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Safety of COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases: A Cross-sectional Study in Egypt

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ABSTRACT

Objectives: To investigate the incidence and associated risk factors of adverse events following COVID-19 vaccination in patients with inflammatory and non-inflammatory rheumatic and musculoskeletal diseases (I-RMD and NI-RMD, respectively). ***Methods***: The Egyptian College of Rheumatology COVID-19 Study Group investigated physician-reported data (ECR-VaXurvey3) of RMD patients vaccinated against COVID-19 from December 2021 to June 2022, including their demographics, vaccination type, RMD diagnosis, treatments, post-vaccine flares, and other adverse events. The control group consisted of healthy, vaccinated individuals. ***Results:*** The ECR-VaXurvey3 included 890 vaccinated RMD patients, predominantly women (73.3%) with a mean age of 44.4 ± 12.1 years, and 172 controls. The RMD group comprised 816 (91.7%) with I-RMD and 74 (8.3%) with 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 adverse event. Post-vaccination COVID-19 infections and disease flares were reported in 2.9% and 12.1% of I-RMD patients and in 8.1% and 9.5% of NI-RMD patients (p = 0.018 and p = 0.497, respectively). The severity of prior COVID-19 infection (odds ratio (OR) = 2.4, 95% CI: 1.0–5.8; p = 0.040) and azathioprine use (OR = 2.6, 95% CI: 1.1–5.9; p = 0.024) were associated with higher post-vaccine adverse events, while biologic use was associated with fewer adverse events (OR = 0.5, 95% CI: 0.3–0.8; p = 0.010). ***Conclusions:*** Adverse events following COVID-19 vaccinations in patients with RMD are comparable to controls.

COVID-19, caused by SARS-CoV-2, was declared a pandemic by the World Health Organization on 11 March 2020.[1] Thereafter, the pandemic led to a dramatic loss of human life and unprecedented challenges 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 authorized for use during December 2020.[3] Later,

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numerous candidate vaccines emerged worldwide. The development of vaccines against COVID-19 was efficacious in reducing infectivity and decreasing morbidity and mortality.

Although vaccination is essential 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] There are a few studies that support the safety and effectiveness of COVID-19 vaccines in patients with RMD.[7–10] However, there is limited data on the vaccine-associated adverse effects and risk factors among these patients, many of whom take immunosuppressants.[11] This study explored rates and risk factors for COVID-19 vaccination-reported side effects in patients with rheumatic disease compared to healthy controls. Additionally, we aimed to determine if there were any significant differences in these parameters between patients with inflammatory RMDs (I-RMDs) and non-inflammatory RMDs (NI-RMDs).

METHODS

This cross-sectional study was carried out by the Egyptian College of Rheumatology-COVID-19 study group, which invited physicians (rheumatologists and internists) across Egypt via social network communications to participate in the ECR-VaXurvey3. Physicians reported data from December 2021 to June 2022. All patients presenting for an appointment who had pre-existing RMD and had received one or more doses of any vaccine against COVID-19 with or without adverse events 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 the research was conducted in compliance with the Helsinki Declaration.[12] The objectives of the study and participant rights were disclosed to all potential participants. Those who provided informed written consent were included.

The RMD cases in the study were divided into I-RMD and NI-RMD types and included primary diseases as chosen by Machado et al,[7] COVID-19 vaccine clinical study on autoimmune rheumatic diseases.

Under I-RMDs, we included these primary diseases: (1) inflammatory arthritis: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, axial spondylarthritis, inflammatory bowel disease, reactive arthritis, and palindromic rheumatism; (2) connective tissue diseases (CTDs): systemic lupus erythematosus (SLE), systemic sclerosis, antiphospholipid syndrome, Sjögren's syndrome, inflammatory myositis (dermatomyositis, polymyositis), overlap syndrome, mixed CTDs, and undifferentiated CTDs; (3) vasculitis (small and medium vasculitis); and (4) others: Behcet Disease, autoinflammatory diseases such as familial Mediterranean fever and sarcoidosis. Under NI-RMD were included: (1) osteoarthritis, (2) osteoporosis, (3) crystal arthropathy, and (4) fibromyalgia syndrome and complex regional pain syndrome.[7]

The following information was collected and entered into an Excel spreadsheet: (1) participant's characteristics including age, sex, educational level, comorbidities including diabetes, obesity, hypertension, respiratory diseases, or cardiovascular disease; (2) details of primary RMD diagnoses and disease activity, as assessed by Physician Global Assessment, as well as immunomodulatory/immunosuppressive treatments at the time of vaccination and I-RMD flare-up following vaccination that required a change in rheumatic medication; and (3) COVID-19 vaccination history including willingness 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 adverse events.

Medications taken by patients at the time of the COVID-19 vaccine were categorized as: (1) conventional synthetic drugs including hydroxychloroquine, sulfasalazine, methotrexate, leflunomide, mycophenolate mofetil, cyclophosphamide, and azathioprine; (2) biologics including tumor necrosis factor inhibitors, abatacept, belimumab, rituximab, interleukin (IL)-6 inhibitors, and IL-17 inhibitors; and (3) targeted synthetic drugs, specifically JAK inhibitors and

glucocorticoids. Any history of discontinuation of anti-rheumatic drugs after the COVID-19 vaccination was included.

Adverse events occurring within six months of receiving a COVID-19 vaccine and lasting for at least two days included symptoms such as pain, redness or swelling at the site of injection, headache, fever, fatigue, chills, generalized muscle pain, joint pain or swelling, low back pain, abdominal pain, vomiting and diarrhea, 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 adverse events were chosen because they have been reported in vaccine clinical trials and were reported by physicians.

