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COVID-19 vaccination and systemic autoimmune rheumatic diseases: No evidence of disproportionately increased reporting in VAERS

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ABSTRACT

Objectives: To investigate whether systemic autoimmune rheumatic diseases (SARDs) were disproportionately reported as adverse events following COVID-19 vaccination compared with other vaccines, using data from the Vaccine Adverse Event Reporting System (VAERS).
Methods: We conducted a retrospective disproportionality analysis of VAERS reports collected between December 2020 and December 2024. Reports were identified using a structured query based on MedDRA terms for specific SARDs, including polymyalgia rheumatica, giant cell arteritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, myositis, and other vasculitides. For each disease, the proportional reporting ratio (PRR), reporting odds ratio (ROR), and Bayesian information component (IC) were calculated, comparing COVID-19 vaccines (BNT162b2, mRNA-1273, Ad26.COV2.S) with all other vaccines in VAERS. Analyses were further stratified by sex to explore consistency.
Results: Among approximately 680,000 valid adverse event reports, encompassing both COVID-19 and non–COVID-19 vaccines, no significant disproportionality signal was identified for any SARD. Polymyalgia rheumatica, giant cell arteritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, and myositis showed no evidence of disproportionate reporting following COVID-19 vaccination. The category "other vasculitides" displayed a lower reporting frequency following COVID-19 vaccination compared with other vaccines. Stratified analyses yielded consistent findings across sex subgroups.
Conclusion: In a large national pharmacovigilance dataset, COVID-19 vaccines were not associated with a disproportionate increase in reports of any SARD. These results support the favorable safety profile of COVID-19 vaccines with respect to autoimmune rheumatic events, while highlighting the value of ongoing post-marketing surveillance for rare immune-mediated reactions.

Introduction

The Vaccine Adverse Event Reporting System (VAERS) was created in 1990 as a joint initiative of the U.S. Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) to enable passive post-marketing surveillance of all vaccines authorized for human use in the United States [1]. This open-access pharmacovigilance platform collects spontaneous reports describing suspected adverse events following immunization (AEFI), encompassing a wide spectrum of clinical manifestations, including systemic, autoimmune, and musculoskeletal reactions.

According to the World Health Organization (WHO), an AEFI refers to *"any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine; the event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease"* [2]. This definition highlights the

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importance of distinguishing true vaccine-related reactions from coincidental medical conditions, a task that becomes particularly challenging within large-scale immunization programs. Vaccination remains one of the cornerstones of modern public health, having dramatically reduced global morbidity and mortality from infectious diseases over the past decades [3]. Since the 1960s, the widespread implementation of national immunization programs has virtually eliminated numerous life-threatening infections, particularly in childhood [4]. The emergence of COVID-19, caused by the novel coronavirus SARS-CoV-2, led to an international effort to design and deploy effective vaccines within a very short timeframe [5]. By late 2020, the U.S. FDA had granted emergency authorization for three COVID-19 vaccines—BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen/-Johnson & Johnson)—marking the beginning of the largest vaccination campaign in history [6].

The unprecedented scale and speed of the global COVID-19 vaccination campaign, which reached billions of individuals within months, has resulted in an equally remarkable volume of safety data [7]. The large number of vaccinated people and the extensive use of post-marketing surveillance systems, such as VAERS, have made it possible to identify and characterize a wide range of AEFIs, including those suggestive of autoimmune or immune-mediated phenomena [8].

Beyond the reports of inflammatory joint disorders occurring after SARS-CoV-2 infection, several authors have reported cases of systemic autoimmune rheumatic diseases (SARDs) occurring in temporal association with COVID-19 vaccination [9,10]. Among these, Ursini et al. described polymyalgia rheumatica (PMR) as the most frequently observed rheumatic condition following vaccination, accounting for nearly one-third of new-onset inflammatory rheumatic diseases in their multicenter cohort [11]. Other SARDs, including vasculitides, systemic lupus erythematosus (SLE), and myositis, have been documented less commonly but with consistent clinical features across independent reports. A systematic review collected over 150 cases of vaccine-associated vasculitis, predominantly of cutaneous, ANCA-associated, or IgA type, typically appearing within two weeks after vaccination and resolving with corticosteroid therapy [12]. In addition, isolated cases of giant cell arteritis (GCA) developing shortly after COVID-19 immunization have been published, some with biopsy confirmation and long-term follow-up, further supporting the need for continued vigilance in older adults [13,14]. Case reports have described new-onset SLE or lupus-like syndromes after COVID-19 vaccination, characterized by cutaneous, renal, or articular manifestations and serologic positivity for antinuclear antibodies (ANA) and anti–double-stranded DNA (anti-dsDNA) antibodies [15,16]. In addition, cases of myositis, some associated with anti–melanoma differentiation-associated gene 5 (anti-MDA5) or anti–transcription intermediary factor 1-γ (anti-TIF1-γ) antibodies, have been reported after COVID-19 immunization [17,18].

While most cases of autoimmune or inflammatory manifestations following COVID-19 vaccination appear to be coincidental, it is noteworthy that similar syndromes have occasionally been reported after other immunizations, including influenza, hepatitis B, and herpes zoster vaccines, suggesting that vaccination may act as a transient immune trigger in predisposed individuals rather than a unique phenomenon of COVID-19 immunization [19–24].

