# Safety of Vaccination Against Coronavirus Disease-19 (COVID-19) in Rheumatic and Musculoskeletal Diseases (Rmds) Patients: Results from the (ECR)-COVID-19 Group

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*Received: 15 April 2024*

*Accepted: 8 July 2024*

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**DOI 10.5001/omj.2024.107**

## *Abstract*

**Objectives:** To examine the frequency of, and risk factors for, adverse events following coronavirus disease 2019 (COVID-19) vaccination in patients with inflammatory rheumatic and musculoskeletal diseases (I-RMDs) and non-inflammatory RMDs (NI-RMDs).

**Methods:** The Egyptian College of Rheumatology-COVID-19 vaccine physician-reported data (ECR-VaXurvey3) of RMD patients vaccinated against COVID-19 included information on demographics, vaccination type, RMD

diagnosis, treatments, and post-vaccine flares, and adverse events. Healthy vaccinated subjects were considered controls.

**Results:** The ECR-VaXurvey3 included 890 vaccinated RMD patients, predominantly females (73.3%) with a mean age of 44.4±12.1 years, and 172 controls. In the RMD group, 816 (91.7%) had I-RMD and 74 (8.3%) had NI-RMD. The frequency of adverse events was comparable between the RMD and control groups. In RMD patients, injection site pain (59.9%) was the most reported AE. Post-vaccination COVID-19 infection and disease flares were reported in 2.9% and 2.9% of I-RMD patients and in 8.1% and 9.5% of NI-RMD patients (p=0.01 and p=0.49; respectively). The severity of prior COVID-19 infection (OR=2.4, 95%CI:1.0,5.8, p=0.04) and azathioprine use (OR= 2.6, 95% CI:1.1,5.9, p= 0.024) were associated with post-vaccine adverse events, while biologic use was associated with fewer AEs (OR=0.48, 95%CI:0.27,0.83, p=0.01).

**Conclusions:** Adverse events of COVID-19 vaccinations in patients with RMD are comparable to controls.

**Keywords:** COVID-19 vaccine; rheumatic and musculoskeletal disease; adverse effect; safety; risk factors.

## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is pandemic as declared by the World Health Organization on 11 March 2020.[1] It has led to a dramatic loss of human life and an unprecedented challenge to public health and healthcare systems worldwide.[2] As a goal of reducing the COVID-19 impact, two vaccines using mRNA technology (Pfizer/BioNTech and Moderna) and one vaccine using a nonreplicating adenoviral vector expressing the spike protein (AstraZeneca/Oxford) were authorised for use in December 2020.[3] Later, there were numerous candidate vaccines worldwide. The development of vaccines against COVID-19 was efficacious in reducing infectivity and decreasing morbidity and mortality.

Although vaccination is especially important for patients with rheumatic and musculoskeletal disease (RMD) as well as those receiving specific medications that may influence the functional competence of their immune system due to an increased risk for poor outcomes from COVID-19,[4] patients with RMD were excluded from the initial COVID-19 vaccine clinical development trials.[5,6]

Although there are few studies that support the safety and effectiveness of COVID-19 vaccine in patients with RMD,[7-10] there is limited data on the risk factors associated with COVID-19 vaccine AEs.[11] Therefore, questions regarding the safety and effectiveness of vaccination against COVID-19 in patients with different RMDs and immunosuppressant therapies still exist. This study explored rates of and risk factors for COVID-19 vaccination-reported side effects in patients with rheumatic disease compared to healthy controls. Additionally, the study aimed to determine if there were any significant differences in these parameters between the two groups: inflammatory rheumatic and musculoskeletal diseases (I-RMDs) and non-inflammatory RMDs (NI-RMDs).

## Methods

This cross-sectional study was carried out by the Egyptian College of Rheumatology (ECR). The ECR-COVID-19 study group invited physicians (rheumatologists and internists) across Egypt via social network communications to participate in the ECR-Coronavirus Vaccine (ECR-VaXurvey3). Physicians reported data for the period from December 2021 to June 2022. All patients coming in for an appointment who have a pre-existing RMD and have received one or more doses of any vaccine against COVID-19 with or without adverse events (AEs) were eligible for inclusion. Healthy individuals who received at least one dose of the COVID-19 vaccine were collected randomly from the community and included as a control group.

The study protocol was approved by the Institutional Research Board of the Faculty of Medicine at Mansoura University (approval registration number: R.24.05.2629), and this research was conducted in compliance with the principles of the Helsinki Declaration.[12] A waiver of consent for reviewing medical records was obtained. The objectives and scope of the study, as well as the rights of all participants, were disclosed. Informed written consent was obtained from all participants.