For statistical analysis, we used Stata software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP.). Continuous variables were expressed as mean (± SD) and categorical variables as percentages. A two-sided independent *t*-test and Chi-square (χ^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 adverse events (no vs. yes) among the population with RMDs. First, we used univariate logistic analysis to investigate the variables associated with the occurrence of any adverse events. Then, multivariate logistic regression included variables with a *p*-value < 0.100. Results were reported as odds ratios (OR) and 95% CI. *P*-values < 0.05 were considered statistically significant.

RESULTS

The study included 890 RMD patients and 172 healthy controls who had received the COVID-19 vaccination. Participant details were received from healthcare practitioners in different specialties, working in 30 different centers located in Egypt. They were mostly affiliated with various medical institutions, except for a few private practitioners.

The demographic features and clinical characteristics of the participating RMD patients and healthy controls are compared in Table 1.

The significant comorbidities among the RMD patients were hypertension in 160 (18.0%) patients, obesity in 120 (13.5%), and respiratory diseases in 48 (5.4%). Apart from the educational level, the demographic characteristics and frequencies of comorbidities were similar in patients and controls. The frequency of prior COVID-19 infection was significantly lower in patients with RMD compared to controls (70.0% vs. 84.8%; $p = 0.002$); however, the severity of prior infection was similar in both groups. The majority (77.2%) of RMD patients and (81.4%) controls reported at least one adverse event following vaccination. Apart from injection site pain, there was no significant difference in the individual adverse events between RMD patients and controls. The most frequently reported adverse event in patients with RMD was injection site pain or swelling (59.9%), fatigue (44.7%), myalgia (38.0%), headache (29.9%), and arthralgia (27.1%). A minority (30, 3.4%) of patients reported post-vaccine COVID-19 infection, while none of the controls did. Table 2 compares the demographic and clinical characteristics of I-RMD and NI-RMD patients.

Our participants were administered different types of vaccines, which had not significant association with adverse events [Table 2]. The vast majority (91.7%) of patients had I-RMDs, while the remaining 8.3% had NI-RMDs. Most I-RMD patients' (78.8%) primary diagnosis was inflammatory joint disease, while osteoarthritis (51.4%) and osteoporosis (23.0%) were the most frequent in NI-RMDs. Hydroxychloroquine, methotrexate, and leflunomide were the most commonly used anti-rheumatic drugs in patients with I-RMD [Table 2].

A comparison of prevalence of post-vaccination adverse events reported by the NI-RMD, IRMD, and control groups are listed in Table 3. Details of adverse events reported by I-RMD patients, stratified by the types of rheumatic flare-up, are given in the Appendix [Supplementary Table 1].

Table 3 shows that the control group was significantly more likely to report injection pain compared to the RMD group (72.1% vs. 59.9%; $p =$

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

Parameters	RMD patients (N = 890) n (%)	Controls (n = 172) n (%)	*p*-value
Age, years, mean ± SD	44.4 ± 12.1	44.4 ± 13.9	0.994
Sex, female	652 (73.3)	114 (66.3)	0.062
Marital status			
Single	58 (6.5)	18 (10.5)	0.140
Married	737 (82.8)	135 (78.5)	
Widowed, divorced, unknown	95 (10.7)	19 (11.0)	
Residency			
Urban	525 (59.0)	110 (64.0)	0.224
Rural	365 (41.0)	62 (36.0)	
Educational level			
Secondary level or lower	360 (40.4)	44 (25.6)	< 0.001*
Higher than secondary level	427 (48.0)	119 (69.2)	
Illiterate	103 (11.6)	9 (5.2)	
Comorbidities			
Diabetes mellitus	93 (10.4)	15 (8.7)	0.490
Hypertension	160 (18.0)	27 (15.7)	0.472
Obesity	120 (13.5)	21 (12.2)	0.652
Chest diseases	48 (5.4)	4 (2.3)	0.088
Cardiovascular	36 (4.0)	10 (5.8)	0.297
Thyroid dysfunction	38 (4.3)	6 (3.5)	0.638
Number of Comorbidities			
None	557 (62.7)	118 (68.6)	0.551
One or more	332 (37.3)	54 (31.4)	
Prior COVID-19 infection			
None	231 (30.0)	24 (15.2)	0.002*
One or more	539 (70.0)	134 (84.8)	
Prior COVID-19 infection severity			
Managed at home	532 (82.0)	117 (85.4)	0.344
Managed at hospital	92 (14.2)	18 (13.1)	
Needed ICU	25 (3.9)	2 (1.5)	
COVID-19 Vaccine type			
BBIBP-CorV-Sinopharm	376 (42.2)	58 (33.7)	0.019*
CoronaVac-Sinovac	192 (21.6)	35 (20.3)	
BNT162b2 (Pfizer-BioNTech)	105 (11.8)	19 (11.0)	
mRNA-1273 (Moderna)	17 (1.9)	2 (1.2)	
Gam-COVID-Vac (Sputnik V)	8 (0.9)	0 (0.0)	
JNJ-78436735 (Johnson & Johnson)	24 (2.7)	4 (2.3)	
ChAdOx1 (Oxford AstraZeneca)	166 (18.7)	53 (30.8)	
Unknown	2 (0.2)	1 (0.6)	
COVID-19 vaccine doses			
One dose	137 (15.4)	11 (6.4)	0.002*
Two doses	753 (84.6)	161 (93.6)	
Booster dose	206 (23.1)	40 (23.3)	0.975
Post-vaccine COVID-19 (breakthrough infection)	30 (3.4)	0 (0.0)	
Post-vaccine COVID-19 infection needing hospitalization	10 (1.1)	0 (0.0)	

**Significance. ICU: intensive care unit.*

Table 2: Demographic and clinical characteristics of patients with inflammatory and non-inflammatory rheumatic and musculoskeletal diseases (I-RMD and NI-RMD) (N = 890).

