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Relapses after SARS-CoV-2 vaccination in patients with neuromyelitis optica spectrum disorder and multiple sclerosis

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ABSTRACT

Background: The COVID-19 pandemic outbreak raises the question of whether immunization is recommended for patients with CNS demyelinating diseases. On the one hand, existing studies suggested that SARS-CoV-2 vaccinations are not associated with increased risk of relapse activity. On the other hand, case reports with acute CNS demyelinating disease post vaccination were emerging and raising clinicians' attention.

Methods: In this longitudinal observational study, we included 556 patients with neuromyelitis optica spectrum disorder (NMOSD) and 280 patients with relapsing-remitting multiple sclerosis (RRMS). Each vaccinated patient was matched to two unvaccinated patients according to age, gender, ARR and immunotherapy status, based on propensity score matching model (PSM). The primary outcome is the short- and medium-term risk of relapse, which were evaluated by Kaplan–Meier analysis between groups.

Results: In our cohort, 649 patients (77.6%) have not yet been vaccinated, mainly due to their concerns about relapse. After PSM, 109 vaccinated patients with NMOSD, 218 PS-matched unvaccinated patients with NMOSD, 78 vaccinated patients with RRMS, and 156 PS-matched unvaccinated patients with RRMS were included in the survival analysis to explore the safety of vaccines, with a median of 9-month follow-up. Following the first vaccination dose, 10 patients with NMOSD (9.2%) and four with RRMS (5.1%) experienced an acute relapse. Meanwhile, in the PS-matched unvaccinated group, 15 patients with NMOSD (6.9%) and 12 patients with RRMS (7.7%) presented with an acute relapse. There was no significant difference between the two curves in both NMOSD and RRMS groups over the course of the observation period. There were no significant differences in demographic characteristics, clinical characteristics, and symptoms of relapses between the vaccinated and PS-matched unvaccinated groups. Post vaccination adverse events (ADE) were reported in 39 individuals (20.9%).

Conclusion: Our results indicate that inactivated SARS-CoV-2 vaccines appear safe for patients with CNS demyelinating diseases.

1. Introduction

With the emergence of COVID-19 pandemic, the world has prioritized SARS-CoV-2 vaccination, which has been proven to be safe and effective in phase 3 trials (Ella et al., 2021, Tanriover et al., 2021, Polack et al., 2020). Currently, there are six types of vaccines against SARS-CoV-2 (Chung et al., 2020) and three of them (mRNA vaccines [Pfizer and Moderna] and vector vaccines [J&J]) have been approved for people with multiple sclerosis (MS) (nationalmssociety). Inactivated vaccines, which are produced by heating or chemically processing the native virus, are replication-defective. There are three widely used brands of inactivated SARS-CoV-2 vaccines in China, including Wuhan Institute of Biological Products (BBIBP-CorV), Sinovac (CoronaVac), and Beijing Institute of Biological Products (Chung et al., 2020, Poland et al., 2020). It remains unknown whether inactivated SARS-CoV-2 vaccines can be recommended for patients with autoimmune diseases (Monschein et al., 2021).

Neuromyelitis optica spectrum disorder (NMOSD) and MS are autoimmune-mediated demyelinating diseases of the central nervous system (CNS) that might lead to potential severe disability. Both diseases are characterized by recurrent attacks of optic neuritis and myelitis. Studies on SARS-CoV-2 vaccines for patients with CNS demyelinating

Abbreviations: NMOSD, Neuromyelitis optica spectrum disorders; MS, Multiple sclerosis.

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diseases suggest that vaccines are safe and that they do not increase the risk of relapse (Lotan et al., 2021, Lotan et al., 2021, Achiron et al., 2021, Ciampi et al., 2022, Alonso et al., 2021, Ali Sahraian et al., 2021). However, the role played by vaccination could be double-edged. Vaccine antigen may provoke an exaggerated autoimmune reaction (Chen et al., 2001, Kivity et al., 2009) and trigger clinical relapses in patients with NMOSD (Apostolos-Pereira et al., 2021) and MS (Michelena et al., 2022). Recently, several cases of acute demyelinating disease of the CNS (optic nerve, brain, and/or spinal cord) following SARS-CoV-2 vaccination have been reported (Pagenkopf & Südmeyer, 2021, Khayat--Khoei et al., 2021, Kaulen et al., 2021, Ismail & Salama, 2021, Chen et al., 2021, Netravathi et al., 2022, Badrawi et al., 2021, Abboud et al., 2020, Fragoso et al., 2022). Thus, cohort studies with larger sample sizes are warranted to investigate the safety of vaccines.

This study aims to: (1) investigate patients' attitudes towards inactivated SARS-CoV-2 vaccines and factors affecting vaccination using questionnaires, (2) explore whether inactivated SARS-CoV-2 vaccines lead to increased risk of relapse in patients with NMOSD and MS using survival analysis; (3) compare the risk for recurrence between vaccinated and propensity score (PS)-matched unvaccinated patients, and (4) determine the incidence rates and types of adverse events (ADE) post-vaccination. This study supplements existing studies on the safety and acceptability of SARS-CoV-2 vaccines.

2. Materials and methods

2.1. Design and patients

From January 2016 to June 2021, we enrolled patients with NMOSD who fulfilled the 2015 IPND criteria for NMOSD (Wingerchuk et al., 2015) or the McDonald 2017 criteria for MS (Thompson et al., 2018) with relapsing-remitting course. The patients with MS recruited between 2016 and 2018 fulfilled the McDonald 2010 criteria (Polman et al., 2011). Moreover, MS diagnosis was confirmed retrospectively according to the 2017 McDonald criteria. All patients were recruited from West China Hospital of Sichuan University, one of the largest medical centers in China serving a patient population comprising over one-fifth of the Chinese population. The clinical data of all the patients were collected and recorded on our database as described (Du et al., 2021, Shi et al., 2020, Chen et al., 2017). The patients were followed up every 3–6 months by routine clinical visits and regular telephone interviews (for patients strictly restricted to wheelchair or bed).