Although these occurrences remain exceedingly rare compared to the massive number of vaccine doses administered, their reproducibility across distinct autoimmune phenotypes has drawn attention to potential shared mechanisms of immune activation and underscored the importance of systematic pharmacovigilance analyses to better delineate the spectrum of vaccine-associated SARDs. Having demonstrated the absence of disproportional reporting for inflammatory arthritis after COVID-19 vaccination, we sought to explore whether other SARDs might display different patterns of association within the VAERS database [25]. Confirming a similar absence of signal across the broader spectrum of SARDs would further strengthen the evidence supporting the vaccine's safety.

Materials and methods

Data source

The present analysis was based on data retrieved from VAERS, a platform for collecting reports of suspected AEFIs, which can be submitted by healthcare professionals, vaccine recipients, caregivers of pediatric patients, vaccine manufacturers, and public health authorities [26]. Each submission contains de-identified information, including demographic data (age, sex, and state of residence), relevant medical history, concomitant medications, comorbid conditions, details of the administered vaccine (type, dose, and lot number), onset date of symptoms, and a narrative description of the clinical event. Data are organized into three complementary datasets—VAERSDATA, VAERSSYMPTOMS, and VAERSVAX—which can be linked through a unique numerical identifier, the VAERS ID, assigned to every report [26]. All records are reviewed by trained personnel who apply standardized medical terminology according to the Medical Dictionary for Regulatory Activities (MedDRA), an internationally recognized and clinically validated classification system [27]. Submitting fraudulent or misleading reports to VAERS is a federal offense and may result in fines or imprisonment [28].

As an open-access resource, VAERS enables continuous pharmacovigilance and signal detection at a population level. Its large scale and inclusiveness allow for the identification of rare or unexpected adverse events that may not emerge during pre-authorization clinical trials, as well as for the exploration of potential patterns or risk factors [29–31]. The database is publicly available, and no institutional approval is required for secondary analyses or for dissemination of research findings derived from its content [32].

Data extraction

Data were obtained from the VAERS database maintained by the CDC [33]. The raw datasets were downloaded in CSV format and included all reports referring to vaccine doses administered between December 2020 and September 2021. This time frame was selected because it corresponds to the period of the two-dose primary COVID-19 vaccination campaign, preceding the widespread administration of booster doses. The first vaccinations were initiated in December 2020, while the Advisory Committee on Immunization Practices (ACIP) formally recommended booster administration in late September 2021 [34–36]. Focusing on this interval minimized the potential for survivorship bias, as individuals who experienced vaccine-related adverse events after the initial series may have been less likely to receive subsequent booster doses [37,38]. To ensure comprehensive coverage, all reports submitted up to December 2024 were included, provided that the vaccination date fell within the primary-series window. The three datasets—VAERSDATA, VAERSSYMPTOMS, and VAERSVAX—were merged using the unique VAERS ID identifier that links records referring to the same adverse event report. Records lacking key demographic or temporal information (age, sex, vaccine administration date, or symptom onset date) were excluded prior to analysis.

Definition of systemic autoimmune rheumatic diseases

After dataset harmonization, a comprehensive list of MedDRA Preferred Terms (PTs) consistent with SARDs was compiled and used as a search strategy within the VAERSSYMPTOMS dataset. The PT selection was performed independently by three rheumatologists and subsequently refined through consensus to ensure both clinical relevance and terminological accuracy. Each report containing one or more relevant PTs was assigned to one of the following seven diagnostic categories:

- PMR: *"Polymyalgia rheumatica"*.

- GCA: *"Giant cell arteritis", "Aortitis", and "Arteritis"*.
- Other vasculitides: *"Anti-neutrophil cytoplasmic antibody positive vasculitis", "Behcet's syndrome", "Cutaneous vasculitis", "Henoch–Schönlein purpura", "Hypersensitivity vasculitis", "Kawasaki's disease", "Pulmonary vasculitis", "Retinal vasculitis", "Vasculitis", "Urticarial vasculitis", "Granulomatosis with polyangiitis", "Eosinophilic granulomatosis with polyangiitis", and "Central nervous system vasculitis"*.
- SLE and related manifestations: *"Systemic lupus erythematosus", "Lupus nephritis", "Lupus-like syndrome", "Cutaneous lupus erythematosus", "Subacute cutaneous lupus erythematosus", "Chronic cutaneous lupus erythematosus", and "Systemic lupus erythematosus rash"*.
- Sjögren's syndrome: *"Sjögren's syndrome"*.
- Systemic sclerosis (SSc): *"Scleroderma" and "Systemic scleroderma"*.
- Myositis: *"Myositis", "Dermatomyositis", "Polymyositis", "Inclusion body myositis", and "Immune-mediated myositis"*.

To enhance statistical robustness and minimize the influence of isolated or spurious entries, only PTs reported in at least three VAERS records were retained for analysis. Each VAERS report containing one or more PTs corresponding to a specific diagnostic category was assigned to that disease group for subsequent analyses.

Handling of duplicate records

Duplicate and multi-entry records in VAERS were carefully managed to preserve data accuracy. Because the VAERS system allows up to five MedDRA-coded symptoms per submission, individuals who reported a greater number of adverse events could generate multiple rows linked to the same VAERS identification code [39]. In such cases, these entries were merged into a single record to ensure that all symptoms associated with the same event were captured. Conversely, records sharing the same identification code along with identical demographic information, vaccination date, symptom onset date, and vaccine dose were considered true duplicates and were therefore removed from the dataset. When the same identification code appeared more than once but with different vaccination dates or doses, the records were retained as distinct entries, as they were assumed to represent separate adverse event reports following different vaccine administrations [40].

