (13.6)	0.63
Gastrointestinal	2 (5.4)	32 (7.8)	0.60

SLE = systemic lupus erythematosus; SD = standard deviation.
* those requiring immunosuppressive therapies (eg. psychosis, acute confusional state, neuropathy, mononeuritis multiplex, myelitis, myasthenia gravis).
** according to American College of Rheumatology criteria for renal involvement.

Table 3
Autoantibodies and medications of SLE patients who did or did not have flares after COVID-19 vaccination.

	SLE flares (N = 37)	No SLE flares (N = 412)	P
Autoantibodies ever	Mean ± SD; Number (%)		
Anti-dsDNA	26 (70.3)	266 (64.6)	0.49
Anti-Ro	26 (70.3)	250 (60.7)	0.25
Anti-La	12 (32.4)	84 (20.4)	0.09
Anti-Sm	14 (37.8)	83 (20.1)	0.01
Anti-nRNP	18 (48.6)	127 (30.8)	0.03
Anti-phospholipid antibody	7/31 (22.6)	105/363 (28.9)	0.45
Lupus serology before vaccination			
Anti-dsDNA titer (IU/ml)	200 ± 212	123 ± 169	0.048
C3 (g/L)	0.81 ± 0.25	0.98 ± 0.28	<0.001
C4 (g/L)	0.17 ± 0.11	0.21 ± 0.10	0.04
Elevated anti-dsDNA*	23 (62.2)	173 (42.0)	0.02
Low C3**	21 (56.8)	124 (30.1)	0.001
Low C4**	22 (59.5)	102 (24.8)	<0.001
Elevated anti-dsDNA or low C3/4	29 (78.4)	240 (58.3)	0.02
Immunosuppressive medications within 6 months before vaccination			
Prednisolone	22 (59.5)	150 (36.4)	0.006
Hydroxychloroquine	24 (64.9)	212 (51.5)	0.12
Azathioprine	4 (10.8)	65 (15.8)	0.42
Mycophenolate mofetil	14 (37.8)	122 (29.6)	0.30
Calcineurin inhibitors	3 (8.1)	35 (8.5)	0.94
Cyclophosphamide	0 (0.0)	0 (0.0)	–
Rituximab	1 (2.7)	2 (0.5)	0.23
Belimumab	0 (0.0)	4 (1.0)	1.00

SLE = systemic lupus erythematosus; SD = standard deviation.
* above 25% of the upper normal range;
** below normal range.

at vaccination in patients who did or did not experience a SLE flares 6-weeks post-vaccination. Patients who experienced flares were significantly younger (42.4 ± 14.1 vs 48.8 ± 13.2; p = 0.008) and were more likely to be receiving glucocorticoid treatment (59.5 % vs 36.4 %; p = 0.006) within 6 months before vaccination. Moreover, patients with history of discoid skin lesions (27.0 % vs 8.6 %; p < 0.001), arthritis (83.8 % vs 64.1 %; p = 0.02), positive anti-Sm/nRNP antibodies and active lupus serology (elevated anti-dsDNA or depressed complements) before vaccination were more likely to flare following SARS-CoV-2 vaccination.

Logistic regression showed that active lupus serology before vaccination (OR 2.63[1.05–6.62]; p = 0.04) and a history of arthritis (OR 2.71[1.05–7.00]; p = 0.04) or discoid skin lesion (OR 4.73[1.90–11.8]; p = 0.001) were associated with SLE flares following vaccination, adjusted for other covariates (Table 4).

3.4. Changes in SLE serology post-vaccination

Among 276 patients who were vaccinated with the BNT162b2 RNA vaccine, the serum anti-dsDNA titer rose significantly from 145 ± 188 to 161 ± 212 IU/ml (p = 0.008). However, the proportion of patients with elevated anti-dsDNA titer to ≥ 25 % of the upper normal range did not change significantly after vaccination (46 % to 48 %; p = 0.61), and so were the levels of complement C3 and C4 (data not shown). In 173 patients who received the inactivated vaccine, anti-dsDNA titer also increased significantly from 106 ± 148 to 130 ± 189 IU/ml (p = 0.004). Similarly, there were no significant increase in the proportion of patients having elevated anti-dsDNA levels post-vaccination (41 % to 43 %; p = 0.66). Again, the levels of complement C3 and C4 did not change significantly (data not shown).

