Prevalence and factors associated with flares following COVID-19 mRNA vaccination in patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis: a national cohort study

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Abstract

Objective To determine prevalence and factors associated with flares post Coronavirus disease 2019 (COVID-19) mRNA vaccination in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA).

Methods A retrospective multi-centre study was conducted (January 2021 to February 2022). Data were collected during index visit, defined as first post-vaccine visit in which the patient had a physician-defined flare, or if at least 3 months had elapsed since first vaccine dose, whichever came first. Factors associated with flares were identified using mixed effects Cox regression and expressed as hazard ratio (HR) and 95% confidence interval (CI).

Results Total of 2377 patients were included (1563 RA, 415 PsA and 399 SpA). Among patients with RA, PsA and SpA, 21.3%, 24.1% and 21.8% experienced a flare respectively. Of those who experienced a flare, only 10.2%, 11.0% and 14.9% were severe in patients with RA, PsA and SpA respectively. Patients with low or moderate/high disease were more likely to flare compared to those in remission in patients with RA only (HR: 1.68, 95% CI 1.22–2.31; HR: 2.28, 95% CI 1.50–3.48, respectively). Receiving the Moderna vaccine was associated with a higher HR of flare compared to the Pfizer vaccine in patients with PsA only (HR: 2.21, 95% CI 1.20–4.08). Patients who had two vaccine doses were found to be less likely to flare (HR: 0.08, 95% CI 0.06–0.10). HRs of flares were not significantly different among RA, PsA and SpA.

Conclusion About one-fifth of patients experienced a disease flare post COVID-19 mRNA vaccination, but most flares were non-severe. Patients with active disease prior to vaccination should be monitored closely for disease flares, especially in patients with RA.

Keywords COVID-19, Autoimmune inflammatory rheumatic diseases, mRNA vaccine, Flares

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Introduction

As compared to the general population, patients with autoimmune inflammatory rheumatic diseases (AIIRD) are more vulnerable to contracting Coronavirus disease 2019 (COVID-19) [1] and are at risk of poorer outcomes [2–4]. Being vaccinated is effective in reducing the risk of COVID-19 and in improving disease-related outcomes such as hospitalisation and mortality in these patients [5–7]. The Pfizer-BioNTech and Moderna vaccines were the first two vaccines approved for use in Singapore and rely on mRNA technology. However, these vaccines bring about a theoretical risk of inducing AIIRD flares—a common barrier against vaccination [8–10]—due to the production of neutralising antibodies and molecular mimicry [11–13]. In addition, the lipid nanoparticles used to encapsulate the mRNA for better vaccine delivery has self-adjuvant properties that might stimulate inflammatory responses [14, 15].

Several observational studies and registries were set up to obtain more data about the safety of COVID-19 vaccinations in patients with AIIRD, which reflected about 2–11% of disease flares [16–20]. However, there were limited studies targeted at patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA) and factors associated with disease flares in these patients. We aimed to determine the prevalence and factors for flares in these patients after receiving the COVID-19 mRNA vaccination.

Patients and methods

Study design and population

This is a sub-study of a multi-centre retrospective cohort study (COronavirus National Vaccine registry for ImmuNe diseases SINGapore) conducted across eight hospitals in Singapore [21], reported in line with the Strengthening of Reporting in Observational studies in Epidemiology (STROBE) guidelines [22] (Additional file 1). Patients clinically diagnosed with RA, PsA or SpA by a rheumatologist, aged 12 years and above and who received at least one dose of an mRNA vaccine (Pfizer-BioNTech or Moderna) were included. National Healthcare Group Domain Specific Review Board approved of this study (Reference number: 2021/00433). Waiver of informed consent was approved for the study.

Data collection

Data were collected from January 2021 through February 2022 through medical records review and entered into an anonymised, secure, online portal. A standardised questionnaire was used for data collection and data fields included the patients' age, sex, race, type of COVID-19 vaccine received, dates of first and second dose of the vaccine, date of post-vaccination index visit, primary diagnosis, physician-defined disease activity prior to vaccination (remission, low, moderate or high disease activity), immunomodulatory/immunosuppressive treatment received at the time of vaccination, whether treatment was interrupted for purposes of the vaccine and whether there was a physician-defined flare at the index visit. We followed-up with participants from their first vaccine dose till index visit, which was defined as the first post-vaccine visit when the patient had flared, or if at least 3 months had elapsed since the first dose of the vaccine, whichever came first. The primary outcome of interest was a physician-defined flare that occurred within 3 months after the first vaccine dose.