From June 2021 to September 2021, 1170 questionnaires were distributed to patients in our database to identify SARS-CoV-2 vaccination exposure, and 942 of them were recovered. Patients with progressive MS course or myelin oligodendrocyte glycoprotein-IgG associated disorder were excluded due to small sample size. Eight hundred and thirty-six patients were included in the final cohort (Fig. 1) and were followed up for at least 6 months.

Data collection regarding this cohort was approved by the Medical Ethics Committee of the West China Hospital of Sichuan University (2018 trial No. 29). Written informed consent was obtained from all participants.

2.2. Data collection

We collected the following information and entered it into our NMOSD database: age, sex, comorbidities, disease duration, history of relapses, and immunotherapy. Comorbidities refer to any additional co-existing ailment (Feinstein, 1970). We defined disease duration as the time period between NMOSD or MS diagnosis and questionnaire completion. Undergoing immunotherapy was defined as taking rituximab (≥ 180 days), mitoxantrone (≥ 90 days), azathioprine (≥ 30 days), mycophenolate mofetil (≥ 30 days), or oral corticosteroids therapy (≥ 7

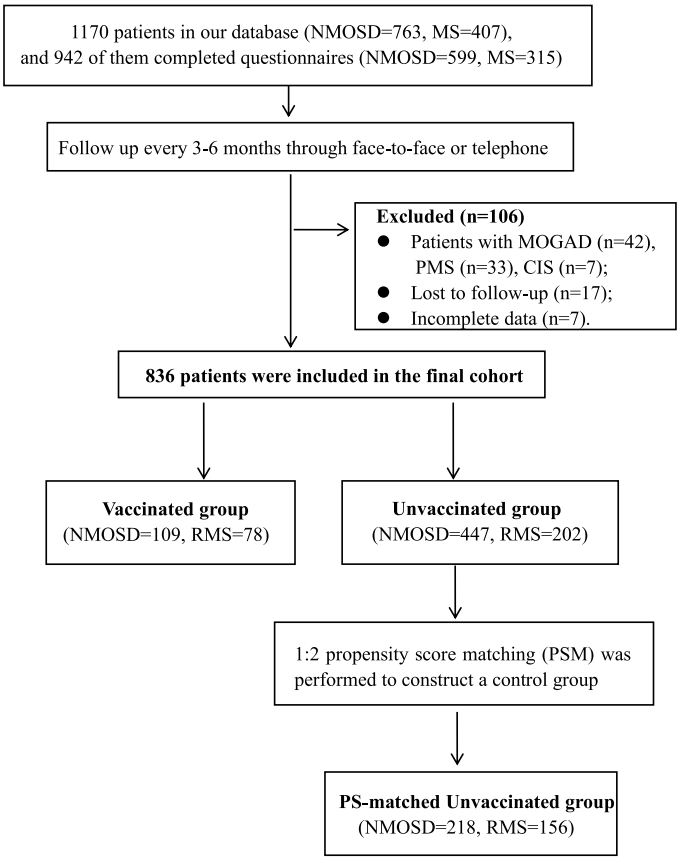

Fig. 1. The flow chart.

days) in NMOSD cases (Stellmann et al., 2017); and disease-modifying therapy (DMT ≥ 180 days) in MS cases (Wang et al., 2016).

Information about vaccination, including vaccine type, date of vaccination, and occurrences of relapses and adverse effects (e.g., pain, redness, or swelling at the injection site; fever; headache; dizziness; fatigue; influenza-like symptoms; gastrointestinal reaction; or other discomfort), was collected using questionnaires. For patients who had not been vaccinated at the time of questionnaire administration, we collected reasons for non-vaccination.

All vaccinated patients were followed up every 3–6 months for any sign of relapse. Once relapse was suspected, a complete neurological investigation (recording history and physical examination) was performed in person. Expanded Disability Status Scale scores were evaluated by two independent neurologists in a blinded manner. Relapse was defined as a patient-reported or objectively observed event typical of an acute inflammatory demyelinating event in the CNS, current or historical, with a duration of at least 24 hours in the absence of fever or infection (Thompson et al., 2018). To distinguish pseudo-relapses from true relapses, the former was defined as cases in which patients experienced only subjective changes, such as numbness, with no change in objective signs, as confirmed by physical examination, Expanded Disability Status Scale assessment, or MRI (Chen et al., 2017).

In this study, all vaccinated patients received inactivated SARS-CoV-2 vaccines enumerated above, with a two-dose schedule.

2.3. Propensity score matching

To exclude the interference of other factors that may affect relapses, we performed propensity score matching (PSM) of baseline characteristics for the unvaccinated and vaccinated groups. PS is defined as the likelihood of a patient being assigned to an intervention group based on a set of covariates (Elze et al., 2017). The estimation algorithm of PS was logistic regression and matching algorithm was k: 1 nearest neighbor matching. The outcome variable was receiving vaccination, and the matching variables were age, sex, annualized relapse rate (ARR), and immunotherapy status (undergoing immunotherapy or not) (Papeix et al., 2021). The caliper width was set at 0.1 to avoid pairing dissimilar individuals, and we finally matched two unvaccinated patients for each vaccinated patient. 2:1 PSM was applied in NMOSD (vaccinated NMOSD=109, PS-matched unvaccinated NMOSD=218) and RRMS groups (vaccinated RRMS=78, PS-matched unvaccinated RRMS=156), respectively, using the R package “MatchIt” (version 4.1.2). The effect of matching was assessed using independent t tests between vaccinated and PS-matched unvaccinated groups, and a p-value > 0.05 was regarded as a “successful” match (Kister et al., 2016).