Table 4
Factors associated with SLE flares in vaccinated patients (logistic regression).

Covariates	Relative risk (95 % CI)	P
Age, year	0.97 (0.94–1.01)	0.12
Women	0.81 (0.21–3.05)	0.75
SLE duration, year	0.98 (0.93–1.04)	0.47
RNA vaccine (vs inactivated vaccine)	0.76 (0.34–1.69)	0.50
Active SLE serology before vaccination	2.63 (1.05–6.62)	0.04
Use of prednisolone at time of vaccination	1.95 (0.91–4.19)	0.09
Anti-Sm	1.67 (0.64–4.39)	0.30
Anti-nRNP	1.31 (0.52–3.33)	0.57
History of arthritis	2.71 (1.05–7.00)	0.04
History of discoid skin lesions	4.73 (1.90–11.8)	0.001

*CI = confidence interval; SLE = systemic lupus erythematosus.

3.5. Other major events after SARS-CoV-2 vaccination

In addition to SLE flares, other events experienced by patients within 42 days of the second dose of vaccination included vertigo (n = 2), worsening diabetes mellitus (n = 1), jaw pain (n = 1), syncope (n = 1), herpes zoster reactivation (n = 2), worsening skin eczema (n = 2), plantar fasciitis/tendinitis (n = 2), back pain (n = 1), gastroenteritis (n = 4), chest pain (n = 1), blurring of vision (n = 1), gastric ulcer with bleeding (n = 1) and urinary tract infection (n = 1). However, none of these events were thought to be related to the SARS-CoV-2 vaccines. Four patients did not receive the second dose of SARS-CoV-2 vaccine because of skin rash or worsening of pre-existing non-SLE skin lesions. None of the patients developed anaphylaxis, neuropathy, demyelinating disease or thromboembolism after vaccination.

4. Discussion

Despite the commencement of COVID-19 vaccination program since February 2021 in our locality, the rate of vaccination of the population had been slow. This could be contributed by many factors that included misinformation and fallacies about the harmful effects of vaccination, perceived low risk of infection in the year 2021 resulting from the stringent immigration and quarantine policy of the Government, worry of exacerbation of pre-existing illnesses by vaccines and the lack of vaccine safety data in vulnerable patients. The vaccination rate of the adult population in Hong Kong only reached 78 % at the time of analysis and that of adult SLE patients in our clinics was significantly lower (49.1 %; p < 0.001). SLE patients with a history of severe neuromuscular manifestations, therapies with cyclophosphamide or calcineurin inhibitors, more organ damage, as well as hypertension on treatment were more reluctant to receive COVID-19 vaccination. Although no significant clinical factors were identified from multivariate analyses, this observation reflects patients with more medical co-morbidities, who are indeed more prone to severe COVID-19 infection, are more unwilling to have vaccination. In addition to the above factors, vaccine hesitancy could be related to the inadequacy of personalized recommendation by physicians and propaganda from the Health Department, cultural belief, educational background, socioeconomic status, trust in health care systems, solidarity, previous experience with vaccines and political ideology [23].

The low vaccination rate to COVID-19 in our SLE patients is consistent with an earlier study in our locality. Li et al. [24] conducted a questionnaire study when the COVID-19 infection rate was low in the year 2021 and showed that among 1367 patients with rheumatic diseases (28.1 % SLE), only 30.2 % had received COVID-19 vaccination. SLE patients had lower vaccination rate (16.9 %) than those with rheumatoid arthritis (27.4 %) or spondyloarthritis (28.1 %). Regression analysis showed that SLE was independently associated with no vaccination. The top three reasons for patients not having received the COVID-19 vaccines were fear of side

effects, disease flares and additional side effects due to the underlying rheumatic diseases. A web-based questionnaire survey study from US show that among 243 participants (25 % response rate overall; 28 % SLE patients), 76 % worried a lot or somewhat about contracting COVID-19. Attitudes towards vaccination were favorable, with 92 % having received influenza vaccination in the past and 84 % would like to have COVID-19 vaccine [25]. Recommendation from physicians was an important factor for the acceptance of the COVID-19 vaccines. On the other hand, another web-based survey conducted in South America in late 2020 showed that half of patients with rheumatic diseases expressed unwillingness or uncertainty about COVID-19 vaccination [26].

