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# Effects of COVID-19 and Influenza Vaccination on Rheumatic Diseases: Results From a Survey of Patient-Reported Outcomes After Vaccination

Ji-Won Kim ,<sup>1</sup> Ju-Yang Jung ,<sup>1</sup> Chang-Hee Suh ,<sup>1</sup> Young-Min Ye ,<sup>2</sup> and Hyoun-Ah Kim <sup>1</sup>

<sup>1</sup>Department of Rheumatology, Ajou University School of Medicine, Suwon, Korea

<sup>2</sup>Department of Allergy & Clinical Immunology, Ajou University School of Medicine, Suwon, Korea



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Address for Correspondence:

Hyoun-Ah Kim, MD, PhD

Department of Rheumatology, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 16499, Republic of Korea.

Email: nakhada@naver.com

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ORCID iDs

Ji-Won Kim

<https://orcid.org/0000-0002-2827-0884>

Ju-Yang Jung

<https://orcid.org/0000-0001-7313-0795>

Chang-Hee Suh

<https://orcid.org/0000-0001-6156-393X>

Young-Min Ye

<https://orcid.org/0000-0002-7517-1715>

Hyoun-Ah Kim

<https://orcid.org/0000-0003-2609-3367>

Disclosure

The authors have no potential conflicts of interest to disclose.

## ABSTRACT

**Background:** This study aimed to compare the occurrence of adverse events (AEs) and disease flares after vaccination against coronavirus disease 2019 (COVID-19) and influenza in patients with autoimmune rheumatic diseases (ARDs).

**Methods:** Between November 2021 and March 2022, a survey was conducted among patients with ARD who received COVID-19 and influenza vaccinations. The questionnaire included 11 mandatory and closed-ended questions, and the following items were collected: medical history, immunization history, type of vaccine, patient-reported AEs, flare-up of the underlying disease after vaccination, and a confirmed diagnosis of COVID-19 or influenza. We compared the occurrence of vaccine-related adverse reactions to the COVID-19 and influenza vaccines based on the survey results. Multivariate logistic regression analysis was used to identify the factors affecting AEs or disease flares and to compare the post-vaccine response to mixed and matched vaccines.

**Results:** We analyzed 601 adults with ARD who received the COVID-19 vaccine, with a mean age of 49.6 years (80.5% female). A total of 255 participants (42.4%) received a complete course of primary vaccination, 342 (56.9%) completed the booster dose, and 132 (38.6%) received a mixed vaccine. The frequencies of AEs (188 [52.2%] vs. 21 [5.8%];  $P < 0.001$ ) and disease flares (58 [16.2%] vs. 5 [1.4%];  $P < 0.001$ ) after COVID-19 vaccination were significantly higher than those after influenza vaccination. In the risk factor analysis, previous allergic reaction to other vaccines (odds ratio, 1.95; confidence interval, 1.07–3.70;  $P = 0.034$ ) was the only factor associated with the occurrence of AEs. There was no difference in the post-vaccine responses between the mixed and matched vaccines.

**Conclusion:** The results of the survey of patients with ARD revealed that patient-reported AEs and underlying disease flares after receiving the COVID-19 vaccine were significantly higher than those after the influenza vaccine.

**Keywords:** COVID-19 Vaccine; Influenza Vaccine; Surveys and Questionnaires; Adverse Events; Underlying Rheumatic Diseases Flare Up

**Author Contributions**

Conceptualization: Ye YM, Kim HA. Data curation: Kim JW, Jung JY, Suh CH. Formal analysis: Kim JW, Ye YM, Kim HA. Investigation: Kim JW, Jung JY, Suh CH, Kim HA. Methodology: Ye YM, Kim HA. Software: Kim JW. Validation: Kim JW, Jung JY, Suh CH, Kim HA. Writing - original draft: Kim JW. Writing - review & editing: Kim HA.

**INTRODUCTION**

Vaccine development is a more time-consuming and resource-intensive process than traditional drug development and focuses on the prevention of disease through administration to healthy individuals. A vaccine for an infectious agent undergoes numerous tests with stringent regulatory requirements and can take up to 5–10 years to be approved and released to the market.<sup>1</sup> Nevertheless, the coronavirus disease 2019 (COVID-19) forced the duration of vaccine development to a minimum as the number of infected individuals increased at an alarming rate after the World Health Organization announced the pandemic in January 2020.<sup>2</sup> The first COVID-19 vaccine research started in March 2020, and on December 30, 2020, emergency authorization was granted in the UK vaccination program. The first vaccination outside of a trial was rolled out on January 4, 2021.<sup>3</sup> This vaccine has since been approved by several medical institutions around the world along with several other types of COVID-19 vaccines. Until recently, about 72% of the world population have been vaccinated against COVID-19.<sup>4</sup>