Inflammatory rheumatic and musculoskeletal diseases (I-RMDs) included the following as primary diseases: 1) Inflammatory arthritis: rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), axial spondyloarthritis (SpA), inflammatory bowel disease (IBD), reactive arthritis (ReA), and palindromic rheumatism (PR); 2) Connective tissue diseases (CTDs): systemic lupus erythematosus (SLE), systemic sclerosis (SSc), antiphospholipid syndrome (APS), Sjögren syndrome (SS), inflammatory myositis (dermatomyositis, polymyositis), overlap syndrome, mixed CTDs (MCTDs), undifferentiated CTDs (UCTDs); 3) Vasculitis (small and medium vasculitis); and 4) Others: Behcet Disease (BD), autoinflammatory diseases such as familial Mediterranean fever (FMF) and sarcoidosis. Non-inflammatory rheumatic and musculoskeletal diseases (NI-RMD) included the following: 1) osteoarthritis; 2) osteoporosis; 3) crystal arthropathy; and 4) fibromyalgia syndrome and complex regional pain syndrome. This classification was chosen as it has been reported in previous vaccine clinical studies and autoimmune rheumatic diseases.[7]

The physicians entered the data directly into an Excel. spreadsheet. There was no duplication of data entry, and data completeness was of high quality. The following information is collected: 1) participant's characteristics including age, gender, educational level, comorbidities including diabetes, obesity, hypertension, respiratory diseases, or cardiovascular disease; 2) details of primary RMD diagnoses, disease activity (assessed by a physician global assessment), as well as immunomodulatory/immunosuppressive treatments at the time of vaccination, I-RMD flare-up following vaccination that required a change in rheumatic medication (e.g. increasing dosages and/or adding new medications); and 3) COVID-19 vaccination history including wiliness to receive the COVID-19 vaccine, type of vaccine received, number of doses, diagnosis of COVID-19 before or after vaccination (breakthrough infection), and vaccine-related AEs.

Medications taken by patients at the time of the COVID-19 vaccine were categorised as: conventional synthetic drugs, including hydroxychloroquine (HCQ), sulfasalazine, methotrexate (MTX), leflunomide, mycophenolate mofetil (MMF), cyclophosphamide, and azathioprine; biologics, including tumour necrosis factor inhibitors (anti-TNF), abatacept, belimumab, rituximab, interleukin (IL)-6 inhibitors, and IL-17 inhibitors; and targeted synthetic drugs, specifically JAK inhibitors as well as glucocorticoids (GCs). Discontinuation of anti-rheumatic drugs used during the COVID-19 vaccine was reported.

Adverse events which occurred at any time within 6 months after receiving any COVID-19 vaccine and last for at least 2 days, include pain, redness, or swelling at the site of injection, headache, fever, fatigue, chills, generalised muscle pain, joint pain or swelling, low back pain, abdominal pain, vomiting and diarrhoea, low back pain, allergic reaction, anaphylaxis, rash, cardiovascular manifestations (palpitations, tachycardia), chest diseases (shortness of breath, pleuritic chest pain, persistent cough), or neurological manifestations (transient ischemic attacks, convulsion, cranial or peripheral neuropathy). These AEs were chosen because they have been reported in vaccine clinical trials and were reported by physicians.

*Statistical analysis*: Continuous variables were expressed as mean (±SD) and categorical variables were expressed as percentages (%). A two-sided independent t-test and Chi-square ($\chi 2$) test were used to compare differences between groups for continuous and categorical variables, respectively. We examined the frequency of COVID-19 vaccine side effects, COVID-19 breakthrough infections and disease flares requiring a change in treatment following COVID-19 vaccination among groups. Next, multivariate logistic regression analyses were conducted to investigate potential risk factors independently associated with COVID-19 vaccine AEs (no *vs.* yes) among the population with RMD. First, we used univariate logistic analysis to investigate the variables associated with the occurrence of any AEs. Then those variables with a p-value <0.1 were included in the multivariate logistic regression. Results were reported as odds ratios (OR) and their 95% confidence intervals. P values < 0.05 were considered statistically significant.

## Results

The study included 890 patients with RMD and 172 healthy controls who received the COVID-19 vaccination. Participants were submitted from 30 centres, and providers were from diverse practices, including academic and non-academic centres, and a minority of private practices. Detailed demographic features and clinical characteristics of the study population are summarized in Supplementary table 1. Patients with RMD were predominantly female (73.26%), and the mean age was 44.4±12.13 years. The most reported comorbidities among patients with RMD were hypertension in 160 patients (17.98%), obesity in 120 (13.48%), and respiratory diseases in 44 (5.39%). Apart from the educational level, the demographic characteristics and frequencies of comorbidities were similar between participants with RMD and healthy subjects. The frequency of prior COVID-19 infection was significantly lower in

