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COVID-19 Vaccination in Autoimmune Diseases (COVAD) Study: Vaccine Safety and Tolerance in Rheumatoid Arthritis

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Key messages:

1. COVID-19 vaccination-related AEs were reported by three quarters of RA patients, but the majority were minor in severity and were comparable to HCs.

2. Despite differences in the AEs between different COVID-19 vaccines, all vaccines were largely well tolerated.

3. Patients on methotrexate and hydroxychloroquine reported fewer minor AEs than those on other disease modifying antirheumatic drugs (DMARDs).

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COVID-19 Vaccination in Autoimmune Diseases (COVAD) Study: Vaccine Safety And Tolerance in Rheumatoid Arthritis

Abstract

Objectives: The COVID-19 vaccination in autoimmune diseases (COVAD) study aimed to assess short-term COVID-19 vaccination-related adverse events (AEs) in rheumatoid arthritis (RA) patients.

Methods: An online self-reported questionnaire (March-December 2021) was used to capture data related to COVID-19 vaccination-related AEs in RA, other autoimmune rheumatic diseases (AIRDs) (excluding RA and inflammatory myositis), non-rheumatic autoimmune diseases (nrAIDs), and healthy controls (HCs). Descriptive and multivariable regression analyses were performed.

Results: Of the 9462 complete respondents, 14.2% (n=1347) had been diagnosed with RA [mean (s.d.) age 50.7 (13.7) years, 74.2% women, 49.3% Caucasian]. In total, 76.9% and 4.2% of patients with RA reported minor and major AEs, respectively. Patients with active and inactive RA had similar AE and hospitalization frequencies. Overall, AEs were reported more frequently by BNT162b2 and mRNA-1273 recipients and less frequently by BBV152 recipients compared with the rest. Major AE and hospitalization frequencies were similar across recipients of different vaccines. Patients receiving methotrexate and hydroxychloroquine reported fewer minor AEs than those patients not on them. Compared with HCs and patients with other AIRDs, patients with RA reported similar total AEs, overall minor AEs, and hospitalizations. Compared to nrAIDs, patients with RA reported lower frequencies of overall AEs, minor AEs (both OR=0.7;95%CI=0.5-0.9), and injection site pain (OR=0.6;95%CI=0.5-0.8) with similar major AE and hospitalization frequencies.

Conclusion

Despite the differences in AE frequency across different COVID-19 vaccines, all were well tolerated in patients with RA and were comparable to HCs providing reassurance to the safety of COVID-19 vaccination in them.

Key messages:

1. COVID-19 vaccination-related AEs were reported by three quarters of RA patients, but the majority were minor in severity and were comparable to HCs.

2. Despite differences in the AEs between different COVID-19 vaccines, all vaccines were largely well tolerated.

3. Patients on methotrexate and hydroxychloroquine reported fewer minor AEs than those on other disease modifying antirheumatic drugs (DMARDs).

Keywords

Introduction

Controversies surrounding coronavirus disease 2019 (COVID-19) vaccination, especially in the context of autoimmune diseases, have attracted much attention in the past few years. This is despite the proven efficacy of vaccines and wide recognition of their positive contribution to health and disease control. For vaccinations against COVID-19, there has been considerable fear and distrust, heightened by their rapid emergence and unavoidable pressure during the critical times of the pandemic for individuals to receive vaccines as a means of controlling the disease and saving lives during the pandemic (1). Although there has been accumulating evidence supporting their general safety and efficacy, there is a general lack of data in more 'vulnerable' groups, such as among those with rheumatic inflammatory disorders and/or on immunosuppressive therapies (2–4). This group has reported significant anxiety and critical health behaviour changes during the pandemic, demonstrating a need for better understanding and awareness-raising of COVID-19 related care (5). Vaccine hesitancy among patients with rheumatic diseases continues with a lack of long-term safety data and fear of delayed adverse effects as the main reasons (6).