2.4. Survival analysis

To investigate the effect of SARS-CoV-2 vaccination on the short-term and long-term recurrence risks, survival analysis was used to calculate the relapse-free rate of vaccinated and PS-matched unvaccinated groups. For vaccinated patients, time zero was taken as the date of the first dose of vaccine. For unvaccinated patients, time zero was set as the same time point of the matched vaccinated patients. The endpoint was the date on which the event (first relapse after vaccination) occurred. For event-free participants, the follow-up period ended on the date of the latest recorded visit. The “survival” and “survminer” packages of R (version 4.1.2, R Foundation for Statistical Computing, Vienna, Austria) were used to perform survival analysis and draw Kaplan–Meier survival curves. Hazard ratio, 95% confidence intervals (95% CI), and p-values were calculated using Log-rank (Mantel-Cox) test. Analyses were carried out for different durations of vaccine exposure, 1, 3, 6 months and the entire follow-up period after the date of vaccine exposure, to facilitate comparison with results from previous studies considering short- and long-term risk periods.

2.5. Statistical analysis

Descriptive statistics are presented as total counts and percentages, medians and ranges. The Mann–Whitney U test and the Chi-square test were applied for between-group comparisons. Statistical analysis was performed using Statistical Package for the Social Sciences version 24.0 (IBM, Armonk, NY, USA). Results were considered statistically significant at a p-value < 0.05.

3. Results

3.1. Baseline characteristics

Among the 556 patients with NMOSD and 280 patients with RRMS included in this study, 109 patients with NMOSD (19.6%) and 78 patients with RRMS (27.9%) received the inactivated SARS-CoV-2 vaccines. The remaining 649 patients (77.6%) were not yet vaccinated due to concerns about relapse (59%) or ADEs (10%). There were 234 patients (28%) who were informed by health workers that vaccination was not recommended (Fig. 2).

Among patients with NMOSD, those who were vaccinated had a mean age of 45.15 years, median disease duration of 6.20 years, median ARR of 0.54, and median follow-up time of 9.3 months. Additionally, 88.1% of the patients were undergoing immunotherapy. Unvaccinated and vaccinated patients had similar baseline characteristics, with the exception of the presence of a higher proportion of females in the unvaccinated group (89.3% vs. 80.7%, p=0.015).

Among patients with RRMS, those who were vaccinated had a mean age of 35.85 years, median disease duration of 4.59 years, median ARR of 0.54, and median follow-up time of 9.4 months. Additionally, 39.7% of the patients were undergoing DMT. The unvaccinated patient group had a higher proportion of females (72.8% vs. 60.3%, p=0.030), higher ARR (0.66 vs. 0.54, p=0.026), and higher proportion of patients undergoing DMT (58.4% vs. 39.7%, p=0.030). Demographic and clinical characteristics are presented in Table 1a & 1b.

3.2. Risk of relapse

To decrease the effects of other confounding factors on the relationship between SARS-CoV-2 vaccination and relapses, we included 218 PS-matched unvaccinated patients with NMOSD and 156 PS-matched unvaccinated patients with RRMS as control using 1:2 PSM as described. The occurrence of the first relapse after the SARS-CoV-2 vaccination was plotted on Kaplan–Meier graphs (Fig. 3a &3b). The hazard ratios of the first relapse post vaccination at different time intervals are demonstrated in Table 2. There was no significant difference in relapse risk in both NMOSD and RRMS groups over the course of the observation period (Table 2).

3.3. Features of relapse

Following the first vaccination dose, 10 patients with NMOSD (9.2%) and four patients with RRMS (5.1%) experienced an acute relapse. Regarding NMOSD, a higher proportion of untreated patients was noted in patients with relapse than those without relapse (p=0.038, Table 3). The patients with RRMS and relapse showed a trend towards shorter disease duration than did those without relapse (p=0.048) (Table 3). Details of the patients with relapses post vaccination, severity of relapses, and treatment responsiveness are provided in Supplementary Material Table 2.

Relapses occurred as early as 3 days after vaccination, as late as 7 months after vaccination, and peaked 1–3 months after vaccination. The most common symptoms were visual loss (NMOSD=5, RRMS=1) and limb weakness or numbness sensory (NMOSD=7, RRMS=3) (Table 4). Meanwhile, in the PS-matched unvaccinated group, 15 patients with NMOSD (6.9%) and 12 patients with RRMS (7.7%) experienced an acute

Fig. 2. Reasons for not accepting SARS-CoV-2 vaccines.

Table 1a
Demographic and clinical characteristics between the vaccinated and unvaccinated group in patients with NMOSD.