If there was a flare, additional data fields included the date of flare, severity of flare, whether hospitalisation was required due to the flare. For patients with SpA and PsA, data on extra-musculoskeletal flares were collected. A mild, self-limiting flare was defined as any flare that did not necessitate treatment escalation or early consult with the rheumatologist, and resolved before the index visit. Moderate flares included any flares that required an early rheumatologist consult and/or increase in treatment (but not exceeding a daily prednisolone dose of 20 mg, requiring intramuscular or intra-articular glucocorticoid injection, initiation of new biological disease modifying anti-rheumatic agents (bDMARDs) or initiation of cytotoxic drugs, such as cyclophosphamide). A severe flare was defined as any flare that required hospitalization, a daily prednisolone dose of more than 20 mg, intramuscular or intra-articular glucocorticoid injection, initiation of bDMARDs or initiation of cytotoxic drugs.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and compared using the Kruskal–Wallis test. Categorical variables were expressed as numbers (percentages), and compared using Chi-square test or Fisher's exact test, as appropriate. Factors associated with flares were identified using multivariable mixed effects Cox regression, while accounting for the clustering effect by Singapore hospital clusters [23], and expressed as hazard ratio (HR) and 95% confidence interval (CI). Potential factors included diagnosis, age, gender, race, disease activity, type of vaccine and number of vaccine doses [16, 18, 24]. Patients who fulfilled the primary outcome (flared within 3 months from first vaccine dose) and who did not flare were included in the mixed effects Cox regression. A sensitivity analysis that included all patients in the regression model was also performed.

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All statistical analyses were conducted using Stata SE 15 (StataCorp LLC, Texas, USA) and a *p* value of < 0.05 was considered to be statistically significant. The design of the online data entry portal ensured that there was no missing data.

Results

Patient characteristics

Patient characteristics are shown in Table 1. A total of 2377 patients were included from January 2021 to February 2022. The median (IQR) age was 62.0 (52.0–71.0)