Statistical analysis

Each VAERS report was treated as a distinct observational unit for the descriptive analyses. Demographic and vaccination characteristics were summarized using means and standard deviations (SD) or medians and interquartile ranges (IQR) for non-normally distributed variables, and as absolute and relative frequencies for categorical data.

The crude reporting rate (CRR) for each SARD category was calculated as the number of reports per one million vaccine doses administered, using official data from the CDC on cumulative COVID-19 vaccinations in the United States up to September 2021. These data encompassed all three authorized SARS-CoV-2 vaccines [41]. A disproportionality analysis was then performed to assess the reporting frequency of each SARD category following COVID-19 vaccination compared with all other vaccines recorded in VAERS. Three statistical indicators were applied: the proportional reporting ratio (PRR), the reporting odds ratio (ROR), and the information component (IC), as recommended in pharmacovigilance research [42–44].

The PRR was calculated by comparing, for each SARD category, the proportion of reports following COVID-19 vaccination with the corresponding proportion observed among recipients of all other vaccines in the VAERS database. Results were presented together with their 95 % confidence intervals (CIs). A signal of disproportionate reporting was considered present when the PRR was ≥ 2, the lower bound of the 95 % CI exceeded 1 and the Chi-squared statistic (with Yates' correction) was ≥ 4.

Similarly, the ROR was calculated by comparing the odds of each SARD being reported following COVID-19 vaccination with the odds of reporting after all other vaccines. A statistically significant signal was defined when the lower limit of the 95 % confidence interval was greater than 1.

In addition to these frequentist measures, we employed the IC, a Bayesian disproportionality metric that estimates the ratio between observed and expected reporting frequencies. Unlike the PRR and ROR, which rely on CIs derived from repeated sampling, the IC is based on the posterior probability distribution and expressed through Bayesian credible intervals (CrIs) [45]. This approach accounts for uncertainty in reporting frequencies and performs particularly well in identifying rare adverse events. A signal of disproportionate reporting was considered present when the lower bound of the 95 % credible interval (IC_{025}) exceeded zero [44].

Initially, disproportionality analyses were performed by comparing the frequency of reports for each SARD following COVID-19 vaccination with that observed after all other vaccines recorded in the VAERS database. To explore potential differences in reporting behavior between men and women, subsequent analyses were stratified by sex. All statistical analyses and graphical visualizations were performed using R Studio (R Foundation for Statistical Computing, Vienna, Austria). Disproportionality analyses were conducted with the "pvda" package.

Ethical considerations

Since VAERS functions as a national vaccine safety monitoring system designed to support public health surveillance, and because this study relied exclusively on de-identified, publicly available data in full compliance with CDC regulations, Institutional Review Board (IRB) approval and informed consent were not required [46].

Results

Demographic description

During the study period, a total of 403.2 million doses of COVID-19 vaccines were administered in the United States [41]. After removal of duplicate records, 679,586 unique reports of AEFIs related to both SARS-CoV-2 and other vaccines were available in the VAERS database. Among the adverse events following COVID-19 vaccination, 1441 cases of SARDs were identified. The largest number of reports referred to other vasculitides ($n = 373$), followed by PMR ($n = 305$), SLE and related manifestations ($n = 299$), and myositis ($n = 244$). Fewer reports involved Sjögren's syndrome ($n = 95$), GCA ($n = 89$), and SSc ($n = 36$). Detailed results of the disproportionality analyses for each SARD are presented in Table 1, while Fig. 1 provides a graphical summary of the corresponding estimates to enhance interpretability.

Polymyalgia rheumatica

A total of 305 VAERS reports described PMR as an adverse event following COVID-19 vaccination, accounting for a CRR of 0.8 cases per million administered doses. Among these, 157 (51 %) involved males and 148 (49 %) involved females. The median age of affected individuals was 69 years (IQR 62–73). Reports were most frequently associated with mRNA-1273 (52 %), followed by BNT162b2 (46 %), and Ad26.COV2.S (3 %). The median time from vaccination to symptom onset was 11 days (IQR 2–36). A previous history of PMR was documented in 12 of 305 reports (4 %), suggesting that a minority of cases may represent disease flares rather than new-onset events.

In the disproportionality analysis, no statistically significant signal emerged for PMR when comparing COVID-19 vaccines with all other vaccines recorded in VAERS. The PRR was 1.288 (95 % CI 0.686–2.418), the ROR was 1.289 (95 % CI 0.686–2.419), and the IC was 0.013 (IC_{025} = –0.153 to 0.170), indicating no evidence of disproportionate reporting.

Table 1
Disproportionality analysis.

