Higher risk of short term COVID-19 vaccine adverse events in myositis patients with autoimmune comorbidities: results from the COVAD study

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Running Title: Higher risk of short term COVID-19 vaccine adverse events in myositis patients with autoimmune comorbidities: results from the COVAD study

Key message: Inflammatory myopathies with comorbid autoimmune disease are associated with increased frequency of AEs following COVID-19 vaccination

Higher risk of short-term COVID-19 vaccine adverse events in myositis patients with autoimmune comorbidities: results from the COVAD study

Dear Editor,

Vaccination against coronavirus disease 2 (COVID-19) is known to reduce adverse infection outcomes in the general population. However, most COVID-19 vaccination studies have excluded immunosuppressed individuals and those with systemic autoimmune diseases (SAIDs), including idiopathic inflammatory myopathies (IIMs), leading to a lack of safety data for this patient group. Studies of self-reported adverse events (AEs) following vaccination against COVID-19 have yielded conflicting results, with either higher or comparable adverse events in IIMs versus healthy controls (HCs) [1, 2]. This could potentially be explained by the effect of coexistent comorbidities on AEs in these patients, especially comorbid autoimmune conditions, an area that remains under-studied.

The COVID-19 Vaccination in Autoimmune Diseases (COVAD) study is an ongoing international collaborative study involving 106 countries and 152 investigators [3, 4]. It captures data including vaccination uptake, AEs, COVID infection and comorbidities in people with SAIDs, by means of an online survey [5, 6]. We previously reported a modest increase in the incidence of severe adverse events 7-day post-vaccination in 1227 patients with IIMs compared to 5033 HCs, as well as other SAIDs [2]. Notably, adverse events were higher in the dermatomyositis (DM) group and active disease [2]. The COVAD study is currently in its second phase which captures data on the long-term efficacy of vaccines, vaccine-induced disease flares, de novo emergence of autoimmune diseases, effects of booster vaccine doses, and specific risks of antenatal vaccination [7].

Patients with IIM often have multiple comorbidities, and the effects and burden of these comorbidities on patient-reported outcomes are seldom accounted for. We hypothesized that harboring multiple autoimmune comorbidities may influence post-vaccination AEs and outcomes. Therefore, we explored the influence of autoimmune multimorbidity (i.e. defined as 1 or more coexistent autoimmune diseases in patients with IIMs) on their self-reported AEs, and the effect of adjustment for these factors in the IIM-SAID group with IIMs alone and HCs.

We previously published the COVAD study protocol and details of the global electronic survey with accompanying methods [3]. The e-survey collected respondent demographics, SAID details, COVID-19 vaccination details, and 7-day vaccine AEs. We compared COVID-19 vaccination-related AE in patients with IIMs with other SAIDs (Table 1) in patients with IIMs only and HCs. We performed multivariable regression analysis with adjustment for age, sex, ethnicity, vaccine type and immunosuppressants received, by number of AID comorbidities, and stratified by country of residence (Baseline Logistic Regression, BLR). We further performed propensity score matching between patients with IIMs with SAIDs and HCs with a tolerance of 0.1. We compared vaccine-related AEs among patients with IIMs with different numbers of SAID comorbidities using the chi-square test, with Bonferroni corrected p values as statistically significant. Statistical analyses were performed using SPSS version 26.

A total of 6099 participants were included, comprising 573 people with IIMs and other SAIDs, 814 with IIMs without other SAIDs, and 4712 HC (Supplementary Table S1). Individuals with IIMs were older than those with HCs (mean age in individual with IIMs and other SAIDs, 54 years; in individuals with IIMs alone, 64 years; HCs, 34 years). The majority of the participants were women (66.3%). The most commonly administered vaccine across all participants was Pfizer-BioNTech (BNT162b2) (37.5%), followed by Oxford/AstraZeneca (ChAdOx1 nCoV-19) (11.1%) and Moderna (mRNA-1273) (8.5%).

Notably, individuals with IIMs with autoimmune multimorbidity (at least one other SAIDs) were more likely to experience any AEs following COVID-19 vaccination than those with IIMs alone (OR 1.50 [1.10-2.10], p=0.003 (Table 1). After adjusting for the number of SAIDs, an increased risk remained for injection site pain (OR 1.40 [1.01-2.00], p=0.044), body ache (OR 1.50 [1.02-2.00], p=0.037), headache (OR 1.7 [1.20-2.40], p=0.004), and nausea and vomiting (OR 2.20 [1.20-4.00], p=0.012). Fortunately, there was no increase in the risk of major AEs in the autoimmune multimorbidity IIM group.

When compared to healthy controls in the multivariable analysis, patients with IIMs and other SAIDs were significantly more likely to experience headache (OR 1.20 [1.01-1.60], p=0.035), nausea and vomiting (OR 1.40 [1.01-2.00], p=0.045), fatigue (OR 1.30 [1.03-1.60], p=0.023), and overall, any major AEs (OR 2.00 [1.20-3.30], p 0.005) (Supplementary Table S2). Conversely, when compared with HCs, patients with IIMs alone were less likely to experience any AEs overall (OR 0.70 [0.56-0.87], p=0.002), suggesting that the AEs were largely limited to the autoimmune multimorbidity group (Supplementary Table S3). When considering patients with inclusion-body myositis or active IIMs with SAIDs, compared to those without SAIDs, patients with multimorbidity were more likely to experience any AEs (minor and major) following vaccination ($p<0.05$).

It is noteworthy that increasing numbers of coexisting SAIDs in people with IIMs were associated with an overall increased likelihood of any minor or major AEs especially: myalgia, nausea and vomiting, hypertension, and dizziness (all $p<0.003$) (Supplementary Table S4).