Table 1 Participant characteristics

	Total (N = 2377)	RA (n = 1563, 65.8%)	PsA (n = 415, 17.5%)	SpA (n = 399, 16.8%)
Age, years, median (IQR)	62.0 (52.0–71.0)	65.0 (58.0–73.0)	59.0 (49.0–68.0)	48.0 (38.0–60.0)
Males, n (%)	820 (34.5)	323 (20.7)	200 (48.2)	297 (74.4)
Race				
Chinese, n (%)	1701 (71.6)	1112 (71.1)	268 (64.6)	321 (80.5)
Malay, n (%)	238 (10.0)	168 (10.7)	48 (11.6)	22 (5.5)
Indian, n (%)	298 (12.5)	186 (11.9)	75 (18.1)	37 (9.3)
Others, n (%)	140 (5.9)	97 (6.2)	24 (5.8)	19 (4.8)
Disease activity before vaccination				
Remission, n (%)	1093 (46.0)	764 (48.9)	169 (40.7)	160 (40.1)
Low disease activity, n (%)	953 (40.1)	632 (40.4)	169 (40.7)	152 (38.1)
Moderate disease activity, n (%)	290 (12.2)	145 (9.3)	72 (17.3)	73 (18.3)
High disease activity, n (%)	41 (1.7)	22 (1.4)	5 (1.2)	14 (3.5)
COVID-19 vaccine type				
Pfizer, n (%)	2082 (87.6)	1387 (88.7)	357 (86.0)	338 (84.7)
Moderna, n (%)	295 (12.4)	176 (11.3)	58 (14.0)	61 (15.3)
Received two vaccine doses, n (%)	2216 (93.2)	1468 (93.9)	381 (91.8)	367 (92.0)
Time from first to second Pfizer dose, days, median (IQR)	21.0 (21.0–22.0)	21.0 (21.0–22.0)	21.0 (21.0–23.0)	21.0 (21.0–24.0)
Time from first to second Moderna dose, days, median (IQR)	28.0 (28.0–32.0)	28.0 (28.0–30.0)	28.0 (28.0–32.0)	29.0 (28.0–35.0)
Treatment with conventional synthetic DMARDs				
Methotrexate, n (%)	1186 (49.9)	921 (58.9)	228 (54.9)	37 (9.3)
Leflunomide, n (%)	217 (9.1)	179 (11.5)	27 (6.5)	11 (2.8)
Sulfasalazine, n (%)	626 (26.3)	426 (27.3)	102 (24.6)	98 (24.6)
Antimalarials (chloroquine/hydroxychloroquine), n (%)	436 (18.3)	423 (27.1)	8 (1.9)	5 (1.3)
Treatment with biological DMARDs				
IL6 inhibitors, n (%)	10 (0.4)	10 (0.6)	0 (0)	0 (0)
IL12/23 inhibitors, n (%)	1 (< 0.1)	0 (0)	1 (0.2)	0 (0)
IL23 inhibitors, n (%)	2 (0.1)	0 (0)	2 (0.5)	0 (0)
IL17 inhibitors, n (%)	32 (1.3)	0 (0)	15 (3.6)	17 (4.3)
TNF inhibitors, n (%)	212 (8.9)	57 (3.6)	78 (18.8)	77 (19.3)
Rituximab, n (%)	5 (0.2)	5 (0.3)	0 (0)	0 (0)
Treatment with JAK inhibitors, n (%)	33 (1.4)	28 (1.8)	2 (0.5)	3 (0.8)
Treatment with immunosuppressants				
Azathioprine, n (%)	10 (0.4)	7 (0.4)	0 (0)	3 (0.8)
Cyclophosphamide, n (%)	3 (0.1)	2 (0.1)	1 (0.2)	0 (0)
Cyclosporine, n (%)	26 (1.1)	10 (0.6)	15 (3.6)	1 (0.3)
Mycophenolate mofetil/mycophenolic acid, n (%)	7 (0.3)	7 (0.4)	0 (0)	0 (0)
Tacrolimus, n (%)	1 (< 0.1)	1 (0.1)	0 (0)	0 (0)
Treatment with glucocorticoids, n (%)	844 (35.5)	749 (47.9)	65 (15.7)	30 (7.5)
Treatment interruption, n (%)	14 (0.6)	8 (0.5)	4 (1.0)	2 (0.5)

COVID-19 Coronavirus disease 2019, *DMARDs* disease modifying antirheumatic agents, *IL* interleukin, *IQR* interquartile range, *JAK* Janus kinase, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *TNF* tumour necrosis factor

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years and 820 (34.5%) were male subjects. Out of all patients, 1701 (71.6%) were Chinese, 1093 (46.0%) were in disease remission before vaccination, 2082 (87.6%) received the Pfizer vaccine and 2216 (93.2%) received two vaccine doses in total. Only 14 (0.6%) had interruption of treatment due to the vaccine.

In terms of disease modifying anti-rheumatic drugs (DMARDs), patients with RA and PsA were mostly on methotrexate (58.9% and 54.9% respectively), whilst patients with SpA were mostly on sulfasalazine (24.6%). In terms of biological DMARDs, majority of patients were on TNF inhibitors (RA: 3.6%, PsA: 18.8%, SpA: 19.3%).

Information regarding flares

Information regarding flares (no flare, flared within 3 months from first dose and outside of 3 months from first dose) is shown in Tables 2 and 3. The median (IQR) follow-up duration from the first vaccine dose to index visit was 4.4 (3.5–5.5) months, of which 1857 (78.1%) did not experience a flare, and the prevalence of flare was not significantly different between the three groups. Five-hundred and twenty (21.9%) flares were observed over 10,362.8 patient-months of follow-up (incidence rate of 5.0/100 patient-months), of which 325 (13.7%) experienced a flare within 3 months from the first vaccine dose and 195 (8.2%) flared outside of the 3 months' time