Group	COVID-19 vaccine Reports of SARD / Total reports	All other vaccines Reports of SARD / Total reports	PRR	PRR 95 % CI	ROR	ROR 95 % CI	IC	IC 95 % CrI
Polymyalgia rheumatica								
Overall	305 / 652,047	10 / 27,539	1.288	0.686 to 2.418	1.289	0.686 to 2.419	0.013	–0.153 to 0.170
Males	157 / 203,881	6 / 10,337	1.327	0.587 to 2.998	1.327	0.587 to 2.999	0.017	–0.217 to 0.234
Females	148 / 448,166	4 / 17,202	1.420	0.526 to 3.834	1.420	0.526 to 3.835	0.016	–0.226 to 0.239
Giant cell arteritis								
Overall	89 / 652,047	3 / 27,539	1.302	0.413 to 4.117	1.303	0.413 to 4.118	0.014	–0.300 to 0.296
Males	37 / 203,881	2 / 10,337	0.938	0.226 to 3.892	0.938	0.226 to 3.892	0.005	–0.507 to 0.423
Females	52 / 448,166	1 / 17,202	1.996	0.276 to 14.439	1.996	0.276 to 14.439	0.027	–0.392 to 0.393
Other vasculitides								
Overall	373 / 652,047	35 / 27,539	0.450	0.318 to 0.636	0.450	0.318 to 0.636	–0.070	–0.220 to 0.073
Males	129 / 203,881	16 / 10,337	0.409	0.243 to 0.687	0.408	0.243 to 0.687	–0.097	–0.357 to 0.141
Females	244 / 448,166	19 / 17,202	0.493	0.309 to 0.786	0.493	0.309 to 0.786	–0.054	–0.241 to 0.122
Systemic lupus erythematosus and related manifestations								
Overall	299 / 652,047	6 / 27,539	2.104	0.938 to 4.722	2.105	0.938 to 4.724	0.031	–0.137 to 0.190
Males	34 / 203,881	1 / 10,337	1.724	0.236 to 12.592	1.724	0.236 to 12.595	0.029	–0.497 to 0.473
Females	265 / 448,166	5 / 17,202	2.034	0.840 to 4.927	2.035	0.840 to 4.930	0.027	–0.152 to 0.196
Sjögren's syndrome								
Overall	95 / 652,047	4 / 27,539	1.003	0.369 to 2.728	1.003	0.369 to 2.728	0.000	–0.305 to 0.276
Males	13 / 203,881	0 / 10,337	NC	NC	NC	NC	0.069	–0.821 to 0.747
Females	82 / 448,166	4 / 17,202	0.787	0.288 to 2.146	0.787	0.288 to 2.147	–0.014	–0.344 to 0.281
Systemic sclerosis								
Overall	36 / 652,047	1 / 27,539	1.520	0.208 to 11.089	1.520	0.208 to 11.090	0.020	–0.490 to 0.452
Males	6 / 203,881	0 / 10,337	NC	NC	NC	NC	0.066	–1.310 to 0.994
Females	30 / 448,166	1 / 17,202	1.151	0.157 to 8.443	1.152	0.157 to 8.444	0.007	–0.556 to 0.477
Myositis								
Overall	244 / 652,047	14 / 27,539	0.736	0.430 to 1.261	0.737	0.429 to 1.261	–0.021	–0.208 to 0.154
Males	99 / 203,881	3 / 10,337	1.673	0.531 to 5.276	1.673	0.531 to 5.279	0.028	–0.270 to 0.298
Females	145 / 448,166	11 / 17,202	0.506	0.274 to 0.934	0.506	0.274 to 0.934	–0.051	–0.295 to 0.174

Table 1 legend: CI: confidence interval; CrI: credible interval; IC: information component; PRR: proportional reporting ratio; ROR: reporting odds ratio; SARD: systemic autoimmune rheumatic disease.

Sex-stratified analyses yielded consistent results. Among males, the PRR was 1.327 (95 % CI 0.587–2.998), the ROR 1.327 (95 % CI 0.587–2.999), and the IC 0.017 (IC_{025} = –0.217 to 0.234). Among females, the PRR was 1.420 (95 % CI 0.526–3.834), the ROR 1.420 (95 % CI 0.526–3.835), and the IC 0.016 (IC_{025} = –0.226 to 0.239), confirming the absence of sex-specific differences in reporting frequency.

Giant cell arteritis

A total of 89 VAERS reports described GCA as an adverse event following COVID-19 vaccination, accounting for a CRR of 0.2 cases per million administered doses. Among these, 52 (58 %) involved females and 37 (42 %) involved males. The median age of affected individuals was 70 years (IQR 61–74), consistent with the expected demographic profile of GCA. Reports were most frequently associated with mRNA-1273 (47 %), followed by BNT162b2 (45 %), and Ad26.COV2.S (8 %). The median time from vaccination to symptom onset was 14 days (IQR 3–60). A history of GCA was reported in 2 of 89 cases (2 %), indicating that most reports likely referred to new-onset disease.

In the disproportionality analysis, no statistically significant signal was observed for GCA when comparing COVID-19 vaccines with all other vaccines in VAERS. The PRR was 1.302 (95 % CI 0.413–4.117), the ROR was 1.303 (95 % CI 0.413–4.118), and the IC was 0.014 (IC_{025} = –0.300 to 0.296).

Sex-stratified analyses yielded consistent results. Among males, the PRR was 0.938 (95 % CI 0.226–3.892), the ROR 0.938 (95 % CI 0.226–3.892), and the IC 0.005 (IC_{025} = –0.507 to 0.423). Among females, the PRR was 1.996 (95 % CI 0.276–14.439), the ROR 1.996 (95 % CI 0.276–14.439), and the IC 0.027 (IC_{025} = –0.392 to 0.393), confirming the absence of sex-specific differences in reporting frequency.