We have recently reported vaccine safety in idiopathic inflammatory myopathies (IIMs) using data from the global COVID-19 vaccination in autoimmune diseases (COVAD) study initiative, demonstrating the overall benefit of vaccination in this group of individuals (7,8). However, in this study, we observed a greater predisposition to specific adverse events, such as skin rashes in certain IIM subgroups, particularly the dermatomyositis subgroup and those with active inflammatory disease, such as the inclusion body myositis subgroup (7). Understanding disease behaviour and vaccination-related adverse effects (AEs) is important for guiding more specific approaches to COVID-19 vaccination based on individual disease and patient characteristics. Such insights and tailored approaches to vaccination can reassure and improve trust in vaccination programs and vaccine uptake. Additionally, the general exclusion of patients with autoimmune diseases or immunosuppressive therapies from vaccine safety trials, as well as the small number of patients and lack of ethnic diversity, calls for more data in order to bridge the gaps in our knowledge, especially regarding safety, in these patient groups (9,10).

This unmet need formed the rationale for this study, which aimed to obtain direct patient insights into how COVID-19 vaccination is received, with a focus on the most common rheumatic inflammatory joint disease, rheumatoid arthritis (RA).

Methods

Study design and data collection

This was an international, online, cross-sectional, multi-centre survey-based study, part of the COVAD initiative. A comprehensive patient-self reported electronic survey was developed, consisting

of a questionnaire on COVID-19- and autoimmune rheumatic disease (AIRD)-related questions, which included demographic details, AIRD-specific diagnosis, treatment details, current symptom status, COVID-19 infection history including symptoms, duration, and complications (hospitalization and requirement of oxygen therapy), COVID-19 vaccination details, 7-day short-term post-vaccination AEs (based on Centre for Disease Control and Prevention criteria), and patient-reported outcome measures as per the Patient Reported Outcomes Measurement Information System (PROMIS) tool (11). After vetting by international experts, pilot testing, revisions, validation, and translation into 18 languages, the survey was hosted on an online platform (surveymonkey.com) and circulated by the international COVAD study group (106 physicians) across healthcare centres in over 94 countries (Supplementary Table S1), as well as through numerous social media platforms and online patient support groups. Convenience sampling was used, and all participants aged over 18 years were included. Duplicate responses were manually removed. The methods have been detailed in the published COVAD study protocol (12).

Informed consent from the participants was obtained via an initial question in the online survey, asking for the patient's consent for participation in the study, before proceeding with the questions. No incentives were offered for completing the survey. Central approval was obtained from the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS) ethics committee as per local guidelines and the Checklist for Reporting results of the Internet E-Surveys was adhered to when reporting the results (13,14).

Data extraction

Data were retrieved at the time of the survey closure on the 30th of December 2021. Subjects who had not received at least one dose of any COVID-19 vaccine at the time of survey completion and those who had not completed the survey in full were excluded from the analysis (Figure 1). Respondents who had received at least one dose of any COVID-19 vaccine and completed the survey in full formed the study population. Multiple relevant variables were extracted from the survey responses, including COVID-19 infection history and 7-day post vaccination AEs.

Active and inactive disease

Active and inactive disease four weeks prior to vaccination was assessed by the patient's response to the question, "What was the status of your autoimmune disease four weeks (prior to) before the first dose of COVID-19 vaccine?" The responses of active and worsening/static/improving diseases were grouped to designate "active disease". Patients who indicated "inactive" as a response formed the inactive disease group. Those who responded "I don't know" and others were assessed for activity based

on other questions (any two of the three answered yes was considered positive), that is, 1. What were the symptoms four weeks prior to vaccination? 2. If you experience any swelling of your joints, how many joints are swollen? 3. Did you require an increase in the dose of any of these immunosuppressant medications, or did you start a new immunosuppressant medicine six months prior to the first COVID-19 vaccine?