Table 2 Information of all flares in the entire patient cohort

	Total (N = 2377)	RA (n = 1563, 65.8%)	PsA (n = 415, 17.5%)	SpA (n = 399, 16.8%)	p value*
Flare					0.70
No flare, n (%)	1857 (78.1)	1230 (78.7)	315 (75.9)	312 (78.2)	
Flare within 3 months from first dose, n (%)	325 (13.7)	206 (13.2)	66 (15.9)	53 (13.3)	
Flare outside of 3 months from first dose, n (%)	195 (8.2)	127 (8.1)	34 (8.2)	34 (8.5)	
Time from first vaccine dose to flare, months, median (IQR)	2.1 (1.0–3.9)	2.0 (1.1–3.9)	2.1 (0.7–3.7)	2.2 (1.1–4.2)	0.37
Number of vaccine doses before flare					0.07
One dose, n (%)	107 (4.5)	62 (4.0)	29 (7.0)	16 (4.0)	
Two doses, n (%)	413 (17.4)	271 (17.3)	71 (17.1)	72 (17.8)	
COVID-19 vaccine type by patients who flared					0.04
Pfizer, n (%)	440 (18.5)	292 (18.7)	79 (19.0)	69 (17.3)	
Moderna, n (%)	80 (3.4)	41 (2.6)	21 (5.1)	18 (4.5)	
Severity of flare					0.37
Mild and self-limiting, n (%)	124 (5.2)	72 (4.6)	27 (6.5)	25 (6.3)	
Mild to moderate, non-self-limiting, n (%)	338 (14.2)	227 (14.5)	62 (14.9)	49 (12.3)	
Severe, n (%)	58 (2.4)	34 (2.2)	11 (2.7)	13 (3.3)	
Flares requiring treatment escalation, n (%)	362 (15.2)	248 (15.9)	64 (15.4)	50 (12.5)	0.25
Flares requiring hospitalisation, n (%)	17 (0.7)	10 (0.6)	6 (1.4)	1 (0.3)	0.16

IQR interquartile range, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

Table 3 Presentation of all flares

	Total (n = 520)	RA* (n = 333)	PsA (n = 100)	SpA (n = 87)
Peripheral arthritis, n (%)	442 (85.0)	333 (100)	67 (67.0)	42 (48.3)
Inflammatory back pain, n (%)	45 (8.7)	–	4 (4.0)	41 (47.1)
Buttock pain– sacroiliitis, n (%)	15 (2.9)	–	2 (2.0)	13 (14.9)
Enthesitis, n (%)	9 (1.7)	–	6 (6.0)	3 (3.4)
Dactylitis, n (%)	5 (1.0)	–	4 (4.0)	1 (1.1)
Skin rashes, n (%)	39 (7.5)	–	37 (37.0)	2 (2.3)
Uveitis, n (%)	9 (1.7)	–	1 (1.0)	8 (9.2)
Nail changes, n (%)	3 (0.6)	–	2 (2.0)	1 (1.1)

*All patients with rheumatoid arthritis were considered to have a flare of peripheral arthritis

PsA psoriatic arthritis, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

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frame. The median (IQR) time to flare for all patients was 2.1 (1.0–3.9) months and was not significantly different between the three groups.

Amongst patients who experienced a disease flare, 107 (20.6%) had a flare after one vaccine dose while 413 (79.4%) flared after two doses. Four-hundred and forty (84.6%) had the Pfizer vaccine and 80 (15.4%) had Moderna. Only a minority had a severe flare (RA: 10.2%, PsA: 11.0%, SpA 14.9%). Of the patients that had a disease flare, majority required treatment escalation (RA: 74.5%, PsA: 64.0%, SpA 57.5%) while few required hospitalisation (RA: 3.0%, PsA: 6.0%, SpA 1.1%). Amongst patients with RA who flared, all had flare of peripheral arthritis. Patients with PsA mainly had flare of peripheral arthritis (67.0%) and psoriasis (37.0%), whilst patients with SpA mainly had flare of peripheral arthritis (48.3%) and inflammatory back pain (47.1%).

Factors associated with flares after vaccination

Factors associated with flares after vaccination are shown in Table 4 and Fig. 1. Higher disease activities in patients with RA before vaccination were associated with experiencing a flare, where patients with low or moderate/high disease activities were more likely to flare compared to those in remission (HR: 1.68, 95% CI 1.22–2.31; HR: 2.28, 95% CI 1.50–3.48, respectively). Disease activity was not correlated with risk of flare in patients with PsA and SpA.