COVID-19 vaccines were approved and used at an unprecedented level compared with previous experiences, which resulted in concerns about vaccination and raising questions about the safety of the vaccines.<sup>5</sup> For this reason, in the early days after initiating COVID-19 vaccine programs, vaccine hesitance existed worldwide, which limited the vaccine acceptance rate.<sup>6</sup> Patients with autoimmune disease and cancer patients showed significantly higher vaccine hesitancy than the healthy population. The main reason for this was safety concerns, as most patients with immunocompromising conditions and patients receiving immunosuppressive medications were excluded from the COVID-19 vaccine clinical trials.<sup>7,8</sup> Over time, numerous studies have emphasized that the benefits of COVID-19 vaccination in autoimmune rheumatic disease (ARD) outweigh the risk of potential vaccine adverse events (AEs),<sup>9–11</sup> however, there are still reports of more vaccine AEs in patients with ARD than healthy individuals.<sup>12</sup> In addition, a growing body of evidence has indicated that the COVID-19 vaccine may induce exacerbations or result in the onset of autoimmune diseases by triggering autoimmunity through mechanisms such as molecular mimicry and the production of specific autoantibodies.<sup>13</sup>

Evidence for a possible link between certain immunizations and the exacerbation or progression of autoimmune disease has increased over the past few decades.<sup>14</sup> Even vaccines that are essential to prevent infection in patients with ARD, such as influenza, pneumococcal, human papillomavirus, and hepatitis B virus vaccines, have reported several cases of worsening underlying autoimmune disease after vaccination.<sup>15,16</sup> Therefore, we compared the occurrence of underlying disease flares after vaccination against COVID-19 and influenza among patients with ARD to determine whether vaccine-induced autoimmunity differs depending on the type of vaccine. Using a survey, this study also aimed to compare the incidence of AEs following COVID-19 and influenza vaccination and identify the factors associated with AEs and disease flares.

**METHODS****Survey participants and data collection**

A patient survey was conducted at the Department of Rheumatology, Ajou University Hospital, between November 2021 and March 2022. To participate, subjects were required

to have been diagnosed with ARD by physicians and vaccinated against COVID-19 and influenza while receiving treatment for ARD. The study included patients aged 18 years and older and who could read and write Korean or English fluently. Participants without physician diagnosis of ARD and participants who were not able to read Korean/English were excluded. Medical and nursing staff selected eligible patients among those scheduled for outpatient visits, explained the purpose of the study, and provided questionnaires only to subjects who expressed a willingness to participate in the survey. All surveys were conducted face-to-face by nursing staff during the outpatient clinic visits, and the medical staff received the completed questionnaires directly. Medical history, including the year of diagnosis, demographic data, laboratory data, signs and symptoms of disease, and treatment, was collected by the medical staff through medical records.

### Questionnaires

The development of this questionnaire was carried out systematically.<sup>17</sup> Five individuals conducted a comprehensive literature review each, and discussed in two groups. After the discussion, 16 items were generated as a draft for the survey questionnaires. Before the main survey, the draft questionnaire was pre-tested with 20 participants of various ages, genders, and underlying ARDs. After completing the questionnaire, participants were required to provide opinions on the necessity, clarity, and relevance of each item. Based on this, three items were removed, and some were merged, resulting in a final survey with a total of 11 items.

The survey consisted of 11 questions (**Supplementary Data 1**). Question 1 required all participants to indicate a previous diagnosis of the following diseases: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), adult-onset Still's disease, primary Sjögren's syndrome, vasculitis, polymyositis/dermatomyositis, and systemic sclerosis (SSc). Questions 2 and 3 related to the types of vaccines previously received (influenza; pneumococcal; zoster; pertussis; hepatitis; human papillomavirus; measles, mumps, and rubella; other vaccines) and reactions or discomfort after vaccination. Questions 4–6 related to COVID-19 vaccination, the patients' vaccination status (incomplete vaccination/full vaccination/booster dose), and type of vaccine (AstraZeneca/Pfizer/Moderna/Johnson & Johnson/mixed schedule). To the participants who answered "Yes" to the question of "Did you have adverse reactions or a worsening of underlying ARD after COVID-19 vaccination?" we inquired about the following symptoms: localized reactions (redness, swelling, pain, or other), fever, myalgia, fatigue, nausea or vomiting, abdominal pain, generalized swelling, acute allergic reactions (itching, skin rash, swelling in the face or mouth, anaphylaxis), delayed allergic reactions, or any other side effects. We also queried the treatment of AEs and disease flares after vaccination. Questions 7–9 were the same as questions 4–6 but related to the influenza vaccine instead of the COVID-19 vaccine. Questions 10 and 11 were self-reported diagnoses of COVID-19 and influenza after vaccination as "Yes/No" variables. This questionnaire took 10–15 minutes to complete.