Other vasculitides

A total of 373 VAERS reports described other vasculitides as adverse events following COVID-19 vaccination, accounting for a CRR of 0.9 cases per million administered doses. Among these, 244 (65 %) involved females and 129 (35 %) involved males. The median age of affected individuals was 54 years (IQR 39–66). Reports were most frequently associated with BNT162b2 (47 %), followed by mRNA-1273 (43 %), and Ad26.COV2.S (9 %), while in 1 % the vaccine manufacturer was not specified. The median time from vaccination to symptom onset was 10 days (IQR 2–28). A pre-existing vasculitic disorder was recorded in 14 of 373 reports (4 %), suggesting that a small subset of cases may reflect exacerbations of known conditions.

In the disproportionality analysis, other vasculitides were less frequently reported after COVID-19 vaccination compared with all other vaccines in VAERS. The PRR was 0.450 (95 % CI 0.318–0.636), the ROR was 0.450 (95 % CI 0.318–0.636), and the IC was –0.070 (IC_{025} = –0.220 to 0.073), indicating a lack of disproportionate reporting.

Sex-stratified analyses showed consistent results. Among males, the PRR was 0.409 (95 % CI 0.243–0.687), the ROR 0.408 (95 % CI 0.243–0.687), and the IC –0.097 (IC_{025} = –0.357 to 0.141). Among females, the PRR was 0.493 (95 % CI 0.309–0.786), the ROR 0.493 (95 % CI 0.309–0.786), and the IC –0.054 (IC_{025} = –0.241 to 0.122), confirming a consistent pattern across sexes.

Systemic lupus erythematosus and related manifestations

A total of 299 VAERS reports described SLE or related manifestations as adverse events following COVID-19 vaccination, accounting for a CRR of 0.7 cases per million administered doses. Among these, 265 (89 %) involved females and 34 (11 %) involved males. The median age of affected individuals was 49 years (IQR 37–59.5). Reports were most frequently associated with BNT162b2 (51 %), followed by mRNA-1273 (43 %) and Ad26.COV2.S (6 %). The median time from vaccination to symptom onset was 5 days (IQR 0–33). A known diagnosis of SLE or related manifestations was present in 12 of 299 cases (4 %), implying that both relapses and de novo presentations contributed to the total number of reports.