	Vaccinated NMOSD (n=109)	Unvaccinated NMOSD (n=447)	PS-matched NMOSD (n=218)	P value before PSM	P value after PSM
Mean age (SD)	45.15 (11.94)	45.66 (13.79)	44.94 (14.07)	0.701	0.887
Female, n (%)	88 (80.7)	399 (89.3)	188 (86.2)	**0.015***	0.129
Comorbidities, n (%)	35 (32.1)	171 (38.3)	80 (36.7)	0.140	0.244
Rheumatic diseases	6 (5.5)	42 (9.4)	32 (14.7)	-	-
Endocrine diseases	17 (15.6)	49 (11.0)	22 (10.1)	-	-
Gastrointestinal diseases	5 (4.6)	32 (7.2)	18 (8.3)	-	-
Lung diseases	2 (1.8)	6 (1.3)	6 (2.8)	-	-
Heart diseases	3 (2.8)	24 (5.4)	9 (4.1)	-	-
Renal disease	0 (0)	5 (1.1)	4 (1.8)	-	-
Malignancy	0 (0)	1 (0.2)	1 (0.2)	-	-
Median disease duration (IQR)	6.20 (3.33, 10.56)	5.17(2.59, 8.81)	5.07(2.59, 8.82)	0.083	0.097
Median ARR (IQR)	0.54 (0.35, 0.82)	0.59 (0.39, 0.97)	0.57 (0.39, 0.96)	0.218	0.333
Prebaseline Immunotheray, n (%)	96 (88.1)	413 (92.4)	198 (90.8)	0.106	0.276
Oral corticosteroids	40 (36.7)	275 (61.5)	106 (48.6)	-	-
MMF	72 (66.1)	274 (61.3)	136 (62.4)	-	-
Azathioprine	12 (11.0)	62 (13.9)	31 (14.2)	-	-
Rituximab	4 (3.7)	11 (2.5)	7 (3.2)	-	-
Median Follow-up time (IQR), months	9.3 (7.5, 10.4)	-	9.3 (7.5, 10.4)	-	-

Table 1b
Demographic and clinical characteristics between the vaccinated and unvaccinated group in patients with RRMS.

	Vaccinated RRMS (n=78)	Unvaccinated RRMS (n=202)	PS-matched unvaccinated RRMS (n=156)	*P* value before PSM	*P* value after PSM
Mean age (SD)	35.85 (9.38)	35.17 (12.13)	36.45 (12.84)	0.662	0.719
Female, n (%)	47 (60.3)	147 (72.8)	104 (66.6)	**0.030***	0.205
Comorbidities, n (%)	17 (21.8)	43 (21.3)	29 (18.6)	0.522	0.339
Rheumatic diseases	0 (0)	2 (1.0)	4 (2.6)	-	-
Endocrine diseases	4 (5.1)	12 (5.9)	3 (1.9)	-	-
Gastrointestinal diseases	2 (2.6)	8 (4.0)	5 (3.2)	-	-
Lung diseases	0 (0)	2 (1.0)	2 (1.3)	-	-
Heart diseases	2 (2.6)	5 (2.5)	2 (1.3)	-	-
Renal disease	2 (2.6)	3 (1.5)	3 (1.9)	-	-
Malignancy	0 (0)	2 (1.0)	0 (0)	-	-
Median disease duration (IQR)	4.59 (2.17, 8.21)	3.59 (1.59, 7.34)	3.75 (1.76, 7.74)	0.153	0.513
Median ARR (IQR)	0.54 (0.33, 0.91)	0.66 (0.40, 1.06)	0.63 (0.39, 1.04)	**0.026***	0.098
Prebaseline DMT, n (%)	31 (39.7)	118 (58.4)	104 (66.6)	**0.030***	0.039
Teriflunomide	20 (25.6)	86 (29.2)	80 (51.3)	-	-
Siponimod	4 (5.1)	12 (9.4)	9 (5.8)	-	-
Rituximab	3 (3.8)	7 (2.5)	6 (3.8)	-	-
Fingolimod	2 (2.6)	10 (4.0)	6 (3.8)	-	-
IFN-β	0 (0)	2 (1.0)	2 (1.3)	-	-
Mitoxantrone	2 (2.6)	0 (0)	0 (0)	-	-
Dimethyl fumarate	0 (0)	1 (0.5)	1 (0.6)	-	-
Median Follow-up time (IQR), months	9.4 (7.8, 10.4)	-	9.4 (7.8, 10.4)	-	-

P value before PSM represents the difference between vaccinated patients and unvaccinated patients.
P value after PSM represents the difference between vaccinated patients and PS-matched unvaccinated patients.
* represents a p-value<0.05.

relapse. There were no significant differences in demographic characteristics, clinical characteristics, and symptoms of relapses between the vaccinated and PS-matched unvaccinated groups (Table 4).