Adverse events post vaccination

Seven-day AEs were categorized as injection site pain and reaction, minor AEs, major AEs, and hospitalization. Minor AEs included myalgia, body aches, fever, chills, nausea and vomiting, headache, rashes, fatigue, diarrhoea, abdominal pain, high pulse rate or palpitations, increase in blood pressure, fainting, difficulty in breathing, dizziness, and chest pain. Major AEs included serious reactions to vaccination, requiring urgent medical attention, anaphylaxis, marked difficulty in breathing, throat closure (choking), and severe rashes. Other AEs that were not listed were reported as "others" as an open-ended question.

Statistical analysis

Since IIM patients formed a disproportionately large subgroup (as the survey was originally designed for IIM patients and was distributed to IIM patient groups), they were excluded from the other AIRDs group before the analysis to avoid selection bias. Patients with RA were excluded from the AIRDs group. Patients with RA were compared for vaccination-related AEs between active and inactive diseases as defined above. In addition, patients with RA were compared with other AIRDs, (which excluded patients with IIM and RA), non-rheumatic autoimmune diseases (nrAIDs), and healthy controls (HCs). RA patients with autoimmune disease comorbidities were compared with those without comorbidities. Autoimmune disease comorbidities included other AIRDs and nrAIDs reported by patients with RA. Chi-square (χ^2) and Mann-Whitney *U* tests were used for comparisons between groups for categorical and continuous variables, respectively. The variables that differed across RA, other AIRDs, nrAIDs, and HCs in univariate analysis were included in multivariable binary logistic regression analysis (BLR) with adjustment for baseline factors defined a priori, that is, age, sex, ethnicity, country defined by human development index (HDI), as well as factors with $P<0.200$ as per the univariable analyses. Stepwise forward regression methodology was used to build the regression models starting with age, sex, ethnicity, and country by HDI first, followed by the addition of other covariates. The results for continuous variables are expressed as median (interquartile range - IQR) in view of the non-normal distribution of the data (by Kolmogorov-Smirnov test and Shapiro-Wilk test). In multivariable models, statistical significance was set at $P<0.05$. Statistical analyses were performed using IBM SPSS version 26 (IBM, Armonk, NY, USA).

Results

Baseline characteristics of study participants

Of the 10679 (56.5%) survey participants with complete responses: 1227 (11.4%) were patients with IIM (11.4%) and were excluded (Figure 1; Table 1). Of the 9462 respondents forming the population under study, 1347 (14.2%) were patients with RA, 2305 (24.3%) patients with other AIRDs, 1079 (11.4%) patients with nrAIDs, and 4741 (50.1%) were HC. Among them, 7028 (74.2%) were female, the mean age was 42.2 (14.8) years, and the most frequently reported origin was Caucasian (49.3%). The three most represented countries were Turkey (16.1%), India (15.3%), and Mexico (13.3%) (Supplementary Table S1). Seventy-two percent had received at least two doses of COVID-19 vaccine, and all had received at least one dose of vaccine. Table 1 shows the type and proportion of patients with other AIRDs, with systemic lupus erythematosus (5.5%) representing the most common disease within this group. The most common vaccine received was Pfizer-BioNTech (BNT162b2) in 39.3% of the cases. The most commonly used immunosuppressants or immunomodulatory agents were methotrexate (10.5%), hydroxychloroquine (10.6%), and glucocorticoids (62.6%) (Table 1). The other sample characteristics are shown in Table 1.

RA patient general characteristics

Among the patients with RA in the study sample, the mean (SD) age was 50.7 (13.7) years, and the majority were female. Most patients with RA were Caucasian, followed by Asians. Seventy-one percent had received two doses of the COVID-19 vaccine. Pfizer-BioNTech (BNT162b2) (39.3%) and Oxford/Astra Zeneca (ChAdOx1 nCoV-19) (23.8%) were the most commonly administered vaccines. The most common co-existing autoimmune diseases in patients with RA were thyroid disorder (10.0%), followed by systemic lupus erythematosus (2.6%) and Sjögren's syndrome (2.5%).