patients with RMD compared to healthy individuals (67.22% and 82.59%, p=0.002); however, the severity of prior infection was similar between both groups. The most frequently received COVID-19 vaccine in the RMD group was the BBIBP-CorV-Sinopharm vaccine (376, 42.34%), followed by Coronavac-Sinovac (192, 21.62%), Oxford AstraZeneca (166, 18.69%), Pfizer-BioNTech (105, 11.82%), Janssen/Johnson & Johnson (50, 1.70%), Moderna (17, 1.91%), and Sputnik V (8, 0.90%). Few subjects received unspecified vaccines (2, 0.22%). Among RMD participants, 687/890 (77.19%) participants reported at least one adverse event, which is comparable to healthy individuals 140/170 (81.40%), p = 0.224. Apart from injection site pain, there was no significant difference in the individual AEs between RMD patients and controls. The most frequently reported AE in patients with RMD was injection site pain or swelling (59.89%), then fatigue (44.72%), myalgia (37.98%), headache (29.89%), and arthralgia (27.08%). Few patients (30, 3.37%) reported postvaccine COVID-19 infection, while none of the controls did.

**Supplementary table 1:** Demographic and clinical characteristics of patients with rheumatic and musculoskeletal diseases (RMD) and healthy controls.

| **Parameter mean± SD or n (%)** | **RMD patients (n=890)** | **Controls (n=172)** | ***p*-value** |
|---|---|---|---|
| Age | 44.40±12.13 | 44.41±13.88 | 0.994 |
| Sex, female | 652 (73.26) | 114 (66.28) | 0.062 |
| Marital status | | | |
| *Single* | 58 (6.52) | 18 (10.47) | 0.140 |
| *Married* | 737 (82.81) | 135 (78.49) | |
| *Others** | 95 (10.67) | 19 (11.05) | |
| Residency | | | |
| *Urban* | 525 (58.99) | 110 (63.95) | 0.224 |
| *Rural* | 365 (41.01) | 62 (36.05) | |
| Educational level | | | |
| *Less than or equal to Secondary level* | 360 (40.45) | 44 (25.58) | <0.001 |
| *More than Secondary level* | 427 (47.98) | 119 (69.18) | |
| *Illiterate* | 103 (11.57) | 9 (5.23) | |
| Comorbidities | | | |
| *Diabetes mellitus* | 93 (10.46) | 15 (8.72) | 0.490 |
| *Hypertension* | 160 (17.98) | 27 (15.70) | 0.472 |
| *Obesity* | 120 (13.48) | 21 (12.21) | 0.652 |
| *Chest diseases* | 48 (5.39) | 4 (2.33) | 0.088 |
| *Cardiovascular* | 36 (4.04) | 10 (5.81) | 0.297 |
| *Thyroid dysfunction* | 38 (4.27) | 6 (3.49) | 0.638 |
| Number of Comorbidities | | | |
| *None* | 557(62.65) | 118 (68.60) | 0.551 |
| *≥ 1* | 332 (37.35) | 54 (31.40) | |
| Prior COVID-19 infection | | | |
| *None* | 231 (30.00) | 24 (15.19) | 0.002 |
| *≥One* | 539 (67.22) | 134 (82.59) | |
| Prior COVID-19 infection severity | | | |
| *Managed at home* | 532 (81.97) | 117 (85.40) | 0.344 |
| *Managed at hospital* | 92 (14.18) | 18 (13.14) | |
| *Needed ICU* | 25 (3.85) | 2 (1.46) | |
| COVID-19 Vaccine type | | | |
| *BBIBP-CorV - Sinopharm* | 376 (42.34) | 58 (33.92) | 0.019 |
| *CoronaVac -Sinovac* | 192 (21.62) | 35 (20.47) | |
| *BNT162b2 (Pfizer-BioNTech)* | 105 (11.82) | 19 (11.11) | |
| *mRNA-1273 (Moderna)* | 17 (1.91) | 2 (1.17) | |
| *Gam-COVID-Vac (Sputnik V)* | 8 (0.90) | 0 (0.00) | |
| *JNJ-78436735 (Johnson & Johnson)* | 24 (2.70) | 4 (2.34) | |
| *ChAdOx1 (Oxford AstraZeneca)* | 166 (18.69) | 53 (30.99) | |
| *Unknown* | 2 (0.22) | 1 (0.58) | |
| COVID-19 vaccine doses | | | |
| Only one dose | 137 (15.39) | 11 (6.40) | 0.002 |
| Two doses | 753 (84.61) | 161 (93.60) | |
| Booster dose | 206 (23.15) | 40 (23.26) | 0.975 |

| | | |
|---|---|---|
| Post vaccine COVID-19 breakthrough infection | 30 (3.37) | 0 (0.00) |
| Post vaccine COVID-19 infection needing hospitalization | 10 (1.12) | 0 (0.00) |

*Abbreviations: RMD rheumatic and musculoskeletal diseases, PGA patient 's global assessment, AEs adverse effects, ICU intensive care unit. Marital status Others: Widow, divorced and unknown.*

**Supplementary table 2:** Demographic and clinical characteristics of patients with immune and non immune rheumatic and musculoskeletal diseases (I-RMD and NI-RMD).