### Statistical analysis

All data are expressed as mean  $\pm$  standard deviation. To determine the normality of distribution, the Shapiro-Wilk test was used. The  $\chi^2$  test or Fisher's exact test was used to compare the statistical significance of the differences in the incidence of AEs or underlying rheumatic disease flares following COVID-19 and influenza vaccination. The frequencies of AEs or underlying ARD flares after the mixed or matched vaccines were compared using the same statistical method. Univariate logistic regression was performed to investigate the factors associated with AEs or worsening of ARD after vaccination. After the univariate

logistic regression analysis, only a few significant variables ( $P < 0.05$ ) were used in the subsequent multivariate logistic analysis. The survey data were analyzed using R software (version 3.6.1; R Studio, Boston, MA, USA). A statistical significance level of  $P$  value  $< 0.05$  was assumed in all analyses.

### Ethics statement

The data collection form, study protocol, and informed consent forms were submitted to and approved by the Institutional Review Board of Ajou University Hospital (AJOURB-SUR-2021-539). Written informed consent was obtained from all the participants.

## RESULTS

### Survey participants characteristics

Between November 2021 and March 2022, we analyzed 601 patients with rheumatic diseases who received the COVID-19 vaccination (mean age 49.6 years, 80.5% female). **Table 1** summarizes the demographic and clinical data of the participants. A total of 286 (47.1%) patients had RA, 152 (25.3%) had SLE, 89 (14.8%) had AS, 37 (6.2%) had Sjögren's syndrome, 21 (3.5%) had SSc, and 19 (3.2%) had other rheumatic diseases. The mean disease duration was  $7.7 \pm 5.3$  years. Of these, 543 (90.3%) patients had a history of receiving other vaccines prior to the COVID-19 vaccine and 56 (9.3%) reported experiencing adverse reactions (**Supplementary Table 1**). Sixty-five (10.8%) patients reported a history of drug allergies and 9 (1.5%) patients reported a history of food allergy. A total of 276 (45.9%) patients with ARD were receiving ongoing treatment with glucocorticoids and 268 (44.6%) were using more than one immunosuppressive agent. Among the patients treated with immunosuppressive drugs, 43.6% used methotrexate, 12.1% used calcineurin inhibitors, 11.8% used leflunomide, 4.7% used mycophenolate mofetil, and 2.7% used azathioprine. A total of 79 (13.1%) patients were treated with biologic therapies: 64 (10.6%) with a tumor necrosis factor inhibitor, 6 (1%) with tocilizumab, 4 (0.7%) with rituximab, 2 (0.3%) with belimumab, 2 (0.3%) with secukinumab, and 1 (0.2%) with abatacept. Sixteen patients (2.7%) were treated with Janus kinase inhibitors (JAKi).

### Vaccination status and dose

**Table 2** lists the types and doses of vaccines administered to the survey participants. Of the 601 patients, 225 (42.4%) completed the primary course, 342 (56.9%) received booster doses, and 4 (0.7%) received only the first dose. The manufacturers of the first dose among the study participants included Pfizer-BioNTech (61.4%), Oxford-AstraZeneca (28.0%), Moderna (8%), and Janssen-Johnson & Johnson (2.7%), and the second dose included Pfizer-BioNTech (68.7%), Oxford-AstraZeneca (21.4%), and Moderna (9.9%). Of those who received a booster dose, 285 (83.3%) patients received Pfizer-BioNTech, 56 (16.4%) received Moderna, and 1 (0.3%) received Oxford-AstraZeneca. A total of 132 (38.6%) patients received mixed vaccines and 210 (61.4%) patients received matching vaccines.

### Comparing AEs occurring after receiving COVID-19 vs. influenza vaccines

The adverse reactions reported after COVID-19 and influenza vaccinations are shown in **Table 3**. After vaccination, the AEs associated with the COVID-19 and influenza vaccines were 52.2% and 5.8%, respectively, with significant differences. No severe AEs related to either vaccine were reported. The most frequently reported AE in the COVID-19 and influenza vaccines was myalgia (27.5% vs. 3.3%,  $P < 0.001$ ). Overall patient-reported AEs occurred more often in the