Patients with RA were older (51 versus. 34 years; $P<0.001$) and had a higher female representation (7:1 versus. 2:1) than the HC group. Furthermore, differences were noted in terms of ethnicity and proportion of vaccines received by patients with RA (Table 1). Patients with RA used glucocorticoids less frequently than other AIRDs (OR=0.7; 95%CI=0.6–0.8) and were more frequently on glucocorticoids than nrAIDs (OR=2.6; 95%CI=2.1-3.3). In addition, they were administered rituximab, methotrexate, and sulfasalazine more frequently than other AIRD patients (Table 1).

Adverse events in RA and comparisons with other subgroups

Overall, AEs 7-day following vaccination were reported by 1037 (76.9%) of the patients with RA, all of whom experienced minor AEs. Major AEs were observed in 56 (4.2%), with three patients (0.2%) reporting hospitalization. Pain at the injection site was reported in 798 (59.2%) patients.

The most commonly reported minor AEs were fatigue (27.2%), headache (25.6%), and body ache (22.7%). The specific major AEs reported were anaphylaxis (0.1%), marked difficulty in breathing (0.5%), throat closure (0.4%), and severe rashes (0.6%).

Of the patients with RA, 996 (74.2%) had active disease prior to vaccination. The reported vaccine-related AEs were similar between those with active and inactive disease, except for higher dizziness in active RA patients (OR=2.1; 95%CI=1.1–3.9; *P*=0.021) (Table 2). The hospitalization frequencies were similar.

Tables 3 and 4, and Figure 2 provide an overview of vaccination-related AEs based on the type of vaccine administered to patients with RA. Overall, AEs were reported more frequently by Pfizer-BioNTech (BNT162b2) (OR=1.3; 95%CI=1.03-1.80; *P*=0.027) and Moderna (mRNA-1273) (OR=3.1; 95%CI=1.4-6.6; *P*=0.003) vaccine recipients and less frequently by Covaxin (Bharat Biotech) (BBV152) (OR=0.2, 95%CI=0.04-0.8; *P*=0.041) vaccine recipients than in the rest. All minor AEs followed similar trends to the overall AEs. Pain at the injection site was reported more frequently by Pfizer-BioNTech (BNT162b2) (OR=2.0; 95%CI=1.5-2.5; *P*<0.001) and Moderna (mRNA-1273) (OR=2.5: 95%CI=1.5-4.3; *P*<0.001) vaccine recipients.

Major AEs were reported to be similar across the different vaccine recipients except Johnson & Johnson (J&J) (JNJ-78436735) (OR=17.X; 95%CI=4.4-65; *P*<0.001) vaccine recipients who reported higher frequencies of any major AEs and major other AEs compared with the rest. Hospitalizations following vaccination were infrequent, with similar frequencies across various vaccine recipients.

Systemic minor AEs such as fever, chills, myalgia, body ache, and headache (all *P*<0.05) were reported more frequently by Oxford/Astra Zeneca (ChAdOx1 nCoV-19), Moderna (mRNA-1273), and Covishield (Serum Institute India) (ChAdOx1 nCoV-19) vaccine recipients and less frequently by Pfizer-BioNTech (BNT162b2), Covaxin (Bharat Biotech) (BBV152), and Sinopharm (BBIBP-CorV) vaccine recipients.

Minor gastrointestinal AEs, such as nausea/vomiting, were reported more frequently by Oxford/Astra Zeneca (ChAdOx1 nCoV-19) (OR=2.1; 95%CI=1.2-3.4; *P*=0.003) and Moderna (mRNA-1273) (OR=3.4; 95%CI=1.8-6.5; *P*<0.001). Autonomic AEs following vaccination such as tachycardia, high blood pressure, chest pain, and dizziness, have been reported infrequently.