Patients who received the Moderna vaccine were more likely to flare compared to those who received the Pfizer vaccine in patients with PsA (HR: 2.21, 95% CI 1.20–4.08), but not in patients with RA and SpA. Patients who had two vaccine doses were found to be less likely to flare (HR: 0.08, 95% CI 0.06–0.10), and this was not significantly different across the three groups. Results from the sensitivity analysis were largely similar (Additional file 2). Compared to RA, the hazard ratio of disease flare was not significantly different in patients with PsA or SpA.

Multivariable mixed effects Cox regression analyses were conducted to identify factors associated having a flare, while accounting for the clustering effect by Singapore hospital clusters. Patients who fulfilled the primary outcome (flared within 3 months from first vaccine dose) and who did not flare were included in the analyses.

Discussion

The prevalence of a flare was seen in 21.3%, 24.1% and 21.8% of patients, and severe flares occurred in 10.2%, 11.0% and 14.9% of the patients with RA, PsA and SpA respectively. This study reported a higher rate of flare

Table 4 Factors associated with flares after vaccination (n = 2182) *

Variables	HR	95% CI
Diagnosis		
Rheumatoid arthritis	ref	
Psoriatic arthritis	1.29	0.96–1.72
Spondyloarthritis	0.83	0.58–1.18
Age	1.00	0.99–1.01
Female sex	1.04	0.81–1.34
Chinese race	1.07	0.83–1.37
Disease activity before vaccination		
Remission	ref	
Low disease activity	1.55	1.20–2.01
Moderate and high disease activity	1.98	1.43–2.74
COVID-19 vaccine type		
Pfizer	ref	
Moderna	1.38	1.03–1.86
Two vaccine doses before index visit	0.08	0.06–0.10

*A multivariable mixed effects Cox regression analysis was conducted to identify factors associated having a flare, while accounting for the clustering effect by Singapore hospital clusters. Patients who fulfilled the primary outcome (flared within 3 months from first vaccine dose) and who did not flare were included in the analysis

CI confidence interval, *COVID-19* Coronavirus disease 2019, *HR* hazard ratio, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

compared to previous studies, where rates ranged from 2 to 11%, possibly due to differences in study methodologies. Previous studies required a change in medication or outpatient consultation to be considered as a flare, or were voluntary reports by patients or physicians, or had a shorter follow-up period from vaccination to index visit (7 days–3 months) [16–20]. In our study however, flares were physician-defined and included those that were mild and self-limiting in nature and did not require up-titration of treatment.

Local guidelines for patients with rheumatic diseases advised that interruption of immunomodulatory drugs for the purposes of COVID-19 vaccination is not necessary, with the exception of rituximab [25]. About 0.6% of patients in this study had treatment interruption during vaccination, which was higher than the percentage of patients receiving rituximab (0.2%). A possible reason might be that patients stopped their medications prior to vaccination without consulting their physicians [26, 27].