**Table 1.** Demographic and clinical characteristics of the participants who responded to the survey

Variables	Participants (n = 601)
Age, yr	49.6 ± 11.9
Female	484 (80.5)
BMI, kg/m <sup>2</sup>	22.7 ± 3.35
Smoking	98 (16.3)
Alcohol	148 (24.6)
Disease duration, yr	7.70 ± 5.34
<b>Rheumatic disease diagnosis</b>	
Rheumatoid arthritis	283 (47.1)
Systemic lupus erythematosus	152 (25.3)
Ankylosing spondylitis	89 (14.8)
Sjögren's syndrome	37 (6.2)
Vasculitis	7 (1.2)
Inflammatory myositis	1 (0.2)
Systemic sclerosis	21 (3.5)
Adult-onset Still's disease	7 (1.2)
Mixed connective tissue disease	2 (0.3)
Behcet's disease	1 (0.2)
Antiphospholipid syndrome	1 (0.2)
<b>Concomitant disease</b>	
Hypertension	105 (17.5)
Diabetes mellitus	24 (4.0)
Hyperlipidemia	94 (15.6)
Previous vaccination history	543 (90.3)
Previous reactions to other vaccination	56 (9.3)
<b>Allergy history</b>	
Food allergy	9 (1.5)
Drug allergy	65 (10.8)
<b>Rheumatic disease medications</b>	
Glucocorticoids	276 (45.9)
Nonsteroidal anti-inflammatory drugs	314 (52.2)
Antimalarial agent	311 (51.7)
Immunosuppressive agents	268 (44.6)
Methotrexate	262 (43.6)
Leflunomide	71 (11.8)
Calcineurin inhibitors	73 (12.1)
Azathioprine	16 (2.7)
Mycophenolate mofetil	28 (4.7)
Biologic therapy	79 (13.1)
TNF inhibitors	64 (10.6)
Rituximab	4 (0.7)
Tocilizumab	6 (1.0)
Abatacept	1 (0.2)
Secukinumab	2 (0.3)
Belimumab	2 (0.3)
JAK inhibitors	16 (2.7)

Values are presented as number (%) or mean ± standard deviation.

BMI = body mass index, TNF = tumor necrosis factor, JAK = Janus kinase.

COVID-19 vaccine than influenza vaccine, including injection site redness (3.6% vs. 0.6%,  $P = 0.004$ ), injection side swelling (5.6% vs. 0.8%,  $P < 0.001$ ), injection side pain (17.5% vs. 2.5%,  $P < 0.001$ ), headache (18.1% vs. 0.8%,  $P < 0.001$ ), fever (17.5% vs. 1.1%,  $P < 0.001$ ), fatigue (20.8% vs. 1.4%,  $P < 0.001$ ), nausea/vomiting (5.0% vs. 0.0%,  $P < 0.001$ ), diarrhea/abdominal pain (3.9% vs. 0%,  $P = 0.002$ ), bleeding/bruises (1.9% vs. 0.3%,  $P = 0.033$ ), chest pain/palpitation (3.3% vs. 0.0%,  $P < 0.001$ ), acute allergic reaction (0.6% vs. 0%,  $P = 0.157$ ), and delayed allergic reaction (3.1% vs. 0%,  $P = 0.001$ ). There was no significant difference in the frequency of AEs according to the vaccine manufacturer ( $P = 0.376$ , **Supplementary Table 2**). Comparing the pattern of treatment for vaccine AEs, most did not require treatment

**Table 2.** Types and frequency of administration of COVID-19 vaccination

Variables	Participants (n = 601)
<b>Vaccination status</b>	
First dose only	4 (0.7)
Complete primary course (the second dose for most vaccine brands)	255 (42.4)
Booster dose	342 (56.9)
<b>Type of COVID-19 vaccine in first dose</b>	
Oxford-AstraZeneca	168 (28.0)
Pfizer-BioNTech	369 (61.4)
Moderna	48 (8.0)
Janssen-Johnson & Johnson	16 (2.7)
<b>Type of COVID-19 vaccine in second dose</b>	
Oxford-AstraZeneca	128 (21.4)
Pfizer-BioNTech	410 (68.7)
Moderna	59 (9.9)
Janssen-Johnson & Johnson	0 (0.0)
<b>Type of COVID-19 vaccine in booster dose</b>	
Oxford-AstraZeneca	1 (0.3)
Pfizer-BioNTech	285 (83.3)
Moderna	56 (16.4)
Janssen-Johnson & Johnson	0 (0.0)
<b>Vaccine regimen</b>	
Mixing vaccine	132 (38.6)
Matching vaccine	210 (61.4)

Values are presented as number (%).  
 COVID-19 = coronavirus disease 2019.

**Table 3.** Adverse events occurring after COVID-19 and influenza vaccination

Variables	COVID-19 vaccine (n = 360)	Influenza vaccine (n = 360)	P value
Any side effects	188 (52.2)	21 (5.8)	< 0.001
Injection site redness	13 (3.6)	2 (0.6)	0.004
Injection site swelling	20 (5.6)	3 (0.8)	< 0.001
Injection site pain	63 (17.5)	9 (2.5)	< 0.001
Headache	65 (18.1)	3 (0.8)	< 0.001
Fever	63 (17.5)	4 (1.1)	< 0.001
Myalgia	99 (27.5)	12 (3.3)	< 0.001
Fatigue	75 (20.8)	5 (1.4)	< 0.001
Nausea/Vomiting	18 (5.0)	0 (0.0)	< 0.001
Diarrhea/Abdominal pain	14 (3.9)	0 (0.0)	0.002
Bleeding/Bruises	7 (1.9)	1 (0.3)	0.033
Chest pain/Palpitation	12 (3.3)	0 (0.0)	< 0.001
Acute allergic reaction	2 (0.6)	0 (0.0)	0.157
Delayed allergic reaction	11 (3.1)	0 (0.0)	0.001
<b>Treatment of adverse events</b>			<b>0.030</b>
No treatment	92 (25.6)	13 (65.0)	
Self-management	227 (63.1)	7 (35.0)	
Additional outpatient visit	27 (7.5)	0 (0.0)	
Emergency room visit	8 (2.2)	0 (0.0)	
Hospitalization	4 (1.1)	0 (0.0)	
Persistent symptoms	2 (0.6)	0 (0.0)	