Parameters	I-RMD (n = 816) n (%)	NI-RMD (n = 74) n (%)	*p*-value
Age, years, Mean ± SD	43.9 ± 12.1	50.0 ± 11.7	< 0.001*
Sex, female	602 (73.8)	50 (67.6)	0.248
Marital status			
Single	51 (6.2)	7 (9.5)	0.044*
Married	684 (83.8)	53 (71.6)	
Widowed, divorced, unknown*	81 (9.9)	14 (18.9)	
Educational level			
Secondary level or lower	340 (41.7)	20 (27.0)	< 0.001*
Higher than secondary level	378 (46.3)	49 (66.2)	
Illiterate	98 (12.0)	5 (6.8)	
Residency			
Urban	463 (56.7)	62 (83.8)	< 0.001*
Rural	353 (43.3)	12 (16.2)	
Comorbidities			
Diabetes mellitus	81 (9.9)	12 (16.2)	0.091
Hypertension	140 (17.2)	20 (27.0)	0.034*
Obesity	109 (13.4)	11 (14.9)	0.716
Chest diseases	44 (5.4)	4 (5.4)	0.996
Cardiovascular	28 (3.4)	8 (10.8)	0.002*
Thyroid dysfunction	32 (3.9)	6 (8.1)	0.088
Number of Comorbidities			
None	525 (64.3)	32 (43.2)	0.010*
One or more	291 (35.7)	42 (56.8)	
Disease duration, years	7.0 ± 5.9	5.1 ± 4.3	0.007*
Age at onset, years	36.9 ± 11.2	44.9 ± 10.4	< 0.001*
PGA (0–10)	4.8 ± 2.4	3.7 ± 2.7	< 0.001*
Medications			
Hydroxychloroquine	505 (61.9)	5 (6.8)	< 0.001*
Methotrexate	422 (51.7)	0 (0.0)	
Leflunomide	238 (29.2)	0 (0.0)	
Azathioprine	150 (18.4)	2 (2.7)	0.001*
Sulfasalazine	53 (6.5)	0 (0.0)	
Mycophenolate mofetil	48 (5.9)	0 (0.0)	
Cyclophosphamide	32 (3.9)	0 (0.0)	
Cyclosporine A	8 (1.0)	0 (0.0)	
Biologics**	174 (21.3)	4 (5.4)	0.001*
Steroid	0.7 ± 0.5	0.1 ± 0.4	< 0.001*
Steroid ≥10 mg/day	40 (13.5)	0 (0.0)	
Prior COVID-19 infection			
None	214 (30.7)	17 (23.6)	< 0.001*
One or more	484 (68.3)	55 (76.4)	
Prior COVID-19 infection severity			
Managed at home	484 (82.6)	48 (76.2)	0.047*
Managed at hospital	83 (14.2)	9 (14.3)	
Needed ICU	19 (3.2)	6 (9.5)	
COVID-19 Vaccine Type			
BBIBP-CorV-Sinopharm	354 (43.5)	22 (29.7)	0.001*
CoronaVac-Sinovac	179 (21.9)	13 (17.6)	
BNT162b2 (Pfizer-BioNTech)	98 (12.0)	7 (9.5)	

Table 2: Demographic and clinical characteristics of patients with inflammatory and non-inflammatory rheumatic and musculoskeletal diseases (I-RMD and NI-RMD) (N = 890).

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Parameters	I-RMD (n = 816) n (%)	NI-RMD (n = 74) n (%)	*p*-value
mRNA-1273 (Moderna)	15 (1.8)	2 (2.7)	
Gam-COVID-Vac (Sputnik V)	8 (1.0)	0 (0.0)	
JNJ-78436735 (Johnson & Johnson)	18 (2.2)	6 (8.1)	
ChAdOx1 (Oxford AstraZeneca)	142 (17.4)	24 (32.4)	
Unknown	2 (0.2)	0 (0.0)	
COVID-19 vaccine doses			
One dose	104 (12.7)	33 (44.6)	< 0.001*
Two doses	712 (87.3)	41 (55.4)	
Booster dose	176 (21.6)	30 (40.5)	< 0.001*
Patient attitudes towards vaccination			
Willing to be vaccinated	426 (52.2)	51 (68.9)	0.006*
Vaccination was encouraged by physician	549 (67.3)	42 (56.8)	0.066
Post vaccination events			
RMD treatment discontinued	176 (21.6)	30 (40.5)	< 0.001*
COVID-19 breakthrough infection	24 (2.9)	6 (8.1)	0.018*
COVID-19 breakthrough infection needing hospitalization	9 (1.1)	1 (1.4)	0.846
Development of rheumatic disease or antibodies	25 (3.1)	10 (13.5)	< 0.001*
RMD flare up requiring treatment or dosage change	99 (12.1)	7 (9.5)	0.497

**Significance; **Biologics include tumor necrosis factor inhibitors (anti-TNF), abatacept, belimumab, rituximab, interleukin (IL)-6 inhibitors, and IL-17 inhibitors, and targeted synthetic drugs, specifically JAK inhibitors.*

0.003). The control group also reported higher rates of other minor events such as fatigue, headache, and myalgia, albeit without statistical significance. The RMD group reported more arthralgia, arthritis, and neurological events, of which only arthritis showed a significant difference between the two groups (7.8% vs. 0%; <0.001).

I-RMD patients reported more overall adverse events than NI-RMD patients (79.3% vs. 45.1%; $p < 0.001$). There was a significantly higher prevalence of injection site pain and constitutional symptoms (headache, myalgia) in the I-RMD group. On the other hand, neurological manifestations were higher in the NI-RMD group (8.1% vs. 3.2% $p = 0.029$). Patients within the I-RMD group had a comparable overall distribution of adverse events when stratified by rheumatic diseases (RDs) [Table 3].