This study identified patients with higher disease activities prior to vaccination as being more likely to flare, similar to previous studies which showed that having a flare 6–12 months prior to receiving the vaccine was associated with experiencing a flare thereafter, and that stable disease activity was a negative predictor of flares [20, 28–30]. Amongst patients who flared, only 11.2% and 3.3% of patients experienced severe flares and flares
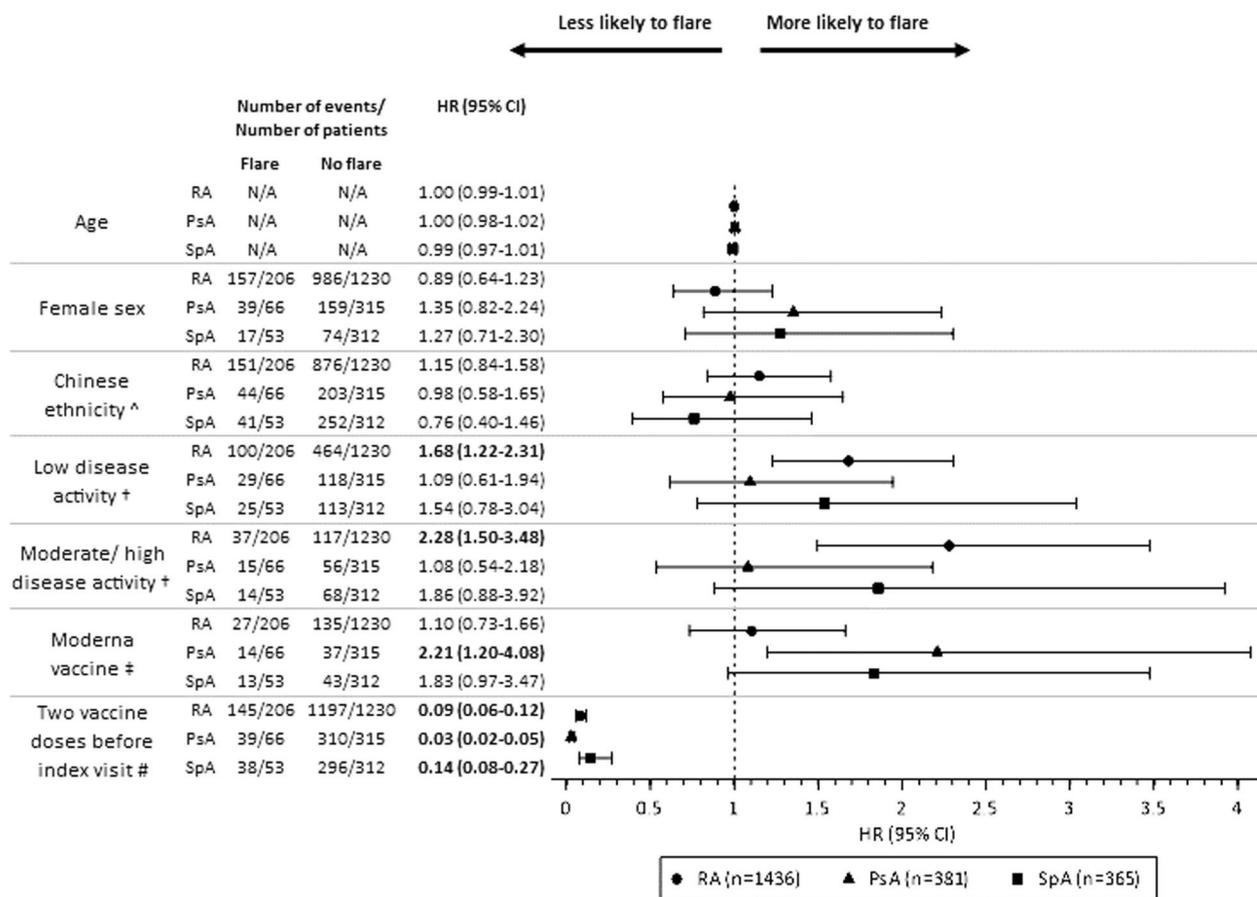
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Fig. 1 Factors associated with flares after vaccination, by disease type

requiring hospitalisation, respectively, and this supports recommendations from both local and international guidelines that advocate for the safety of vaccination in patients with active disease, except in patients afflicted with life-threatening illnesses [25, 31, 32].

Patients who took the Moderna vaccine were also found to be more likely to flare, possibly due to the higher mRNA content in the Moderna vaccine [33, 34], although prior studies did not prove disease flares to be associated with the type of mRNA vaccine [19, 35]. Receiving two doses of the vaccine was also associated with a lower risk of flare, possibly because patients who experienced adverse events after the first vaccination would be less likely to proceed with the second dose. However, 17.4% of all patients flared after the second dose and

might highlight the need for close monitoring of patients even if they did not experience any adverse events after the first dose. Age was not found to be associated with experiencing a flare, in contrast with another study which showed that being elderly was a risk factor for a flare of underlying AIIRDs [28]. In this study, we did not observe significant differences in the hazard ratios for flares between patients with RA, PsA or SpA, in contrast to the Global Rheumatology Alliance registry, which found that patients with PsA were more likely to flare as compared to RA [16].