| **Parameter mean±SD or n (%)** | **I-RMD (n=816)** | **NI-RMD (n=74)** | ***p*-value** |
|---|---|---|---|
| **Age** | 43.88±12.05 | 50.07±11.69 | **<0.001** |
| **Sex, female** | 602 (73.77) | 50 (67.57) | 0.248 |
| **Marital status** | | | |
| *Single* | 51 (6.25) | 7 (9.46) | **0.044** |
| *Married* | 684 (83.82) | 53 (71.62) | |
| *Others** | 81 (9.92) | 14 (18.92) | |
| **Educational level** | | | |
| *Less than or equal to Secondary level* | 340 (41.67) | 20 (26.67) | **<0.001** |
| *More than Secondary level* | 378 (46.32) | 49 (66.22) | |
| *Illiterate* | 98 (12.01) | 5 (6.76) | |
| **Residency** | | | |
| *Urban* | 463 (56.74) | 62 (83.78) | **<0.001** |
| *Rural* | 353 (43.26) | 12 (16.22) | |
| **Comorbidities** | | | |
| Diabetes mellitus | 81 (9.94) | 12 (16.22) | 0.091 |
| Hypertension | 140 (17.16 | 20 (27.03) | **0.034** |
| Obesity | 109 (13.36) | 11 (14.86) | 0.716 |
| Chest diseases | 44 (5.39) | 4 (5.41) | 0.996 |
| Cardiovascular | 28 (3.43) | 8 (10.81) | **0.002** |
| Thyroid dysfunction | 32 (3.92) | 6 (8.11) | 0.088 |
| **Number of Comorbidities** | | | |
| None | 525 (64.42) | 32 (43.24) | **0.010** |
| ≥ 1 | 291 (35.66) | 42 (56.76) | |
| **Disease duration (years)** | 7.00±5.89 | 5.12±4.28 | **0.007** |
| **Age at onset (years)** | 36.88±11.20 | 44.95±10.37 | **<0.001** |
| **PGA (0-10)** | 4.77±2.38 | 3.72±2.67 | **<0.001** |
| **Medications** | | | |
| Hydroxychloroquine users | 505 (61.89) | 5 (6.76) | <0.001 |
| Methotrexate users | 422 (51.72) | 0 (0.00) | |
| Leflunomide users | 238 (29.17) | 0 (0.00) | |
| Azathioprine users | 150 (18.38) | 2 (2.70) | 0.001 |
| Sulfasalazine users | 53 (6.50) | 0 (0.00) | |
| Mycophenolate mofetil users | 48 (5.88) | 0 (0.00) | |
| Cyclophosphamide users | 32 (3.92) | 0 (0.00) | |
| Cyclosporine A users | 8 (0.98) | 0 (0.00) | |
| Biologics | 174 (21.32) | 4 (5.41) | 0.001 |
| Steroid users | 0.66±0.47 | 0.14±0.36 | <0.001 |
| Steroid ≥10 mg/day users | 40 (13.47) | 0 (0.00) | |
| **Prior COVID-19 infection** | | | |
| None | 214 (30.66) | 17 (23.61) | **<0.001** |
| ≥once | 484 (68.34) | 55 (76.39) | |
| **Prior COVID-19 infection severity** | | | |
| Managed at home | 484 (82.59) | 48 (76.19) | **0.047** |
| Managed at hospital | 83 (14.16) | 9 (14.29) | |
| Needed ICU | 19 (3.24) | 6 (9.52) | |
| **COVID-19 Vaccine type** | | | |
| BBIBP-CorV - Sinopharm | 354 (43.49) | 22 (29.73) | **0.001** |
| CoronaVac -Sinovac | 179 (21.99) | 13 (17.57) | |

| | | | |
|---|---|---|---|
| BNT162b2 (Pfizer-BioNTech) | 98 (12.04) | 7 (9.46) | |
| mRNA-1273 (Moderna) | 15 (1.84) | 2 (2.70) | |
| Gam-COVID-Vac (Sputnik V) | 8 (0.98) | 0 (0.00) | |
| JNJ-78436735 (Johnson & Johnson) | 18 (2.21) | 6 (8.11) | |
| ChAdOx1 (Oxford AstraZeneca) | 142 (17.44) | 24 (32.43) | |
| Unknown | 2 (0.24) | 0 (0.00) | |
| **COVID-19 vaccine doses** | | | |
| One dose | 104 (12.75) | 33 (44.59) | **<0.001** |
| Two doses | 712 (87.25) | 41 (55.41) | |
| Booster dose | 176 (21.57) | 30 (40.54) | **<0.001** |
| **COVID-19 vaccine encouraged by physician** | 549 (67.28) | 42 (56.76) | 0.066 |
| **COVID-19 vaccine willing by patient** | 426 (52.21) | 51 (68.92) | **0.006** |
| **Discontinued treatment during COVID-19 vaccine period** | 176 (21.57) | 30 (40.54) | **<0.001** |
| **Post vaccine COVID-19 breakthrough infection** | 24 (2.94) | 6 (8.11) | **0.018** |
| **Post vaccine COVID-19 infection needing hospitalization** | 9 (1.10) | 1 (1.35) | 0.846 |
| **Post vaccine developing rheumatic disease or antibodies** | 25 (3.06) | 10 (13.51) | **<0.001** |
| **Disease flare requiring change dose of treatment** | 99 (12.13) | 7 (9.46) | 0.497 |