3.4. ADEs post vaccination

Eighteen patients with NMOSD (16.5%) and 21 patients with RRMS

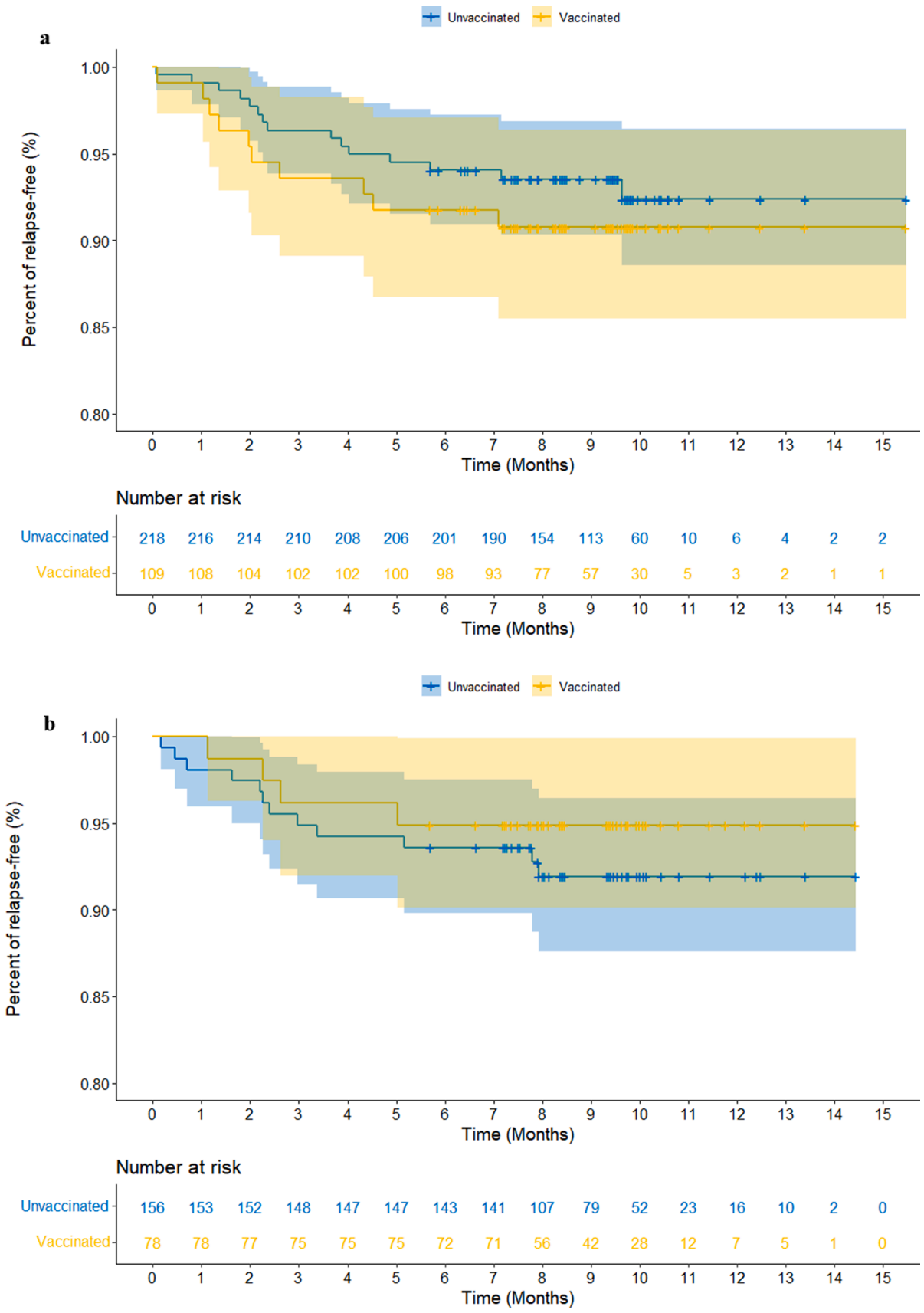

Fig. 3. a: Relapse-free survival curve for vaccinated and unvaccinated PS-matched patients with NMOSD.b: Relapse-free survival curve for vaccinated and unvaccinated PS-matched patients with RRMS.

Table 2
Survival analysis of the effect of SARS-CoV-2 vaccines on relapse in patients with NMOSD and RRMS.

Subgroup	Time period after vaccination	Vaccinated patients Number of patients with a relapse	HR	95% CI	*p* values	PS-matched unvaccinated patients Number of patients with a relapse	HR	95% CI
NMOSD	First 1 month	1	1	(0.09, 11.03)	>0.99	2	1	Reference
	First 6 weeks	4	2.95	(0.61, 14.23)	0.18	3		
	First 8 weeks	4	2.14	(0.49, 9.34)	0.31	4		
	First 3 months	7	1.86	(0.63, 5.46)	0.26	8		
	First 6 months	9	1.44	(0.59, 3.50)	0.42	13		
	The entire study period	10	1.38	(0.60, 31.7)	0.45	15		
RRMS	First 1 month	0	0.22	(0.02, 2.45)	0.22	3		
	First 6 weeks	1	0.68	(0.09, 5.43)	0.72	3		
	First 8 weeks	1	0.54	(0.09, 3.49)	0.52	4		
	First 3 months	3	0.75	(0.22, 2.63)	0.66	8		
	First 6 months	4	0.80	(0.26, 2.39)	0.69	10		
	The entire study period	4	0.68	(0.24, 1.91)	0.46	12		

HR = hazard ratio, and the 95% CI represents the confidence interval of the ratio.
PS-matched unvaccinated patients are the reference group.

Table 3
Demographic and clinical characteristic of patients with and without relapse post vaccination.