In the disproportionality analysis, a non-significant trend toward

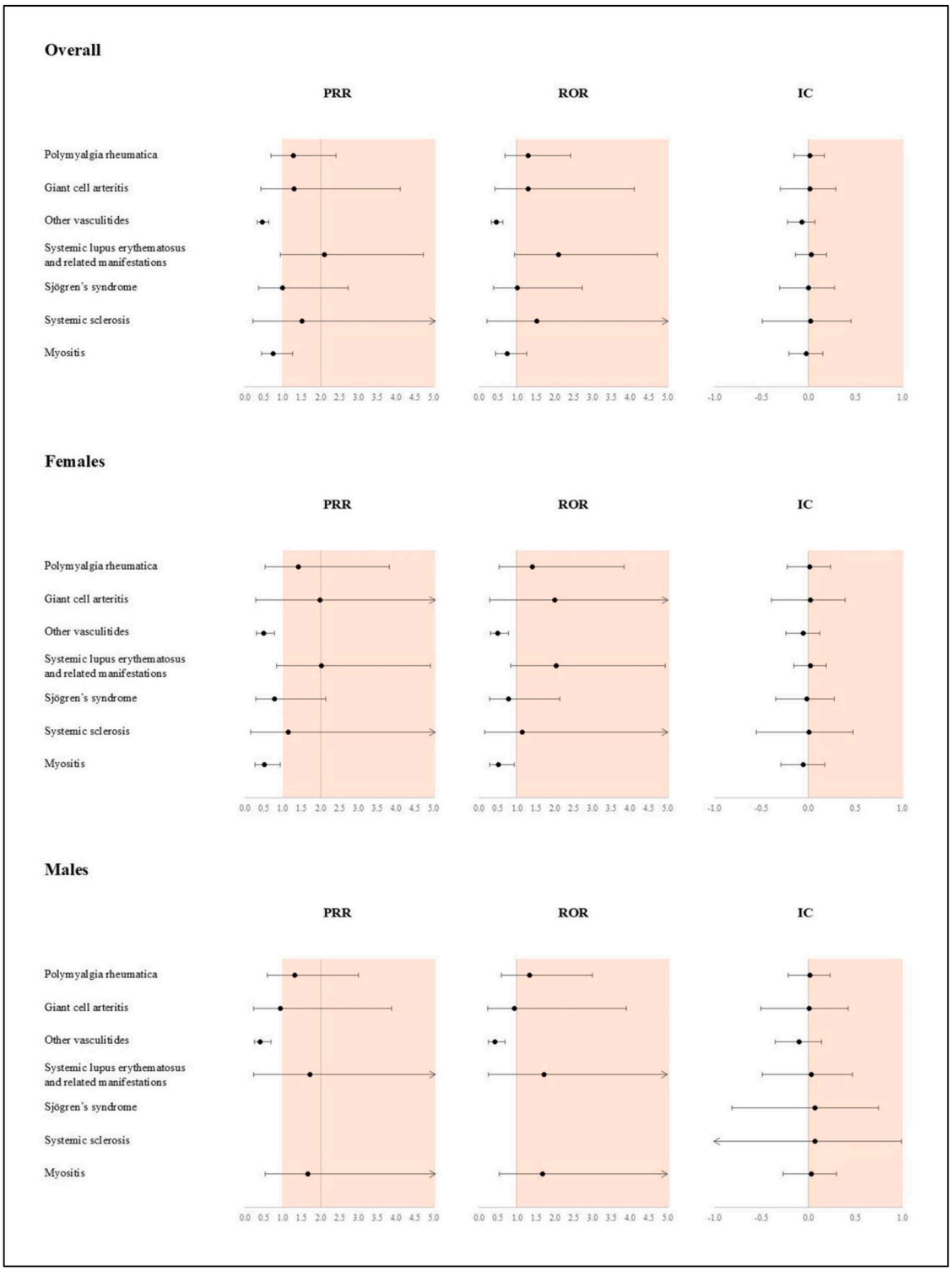

Fig. 1. Graphical summary of disproportionality analyses for systemic autoimmune rheumatic diseases (SARDs) reported in VAERS between December 2020 and December 2024. Each point represents the disproportionality estimate for a given disease, with horizontal bars indicating 95 % confidence or credibility intervals. Results are shown both overall and stratified by sex.

Interpretation:

• **PRR:** a disproportionality signal suggestive of a higher reporting risk for COVID-19 vaccines is observed when the point estimate exceeds PRR = 2 and the 95 % confidence interval does not cross 1, falling entirely within the shaded red area.

• **ROR:** a disproportionality signal suggestive of a higher reporting risk for COVID-19 vaccines is observed when the point estimate exceeds ROR = 1 and the 95 % confidence interval does not cross 1, falling entirely within the shaded red area.

• **IC:** a disproportionality signal, suggestive of a higher reporting risk for COVID-19 vaccines compared to what would be expected under independence, is observed when the 95 % credibility interval is greater than 0, falling entirely within the shaded red area.

higher reporting of SLE and related manifestations was observed following COVID-19 vaccination compared with all other vaccines in VAERS. The PRR was 2.104 (95 % CI 0.938–4.722), the ROR was 2.105 (95 % CI 0.938–4.724), and the IC was 0.031 (IC_{025} = –0.137 to 0.190).

Sex-stratified analyses yielded consistent findings. Among males, the PRR was 1.724 (95 % CI 0.236–12.592), the ROR 1.724 (95 % CI 0.236–12.595), and the IC 0.029 (IC_{025} = –0.497 to 0.473). Among females, the PRR was 2.034 (95 % CI 0.840–4.927), the ROR 2.035 (95 % CI 0.840–4.930), and the IC 0.027 (IC_{025} = –0.152 to 0.196), confirming the absence of statistically significant sex-specific disproportionality

Sjögren's syndrome

A total of 95 VAERS reports described Sjögren's syndrome as an adverse event following COVID-19 vaccination, accounting for a CRR of 0.2 cases per million administered doses. Among these, 82 (86 %) involved females and 13 (14 %) involved males. The median age of affected individuals was 52 years (IQR 40–61.5). Reports were most frequently associated with BNT162b2 (53 %), followed by mRNA-1273 (38 %), and Ad26.COV2.S (Janssen, 9 %). The median time from vaccination to symptom onset was 7 days (IQR 0.5–25). A history of Sjögren's syndrome was reported in 12 of 95 cases (13 %), suggesting that a relevant share of reports might reflect disease reactivation.

In the disproportionality analysis, no statistically significant signal was observed for Sjögren's syndrome when comparing COVID-19 vaccines with all other vaccines in VAERS. The PRR was 1.003 (95 % CI 0.369–2.728), the ROR was 1.003 (95 % CI 0.369–2.728), and the IC was 0.000 (IC_{025} = –0.305 to 0.276).

Sex-stratified analyses showed consistent findings. Among females, the PRR was 0.787 (95 % CI 0.288–2.146), the ROR 0.787 (95 % CI 0.288–2.147), and the IC –0.014 (IC_{025} = –0.344 to 0.281). Among males, the PRR and ROR were not calculable due to the absence of comparator events, while the IC was 0.069 (IC_{025} = –0.821 to 0.747), indicating no evidence of disproportionate reporting.

Systemic sclerosis

A total of 36 VAERS reports described SSc as an adverse event following COVID-19 vaccination, accounting for a CRR of 0.1 cases per million administered doses. Among these, 30 (83 %) involved females and 6 (17 %) involved males. The median age of affected individuals was 53 years (IQR 39–60.75). Reports were most frequently associated with BNT162b2 (50 %), followed by mRNA-1273 (44 %), and Ad26.COV2.S (6 %). The median time from vaccination to symptom onset was 10.5 days (IQR 1.25–100.75). Pre-existing SSc was documented in 5 of 36 reports (14 %), representing the highest proportion of pre-existing disease among the examined SARD categories.

In the disproportionality analysis, no statistically significant signal was observed for SSc when comparing COVID-19 vaccines with all other vaccines recorded in VAERS. The PRR was 1.520 (95 % CI 0.208–11.089), the ROR was 1.520 (95 % CI 0.208–11.090), and the IC was 0.020 (IC_{025} = –0.490 to 0.452).