The frequency of post-vaccine fatigue was highest in the CTDs group (59.3%) and vasculitis group (47.8%), and the frequency of palpitation was lowest in subjects with CTDs (2.8%), followed by inflammatory arthritis (3.6%). Disease flares requiring changes in treatment following COVID-19 vaccination were reported by 12.1% of I-RMD patients and by 9.8% of NI-RMD patients. Patients with NI-RMD had a higher frequency of post-COVID-19 breakthrough infections compared to I-RMD (8.1% vs. 2.9%, $p = 0.018$).

Among all RMD patients, I-RMD (OR = 4.8, 95% CI: 2.2–10.6; $p < 0.001$), disease flare requiring change dose of treatment (OR = 4.8, 95% CI: 1.8–13.1; $p = 0.002$), azathioprine use during the time of vaccine (OR = 3.3, 95% CI: 1.5–7.5; $p = 0.004$), hydroxychloroquine use (OR = 0.4, 95% CI: 0.2–0.7; $p = 0.003$), and biologic use (OR = 0.4, 95% CI: 0.2–0.7; $p = 0.001$) were associated with COVID-19 vaccine adverse events in a multivariate analysis (data not shown).

A multivariate analysis of the risk factors for post-vaccine adverse events among patients with I-RMD was performed. Previous COVID-19 infections requiring hospitalization were associated with more post-vaccine adverse events (OR = 2.4, 95% CI: 1.0–5.8; $p = 0.040$). Azathioprine use during the time of vaccination was associated with a higher incidence of adverse events (OR = 2.6, 95% CI: 1.1–5.9; $p =$

Table 3: Comparison of frequencies of adverse events after COVID-19 vaccination between patients with rheumatic and musculoskeletal diseases (RMD) and the control group, as well as between patients with inflammatory and non-inflammatory types of RMD.

Variables	Total study participants			RMD group		
	Control group (n = 172) n (%)	RMD group (N = 890) n (%)	*p*-value	NI-RMD (n = 74) n (%)	I-RMD (n = 816) n (%)	*p*-value
Any adverse events	140 (81.4)	687 (77.2)	0.224	40 (54.1)	647 (79.3)	< 0.001*
Injection site pain	124 (72.1)	533 (59.9)	0.003*	26 (35.1)	507 (62.1)	< 0.001*
Dizziness	31 (18.0)	135 (15.2)	0.345	8 (10.8)	127 (15.6)	0.275
Fatigue	71 (41.3)	398 (44.7)	0.406	20 (27.0)	378 (46.3)	0.001*
Fever	43 (25.0)	261 (29.3)	0.251	15 (20.3)	246 (30.1)	0.074
Chills	23 (13.4)	100 (11.2)	0.426	5 (6.8)	95 (11.6)	0.202
Sleepiness	7 (4.1)	70 (7.9)	0.078	6 (8.1)	64 (7.8)	0.938
Headache	43 (25.0)	266 (29.9)	0.196	9 (12.2)	257 (31.5)	0.001*
Myalgia	56 (32.6)	338 (38.0)	0.178	15 (20.3)	323 (39.6)	0.001*
Arthralgia	40 (23.3)	241 (27.1)	0.298	8 (10.8)	233 (28.6)	0.001*
Arthritis	0 (0.0)	69 (7.8)	< 0.001*	5 (6.8)	64 (7.8)	0.738
Low back pain	5 (2.9)	44 (4.9)	0.244	2 (2.7)	42 (5.1)	0.353
Allergic reaction	0 (0.0)	14 (1.6)	0.098	0 (0.0)	14 (1.7)	0.256
Anaphylaxis	0 (0.0)	5 (0.6)	0.324	0 (0.0)	5 (0.6)	0.500
Rash	0 (0.0)	13 (1.5)	0.111	0 (0.0)	13 (1.6)	0.274
Cardiovascular	2 (1.2)	12 (1.4)	0.845	0 (0.0)	12 (1.5)	0.294
Chest pain	4 (2.3)	33 (3.7)	0.365	2 (2.7)	31 (3.8)	0.633
Palpitation	7 (4.1)	33 (3.7)	0.819	3 (4.1)	30 (3.7)	0.869
Dyspnea	3 (1.7)	30 (3.4)	0.514	3 (4.1)	27 (3.3)	0.882
Nausea/vomiting	5 (2.9)	51 (5.7)	0.129	3 (4.1)	48 (5.9)	0.516
Diarrhea	8 (4.7)	44 (4.9)	0.871	5 (6.8)	39 (4.8)	0.452
Abdominal pain	9 (5.2)	48 (5.4)	0.932	4 (5.4)	44 (5.4)	0.996
Neurological events	2 (1.2)	32 (3.6)	0.101	6 (8.1)	26 (3.2)	0.029*

**p <0.05; I-RMD: inflammatory RMD; NI-RMD: non-inflammatory RMD.*

0.024), while it was lower with biologics use (OR = 0.5, 95% CI: 0.3–0.8; $p = 0.010$) [Tables 4 and 5].

Demographics, comorbidities, and glucocorticoid use were not significantly associated with the prevalence of adverse events. However, Oxford AstraZeneca vaccine administration was associated with higher adverse events ($p = 0.009$) [Table 4].

DISCUSSION

This large nationally representative study in Egypt investigated the adverse events following COVID-19 vaccination among patients with various types of RMD from different parts of Egypt.

Interestingly, our control subjects were more likely than RMD patients to report minor post-vaccine adverse events, particularly injection pain ($p = 0.003$). Similar findings were also reported in a major study by Machado et al.[7] However, this is counterintuitive, because RMD patients typically have a lower pain threshold than healthy individuals. The explanation is likely psychological, related to how past pain is remembered. People whose daily lives are pain-free may experience less pain but *recall* those moments more vividly when asked later. Conversely, individuals who deal with chronic pain may have less vivid memories of minor adverse events. If so, future studies that rely on patients' memories of past adverse events need to consider whether this phenomenon is a potential confounder.