Table 5, Supplementary Table S2, and Figure 2 provide an overview of vaccination-related AEs based on the type of immunosuppression received among patients with RA. The patients on methotrexate reported lower tachycardia (OR=0.3; 95%CI=0.1-0.6; *P*=0.002), difficulty breathing (OR 0.15, 95%CI 0.03-0.6, p 0.002), dizziness (adjusted OR=0.6, 95%CI=0.4-0.9, *P*=0.022), and chest pain (adjusted OR=0.3, 95%CI=0.1-0.8, *P*=0.026) compared with the rest of the immunosuppression. Those

who received hydroxychloroquine more frequently reported body ache (adjusted OR=1.3, 95%CI=1.03-1.7X, *P*=0.028) and less frequently reported headache (adjusted OR 0.7, 95% CI 0.5-0.9, *P*=0.024), fatigue (adjusted OR=0.5, 95%CI=0.4-0.7, *P*<0.001), and dizziness (adjusted OR=0.5, 95%CI=0.3-0.9, *P*=0.020). The vaccination-related AEs were similar in recipients of other immunosuppression. Hospitalization frequencies were similar across the various immunosuppression groups.

Supplementary Tables S3, S4, and S5, and Figure 3 provide an overview of vaccination-related AEs between RA and HC, other AIRDs, and nrAIDs, respectively. When compared with HC, patients with RA had similar frequencies of overall vaccination-related AEs, including injection site pain, overall minor AEs, and hospitalizations. Major AEs (OR=1.5; 95%CI=1.03-2.2; *P*=0.032) and other major AEs (OR=2.1; 95%CI=1.3-3.4; *P*=0.002) were higher in patients with RA than in HC. When compared with AIRD patients, patients with RA had similar frequencies of overall AEs, minor AEs, and major AEs, except for fatigue (OR=0.8; 95%CI=0.6-0.9; *P*=0.015) and minor other AEs (OR=0.6; 95%CI=0.5-0.9; *P*=0.006) for which frequencies were lower in RA patients. When compared with non-AIRD patients, RA patients had lower frequencies of overall AEs (OR=0.7; 95%CI=0.5-0.9; *P*=0.017), injection site pain (OR=0.6; 95%CI=0.5-0.8; *P*=0.002), and any minor AEs (OR=0.7; 95%CI=0.5-0.9; *P*=0.017). Major AEs and hospitalizations were similar between the two groups.

Supplementary Table S6 shows that RA patients with autoimmune comorbidities (17.9%) has reported similar overall, minor, and major AEs compared to those without autoimmune comorbidities (82.1%). A few minor AEs, such as rash, abdominal pain, high pulse rate, difficulty in breathing, dizziness, and chest pain were reported more frequently by those with autoimmune comorbidities (OR ranging 1.8-2.8, *P*<0.05).

Discussion

This is the first study of this scale, in terms of number, ethnic diversity, and global reach, to address COVID-19 vaccination-related AEs at 7-day post-vaccination period, with a focus on patients with RA and comparisons with other AIRD populations and healthy individuals. The study showed that despite observed differences in the frequencies of AEs between different COVID-19 vaccines, all were well tolerated in patients with RA, with no differences observed based on disease activity status. This finding is in line with other studies that have demonstrated low AEs associated with COVID-19 vaccines (7,15,16).

Vaccination-related AEs were reported by three-quarters of the patients with RA, but they were mostly minor in severity. This is higher than one-third reported in the EULAR Coronavirus Vaccine (COVAX) study, where AEs were recorded by physicians (16). This might be due to the better scrutiny of adverse events reported by patients than by physicians. These findings are in line with our observations in the IIM group, where the overall safety of COVID-19 vaccination was demonstrated, with only minor flares in cutaneous disease following vaccination in IIM subgroups, particularly

dermatomyositis (7). In terms of the type of vaccine, BNT162b2 (Pfizer) and mRNA 1273 (Moderna) vaccine recipients among patients with RA generally had higher frequencies of vaccination-related AEs. This is consistent with other studies in healthy populations and rheumatic diseases, wherein mRNA 1273 (Moderna) vaccine recipients were reported to have a higher frequency of overall AEs, although most were minor (16–18). Despite differences in the frequencies of AEs between the different COVID-19 vaccines, all were generally well tolerated in patients with RA.