This pattern was also seen in specific subgroups of IIM, particularly we noted patients with Dermatomyositis (DM) and other co-existent SAIDs at a higher risk of major AEs [OR 3.1 (1.3-7.6), p=0.006] compared to those with DM alone (Supplementary Table S5)

Thus, to conclude, patients with IIMs and coexisting SAIDs experience more frequent AEs following vaccination against COVID-19 compared to those with IIMs alone and HCs. Our study adds to the growing body of evidence on the safety of COVID-19 vaccination in people with SAIDs, specifically contributing more granular detail on patients with IIMs including the vulnerable and relatively understudied proportion of these patients with autoimmune multimorbidity, compared to other global studies on COVID-19 vaccination related adverse events [1].

Fortunately, the associated risks are minor and the frequency of major AEs is not significant in the majority of cases. People with a greater number of SAIDs in addition to IIMs are more likely to experience certain AEs and have an overall increased risk of AEs. It is important to ascertain the long-term outcomes after vaccination in this group [8].

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Conflicts of Interest/Competing interests:

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Table 1. Comparison of vaccine related AE among IIM with and without other AIDs

N (%)	IIMs with other AIDs (n=573)	IIMs only (n=814)	Univariate		BLR[1]		BLR[2]	
			OR (CI)	P value	OR (CI)	Adjusted P value	OR (CI)	Adjusted P value
Any AEs	479 (83.6)	541 (66.5)	2.5 (1.9-3.3)	<0.001	1.5 (1.1-2.1)	0.003	1.8 (1.2-2.8)	0.003
Injection site pain	395 (69)	458 (56.3)	1.2 (1.1-1.3)	<0.001	-	0.303	1.4 (1.01-2.0)	0.044
Minor AEs to vaccine								
Any minor AEs	479 (83.6)	541 (66.5)	2.5 (1.9-3.3)	<0.001	1.5 (1.1-2.1)	0.003	1.8 (1.2-2.8)	0.003
Fatigue	203 (35.4)	191 (23.5)	1.2 (1.1-1.4)	<0.001	1.3 (1.1-1.7)	0.033	1.4 (1.01-1.9)	0.044
Headache	166 (29.0)	136 (16.7)	1.3 (1.2-1.5)	<0.001	1.4 (1.1-1.9)	0.006	1.7 (1.2-2.4)	0.004
Body ache	142 (24.8)	104 (12.8)	1.4 (1.2-1.7)	<0.001	1.6 (1.2-2.2)	0.001	1.5 (1.02-2.0)	0.037
Chills	91 (15.9)	96 (11.8)	1.1 (1-1.3)	0.028	-	0.645	-	0.841
Myalgia	88 (15.4)	68 (8.4)	1.3 (1.1-1.6)	<0.001	1.6 (1.1-2.3)	0.011	-	0.314
Fever	81 (14.1)	89 (11.x)	-	0.073	-	-	-	-
Nausea and vomiting	51 (8.9)	26 (3.2)	1.7 (1.2-2.4)	<0.001	2.3 (1.3-3.8)	0.001	2.2 (1.2-4.0)	0.012
Dizziness	36 (6.3)	26 (3.2)	1.4 (1.1-1.9)	0.006	-	0.065	-	0.874
Rashes	16 (2.8)	18 (2.2)	-	0.491	-	-	-	-
Diarrhoea	16 (2.8)	16 (2.0)	-	0.313	-	-	-	-
Abdominal pain	16 (2.8)	10 (1.2)	1.5 (0.9-2.5)	0.034	-	0.186	-	0.216
High pulse rate or palpitations	16 (2.8)	13 (1.6)	-	0.126	-	-	-	-
Difficulty in breathing	8 (1.4)	8 (1.0)	-	0.478	-	-	-	-
Chest pain	6 (1.0)	5 (0.6)	-	0.371	-	-	-	-
Rise in blood pressure	5 (0.9)	8 (1.x)	-	0.105	-	-	-	-
Fainting	4 (0.7)	2 (0.2)	-	0.206	-	-	-	-
Others	51 (8.9)	43 (5.3)	1.7 (1.1-2.6)	0.008	-	0.077	-	0.662
Minor AEs to vaccine								
Any major AEs	33 (5.8)	17 (2.1)	2.8 (1.5-5.1)	<0.001	3.0 (1.5-5.8)	0.001	-	0.185
Marked difficulty in breathing	7 (1.2)	2 (0.2)	2.6 (1-9)	0.026	-	0.146	-	0.213
Severe rashes	4 (0.7)	3 (0.4)	-	0.394	-	-	-	-
Anaphylaxis	0 (0)	2 (0.2)	-	0.235	-	-	-	-

Throat closure	0 (0)	1 (0.1)	-	0.401	-	-	-	-
Others	30 (5.2)	12 (1.5)	3.6 (1.8-7.2)	<0.001	3.9 (1.9-8.3)	<0.001	-	0.064
Hospitalization	4 (0.7)	2 (0.2)	-	0.206	-	-	-	-

AEs: adverse events, AIDs: autoimmune diseases, IIMs: idiopathic inflammatory myopathies, OR: odds ratio, CI: confidence interval

[1]BLR: binary logistic regression was adjusted for age, sex, ethnicity, vaccine type, number of doses of vaccine received, IS dose and stratified by the country of origin

[2] BLR: binary logistic regression was adjusted for age, sex, ethnicity, vaccine type, number of doses of vaccine received, IS dose, the number of AIDs comorbidities and stratified by the country of origin