	NMOSD (n=109)				RRMS (n=78)				**NMOSD vs. RRMS**
	All vaccinated patients with NMOSD (n=109)	With relapse (n=10)	Without relapse (n=99)	*p*1	All vaccinated patients with RRMS (n=78)	With relapse (n=4)	Without relapse (n=74)	***p*2**	***p*3**
Mean age (SD)	45.15 (11.95)	47.78 (7.00)	44.88 (12.33)	0.467	35.85 (9.83)	29.07 (9.78)	36.22 (9.76)	0.158	**<0.001***
Female, n (%)	88 (80.7)	8 (80.0)	80 (80.8)	>0.999	47 (60.3)	3 (75.0)	44 (59.5)	>0.999	**0.003***
Comorbidities, n (%)	36 (33.0)	6 (60.0)	30 (30.3)	0.079	16 (20.5)	0 (0)	16 (21.6)	0.576	0.069
Mean age at onset (SD)	37.09 (12.64)	39.20 (11.03)	36.88 (12.82)	0.583	29.65 (8.94)	26.56 (6.06)	29.81 (9.07)	0.483	**<0.001***
Median Disease duration (IQR)	6.53 (3.85, 11.02)	5.48 (4.16, 13.36)	6.67 (3.75, 11.01)	0.807	4.95 (2.53, 8.64)	0.62 (0.04, 6.86)	6.67 (3.75, 11.01)	**0.048***	**0.027***
Median ARR (IQR)	0.50 (0.35, 0.72)	0.61 (0.22, 0.90)	0.49 (0.36, 0.71)	0.832	0.51 (0.35, 0.83)	-※	0.49 (0.36, 0.71)		0.709
Prebaseline Immunotherapy, n (%)	93 (85.3)	6 (60.0)	87 (87.9)	**0.038***	40 (51.3)	1 (25.0)	39 (52.7)	0.352	**<0.001***
Patients with ADE post-vaccination, n (%)	18 (16.5)	2 (20.0)	16 (16.2)	0.669	21 (26.9)	1 (25.0)	20 (27.0)	>0.999	0.101
Median Follow-up time (IQR), months	9.47 (8.32, 10.50)	9.2 (7.7, 10.4)	9.5 (8.4, 10.5)	0.672	9.47 (8.05, 10.5)	10.3 (7.8, 13.2)	9.5 (8.1, 10.5)	0.595	0.430

*p*1 represents the difference between patients with relapse and without relapse in NMOSD, *p*2 represents the difference between patients with relapse and without relapse in RRMS, and *p*3 represents the difference between vaccinated patients with NMOSD and RRMS.
※: Since 2 of the 4 RRMS patients (No.11 and 12 in Table 7) with relapse had less than 6 months of disease duration, we cannot calculate the median ARR. The ARR of other 2 patients were 0.34 and 0.85, respectively.

Table 4
Characteristics of vaccinated and PS-matched unvaccinated patients and relapses.

	NMOSD (n=25)			RRMS (n=16)		
	Vaccinated (n=10)	PS-matched unvaccinated (n=15)	p1	Vaccinated (n=4)	PS-matched unvaccinated (n=12)	p2
Mean age (SD)	47.78 (7.00)	40.11 (17.74)	0.147	29.07 (9.78)	33.83 (12.29)	0.496
Female, n (%)	8 (80.0)	13 (86.7)	>0.999	3 (75.0)	10 (83.3)	>0.999
Comorbidities, n (%)	4 (40.0)	4 (26.7)	0.667	0 (0)	4 (33.3)	0.516
Median Disease duration (IQR)	5.48 (4.16, 13.36)	3.77 (1.13, 7.59)	0.062	0.62 (0.04, 6.86)	2.88 (1.73, 7.11)	0.170
Median ARR (IQR)	0.61 (0.22, 0.90)	0.80 (0.40, 1.17)	0.389	1.15 (0.47, 1.47)	0.91 (0.38, 1.92)	0.862
Immunotherapy, n (%)	9 (90.0)	13 (86.7)	>0.999	3 (75.0)	10 (83.3)	>0.999
Symptoms, n (%)						
Visual loss	5 (50.0)	5 (33.3)	0.442	1 (25.0)	4 (33.3)	>0.999
Limb weakness or numbness	7 (70.0)	12 (80.0)	0.653	3 (75.0)	10 (66.7)	>0.999
Ataxia/ Diplopia/ Slurred speech/ Facial numbness/ Frequent choking	0 (0)	0 (0)	-	2 (50.0)	5 (41.7)	>0.999

*p*1 represents the difference between vaccinated and PS-matched unvaccinated patients with NMOSD, *p*2 represents the difference between vaccinated and PS-matched unvaccinated patients with RRMS.

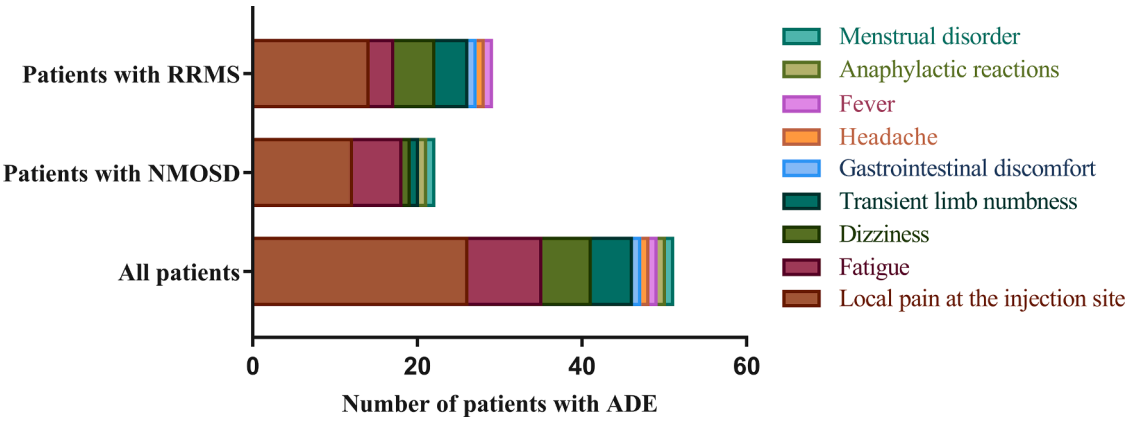

Fig. 4. Rate of ADE following the SARS-CoV-2 vaccines in patients with NMOSD and RRMS.