Values are presented as number (%).  
 COVID-19 = coronavirus disease 2019.

after the influenza vaccine (65%), whereas most COVID-19 vaccine-related AEs required self-management (63.1%). There were cases of additional outpatient visits (7.5%), emergency room visits (2.2%), and hospitalizations (1.1%) after receiving the COVID-19 vaccine; however, no patients required such treatment after receiving the influenza vaccine.

### Comparing underlying disease flares after receiving the COVID-19 vs. influenza vaccines

The incidence of ARD flares was higher after the COVID-19 vaccine than after the influenza vaccine (16.2% vs. 1.4%,  $P < 0.001$ ) (Table 4). Joint pain or swelling (68.3%) was the most common symptom of ARD flares after COVID-19 vaccination. Fever (18.3%), skin rash (5.3%), myalgia (3.3%), thrombocytopenia (2.5%), and dryness (2.2%) were also included in the disease flare symptoms after COVID-19 vaccination. Nearly 80% of the patients developed symptoms of ARD flares within 3 days of COVID-19 vaccination. After influenza vaccination, patients experienced fever (40%), joint pain/swelling (20%), myalgia (20%), and thrombocytopenia (20%), due to ARD flares. Additional outpatient clinic visits were the most common treatment method for ARD flares after COVID-19 and influenza vaccination (67.2% vs. 60%), followed by hospitalization (19% vs. 40%).

### Factors associated with AEs and underlying rheumatic disease flares after COVID-19 vaccination

Table 5 shows the results of the analysis of the factors related to AEs after COVID-19 vaccination. AEs occurrence was significantly higher after COVID-19 vaccination in patients who had previously experienced other vaccine AEs (odds ratio [OR], 1.95; 95% confidence interval [CI], 1.07–3.7;  $P = 0.034$ ), whereas the frequency of AEs decreased significantly in patients who received a booster dose (OR, 0.69; 95% CI, 0.49–0.98;  $P = 0.040$ ). We also analyzed the risk factors associated with ARD flares after COVID-19 vaccination (Table 6). Multivariate logistic regression analysis revealed that the female sex (OR, 2.64; 95% CI, 1.29–6.17;  $P = 0.014$ ), food allergy (OR, 4.57; 95% CI, 1.07–18.68;  $P = 0.031$ ), and first dose only (OR, 10.7; 95% CI, 1.34–220.8;  $P = 0.041$ ) were associated with ARD flares after COVID-19 vaccination.

**Table 4.** Flare of rheumatic diseases after COVID-19 and influenza vaccination

Variables	COVID-19 vaccine (n = 360)	Influenza vaccine (n = 360)	P value
Disease flare after vaccination	58 (16.2)	5 (1.4)	< 0.001
Flare symptoms			< 0.001
Joint pain/Swelling	246 (68.3)	1 (20.0)	
Fever	66 (18.3)	2 (40.0)	
Skin rash	19 (5.3)	0 (0.0)	
Myalgia	12 (3.3)	1 (20.0)	
Dryness	8 (2.2)	0 (0.0)	
Thrombocytopenia	9 (2.5)	1 (20.0)	
Timing of flare			
After first dose	14 (24.1)		
After second dose	12 (20.7)		
After booster dose	6 (10.3)		
After first and second dose	17 (29.3)		
After first, second, and booster dose	9 (15.5)		
Days from vaccine to flare, day			0.754
1	27 (46.6)	2 (40.0)	
2–3	18 (31.0)	1 (20.0)	
4–7	8 (13.8)	1 (20.0)	
8–14	3 (5.2)	1 (20.0)	
> 14	2 (3.4)	0 (0.0)	
Treatment of disease flare after vaccination			0.788
Hospitalization	11 (19.0)	2 (40.0)	
Additional outpatient visit	39 (67.2)	3 (60.0)	
Emergency room visit	1 (1.7)	0 (0.0)	
Self-management	6 (10.3)	0 (0.0)	
No treatment	1 (1.7)	0 (0.0)	

Values are presented as number (%).  
 COVID-19 = coronavirus disease 2019.