*Biologics namely tumour necrosis factor inhibitors (anti-TNF), abatacept, belimumab, rituximab, interleukin (IL)-6 inhibitors, and IL-17 inhibitors) and targeted synthetic drugs, specifically JAK inhibitors. Marital status Others: Widow, divorced and unknown.*

Among 890 patients with RMD diagnosis, n= 816 (91.69%) had I-RMDs; 602/816 (73.77%) were female, with a mean age 43.88±12.05 years; and 74 (8.31%) had NI-RMDs; 50/74 (67.57%) were female, with mean age 50.07±11.69 years (Supplementary table2). Among I-RMD patients, 643 (65.08%) had inflammatory joint disease as their primary diagnosis, 145 (14.68%) had a CTD, 23 (2.33%) vasculitis, and 177 (17.41%) other I-RMD. Osteoarthritis (38, 51.35%) and osteoporosis (17, 22.97%) were the most frequent NI-RMDs. Hydroxychloroquine, methotrexate, and leflunomide were the three most commonly used anti-rheumatic drugs in patients with I-RMD. 13.47% of I-RMD patients used systemic GC (≥10mg/day) and 17.61% used biologics.

The highest vaccine intake in I-RMD patients was BBIBP-CorV-Sinopharm vaccine in 43.49%, followed by Coronavac-Sinovac in 21.99%, Oxford AstraZeneca in 17.44%, Pfizer-BioNTech in 12.04%, Janssen/Johnson & Johnson in 2.21%, Moderna in 1.84%, Sputnik V in 0.98%, and unspecified in 0.24%. While NI-RMD highest detected vaccine intake was Oxford AstraZeneca (32.43%), followed by BBIBP-CorV–Sinopharm vaccine in 29.73%, then Coronavac- Sinovac in 17.57%, Pfizer-BioNTech in 9.46%, Janssen/Johnson & Johnson in 8.11%, and lastly Moderna in 2.7%.

Overall, a higher proportion of subjects with I-RMD reported at least one AE compared to NI-RMD (79.29% vs. 45.05%, p<0.001). Injection site pain and constitutional symptoms (headache, myalgia) were higher in the I-RMD group, while neurological manifestations were higher in patients with NI-RMD. Patients with I-RMD stratified by rheumatic diseases have a similar overall distribution of COVID-19 vaccination AEs. The frequency of post-vaccine fatigue was highest in the CTDs group (59.31%), and vasculitis group (47.83%), and the frequency of palpitation was lowest in subjects with CTDs (2.76%), followed by inflammatory arthritis (3.58%). Disease flares requiring changes in treatment following COVID-19 vaccination were reported by 12.13% of I-RMD patients and by 9.46% of NI-RMD patients. Patients with NI-RMD had a higher frequency of post-COVID-19 breakthrough infections compared to those with I-RMD (8.11% vs. 2.94%, p=0.018).

Among all RMD patients, I-RMD (OR=4.81, 95%CI: 2.19, 10.56, p<0.001), disease flare requiring change dose of treatment (OR=4.81, 95%CI: 1.76, 13.11, p= 0.002), azathioprine use during the time of vaccine (OR=3.32, 95%CI: 1.45, 7.58, p= 0.004), hydroxychloroquine use (OR=0.41, 95%CI: 0.23, 0.74, p= 0.003), and biologic use (OR=0.36, 95%CI: 0.19, 0.67, p= 0.001) were associated with COVID-19 vaccine AEs in a multivariate analysis (data not shown). A multivariate analysis of the risk factors for COVID-19 vaccine AEs among patients with IRMD was performed. Previous COVID-19 infections requiring hospitalization were associated with more postvaccine AEs (OR= 2.45, 95%

CI: 1.04, 5.78, p= 0.04). Azathioprine use during the time of vaccination was associated with a higher incidence of AEs (OR= 2.6, 95% CI: 1.13, 5.95, p= 0.024), while it was lower with biologics use (OR=0.48, 95%CI: 0.27, 0.83, p= 0.01) (Table 1 and Table 2). Demographics, comorbidities, glucocorticoid use, and vaccination types were not associated with excess AEs.