Our patients with I-RMD were significantly more likely to report adverse events compared to those with NI-RMD. We also found that the severity of prior COVID-19 infection and use of azathioprine were associated with higher odds of

Table 4: Univariate analysis of factors associated with experiencing side effects of the vaccine among patients with inflammatory rheumatic and musculoskeletal diseases (I-RMD).

Variables	OR (95% CI)	*p*-value
Age, years	0.9 (0.9–1.0)	0.186
Sex, male	1.2 (0.8–1.8)	0.396
Disease duration	0.9 (0.9–0.9)	0.017*
Age of onset, years	0.9 (0.9–1.0)	0.791
I-RMD types		
Arthritis	Reference	
CTDs	1.6 (1.0–2.6)	0.061
Vasculitis	1.9 (0.6–6.5)	0.303
Others	1.1 (0.1–10.3)	0.905
RMD medications		
Methotrexate	0.8 (0.5–1.1)	0.138
Hydroxychloroquine	1.0 (0.7–1.4)	0.916
Sulfasalazine	1.3 (0.6–2.7)	0.489
Azathioprine	3.2 (1.8–5.8)	< 0.001*
Leflunomide	0.9 (0.6–1.3)	0.481
Cyclophosphamide	0.6 (0.3–1.2)	0.138
Biologics	0.5 (0.3–0.7)	< 0.001*
Steroids	1.4 (0.9–2.2)	0.156
Steroid dosage		
< 10 mg/day	Reference	0.262
≥ 10 mg/day	1.7 (0.7–4.2)	
Other chronic conditions		
Diabetes mellitus	1.6 (0.8–.0)	0.169
Hypertension	0.7 (0.5–1.1)	0.110
Obesity	0.8 (0.5–1.3)	0.385
Chest diseases	0.7 (0.3–1.3)	0.272
Cardiovascular	1.6 (0.5–4.6)	0.397
Thyroid dysfunction	0.8 (0.3–1.8)	0.542
Number of comorbidities		
None	Reference	0.135
One or more	0.7 (0.5, 1.0)	
Prior COVID-19 infection		
None	Reference	
Once	0.9 (0.6–1.3)	0.581
≥ 2	4.1 (1.9–9.0)	< 0.001*
COVID-19 vaccine type		
BBIBP-CorV-Sinopharm	Reference	
CoronaVac-Sinovac	0.8 (0.5–1.2)	0.312
BNT162b2 (Pfizer-BioNTech)	1.6 (0.9–2.9)	0.133
mRNA-1273 (Moderna)	0.8 (0.2–2.5)	0.693
Gam-COVID-Vac (Sputnik V)	0.9 (0.2–4.3)	0.857
JNJ-78436735 (Johnson & Johnson)	1.0 (0.3–3.1)	0.993
ChAdOx1 (Oxford AstraZeneca)	2.1 (1.2–3.7)	0.009*
Treatment discontinued after vaccination	1.8 (1.2–3.0)	0.010*
Prior COVID-19 Severity		
Managed at home	Reference	
Managed at hospital	2.0 (0.9–4.5)	0.089
Needed ICU	0.5 (0.2–1.5)	0.224
Post-vaccine flare required higher MRD medication dosage	4.6 (2.0–10.6)	< 0.001*

**Significance; OR: odds ratio; CTD: connective tissue disease; MRD: multidrug resistance; ICU: intensive care unit.*

reporting adverse events, while the use of biologics was associated with lower odds.

As stated earlier, overall adverse events were reported at slightly higher rates by controls (81.3%) than by RMD patients (77.2%), mainly due to higher reportage of non-serious adverse events by controls. In previous studies, rates of post-COVID-vaccine adverse events in RMD patients were similar to ours, 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 USA, 8947 of 11 140 (80.3%) reported adverse events.[15] A study from the Netherlands reported that 51% of patients and 52% of controls had at least one mild adverse event, while 21% of patients and 19% of controls reported moderate adverse events after the first COVID-19 vaccine dose.[8] In our study, systemic symptoms such as localized pain (72.1%), fatigue (41.3%), myalgia (32.6%), headache, and fever (25.0%) were the most common adverse events similar to findings elsewhere.[7,10,13]

Overall, the current study's findings support the safety of COVID-19 vaccines in Egyptian patients with RMD, and are reinforced by recommendation by the American College of Rheumatology to vaccinate RMD patients.[15]

In the current study, the frequency of post-vaccine adverse events varied across RMD types and was higher in I-RMD patients. Regarding adverse events of special interest, neurological symptoms

Table 5: Multivariate analysis of factors associated with vaccine side effects among patients with inflammatory rheumatic and musculoskeletal diseases (I-RMD).

Variables	OR (95%CI)	*p*-value
Age, years	1.0 (1.0–1.0)	0.929
Sex, male	1.2 (0.7–1.5)	0.680
Duration of the I-RMD	1.0 (0.9–1.0)	0.466
Arthritis	Reference	
CTDs	0.9 (0.5–1.6)	0.671
Vasculitis	1.8 (0.4–8.2)	0.404
Others	0.8 (0.9–7.3)	0.814
Azathioprine	2.6 (1.1–5.9)	0.024*
Biologics	0.5 (0.3– 0.8)	0.010*
Prior COVID-19 infection		
None	Reference	
Once	0.1 (0.0–0.3)	< 0.001*
≥ 2	0.3 (0.1–1.3)	0.094
COVID-19 vaccine type		
BBIBP-CorV-Sinopharm	Reference	0.303
CoronaVac-Sinovac	0.7 (0.4–1.3)	0.390
BNT162b2 (Pfizer-BioNTech)	1.4 (0.6–3.7)	0.826
mRNA-1273 (Moderna)	0.8 (0.1–7.7)	-
Gam-COVID-Vac (Sputnik V)	-	0.771
JNJ-78436735 (Johnson & Johnson)	0.8 (0.2–3.4)	0.546
ChAdOx1 (Oxford AstraZeneca)	1.8 (0.6–2.3)	
Treatment discontinued after COVID-19 vaccination	1.2 (0.8–3.8)	0.140
Prior COVID-19 severity and management		
Managed at home	Reference	
Managed at hospital	2.4 (1.0–5.8)	0.040*
Needed ICU	0.7 (0.2–2.3)	0.565
Post-vaccine flare required higher MRD medication dosage	2.7 (1.0–7.2)	0.049*