When exploring AE type and frequency between active and inactive RA disease status, no differences were observed, suggesting that the disease activity level is not a defining parameter for vaccine-related AEs. Along these lines, reports of AEs according to different DMARD use were very similar, although patients on methotrexate and hydroxychloroquine reported significantly fewer minor AEs. This is in accordance with recent data, which suggests that methotrexate does not tend to contribute to severe COVID-19; on the contrary, they may even experience a milder COVID-19 disease (19).

In terms of major AEs, patients with RA had similar frequencies of AEs and hospitalization compared with HC and patients with other AIRDs. The hospitalization frequencies were similar to those reported in the COVAX study (<1%) among those with inflammatory arthritis (n=4604) (16). The number of serious AEs were 0.5% and all AEs were 37% in the physician-recorded registry. No mortality due to vaccination-related AEs was observed in this study (16).

Our study had some limitations. First, our study was entirely based on self-reported patient data, without verification through medical records or by healthcare professionals' verification. As with any online survey, there is also the issue of selection bias in the sample under study, since lack of internet access and potentially patients with lower socioeconomic status and severe disability are less likely to contribute data. Additionally, the focus was on the short-term safety of COVID-19 vaccination, thus not contributing to the knowledge on safety over the longer term. Furthermore, it was beyond the scope of this study to explore humoral responses to vaccines, which may have also affected the development of AEs. However, a large number of patients, a high frequency of full questionnaire completion, and the wide geographical spread of the survey participants represent important strengths of this study. The anonymised, patient-self-reported nature of the questionnaire is also a potential strength of the study, reflecting the direct and likely unbiased (without external influence) patient voice.

In conclusion, the findings of the present study provide reassurance on the safety of COVID-19 vaccination in RA, adding to the body of literature addressing the concerns and controversies surrounding COVID-19 vaccination (16,17). The study will hopefully pave the way forward for greater confidence and better uptake of COVID-19 vaccines in this particularly vulnerable group of individuals, as advocated by the recent European and American guidelines (20,21).

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ALT has received honoraria for advisory boards and speaking for Abbvie, Gilead, Janssen, Lilly, Novartis, Pfizer, and UCB.

EN has received speaker honoraria/participated in advisory boards for Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, and Lilly, and holds research grants from Pfizer and Lilly.

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Rest of the authors have no conflict of interest relevant to this manuscript.

Contribution of authors:

Conceptualisation: LG, EN, JL and IP. Data curation: All authors. Formal analysis: NR; Funding acquisition: N/A. Investigation: LG, NR, IP, and EN. Methodology: LG, NR, IP, and EN; Software: LG. Validation: VA, RA, JBL, and HC. Visualisation: RA, VA, and LG. Writing-original draft: NR, EN, and IP. Writing-review and editing: all authors.

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Figure legends

Figure 1. Flow diagram of patients included in the study.

Figure 2. Forest plot of selected vaccination related adverse events in patients with rheumatoid arthritis

Figure 3. Comparison of vaccination-related adverse events between patients with rheumatoid arthritis, patients with other autoimmune rheumatic diseases, healthy controls, and patients with non-autoimmune rheumatic diseases.