**Table 1:** Univariate analysis of factors associated with experiencing side effects of the vaccine among patients with IRMD.

| **Variables** | **OR (95%CI)** | ***p*-value** |
|---|---|---|
| **Age** | 0.99 (0.98, 1.00) | 0.186 |
| **Male** | 1.19 (0.79, 1.76) | 0.396 |
| **Disease duration** | 0.97 (0.94, 0.99) | **0.017** |
| **Age of onset** | 0.99 (0.98, 1.01) | 0.791 |
| **I-RMD types** | | |
| **Arthritis** | Reference | |
| **CTDs** | 1.60 (0.97, 2.61) | 0.061 |
| **Vasculitis** | 1.91 (0.56, 6.51) | 0.303 |
| **Others** | 1.14 (0.13, 10.31) | 0.905 |
| **Medications** | | |
| Methotrexate | 0.77 (0.54, 1.08) | 0.138 |
| Hydroxychloroquine | 1.02(0.72, 1.44) | 0.916 |
| Sulfasalazine | 1.29 (0.62, 2.71) | 0.489 |
| Azathioprine | 3.22 (1.77, 5.85) | **<0.001** |
| Leflunomide | 0.88 (0.61, 1.27) | 0.481 |
| Cyclophosphamide | 0.56 (0.26, 1.21) | 0.138 |
| Biologics | 0.48 (0.33, 0.71) | **<0.001** |
| Steroid | 1.39 (0.88, 2.21) | 0.156 |
| Steroid | | |
| < 10 mg/day | Reference | 0.262 |
| ≥ 10 mg/day | 1.69 (0.68, 4.22) | |
| **PGA** | 1.01 (0.94, 1.09) | 0.732 |
| **Diabetes mellitus** | 1.56 (0.83, 2.96) | 0.169 |
| **Hypertension** | 0.71 (0.46, 1.08) | 0.110 |
| **Obesity** | 0.81 (0.50, 1.30) | 0.385 |
| **Chest diseases** | 0.68 (0.34, 1.35) | 0.272 |
| **Cardiovascular** | 1.59 (0.54, 4.64) | 0.397 |
| **Thyroid dysfunction** | 0.77 (0.34, 1.76) | 0.542 |
| **Number of comorbidities** | | |
| None | Reference | |
| ≥ 1 | 0.74 (0.49, 1.00) | 0.135 |
| ***Prior COVID-19 infection*** | | |
| *None* | Reference | |
| *Once* | 0.88 (0.58, 1.35) | 0.581 |
| ≥ 2 | 4.11 (1.87, 9.03) | **<0.001** |
| ***COVID-19 Vaccine type*** | | |
| BBIBP-CorV - Sinopharm | Reference | |
| CoronaVac -Sinovac | 0.81 (0.53, 1.22) | 0.312 |
| BNT162b2 (Pfizer-BioNTech) | 1.59 (0.87, 2.91) | 0.133 |
| mRNA-1273 (Moderna) | 0.79 (0.25, 2.55) | 0.693 |
| Gam-COVID-Vac (Sputnik V) | 0.86 (0.17, 4.35) | 0.857 |
| JNJ-78436735 (Johnson & Johnson) | 1.00 (0.32, 3.14) | 0.993 |
| ChAdOx1 (Oxford AstraZeneca) | 2.11(1.20, 3.72) | **0.009** |
| ***Discontinued treatment during COVID-19 vaccine*** | 1.85 (1.16, 2.96) | **0.010** |
| ***Prior COVID-19 Severity*** | | |
| Managed at home | Reference | |
| Managed at hospital | 2.02 (0.90, 4.55) | 0.089 |

| | | |
|---|---|---|
| Needed ICU | 0.53 (0.18, 1.49) | 0.224 |
| Post vaccine flare required increase dose | 4.56 (1.96, 10.60) | **<0.001** |

**Table 2:** Multivariate analysis of factors associated with experiencing side effects of the vaccine among patients with IRMD.

| **Variables** | **OR (95%CI)** | ***p*-value** |
|---|---|---|
| Age | 1.00 (0.97, 1.02) | 0.929 |
| **Male** | 1.08 (0.75, 1.54) | 0.680 |
| **Disease duration** | 0.98 (0.94, 1.03) | 0.466 |
| **Arthritis** | Reference | |
| **CTDs** | 0.87 (0.47, 1.62) | 0.671 |
| **Vasculitis** | 1.81 (0.40, 8.16) | 0.404 |
| **Others** | 0.76 (0.08, 7.32) | 0.814 |
| Azathioprine | **2.60 (1.13, 5.95)** | **0.024** |
| Biologics | **0.48 (0.27, 0.83)** | **0.010** |
| ***Prior COVID-19 infection*** | | |
| *None* | Reference | |
| *Once* | 0.09 (0.03, 0.27) | **<0.001** |
| ≥ 2 | 0.35 (0.09, 1.29) | 0.094 |
| ***COVID-19 Vaccine type*** | | |
| BBIBP-CorV - Sinopharm | Reference | |
| CoronaVac -Sinovac | 0.73 (0.40, 1.33) | 0.303 |
| BNT162b2 (Pfizer-BioNTech) | 1.45 (0.60, 3.72) | 0.390 |
| mRNA-1273 (Moderna) | 0.77 (0.08, 7.66) | 0.826 |
| Gam-COVID-Vac (Sputnik V) | Empty | |
| JNJ-78436735 (Johnson & Johnson) | 0.81 (0.19, 3.38) | 0.771 |
| ChAdOx1 (Oxford AstraZeneca) | 1.81 (0.64, 2.30) | 0.546 |
| ***Discontinued treatment during COVID-19 vaccine*** | 1.17 (0.82, 3.80) | 0.140 |
| ***Prior COVID-19 Severity*** | | |
| Managed at home | Reference | |
| Managed at hospital | 2.45 (1.04, 5.78) | **0.040** |
| Needed ICU | 0.71 (0.22, 2.27) | 0.565 |
| Post vaccine flare required increase dose | 2.70 (1.00, 7.23) | **0.049** |