**Significance; OR: odds ratio; CTD: connective tissue disease; ICU: intensive care unit; MRD: multidrug resistance.*

were higher in NI-RMD (8.1%) compared with I-RMD (3.9%) patients. Machado et al,[7] reported a similar adverse event 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 adverse events collected. The frequencies of most adverse events in our patients were similar across RMD types; however, a larger proportion of the I-RMD patients reported injection site pain and general constitutional symptoms compared to NI-RMD patients.

Common reasons for vaccination hesitancy center around fears of RD flare-ups, as reported in previous studies.[16–18] Because some post-vaccination adverse events such as fatigue and arthralgia resemble symptoms of underlying RMD flare, we included only flares that required a medication change or an increased medication dose to enhance the specificity of the flare detection.

The risk of post-vaccine flare was 12.1% among our I-RMD patients. Flares requiring a change in treatment following COVID-19 vaccination were reported by 11% in a study of 1377 patients with systemic RDs receiving mRNA vaccines,[19] and 15% in a study of > 1000 RD patients in New York,[20] while another study observed much lower frequencies (4.9%).[21] Prior studies in patients with RDs and SLE found that the occurrence of a flare six to 12 months before COVID-19 vaccination made post-vaccination flares more likely.[19,22] In the present study, we lacked information about prior flare history. It is also possible that the natural history of the disease is more predictive of flare recurrence than COVID-19 vaccination. Future long-term prospective studies are needed to determine predictors of disease flare after COVID-19 vaccination in patients with RMD.

In the current study, post-vaccine breakthrough infections occurred in 2.9% of the I-RMD group and 8.1% of the NI-RMD group. Such reinfections have been attributed to the greater infectivity of later strains of the SARS-CoV-2, particularly the Omicron and the Delta variants.[23] A study in the Netherlands detected Omicron breakthrough infections in 23% of 1882 patients with immune-mediated inflammatory diseases and 30% of controls.[23] Most of them had received a COVID-19 vaccine dose less than three months before being reinfected. In another Dutch study, breakthrough Delta variant infections occurred in 5% of 2206 vaccinated patients with autoimmune inflammatory diseases.[24] On the other hand, post-vaccine breakthrough infections were significantly lower in the COVAX registry database (0.7% and 1.1% of cases in the I-RMD and NI-RMD groups, respectively).[7] In the current study, hospitalization after a breakthrough infection was required for 1.1% of 890 patients with RMD, which is comparable to results from the earlier mentioned Dutch study where 1% of 431 patients with immune-mediated diseases experienced breakthrough infections.[24]

Observational studies on patients using immunosuppressive regimens have yielded mixed

results. Some reports suggest an increased risk of COVID-19 and its complications for patients who take specific anti-rheumatic therapies, while others indicate the same or even a decreased risk compared with those not on such therapies.[25–28,29] The American College of Rheumatology recommended patients with controlled RMD to pause using methotrexate, JAK inhibitors, abatacept, mycophenolate mofetil, and rituximab after receiving COVID-19 vaccinations.[15] Nearly a quarter (23.1%) of RMD patients in the current study temporarily discontinued their anti-rheumatic medications after vaccination. Similar behavior was reported by 28.9% of RMD patients who participated in the COVID-19 Global Rheumatology Alliance Vaccine Survey.[14] In contrast, the European Alliance of Associations for Rheumatology 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.[30] Future studies are needed to establish an evidence base for temporarily holding specific anti-rheumatic therapies to balance vaccine efficacy with the risk of disease flare.

Our study has identified several characteristics as potential risk factors for adverse events following COVID-19 vaccination in patients with I-RMD. Biologic use was associated with a lower incidence of post-vaccine adverse events. Most previous studies suggest that patients with immune-mediated inflammatory diseases receiving biologic therapies may not be at additional risk for adverse events after COVID-19 vaccination.[31–33] However, azathioprine use was independently associated with a higher incidence of post-vaccination adverse events. Including the type of I-RMD (arthritis, CTD, vasculitis, and others) in the multivariate analysis supports the conclusion that the associations between RMD drugs and COVID-19 adverse events depend on the specific drug and not the underlying I-RMD.

In the present study, the Oxford-AstraZeneca vaccine was the only one that showed a significant risk of adverse events in RMD patients. The choice of type of COVID-19 vaccine should be based on a risk-benefit analysis. In harmony, the Oxford-AstraZeneca vaccine was associated with the risk of adverse events after COVID-19 vaccination[8] as well as the risk of thrombotic events.[34] There was no independent association between the demographic variables or comorbidities and the frequency of adverse events. Importantly, no causal conclusions regarding vaccination and the development of adverse events can be firmly drawn from this study.

Strengths of this study include the rapid dissemination of nationwide data reported by rheumatologists and internists through the Egyptian College of Rheumatology networks. Furthermore, defining a post-vaccination flare as one that required a change in treatment reduced the potential misclassification of outcomes, making it less likely to be confused with common vaccine side effects, such as fatigue, fever, and joint pain. However, our study has important limitations. Firstly, this data is physician-reported, leading to possible misestimations of adverse events. Secondly, the short time between vaccination and adverse events limits our ability to draw conclusions regarding the long-term safety profile of COVID-19 vaccines. Moreover, the control group was significantly smaller than the RMD group. Finally, the cross-sectional design prevented us from establishing a causal relationship between the COVID-19 vaccine and adverse events.