(26.9%) experienced at least one ADE of varying severity within the first 3 days following the first vaccination dose (Fig. 4). Local pain at the injection site was the most common early reaction and was reported in 28 individuals. Fatigue and dizziness were the most common systemic reactions, followed by transient limb numbness and gastrointestinal discomfort. Other ADEs included headache, fever, anaphylactic reactions, and menstrual disorder, which were experienced by <1% of the study population. All these ADEs were transient, of mild to moderate intensity, and resolved without therapeutic intervention. Details of post vaccination ADE are presented in Supplementary Material Table 3.

4. Discussion

As various types of vaccines have been rolled out, vaccine hesitancy has gradually increased among patients with NMOSD and MS. In this study, questionnaire-based analyses showed that 649 patients (77.6%) had low intention to get vaccinated, mainly due to concerns about relapse. Our results indicated that there was no increased risk of relapses in vaccinated patients within 1, 3, 6 months post vaccination. Therefore, inactivated SARS-CoV-2 vaccines appear safe for patients with CNS demyelinating diseases. The strength of this study is that we used PSM to balance baseline characteristics that might have potentially affected the outcomes.

Some studies indicated that there might be a possible link between vaccine and MS activity within 30 days following vaccination (McDonald et al., 2021, Coyle et al., 2021). However, other studies supported a 6-week interval as an appropriate threshold (Netravathi et al., 2022). Since the time frame of vaccine-related relapses has not been established, we compared the risk of relapse between vaccinated and PS-matched unvaccinated patients at different time intervals.

In our study, over 70% of the enrolled patients have not yet received SARS-CoV-2 vaccine, which may be related to vaccine hesitancy. Vaccine hesitancy is a complex public health issue, and is defined as “delay in acceptance or refusal of vaccines despite availability of vaccine services (MacDonald, 2015). A recent nationwide cross-sectional online survey that included 3,541 responses in China, reported a 54.6% of “probably yes intent” and a 28.7% of “definite yes intent” to receive SARS-CoV-2 vaccine (Lin et al., 2020). Data from patients with MS showed different proportions of vaccine hesitancy, with 23.4% in US (Uhr & Mateen, 2021), 32% in Iran (Nabavi et al., 2022), and 48.3% in the UK (Huang et al., 2021). Few studies have investigated vaccine hesitancy in patients with NMOSD. Xu et al used the Adult Vaccine Hesitancy Scale to investigate 262 patients with NMOSD, and illustrated that patients with NMOSD did not have vaccine hesitancy (Xu et al., 2021). Thus, the limited number of vaccinated patients in our study can also be explained by the study period, which was at the initial stage of vaccination efforts in China.

Studies propose four possible determinants for vaccine hesitancy: vaccine safety, vaccine incident response, unprofessional medical conduct, and parental belief (Yang et al., 2019). Similar to other published studies, our study demonstrated that the main reasons for non-vaccination were concerns about relapse or exacerbation of the disease (59%), followed by physician recommendations (28%) (Uhr & Mateen, 2021, Nabavi et al., 2022, Huang et al., 2021). Therefore, additional high-quality, large-scale, and long follow-up period clinical studies are needed to verify the safety of SARS-CoV-2 vaccines. Table 5 summarized the published safety studies of various types of SARS-CoV-2 vaccines in patients with CNS demyelinating diseases.

In this study, we compared the risk of relapse between vaccinated and PS-matched unvaccinated patients over different time period, and found no increased risk of relapse in patients with NMOSD and RRMS, respectively. Our findings are similar to those reported in mRNA SARS-CoV-2 vaccine studies (Lotan et al., 2021, Achiron et al., 2021). The current safety data on the inactivated SARS-CoV-2 vaccines are available from three studies performed in patients with MS in Iran (Ali Sahraian et al., 2021), Chile (Ciampi et al., 2022) and Latin America (Alonso et al., 2021), with relapse rates of 0.9% (5/583), 3.3% (4/123), and 0.7% (1/150), respectively. We reported a relatively higher relapse rate of 5.1% in patients with MS. Probable reasons are racial differences and a longer follow-up time. The discrepancy could also be associated with the relatively lower DMT treatment rate in our study, which may result in more frequent relapses. Similar to other published studies, the manifestations of relapses were diverse and included visual loss, limb weakness or numbness, facial numbness, and ataxia (Ciampi et al., 2022, Alonso et al., 2021, Ali Sahraian et al., 2021). Additionally, there is a recent report of 8 patients with NMOSD receiving inactivated SARS-CoV-2 vaccines (Jovicevic et al., 2022). In this report, no vaccine-associated NMOSD relapse was confirmed during at least two months of follow-up, indicating overall encouraging safety profile of vaccines in patients with NMOSD.

However, in this study, the hazard ratios were >1 in vaccinated patients with NMOSD and were <1 in vaccinated patients with RRMS at all the time intervals. To explain this finding, we performed survival analysis between vaccinated patients with NMOSD and RRMS (Supplementary Material Table 1). The above differences did not reach statistical significance, possibly due to the limited sample size and the small number of patients who developed the main outcome event of relapse during the observation period. Based on the available data, we are unable to conclude that patients with NMOSD have an increased risk of vaccine-induced relapses compared to patients with RRMS. Further prospective and well-designed studies are needed to evaluate the effect of SARS-CoV-2 vaccines on the relapse risk in patients with CNS demyelinating diseases.

Several limitations of this study should be addressed. First, this study was a single-center observational study of patients mainly from Southwest China, and the results may not be generalized to other countries

Table 5
Overview of the published safety studies of various types of SARS-CoV-2 vaccines in patients with CNS demyelinating diseases.