## Discussion

This large national study of COVID-19 vaccination in 890 patients with RMD enabled investigating the risk factors for post-COVID-19 vaccine AEs among a diverse sample of systemic rheumatic disease diagnoses and following a variety of COVID-19 vaccines. In this work, there was no significant difference in the frequency and pattern of reported post-vaccine AEs between RMD patients and controls. Severity of prior COVID-19 infection and use of azathioprine were associated with higher odds of reporting AEs, while biologic use was associated with lower odds. These findings support the safety of COVID-19 vaccines in patients with RMD.

The AEs, which were non-serious and involved local and systemic symptoms, were observed at a similar rate in RMD patients (77.19%) and controls (81.40%). Previous rates of post-COVID-vaccine AEs in RMD patients were similar to this work, ranging from 70.2% to 81%,[10,13] but lower rates were observed in the European Coronavirus Vaccine (COVAX) registry (47%), and in the COVID-19 Global Rheumatology Alliance Vaccine Survey (37%).[7,14] In a real-world digital cohort study including fully vaccinated healthy adults from the US, 8947 of 11 140 (80.3%) reported AEs[15]. A questionnaire from the Netherlands reported that 258 (51%) patients and 106 (52%) controls had at least one mild AE, and 105 (21%) patients and 38 (19%) controls reported moderate AEs after the first COVID-19 vaccine dose.[8] Localized pain was the most frequent AE (72.1%). Fatigue (41.3%), myalgia (32.6%), headache, and fever (25%) were the most common systemic symptoms, as in prior studies.[7,10,13]The American College of Rheumatology (ACR) recommends COVID-19 vaccination in RMD patients.[16] Current findings are in favor of these recommendations and offer reassurance regarding the safety profile of the vaccine.

The frequency of post-vaccine AEs was variable across RMD types, being higher in I-RMD patients. *Machado et al*[7] reported a similar AE profile in patients with I-RMDs and NI-RMDs in the COVAX registry. These variations are likely related to differences in the study populations, type of vaccine exposure, and diversity of AEs collected. The frequencies of most AEs were similar across RMD types; however, a larger proportion of I-RMD cases had injection site pain and general constitutional symptoms compared to NI-RMD cases. Regarding AEs of special interest, neurological symptoms were higher in NI-RMD (8.1%) compared with I-RMD (3.2%) patients.

Common reasons for vaccination hesitancy center around fears of rheumatic disease flare-ups, which have been reported in previous studies.[17-19] Because some vaccine AEs may resemble symptoms of underlying RMD flare, such as fatigue and arthralgia, we included only flares that required a medication change or an increased medication dose to enhance the specificity of the flare detection. The current data suggest that the risk of I-RMD post-vaccine flare is low (12.13%). Flares requiring a change in treatment following COVID-19 vaccination were reported by 11% in a study of 1377 patients with systemic rheumatic diseases (RDs) receiving mRNA vaccines,[20] and 15% in a study of >1000 patients in New York.[21] Another study has observed lower frequencies of disease flares requiring a change in treatment in 4.9% of patients with RDs.[22] Prior studies in patients with rheumatic diseases and systemic lupus erythematosus found a flare within 6 or 12 months prior to the COVID-19 vaccine to be associated with flares following vaccination.[20,23] A possible link is compatible with the natural history of the disease rather than being necessarily caused by COVID-19 vaccines. In the present study, we lacked information about prior flare history. Future long-term prospective studies to determine predictors of disease flare after COVID-19 vaccination in patients with RMD are needed.