CONCLUSION

Our findings showed that the rate and type of adverse events 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 adverse events of I-RMD following COVID-19 vaccination. 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.

Disclosure
The authors declare no conflicts of interest. No funding was received for this study.

Data Availability Statement
Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed 2020 Mar;91(1):157-160.
2. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2022 [cited 2022 Oct 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776/.
3. 3. Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO. SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. NPJ Vaccines 2021;6(1):1-17.
4. Fagni F, Simon D, Tascilar K, Schoenau V, Sticherling M, Neurath MF, et al. COVID-19 and immune-mediated inflammatory diseases: effect of disease and treatment on COVID-19 outcomes and vaccine responses. Lancet Rheumatol 2021 Oct;3(10):e724-e736.
5. Schulze-Koops H, Specker C, Skapenko A. Vaccination of patients with inflammatory rheumatic diseases against SARS-CoV-2: considerations before widespread availability of the vaccines. RMD Open 2021 Feb;7(1):e001553.
6. Furer V, Rondaan C, Agmon-Levin N, van Assen S, Bijl M, Kapetanovic MC, et al. Point of view on the vaccination against COVID-19 in patients with autoimmune inflammatory rheumatic diseases. RMD Open 2021 Feb;7(1):e001594.
7. Machado PM, Lawson-Tovey S, Strangfeld A, Mateus EF, Hyrich KL, Gossec L, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR coronavirus vaccine (COVAX) physician-reported registry. Ann Rheum Dis 2022 May;81(5):695-709.
8. Boekel L, Kummer LY, van Dam KP, Hooijberg F, van Kempen Z, Vogelzang EH, et al. Adverse events after first COVID-19 vaccination in patients with autoimmune diseases. Lancet Rheumatol 2021 Aug;3(8):e542-e545.
9. Aboud FM, Hussein RS, Hassan RM. Safety and reported adverse effects of coronavirus disease-2019 (COVID-19) vaccines in patients with rheumatic diseases. Egypt Rheumatol 2023 Apr;45(2):133-137.
10. Esquivel-Valerio JA, Skinner-Taylor CM, Moreno-Arquieta IA, Cardenas-de la Garza JA, Garcia-Arellano G, Gonzalez-Garcia PL, et al. Adverse events of six COVID-19 vaccines in patients with autoimmune rheumatic diseases: a cross-sectional study. Rheumatol Int 2021 Dec;41(12):2105-2108.
11. Wieske L, Kummer LY, van Dam KP, Stalman EW, van der Kooi AJ, Raaphorst J, et al; T2B! immunity against SARS-CoV-2 study group. Risk factors associated with short-term adverse events after SARS-CoV-2 vaccination in patients with immune-mediated inflammatory diseases. BMC Med 2022 Mar;20(1):100.
12. Cantín M. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. Reviewing the latest version. International Journal of Medical and Surgical Sciences 2014;1(4):339-346.
13. Li YK, Lui MP, Yam LL, Cheng CS, Tsang TH, Kwok WS, et al. COVID-19 vaccination in patients with rheumatic diseases: vaccination rates, patient perspectives, and side effects. Immun Inflamm Dis 2022 Mar;10(3):e589.
14. Sattui SE, Liew JW, Kennedy K, et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open 2021;7(3):e001814.
15. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, et al. American college of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 4. Arthritis Rheumatol 2022 May;74(5):e21-e36.
16. Abualfadl E, Ismail F, Shereef RR, Hassan E, Tharwat S, Mohamed EF, et al; ECR COVID19-Study Group. Impact of COVID-19 pandemic on rheumatoid arthritis from a multi-centre patient-reported questionnaire survey: influence of gender, rural-urban gap and north-south gradient. Rheumatol Int 2021 Feb;41(2):345-353.
17. Boekel L, Hooijberg F, van Kempen ZL, Vogelzang EH, Tas SW, Killestein J, et al. Perspective of patients with autoimmune diseases on COVID-19 vaccination. Lancet Rheumatol 2021 Apr;3(4):e241-e243.
18. Priori R, Pellegrino G, Colafrancesco S, Alessandri C, Ceccarelli F, Di Franco M, et al. SARS-CoV-2 vaccine hesitancy among patients with rheumatic and musculoskeletal diseases: a message for rheumatologists. Ann Rheum Dis 2021 Jul;80(7):953-954.
19. Connolly CM, Ruddy JA, Boyarsky BJ, Barbur I, Werbel WA, Geetha D, et al. Disease flare and reactogenicity in patients with rheumatic and musculoskeletal diseases following two-dose SARS-CoV-2 messenger RNA vaccination. Arthritis Rheumatol 2022 Jan;74(1):28-32.
20. Barbhaiya M, Levine JM, Bykerk VP, Jannat-Khah D, Mandl LA. Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City. Ann Rheum Dis 2021 Oct;80(10):1352-1354.
21. Rider LG, Parks CG, Wilkerson J, Schiffenbauer AI, Kwok RK, Noroozi Farhadi P, et al; COVID-19 Global Rheumatology Alliance Vaccine Survey Group. Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults with systemic rheumatic disease: results from the COVID-19 global rheumatology alliance vaccine survey. Rheumatology (Oxford) 2022 Jun;61(SI2):SI143-SI150.
22. Felten R, Kawka L, Dubois M, Ugarte-Gil MF, Fuentes-Silva Y, Piga M, et al. Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: the international VACOLUP study. Lancet Rheumatol 2021 Sep;3(9):e613-e615.
23. Boekel L, Besten YR, Hooijberg F, Wartena R, Steenhuis M, Vogelzang E, et al. SARS-CoV-2 breakthrough infections in patients with immune-mediated inflammatory diseases during the omicron dominant period. Lancet Rheumatol 2022 Nov;4(11):e747-e750.
24. Boekel L, Stalman EW, Wieske L, Hooijberg F, van Dam KP, Besten YR, et al; T2B! immunity against SARS-CoV-2 study group. Breakthrough SARS-CoV-2 infections with the delta (B.1.617.2) variant in vaccinated patients with immune-mediated inflammatory diseases using immunosuppressants: a substudy of two prospective cohort studies. Lancet Rheumatol 2022 Jun;4(6):e417-e429.
25. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis 2020 Jul;79(7):859-866.
26. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al; COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis 2021 Jul;80(7):930-942.