Strengths of this study include the large sample size and the inclusion of patients of a large age range, which increases the generalisability of results. Patient demographics were also similar to previous reports [36, 37]. We

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required the index visit to be at least 3 months after the first vaccine dose for cases with no flares to ensure a sufficient observation period. Flares not requiring a change in treatment were also included to obtain a more comprehensive spectrum of data as some patients might not seek a change in medication for their flares [38]. The study was also conducted using a detailed chart review rather than just using administrative data collected, and flares were physician-defined and documented in the clinical notes.

Given the retrospective nature of this study, results are prone to information bias and there are also several limitations which restrict the interpretation of results. There was no control group (non-vaccinated patients with AIIRD). Given the rigorous vaccination efforts conducted locally in line with national policies, the numbers of unvaccinated individuals in Singapore were low (only 7% of population unvaccinated) [39]. Also, no causal relationships between taking the vaccine and experiencing a flare can be deduced from this study. As this study was initiated after the COVID-19 pandemic, data of flares prior to the pandemic and vaccination were unavailable, which might restrict the interpretation of findings from this study. Although previous literature had reported on the background rates of flares before vaccine availability [38, 40, 41], definitions of flare were heterogenous and no definitive comparisons could be made. In addition, myalgias and arthralgias are well described side effects of the mRNA vaccines, which could be mistaken to be a disease flare. Adverse events which could overlap with manifestations of rheumatic diseases were also not collected. However, we had aimed to reduce any misclassification by using a physician-defined flare as the outcome of interest as well as a standardised questionnaire for data collection. Prior to study initiation, a consensus meeting was held and practice cases were also used to harmonise definitions of pre-vaccine disease activity and adjudication of flare. Although we collected details of the dates of the first and second vaccinations, data collection was truncated after the first flare. For patients who flared after the first dose, we were unable to determine the prevalence and severity of flares should they proceed with the second dose, which might be important information to patients. Data for other potential confounders such as comorbidities were also not collected in this study [42].

Conclusions

This study showed that about one in five patients with RA, PsA and SpA experienced a disease flare post COVID-19 mRNA vaccination, but most flares were non-severe. Patients with active disease prior to vaccination should be more closely monitored for disease flares post-vaccination, especially for patients with RA.

Abbreviations

AIIRD	Autoimmune inflammatory rheumatic diseases
CI	Confidence interval
COVID-19	Coronavirus disease 2019
DMARDs	Biological disease modifying anti-rheumatic drugs
HR	Hazard ratio
IQR	Interquartile range
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
SpA	Spondyloarthritis
SD	Standard deviation
STROBE	Strengthening of Reporting in Observational Studies in Epidemiology
TNF	Tumour necrosis factor

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42358-023-00316-0.

Additional file S1: STROBE Statement—Checklist of items that should be included in reports of cohort studies

Additional file S2: Sensitivity analysis for factors associated with flares*

Declarations

Ethics approval and consent to participate
This study was approved by National Health Group Domain Specific Review Board (Reference number: 2021/00433). Waiver of consent was approved for this study.

Consent for publication
Not applicable.

Competing interests
WF: Speakers bureau: Abbvie, DKSH, GSK and Novartis; THW: None declared; LCC: Speakers bureau: Pfizer and Abbvie, Consultant of: Pfizer and Abbvie Advisory Board meetings, Grant/research support: Abbvie educational grant; ALow: Speakers bureau: Boehringer Ingeilheim, Consultant of: Boehringer Ingeilheim and J&J consultant/ steering group committee; ALaw: None declared; YJP: None declared; SIY: Grant/research support: Multiple pharmaceutical companies for the support of the National Biologics Registry; YYL: Speakers bureau: Abbvie, DKSH, Jassen, Novartis and Pfizer; MM: Grant/research support: Multiple pharmaceutical companies for the support of the National Biologics Registry; AS: Speakers bureau: Amgen Talk, Consultant of: Pfizer ad board; KOK: None declared; CX: None declared; GGT: Speakers bureau: Boehringer Ingleheim; AM: Speakers bureau: J&J and GSK, Grant/research support: GSK—the supported studies programme; SHT: None declared; TYC: None declared; NER: None declared; SA: Speakers bureau: Boehringer Ingeilheim, Consultant of: Abbvie and DKSH; KFP: None declared; MS: None declared; TCT: None declared; PC: Consultant of: Boehringer Ingleheim ad board, Novartis, Janssen and Abbvie, Grant/research support:

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