**Table 5.** Multivariable analyses of risk factors for adverse events after coronavirus disease 2019 vaccination

Variables	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
(Intercept)	-	-	1.03 (0.57–1.83)	0.933
Age	0.99 (0.98–1.00)	0.178		
Female	1.99 (1.32–3.01)	0.001	1.62 (0.95–2.79)	0.079
BMI	1.00 (0.96–1.05)	0.867		
Disease duration	1.02 (0.99–1.05)	0.155		
Smoking	0.51 (0.33–0.79)	0.003	0.62 (0.34–1.10)	0.101
Alcohol	1.00 (0.69–1.45)	0.997		
Rheumatoid arthritis	Ref.			
Systemic lupus erythematosus	1.46 (0.97–2.19)	0.069		
Ankylosing spondylitis	0.64 (0.40–1.04)	0.072		
Sjögren’s syndrome	1.52 (0.76–3.20)	0.247		
Vasculitis	0.33 (0.05–1.56)	0.190		
Systemic sclerosis	0.26 (0.08–1.68)	0.110		
Adult-onset Still’s disease	0.62 (0.12–2.86)	0.535		
Mixed connective tissue disease	0.83 (0.03–21.02)	0.893		
Previous reactions to other vaccination	2.17 (1.20–4.09)	0.012	1.95 (1.07–3.70)	0.034
Food allergy	1.03 (0.27–4.21)	0.961		
Drug allergy	0.68 (0.40–1.14)	0.143		
Glucocorticoids	1.00 (0.72–1.38)	0.988		
NSAID	1.16 (0.84–1.61)	0.354		
Antimalarial agent	1.34 (0.97–1.85)	0.078		
Immunosuppressive agents	0.90 (0.65–1.25)	0.541		
TNF inhibitors	0.81 (0.48–1.36)	0.421		
Rituximab	0.83 (0.10–6.92)	0.849		
Tocilizumab	1.24 (0.20–9.48)	0.813		
Secukinumab	0.83 (0.03–20.96)	0.893		
Belimumab	0.83 (0.03–20.96)	0.893		
JAK inhibitors	1.06 (0.39–3.02)	0.902		
First dose only	-	0.974		
Complete primary course	-	0.974		
Booster dose	0.65 (0.47–0.90)	0.010	0.69 (0.49–0.98)	0.040
Oxford-AstraZeneca	Ref.			
Pfizer-BioNTech	1.21 (0.84–1.74)	0.312		
Moderna	1.78 (0.93–3.52)	0.089		
Janssen-Johnson & Johnson	1.26 (0.45–3.66)	0.666		

OR = odds ratio, CI = confidence interval, BMI = body mass index, NSAID = nonsteroidal anti-inflammatory drugs, TNF = tumor necrosis factor, JAK = Janus kinase.

### Comparison of mixed and matched COVID-19 booster vaccines

No significant difference was found in the occurrence of reactions after COVID-19 vaccine according to mixed or matched (Supplementary Table 3). Mixed and matched COVID-19 booster vaccinations showed similar frequencies of AEs (48.5% vs. 51.4%,  $P = 0.596$ ), ARD flares (12.9% vs. 13.3%,  $P = 0.89$ ), and COVID-19 infections (14.4% vs. 15.2%,  $P = 0.831$ ). COVID-19 and influenza infection after vaccination were shown in Supplementary Figure 1.

## DISCUSSION

To reach the end of the COVID-19 pandemic, it is important to better understand vaccine safety profiles. This can be achieved through post-marketing safety studies by collecting data on the safety, efficacy, and potential risks. Therefore, we conducted a post-vaccination questionnaire survey of patients undergoing treatment for ARD. To the best of our knowledge, this is the first study to compare the incidence of AEs and underlying disease flares after COVID-19 and influenza vaccinations in patients with ARD. AEs after vaccination showed a significant



**Table 6.** Multivariable analyses of risk factors for rheumatic disease flares after coronavirus disease 2019 vaccination

Variables	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
(Intercept)	-	-	0.09 (0.04–0.18)	< 0.001
Age	1.00 (0.98–1.02)	0.836		
Female	3.08 (1.54–7.08)	0.003	2.64 (1.29–6.17)	0.014
BMI	0.97 (0.90–1.03)	0.304		
Disease duration	1.01 (0.97–1.05)	0.751		
Smoking	0.60 (0.29–1.13)	0.138		
Alcohol	0.86 (0.51–1.43)	0.578		
Rheumatoid arthritis	Ref.			
Systemic lupus erythematosus	1.21 (0.72–2.01)	0.468		
Ankylosing spondylitis	0.65 (0.30–1.30)	0.246		
Sjögren’s syndrome	1.42 (0.57–3.17)	0.420		
Systemic sclerosis	0.26 (0.01–1.28)	0.190		
Adult-onset Still’s disease	2.05 (0.29–9.84)	0.399		
Mixed connective tissue disease	5.13 (0.20–131.31)	0.251		
Previous reactions to other vaccination	1.65 (0.82–3.14)	0.141		
Food allergy	4.23 (1.03–16.27)	0.034	4.57 (1.07–18.68)	0.032
Drug allergy	1.63 (0.85–2.98)	0.122		
Glucocorticoids	1.49 (0.96–2.30)	0.074		
NSAID	1.04 (0.68–1.61)	0.846		
Antimalarial agent	1.58 (1.02–2.47)	0.043	1.30 (0.82–2.07)	0.269
Immunosuppressive agents	0.92 (0.59–1.43)	0.721		
TNF inhibitors	0.40 (0.14–0.94)	0.059		
Tocilizumab	3.47 (0.45–21.18)	0.177		
First dose only	15.79 (2.00–321.06)	0.017	10.77 (1.34–220.86)	0.042
Complete primary course	0.06 (0.00–0.50)	0.017		
Booster dose	0.59 (0.38–0.91)	0.017	0.65 (0.41–1.01)	0.058
Oxford-AstraZeneca	Ref.			
Pfizer-BioNTech	1.18 (0.72–1.98)	0.517		
Moderna	1.51 (0.64–3.33)	0.326		
Janssen-Johnson & Johnson	-	0.980		