Sex-stratified analyses yielded comparable findings. Among females, the PRR was 1.151 (95 % CI 0.157–8.443), the ROR 1.152 (95 % CI 0.157–8.444), and the IC 0.007 (IC_{025} = –0.556 to 0.477). Among males, disproportionality measures were not calculable due to the absence of comparator events, and the IC was 0.066 (IC_{025} = –1.310 to 0.994), confirming the lack of evidence for sex-specific disproportionality.

Myositis

A total of 244 VAERS reports described myositis as an adverse event following COVID-19 vaccination, accounting for a CRR of 0.6 cases per million administered doses. Among these, 145 (59 %) involved females and 99 (41 %) involved males. The median age of affected individuals was 51 years (IQR 37–65). Reports were most frequently associated with mRNA-1273 (46 %) and BNT162b2 (45 %), while Ad26.COV2.S accounted for 21 reports (9 %). The median time from vaccination to symptom onset was 7 days (IQR 1–26.5). A prior diagnosis of myositis was noted in 14 of 244 cases (6 %), indicating that most reports corresponded to new-onset manifestations.

In the disproportionality analysis, no statistically significant signal was observed for myositis when comparing COVID-19 vaccines with all other vaccines in VAERS. The PRR was 0.736 (95 % CI 0.430–1.261), the ROR was 0.737 (95 % CI 0.429–1.261), and the IC was –0.021 (IC_{025} = –0.208 to 0.154).

Sex-stratified analyses yielded partially heterogeneous results. Among males, the PRR was 1.673 (95 % CI 0.531–5.276), the ROR 1.673 (95 % CI 0.531–5.279), and the IC 0.028 (IC_{025} = –0.270 to 0.298). Among females, the PRR was 0.506 (95 % CI 0.274–0.934), the ROR 0.506 (95 % CI 0.274–0.934), and the IC –0.051 (IC_{025} = –0.295 to 0.174), suggesting a slightly lower reporting frequency in women but without evidence of disproportionate association.

Discussion

Since the launch of the vaccination campaign in December 2020, the VAERS database has continuously collected reports of AEFIs, including autoimmune and inflammatory manifestations [47]. Although these events represent only a small proportion of all reported AEFIs, they have attracted increasing attention within the rheumatology community because of their potential immune-mediated nature [48–51].

In a previous VAERS-based analysis, we separately investigated inflammatory arthritis as a potential AEFI following COVID-19 vaccination and found no evidence of disproportional reporting compared with other vaccines, suggesting that the occurrence of arthritis after vaccination most likely reflects coincidental events within the background incidence of rheumatic disease [25]. Building on those findings, the present study broadens the analysis to additional SARDs, with the scope of clarifying whether reports of these autoimmune conditions following COVID-19 vaccination show patterns distinct from those associated with other vaccines.

In the pooled analysis of nearly 680,000 adverse event reports from both COVID-19 and non–COVID-19 vaccines, no clear disproportionality signals emerged across the SARDs analyzed. Specifically, PMR, GCA, Sjögren's syndrome, SSc, and myositis showed no evidence of disproportionate reporting following COVID-19 vaccination. A non-significant upward trend was observed for SLE and related manifestations, while the category of other vasculitides displayed a lower reporting frequency compared with other vaccines.

The biological plausibility of a link between vaccination and autoimmune phenomena has long been debated, and several mechanisms have been proposed to explain new-onset or flares of autoimmune conditions after immunization [52]. Among these, molecular mimicry between SARS-CoV-2 spike antigens and human self-proteins may allow cross-reactive antibody formation and subsequent loss of tolerance in genetically predisposed hosts [53]. Another plausible mechanism is adjuvant-driven innate activation, in which vaccine components engage pattern-recognition receptors such as Toll-like receptors, triggering downstream NF-κB and type I interferon signaling that can amplify adaptive immune responses [54–57]. These pathways overlap with bystander activation of autoreactive lymphocytes in cytokine-rich inflammatory milieus, potentially lowering the threshold for transient autoimmune reactivity [58]. In addition, autoantibody-mediated mechanisms have been described, as exemplified by vaccine-induced immune thrombotic thrombocytopenia (VITT), where anti-PF4 antibodies lead to platelet and complement activation [59]. The ASIA (autoimmune/inflammatory syndrome induced by adjuvants) framework has also been invoked as a unifying model linking adjuvant exposure and autoimmunity, integrating genetic predisposition and historical clusters of giant cell arteritis or polymyalgia rheumatica reported after influenza vaccination—concepts now reconsidered in the

context of COVID-19 vaccines, though such events remain rare and causality unproven [20,57]. Taken together, these mechanisms delineate a biologically plausible but largely theoretical framework in which COVID-19 vaccination could, in rare cases, act as a trigger in genetically susceptible individuals rather than as a direct cause of SARDs.

However, translating these theoretical mechanisms into real-world evidence requires population-based pharmacovigilance analyses, as illustrated by the recent European study by Fraenza et al., which used the EudraVigilance database to evaluate immune-mediated and rheumatic adverse events following COVID-19 vaccination [60,61]. The analysis included 45,352 individual case safety reports collected between January 2021 and October 2023, classified into five standardised MedDRA categories: arthritis, tendinopathies, vasculitis, systemic lupus erythematosus, and other immune-mediated disorders [60]. Disproportionality was assessed using the ROR as the sole metric and, importantly, the comparator group consisted of other COVID-19 vaccines, allowing for intra-platform evaluation of reporting patterns rather than comparison with non-COVID vaccines. In this framework, mRNA vaccines showed higher reporting odds for arthritis and vasculitis relative to Ad26.COV2.S, whereas no significant associations were detected for SLE, tendinopathies, or other immune-mediated disorders [60].