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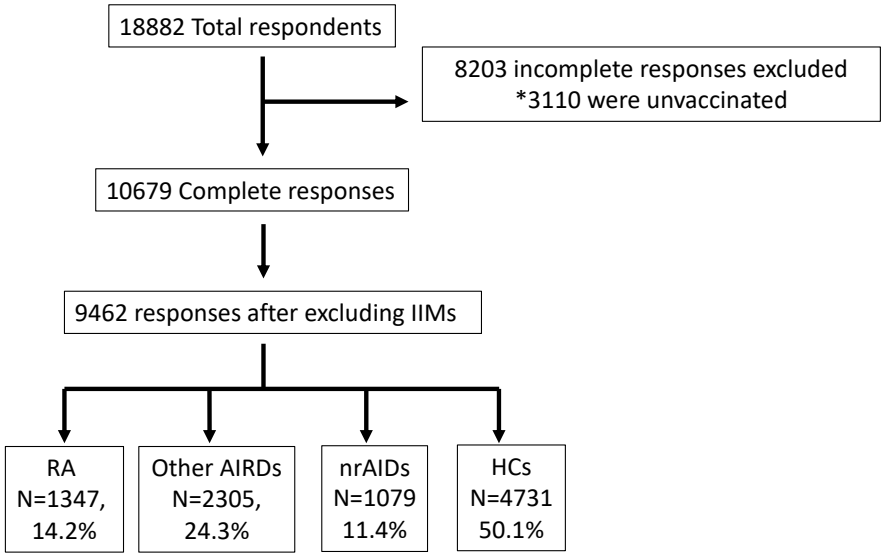


Legends: * An electronic protocol terminated the survey automatically if respondents indicated not having received any COVID-19 vaccine. RA: Rheumatoid arthritis; Other AIRDs: Autoimmune rheumatic diseases excluding RA and IIM; nrAIDs: non-rheumatic autoimmune diseases; HCs: Healthy controls; IIM: Idiopathic inflammatory myopathies