OR = odds ratio, CI = confidence interval, BMI = body mass index, NSAID = nonsteroidal anti-inflammatory drugs, TNF = tumor necrosis factor.

difference of 52.2% for the COVID-19 vaccine and 5.8% for the influenza vaccine; fortunately, most AEs of the COVID-19 vaccine-related AEs could be improved with self-treatment. Participants widely reported common and mild AEs such as myalgia, fatigue, headache, fever, and injection site pain/swelling as post-vaccination reactions, and these findings were consistent with previous studies or manufacturer’s factsheets.<sup>18,19</sup> A comparative analysis of AEs after vaccination with the COVID-19 mRNA and influenza vaccines in the general population, with data reported on Vigibase, also suggested that mild systemic reactions are more prominent after receiving the COVID-19 vaccine.<sup>20</sup> Whereas serious and rare AEs, including cardiovascular or neurologic complications, have been reported with different safety profiles for COVID-19 and influenza vaccines.<sup>19,20</sup> In this study, there were no severe AEs associated with the COVID-19 and influenza vaccines, such as myocarditis, deep vein thrombosis, or intracerebral hemorrhage, presumably because the survey participants were patients visiting outpatient clinics.

The rate of AEs after influenza vaccination in our study was similar to that of other studies.<sup>21,22</sup> The proportion of ARD patients who experienced AEs from the COVID-19 vaccine has been reported in a wide range of 30% to 94% (including our results), with differences according to underlying disease, race, and vaccine manufacturer.<sup>10,12,23–26</sup> In other Asian countries, such as Japan, China, and Hong Kong, the incidence of AEs was around 70–80%, which is slightly higher than our results.<sup>27,28</sup> In addition, the frequency of AEs did not differ significantly by vaccine manufacturer in our study; however, when comparing symptoms, injection site

redness, diarrhea or abdominal pain, general edema, and chest pain or palpitations were significantly higher in the Moderna vaccine. In the past three years, information on the AEs associated with the COVID-19 vaccine in patients with ARD has become abundant, and it has become difficult to obtain consistent results on the superiority of vaccines according to manufacturer.<sup>29-32</sup> Based on the cumulative AE reports from patients with ARD, physicians can recommend a suitable vaccination approach for individual patients, which may help reduce hesitancy and the occurrence of COVID-19 vaccination-related AEs.<sup>33</sup>

Significant differences were also observed between COVID-19 and influenza vaccinations in terms of underlying disease flares, which is a major post-vaccination problem for patients with ARD. Approximately 11% of the participants reported flares of their underlying diseases after COVID-19 vaccination, consistent with previous findings.<sup>11, 34-38</sup> Joint pain or swelling was the most common symptom of disease flare, which was expected due to vaccine reactogenicity, and there were no reports of severe disease flares in our study. In contrast, only 1.4% of patients with ARD experienced underlying disease flares after influenza vaccination, which supports the findings of previous studies that showed no correlation between influenza vaccine and rheumatic disease flares.<sup>35</sup> The tendency for underlying disease flares to occur within 3 days of vaccination and the required treatment for symptoms did not differ between COVID-19 and influenza vaccines, which was also similar to the results published in several countries.<sup>34-36,39</sup>

COVID-19 vaccine development utilizes novel technologies, such as mRNA- and vector-associated vaccines, which differ from conventional influenza vaccines. These technologies result in a higher incidence of AEs and underlying rheumatic disease flares after COVID-19 vaccination than the continuously used influenza vaccines, mainly because of the activation of the immune response caused by COVID-19 vaccines. The mRNA and vector vaccines work by introducing small fragments of the virus's genetic material into the body. Subsequently, the immune system recognizes this virus fragment and reacts to activate innate immunity, and these small pieces may lead to immune cross-reactivity through molecular mimicry with human proteins.<sup>40</sup> Although the COVID-19 vaccine developers modified some structures to reduce these immune responses and safety was carefully evaluated through clinical trials, most of the clinical trials were limited to healthy populations, which would have resulted in different results than that of real-world data.