27. Bachiller-Corral J, Boteanu A, Garcia-Villanueva MJ, de la Puente C, Revenga M, Diaz-Miguel MC, et al. Risk of severe COVID-19 infection in patients with inflammatory rheumatic diseases. J Rheumatol 2021 Jul;48(7):1098-1102.

28. Sparks JA, Wallace ZS, Seet AM, Gianfrancesco MA, Izadi Z, Hyrich KL, et al; COVID-19 Global Rheumatology Alliance. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: results from the COVID-19 global rheumatology alliance physician registry. Ann Rheum Dis 2021 Sep;80(9):1137-1146.

29. Izadi Z, Brenner EJ, Mahil SK, Dand N, Yiu ZZ, Yates M, et al; Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect); the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD); and the COVID-19 Global Rheumatology Allianc; Psoriasis Patient Registry for Outcomes, Therapy and Epidemiology of COVID-19 Infection (PsoProtect); the Secure Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD); and the COVID-19 Global Rheumatology Alliance (GRA). Association between tumor necrosis factor inhibitors and the risk of hospitalization or death among patients with immune-mediated inflammatory disease and COVID-19. JAMA Netw Open 2021 Oct;4(10):e2129639.

30. Bijlsma JW; EULAR COVID-19 Task Force. EULAR 2021 updated viewpoints on SARS-CoV-2 vaccination in patients with RMDs: a guidance to answer patients' questions. Ann Rheum Dis 2022 Jun;81(6):786-788.

31. Hadi YB, Thakkar S, Shah-Khan SM, Hutson W, Sarwari A, Singh S. COVID-19 vaccination is safe and effective in patients with inflammatory bowel disease: analysis of a large multi-institutional research network in the United States. Gastroenterology 2021 Oct;161(4):1336-1339.

32. Wack S, Patton T, Ferris LK. COVID-19 vaccine safety and efficacy in patients with immune-mediated inflammatory disease: review of available evidence. J Am Acad Dermatol 2021 Nov;85(5):1274-1284.

33. Skroza N, Bernardini N, Tolino E, Proietti I, Mambrin A, Marchesiello A, et al. Safety and impact of anti-COVID-19 vaccines in psoriatic patients treated with biologics: a real life experience. J Clin Med 2021 Jul;10(15):3355.

34. Klok FA, Pai M, Huisman MV, Makris M. Vaccine-induced immune thrombotic thrombocytopenia. Lancet Haematol 2022 Jan;9(1):e73-e80.

APPENDIX

Supplementary Table 1: Frequency of adverse events post COVID-19 vaccine among patients with inflammatory rheumatic disease (I-RMD) stratified by the types of rheumatic flareup reported.

Adverse eevents	Inflammatory arthritis	Connective tissue diseases	Vasculitis	Other I-RMD	*p*-value
Any adverse event	500 (77.8)	123 (84.8)	20 (87.0)	4 (80.0)	0.217
Injection site pain	384 (59.7)	104 (71.7)	15 (65.2)	4 (80.0)	0.045
Dizziness	90 (14.0)	33 (22.8)	3 (13.0)	1 (20.0)	0.069
Fatigue	279 (43.4)	86 (59.3)	11 (47.8)	2 (40.0)	0.007*
Fever	169 (26.3)	67 (46.2)	7 (30.4)	3 (60.0)	< 0.001*
Chills	61 (9.5)	34 (23.5)	0 (0.0)	0 (0.0)	< 0.001*
Sleepiness	46 (7.2)	17 (11.7)	1 (4.4)	0 (0.0)	0.237
Headache	191 (29.7)	63 (43.5)	2 (8.7)	1 (20.0)	0.001*
Myalgia	252 (39.2)	65 (44.8)	6 (26.1)	0 (0.0)	0.081
Arthralgia	185 (28.8)	44 (30.3)	3 (13.0)	1 (20.0)	0.371
Arthritis	51 (7.9)	12 (8.3)	0 (0.0)	1 (20.0)	0.388
Low back pain	34 (5.3)	7 (4.8)	1 (4.4)	0 (0.0)	0.949
Allergic reaction	12 (1.9)	2 (1.4)	0 (0.0)	0 (0.0)	0.880
Anaphylaxis	3 (0.50)	2 (1.4)	0 (0.0)	0 (0.0)	0.616
Rash	8 (1.2)	5 (3.5)	0 (0.0)	0 (0.0)	0.247
Cardiovascular	10 (1.6)	2 (1.4)	0 (0.0)	0 (0.0)	0.928
Chest pain	24 (3.7)	6 (4.1)	1 (4.4)	9 (0.0)	0.966
Palpitation	23 (3.6)	4 (2.8)	2 (8.7)	1 (20.0)	0.124
Dyspnea	20 (3.1)	5 (4.0)	1 (4.4)	0 (0.0)	0.550
Nausea/vomiting	35 (5.5)	12 (8.3)	9 (0.0)	1 (20.0)	0.176
Diarrhea	27 (4.2)	11 (7.6)	0 (0.0)	1 (20.0)	0.083
Abdominal pain	29 (4.5)	14 (9.7)	0 (0.0)	1 (20.0)	0.023
Neurological	17 (2.6)	9 (6.2)	0 (0.0)	0 (0.0)	0.121

**Significance.*