The hesitancy of SLE patients to various vaccines is observed across different ethnicities. A pooled analysis of studies about influenza vaccine in SLE showed that the vaccination rate was only 40.0 % (33.7 %-46.5 %) [5]. Barriers to vaccination were the lack of doctor recommendation (57.4 %) and concerns over the safety or efficacy of the vaccine (12.7 %). A questionnaire study in US revealed that 69 % of 94 eligible SLE patients had either been recommended or administered the 23-polyvalent pneumococcal vaccine [27]. Age, SLE duration, current use of hydroxychloroquine or mycophenolate mofetil, and rheumatologist's patient volume were correlates of the recommendation or receipt of the vaccine. Among 1130 Latin American patients with SLE who had SLE duration of more than 7 years, the coverage for influenza and pneumococcus vaccination was only 42.7 % and 25 %, respectively [28].

As patients treated with immunosuppressive or immunomodulatory drugs were generally excluded from the pivotal COVID-19 vaccine trials [29], there is a lack of data of the safety of these vaccines in patients with rheumatic diseases. Two studies reported similar adverse event profile of patients with rheumatic diseases as compared to the general population after COVID-19 vaccination [30,31]. In particular, flares of the underlying rheumatic diseases were reported in 5–11 % of patients, which were considered uncommon and reassuring.

The pathophysiology of SARS-CoV-2 infection and SLE shares some similarities. Both involve the activation of certain molecular pathways, including the type I interferon and proinflammatory cytokines [32,33]. The COVID-19 vaccines may trigger these pathways by signaling through the Toll-like receptors, raising the concern of SLE flares after vaccination [34]. Several studies focused on the risk of disease flares in patients with SLE after COVID-19 vaccination [13,35]. Izmirly et al. [13] studied 90 SLE patients who received COVID-19 vaccination and reported similar percentages of patients with abnormal anti-dsDNA and/or complement levels before and after vaccination. Flares occurred in 11.4 % of patients, 1.3 % of which were serious. Another survey of 466 SLE patients in US revealed a flare rate of 8.1 % [36]. However, whether these self-reported flares were actually adverse effects of the vaccines could not be verified. Felten et al. [35] reported disease flares in only 3 % of 696 SLE patients after a median of 3 days following COVID-19 vaccination, leading to treatment change in 71 % and hospitalization in 19 % of these patients. A prospective study of 126 SLE patients showed that vaccination with the BNT162b2 SARS-CoV-2 vaccine was well-tolerated and not associated with statistically significant variations of the BILAG or SLEDAI scores in patients with SLE with active and inactive disease at baseline [37]. The rate of SLE flares (8.4 %) post-COVID-19 vaccination in our study is in keeping with the above studies [13,35]. In fact, most (91 %) SLE flares in our study were mild/moderate and serious flares only occurred in 3 patients (9 %). All flares were confirmed by attending physicians and manageable by change in therapies. Compared with SLE controls matched for the post-vaccination observation period, no significant increase in the incidence of SLE flares was observed. Taken all these data together, the safety of COVID-19 vaccination in SLE patients in terms of disease flares is reassuring. As we observed that patients with active SLE serology and a history of articular and mucocutaneous disease were more prone to disease flares post-vaccination, these patient subgroups should be monitored more closely after COVID-19 vaccination.

Our study has several limitations. First, the sample size of our study and the relatively low number of SLE flares did not allow multivariate analyses of all factors associated with vaccine hesitancy and post-vaccination disease flares. Second, our study was not designed to look at the reasons for vaccine hesitancy in individual patients. Finally, we did not have data on the immunogenicity of the COVID-19 vaccines and the effect of concomitant medications on immunogenicity.

In conclusion, the benefit of the SARS-CoV-2 vaccines far outweighs the risk of side effects or disease flares in patients with SLE. The knowledge that SLE patients with neuromuscular manifestations, organ damage and medical comorbidities tend to be more hesitant to receive COVID-19 vaccination should alert physicians to give extra counseling to these patient subsets. SLE patients should be reassured that disease flares do not occur more commonly after SARS-CoV-2 vaccination. Patients with active serology and a history of arthritis and discoid skin lesions should be monitored more closely for the possibility of SLE flares after vaccination. Recommendations by physicians appear to be the most important measure to alleviate the worries from patients and clarify the fallacies about vaccination.

Declaration

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Data availability

The authors do not have permission to share data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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