This mechanism has raised concerns that cross-vaccination with other types of COVID-19 vaccines may increase the frequency or intensity of AEs or cause acute flares of ARDs.<sup>41</sup> In South Korea, the AstraZeneca vaccine was the first to be approved and was administered to the initial priority groups, which included immunocompromised patients, with nearly 30% of the AstraZeneca vaccinated patients in the primary course of our study. While booster vaccination in South Korea was mostly provided by Pfizer, and 40% of the patients included in our study received a mixed booster vaccination, there were no significant differences in the incidence of AEs and underlying disease flares. Some studies have reported that mixed vaccination had higher vaccine effectiveness than matched vaccination; however, in this study, there was no difference between mixed and matched in the rate of COVID-19 infection after vaccination.<sup>42</sup>

After evaluating the benefits and risks associated with COVID-19 vaccines, vaccination can be considered essential, and it is important to determine which features among patients with ARD are associated with AEs or ARD flares. Among the various factors, the only risk factor that increased AEs through multivariate analysis was a previous allergic reaction to other

vaccinations. Similar to our findings, there have been several reports of many AEs of the COVID-19 vaccine in patients with a history of allergic reactions to other vaccinations.<sup>23,43</sup> mRNA vaccines are not an absolute contraindication, even if there is a past vaccine allergic reaction in which excipients such as polyethylene glycol contribute greatly. However, it is recommended that such patients be informed before vaccination that the possibility of minor allergic reactions to COVID-19 vaccines may increase. Other published analysis identified that female sex and an age below 50 were factors related to the risk of AEs.<sup>44</sup> On the other hand, patients who received the booster vaccination had a lower frequency of AEs, which can be interpreted as the high rate of booster doses for patients who did not have AEs after the first and second COVID-19 vaccinations. In addition, no significant results were found in our attempt to find a possible correlation between occurrence of AEs and the drugs to treat several rheumatic diseases, especially biologic agents, which was estimated to be due to the insufficient number of patients for each biologic as the study included various ARDs. There have been reports of disease flare after COVID-19 vaccination in patients with RA treated with JAKi and interleukin (IL)-6 inhibitor, and in patients with psoriatic arthritis with IL-12/23 inhibitor.<sup>45</sup>

Our data also revealed that female sex, a single vaccine dose, and food allergies were factors associated with the occurrence of underlying rheumatic disease flares. This can be explained by the fact that no additional vaccination was received owing to disease flares after the first vaccine dose. The inclusion of female sex in the risk factors for underlying rheumatic disease flares is consistent with previous studies.<sup>46</sup> As demonstrated by our results, most of the reports analyzed based on the survey showed that women tended to report more symptoms than men; thus, differences in gender sensitivity may also have contributed to these results.

A significant strength of our study is that, to the best of our knowledge, this is the first study to compare the incidence of AEs of COVID-19 and influenza vaccines in patients with ARD and their effects on underlying diseases. In addition, all surveys were conducted face-to-face, which ensures more information without missing items and a larger number of respondents. However, this study has some limitations. First, there was a lack of information regarding disease activity and the timing, dose, and discontinuation of immunosuppressive agents related to the time of vaccination. Second, although the potential risk of flares varies depending on the ARDs, a sub-analysis was not conducted according to each disease. For the RA, SLE, and AS groups, which include many participants, further research is needed to collect information on disease activities, immunosuppressive agent types, and doses to better understand the risk factors for reactions after vaccination. Finally, the subjective nature of the study design, which was based on self-reported patient data, may have led to an overestimation or underestimation of post-vaccination symptoms, and mild reactions, including myalgia, fever, and joint pain, may have been compounded by AEs or disease flares.

This study compared the incidence of self-reported AEs and underlying disease flares after COVID-19 and influenza vaccines through a survey of patients with ARD. We found that the incidence of AEs and ARD flares after the COVID-19 vaccine was higher than that after the influenza vaccine. We also identified several factors associated with potential disease flares and AEs following COVID-19 vaccination; an allergic reaction history of previous vaccination was found to be related to AEs after COVID-19 vaccination, and female sex was related to the flares of underlying rheumatic diseases.

## SUPPLEMENTARY MATERIALS

### Supplementary Data 1

Vaccination questionnaire

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### Supplementary Table 1

Previous vaccine histories and vaccine related allergic reactions of participants

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### Supplementary Table 2

Adverse events occurring after coronavirus disease 2019 vaccination according to the vaccine type

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### Supplementary Table 3

Comparison of adverse events and underlying disease flares between mixing and matching vaccines

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### Supplementary Fig. 1

Coronavirus disease 2019 and influenza infection after vaccination.

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