Regarding post-vaccine breakthrough infections, we found that 2.9% and 8.1% of cases in the I-RMD and NI-RMD groups reported these events, respectively. The rate of COVID-19 infections post-vaccination can vary across COVID-19 variants. SARS-CoV-2 omicron breakthrough infections were detected in 431 (23%) of 1882 patients with immune-mediated inflammatory diseases and 210 (30%) of 708 controls, of whom the majority had received a COVID-19 vaccine dose within 3 months prior to infection.[24] In patients with autoimmune inflammatory diseases, delta-breakthrough infections occurred in 104 (5%) of 2206 vaccinated patients.[25] On the other hand, post-vaccine breakthrough infections occurred infrequently in the COVAX registry database (0.7% and 1.1% of cases in the I-RMD and NI-RMD groups, respectively).[7] Hospitalisation after a breakthrough infection was required in 1% of 890 patients with RMD, which is comparable to a previous study in patients with immune-mediated diseases (1% in 431 patients).[25]

Data from observational studies of patients receiving various immunosuppressive regimens are mixed, with some reports suggesting that patients receiving some anti-rheumatic therapies may be at increased risk of COVID-19 and its complications, while other studies suggest the same or a decreased risk compared with those not taking such therapies.[26-30] We found that temporary discontinuation of antirheumatic medications was frequent (206, 23.1%). This attitude resembles the results from the COVID-19 Global Rheumatology Alliance Vaccine Survey: 764 (28.9%) who decided to discontinue their medication use during the vaccination period.[14] The ACR recommended holding methotrexate, JAK inhibitors, abatacept, mycophenolate mofetil, and rituximab in certain patients with controlled disease.[16] In contrast, the EULAR did not advise temporarily stopping any of these medications (with the exception of rituximab) relative to when the vaccine against SARS-CoV-2 is administered.[31] Future studies are needed to firmly establish an evidence base for temporarily holding specific antirheumatic therapies to balance vaccine efficacy with the risk of disease flare.

Our study has identified several characteristics as potential risk factors for AEs following COVID-19 vaccination in patients with I-RMD. Biologic use was associated with a lower incidence of postvaccine AEs. The majority of studies emphasize that patients with immune-mediated inflammatory diseases receiving biologic therapies do not run any extra risk for AEs after COVID-19 vaccination[32-34] when compared with the general population. During the time of the vaccine, azathioprine use was independently associated with a higher incidence of post-vaccine AEs. Including the type of I-RMD (arthritis, CTD, vasculitis, and others) in the multivariate analysis support the conclusion that the association between these drugs and COVID-19 AEs depends on the drug specifically and not the underlying I-RMD.

The choice of type of COVID-19 vaccine should be based on a risk-benefit analysis. The Oxford-AstraZeneca vaccine tended to be associated with the risk of AEs following COVID-19 vaccination. In harmony, the Oxford-AstraZeneca vaccine was associated with the risk of AEs after COVID-19 vaccination[8] as well as the risk of thrombotic events.[35] There was no independent association between the demographic variables or comorbidities and the frequency of AEs. Importantly, no causal conclusions regarding vaccination and the development of AEs can be firmly drawn from this study.

Strengths of this study include the rapid dissemination via Egyptian College of Rheumatology networks, which that resulted in a large number of cases reported by rheumatologists and internists over a short period of time. Furthermore, requiring a change in treatment to define flare reduced the potential misclassification of outcome such that flare was less likely to be confused with common vaccine side effects, including fatigue, fever, and joint pain. However, our study has important limitations. This data is physician-reported, leading to possible over-reporting of flares and AEs. Time between vaccination and AEs is relatively short, not allowing us to draw conclusions regarding the long-term safety profile of vaccines against COVID-19. Moreover, the sample size of control group is substantially smaller. Finally, the cross-sectional design prevented a possible causal relationship with the COVID-19 vaccine AEs.

## Conclusion

In conclusion, our findings showed that the rate and type of AEs were comparable between RMD and healthy subjects, thus providing overall confidence in the COVID-19 vaccine's safety in people with RMDs. Interestingly, azathioprine use, prior COVID-19 infection and hospitalization are the most important risk factors associated with AEs of I-RMD following COVID-19 vaccines. Future studies should address the importance of continued long-term evaluation of the risks and benefits of specific medications in patients with RMDs during the COVID-19 vaccine.

## Acknowledgments

Hala A Raafat (Cairo), Samah A El-Bakry (Ain Shams), Alaa Mohamed (Assuit), Iman I El-Gazzar (Cairo), Samar M Fawzy (Cairo), Nahla N Eesa (Cairo), Amany El-Bahnasawy (Mansoura), Mohamed N Salem (Beni-Suef), Rasha M Fawzy (Benha), Ahmed Elsaman (Sohag), Nouran M Abaza (Ain Shams), Ahmed M Abdalla (Aswan), Amany R El-Najjar (Zagazig), Soha Senara (Fayoum), Safaa Sayed (Cairo), Emad El-Shebini (Menoufiya), Dina H El-Hammady (Helwan), Shereen Elwan (Tanta), Marwa A Amer (Alexandria), Maha E Ibrahim (Suez-Canal), Gehad Elsehrawy (Suez Canal), Ahmed Y Ismail (Beni-Suef), Wael Abdel Mohsen (South-Valley).

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