Figure 1. Flow diagram of patients included in the study

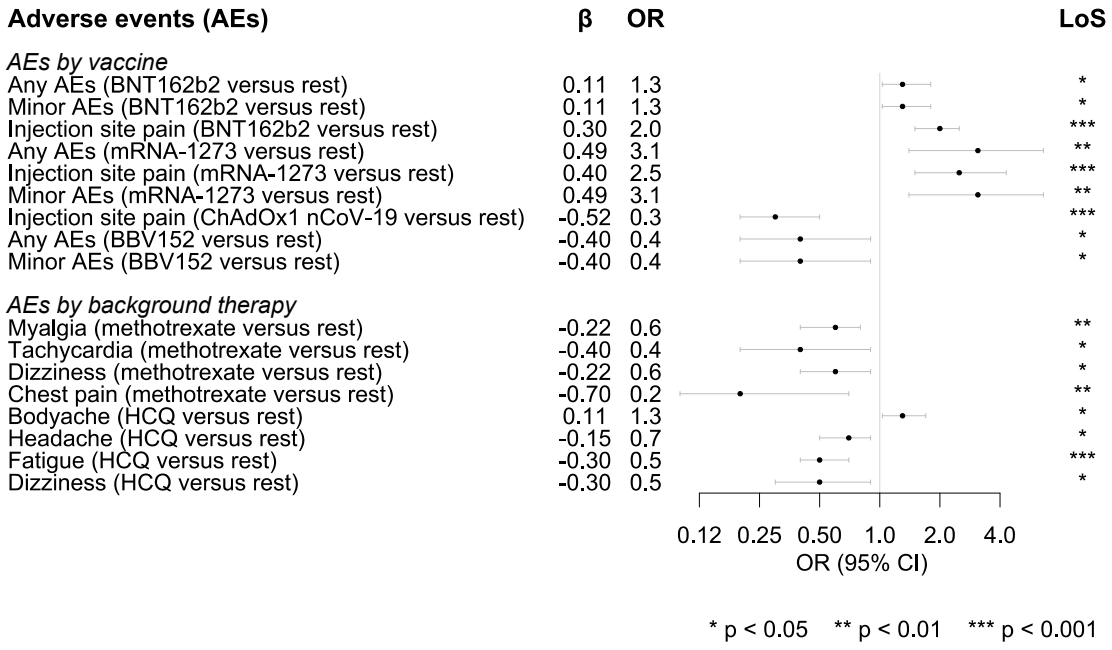
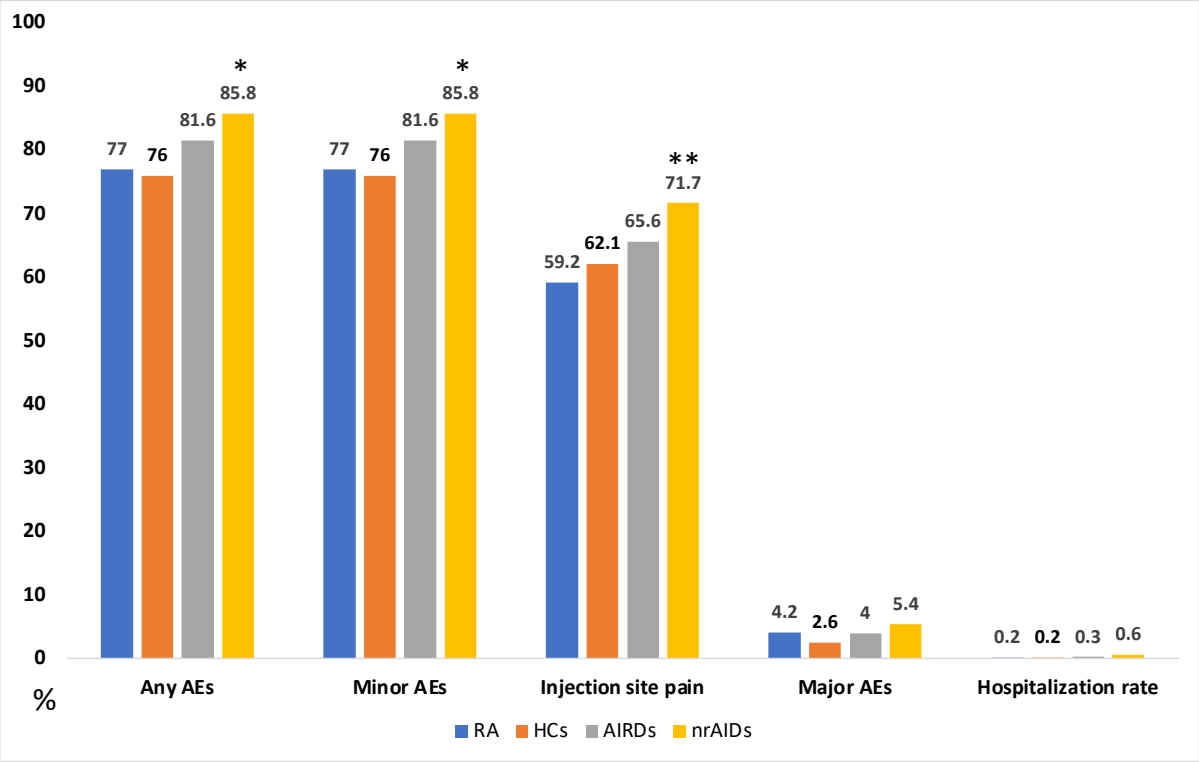


Figure 2. Forest plot of selected vaccination related adverse events in patients with rheumatoid arthritis

Legends: AEs: Adverse events; HCQ: Hydroxychloroquine; OR: Odd's ratio; 95%CI: 95% Confidence interval; LoS: Level of significance (P value *<0.05, **<0.005, ***<0.001)



*P<0.05; **P<0.005; AEs: Adverse events; RA: Rheumatoid arthritis; Other AIRDs: Autoimmune rheumatic diseases excluding RA and IIM, nrAIDs: non-rheumatic autoimmune diseases; HCs: Healthy controls

Figure 3. Comparison of vaccination related adverse events between rheumatoid arthritis, other autoimmune rheumatic diseases, non-rheumatic autoimmune diseases, and healthy controls