However, methodological and conceptual distinctions are crucial when comparing results across pharmacovigilance systems [62]. While the EudraVigilance study examined relative differences among COVID-19 vaccine platforms, our VAERS-based analysis assessed whether COVID-19 vaccines as a group exhibited disproportionate reporting of well-defined SARDs compared with all non-COVID vaccines. Furthermore, our approach incorporated three complementary disproportionality metrics (PRR, ROR, and IC) to strengthen signal validation. In settings where event numbers are relatively low, frequentist indicators such as PRR and ROR may become unstable, as small fluctuations in counts can disproportionately affect the estimates and inflate the risk of spurious associations [63]. Conversely, the IC, derived from a Bayesian framework, is inherently less sensitive to random variability because it incorporates prior probability distributions and adjusts for heterogeneity in reporting patterns [64]. This approach tends to yield more robust and conservative estimates, particularly when data sparsity or reporting imbalance may otherwise distort frequentist metrics. For these reasons, we consider the Bayesian estimates more reliable for interpreting disproportionality signals in this context.

The absence of significant disproportionality in our data therefore does not contradict the European findings; rather, it reflects differences in comparator groups, statistical thresholds, and case ascertainment frameworks between the two systems. Collectively, both studies contribute complementary perspectives—EudraVigilance offering tightly curated, regulator-verified data for intra-COVID comparisons, and VAERS providing broader, early signal detection capacity across the entire vaccine landscape [60].

Despite the complementary nature of these findings, the present study shares the intrinsic methodological limitations of passive surveillance systems, which warrant careful consideration. First, VAERS is a passive, spontaneous surveillance system and is therefore inherently affected by underreporting, stimulated reporting, and variable data completeness [65,66]. The likelihood of reporting may fluctuate according to media coverage, temporal proximity to vaccination, and public awareness of specific adverse events [67]. Clinical information is often self-reported and therefore may lack diagnostic confirmation or standardized terminology. Despite our efforts to exclude records with missing demographic or essential temporal information, residual inaccuracies and potential duplicate submissions cannot be completely ruled out.

Second, causal inference cannot be drawn from disproportionality analyses. Metrics such as PRR, ROR, and IC quantify statistical associations within the reporting database but do not incorporate individual clinical trajectories or adjust for external confounders [68]. These methods are designed to generate safety signals rather than establish causation, and the possibility of confounding by indication remains. Individuals with pre-existing autoimmune or rheumatic diseases may have had different vaccination priorities, altered healthcare-seeking behavior, or heightened symptom vigilance, all of which could influence reporting probabilities independently of any biological effect [69].

Third, the relatively low number of SARD-specific reports within certain strata, coupled with the inherent clinical heterogeneity of pharmacovigilance data, may limit the precision of our estimates. MedDRA coding encompasses a broad spectrum of autoimmune manifestations—from mild, transient reactions to chronic, well-characterized diseases—and does not always allow a clear distinction between new-onset cases and flares of pre-existing conditions. Under these circumstances, disproportionality metrics should be interpreted cautiously, as statistical instability and diagnostic uncertainty may both contribute to apparent fluctuations in signal strength.

Lastly, as with all pharmacovigilance research, the absence of a disproportionality signal does not necessarily imply the absence of risk, but rather indicates that, at the population level, no statistically robust deviation from background reporting has been observed. The VAERS data should therefore be interpreted as hypothesis-generating. Any potential signal emerging from data-mining analyses warrants follow-up using controlled epidemiological designs—such as cohort or self-controlled case-series studies—capable of disentangling true vaccine-related associations from confounding and reporting bias.

Despite these intrinsic limitations, the overall consistency of disproportionality estimates across different statistical approaches, together with the absence of clear signals for any SARD, provides further reassurance regarding the favorable safety profile of COVID-19 vaccines in this setting. Nevertheless, continued post-marketing surveillance remains essential to promptly identify and contextualize potential immune-mediated events as vaccination programs evolve.

In conclusion, by systematically analyzing VAERS reports of SARDs, this study expands current pharmacovigilance knowledge beyond individual disease entities, offering a comprehensive overview of autoimmune safety signals across the COVID-19 vaccine spectrum. The absence of significant disproportionality supports the interpretation that post-vaccination autoimmune events largely reflect the background incidence of these conditions rather than vaccine-induced pathology. The study highlights the importance of contextualizing spontaneous reports within the broader epidemiological and immunological landscape, bridging pharmacovigilance data with mechanistic understanding. As vaccination strategies continue to evolve, integrating passive surveillance with prospective, population-based approaches will be key to further refining risk assessment and guiding evidence-based communication between clinicians and patients.

Contributors

JC, GT, and AZ contributed to data analysis and interpretation of results. JC, PR, and FU were responsible for drafting the manuscript. GT and AZ were involved in sample and data collection. PR, FU, and AZ contributed to the study design. JC is the guarantor and accepts full responsibility for the integrity of the work and the accuracy of the data. All authors critically reviewed and revised the manuscript and approved the final version for submission.

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Data availability statement

All data analysed in this study are publicly available.

Ethics approval

Not required for analysis of publicly available VAERS data.

Patient consent for publication

Not applicable.

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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