Author (country, year)	Vaccine type	Design	Number of vaccinated patients	Mean age (SD)	Gender ratio, F (%)	Number of patients with pseudo-relapses post vaccination (%)	Number of patients with relapses post vaccination (%)	Time to relapse	Risk of Relapses	Follow-up	Conclusions
Sahraian MA, et al (Iran, 2021)	Sinopharm BBIBP-CorV (inactivated vaccine)	Cross-sectional study	583 MS	36.2 (8.2)	449 (77.02)	2 (0.34)	5 (0.86)	7 (4-8.5) days	-	2 weeks	-
Achiron A, et al (Israel, 2021)	Pfizer (mRNA vaccine)	Observational study	555 MS (first dose)	18-55 years, 370 (66.7%); >55 years, 185 (33.3%)	364 (65.6)	11 (2.0)	8 (2.1)	16 (10-19) days	-	38 (33-43) days	COVID-19 BNT162b2 vaccine proved safe for MS patients. No increased risk of relapse activity was noted.
			435 MS (second dose)	18-55 years, 274 (63%); >55 years, 161 (37%)	284 (65.3)	21 (4.8)	5 (1.6)	15 (14-21) days	-	20 (15-22) days	
Lotan I, et al (USA, 2021)	mRNA vaccine	Cross-sectional study	404 patients with neuroimmunological diseases[a]	Median age 51 years; range 18-82 years.	366 (83.6)	70 (16.0%) experiencing new or worsening neurological symptoms		First 24h: 20 patients; Within 2-7 days: 40 patients; Within 8-14 days: 6 patients; More than 14 days: 7 patients.	-	-	This survey indicates an overall favorable safety and tolerability profile of the COVID-19 vaccines among persons with rare neuroimmunological diseases.
	Adenovirus vaccine		34 patients with neuroimmunological diseases[a]			10 (2.3%) experiencing new or worsening neurological symptoms			-	-	
Alonso R, et al (Latin American, 2022)	mRNA vaccine	Cross-sectional study	51 MS	41.9 (11.8)	324 (82.4)	2 (3.9), associated with flu-like symptoms		12days; 13 days	-	22.2 ± 23.5 days (first dose); 16.5 ± 19.2 (second dose)	COVID-19 vaccines applied in LATAM proved safe for MS patients.
	Inactivated virus vaccine		150 MS			1 (0.67), associated with flu-like symptoms		15 days	-		
	Adenovirus vaccine		192 MS			2 (1.04), associated with flu-like symptoms		9 days; 25 days	-		
Ciampi E, et al (Chile, 2022)	mRNA vaccine	Ongoing, multicentric, prospective, observational study	51 MS	39.7 (11.2)	121 (68)	-	0	Within 8 weeks	the relapse rate within the 8 weeks before vaccination (11 relapses, 6.2%) and the 8 weeks after vaccination (4 relapses, 2.2%) (Chi-squared 3.41, p = 0.06)	At least 1 year	In this MS patient cohort, inactivated and mRNA vaccines against SARS-CoV-2 appear to be safe, with no increase in relapse rate.
	Inactivated virus vaccine		123 MS			-	4 (2.0)				
	Adenovirus vaccine		4 MS			-	0				
Dinoto A, et al (Italy, 2022)	mRNA vaccine	Retrospective study	30 MOGAD; 26 AQP4-IgG+ NMOSD	47 (range: 23-84)	44 (79)	-	3	85 (10-97) days	-	5 (1-8) months	SARS-CoV-2 vaccination is safe in patients with MOGAD and AQP4-IgG+NMOSD.
König M, et al (Norway, 2022)	mRNA vaccine	Ongoing observational cohort study	130 MS	47.5 (40.6-56.0)	97 (74.6)	-	0	-	-	3-5 weeks	A third dose of the mRNA COVID-19 vaccine was safe.
Jovicevic, V. (Serbia, 2022)	Inactivated virus vaccine	Observational cohort	8 NMOSD	54.4 (11.0)	5 (62.5)	0	0	-	-	2-7 months	Our survey indicates overall favourable COVID-19 outcome and encouraging safety profile of the vaccines in persons with NMOSD.
	mRNA vaccine		1 NMOSD	53.0	1 (100.0)	0	0	-	-	5 months	

[a] represents neuromyelitis optica spectrum disorder (NMOSD), myelin oligodendrocyte antibody-mediated disease (MOGAD), transverse myelitis, recurrent optic neuritis, isolated optic neuritis and acute demyelinating encephalomyelitis (ADEM) in the study of Lotan I et al.

and regions due to the differences in race, region, and type of vaccines. Second, our results are based on a small sample size and limited follow-up periods, which may not be sufficient to determine the impact of inactivated SARS-CoV-2 vaccines on the disease activity of NMOSD and MS in general. Thus, our findings should be validated with prospective and large-scale studies with longer follow-up duration.

In conclusion, our results indicate that inactivated SARS-CoV-2 vaccines are safe for patients with CNS demyelinating diseases and do not appear to increase the risk of relapse within a median of 9-month follow-up. Although our results should be interpreted with caution, it provides useful information for further vaccination initiatives.

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CRediT authorship contribution statement

Lingyao Kong: Methodology, Formal analysis, Investigation, Data curation, Writing – original draft. **Xiaofei Wang:** Methodology, Validation, Formal analysis. **Hongxi Chen:** Investigation, Validation, Data curation. **Ziyan Shi:** Investigation, Data curation, Formal analysis. **Yanlin Lang:** Investigation, Data curation, Formal analysis. **Ying Zhang:** Investigation, Data curation. **Hongyu Zhou:** Conceptualization, Methodology, Validation, Supervision, Writing – review & editing, Funding acquisition.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104167.

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