COVID-19 vaccination-related adverse events among autoimmune disease patients: results from the COVAD study

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Running Title: COVID-19 vaccination-related adverse events in autoimmune disease patients

Abstract

Objectives

COVID-19 vaccines have been proven to be safe in the healthy population. However, gaps remain in the evidence of their safety in patients with systemic autoimmune and inflammatory disorders (SAIDs). COVID-19 vaccination related adverse events (ADEs) in patients with SAIDs and healthy controls (HC) seven days post-vaccination were assessed in the COVAD study, a patient self-reported cross-sectional survey.

Methods

The survey was circulated in early 2021 by >110 collaborators (94 countries) to collect SAID details, COVID-19 vaccination details, and 7-day vaccine ADEs, irrespective of respondent vaccination status. Analysis was performed based on data distribution and variable type.

Results

10900 respondents [42 (30-55) years, 74% females and 45% Caucasians] were analyzed. 5,867 patients (54%) with SAIDs were compared with 5033 HCs.

79% had minor and only 3% had major vaccine ADEs requiring urgent medical attention (but not hospital admission) overall. Headache [SAIDs=26%, HCs=24%; OR=1.1 (1.03-1.3); p=0.014], abdominal pain [SAIDs=2.6%, HCs=1.4%; OR=1.5 (1.1-2.3); p=0.011], and dizziness [SAIDs=6%, HCs=4%; OR=1.3 (1.07-1.6); p=0.011], were slightly more frequent in SAIDs. Overall, major ADEs [SAIDs=4%, HCs=2%; OR=1.9 (1.6-2.2); p<0.001] and, specifically, throat closure [SAIDs=0.5%, HCs=0.3%; OR=5.7 (2.9-11); p=0.010] were more frequent in SAIDs though absolute risk was small (0-4%). Major ADEs and hospitalizations (less than 2%) were comparable across vaccine types in SAIDs.

Conclusion

Vaccination against COVID-19 is relatively safe in SAID patients. SAIDs were at a higher risk of major ADEs than HCs, though absolute risk was small. There are small differences in minor ADEs between vaccine types in SAID patients.

Key message:

- COVID-19 vaccination is safe in SAIDs and HCs.
- There are minor differences in the risk of specific vaccine ADEs between SAIDs and HCs, between vaccines.
- The absolute risk of major ADEs and hospitalizations due to vaccination is very small.

Key words: adverse reaction, autoimmune disease, COVID-19, rheumatic disease, vaccine

Introduction

The COVID-19 pandemic has had an unprecedented impact on societies and economics across the globe, with even the most robust healthcare systems grappling to cope with the ever-growing needs of health care delivery [1]. The clinical outcomes and morbidity of COVID-19 in patients with systemic autoimmune and inflammatory disorders

(SAIDs) has been largely understudied and poorly characterized. Given the limited evidence available, stringent shielding for avoidance of COVID-19 infection has remained the primary advice to avoid poor clinical outcome in this already vulnerable group [2, 3].

The safety and effectiveness of COVID-19 vaccination has been suitably demonstrated by large multicentric clinical trials in the healthy population with only limited adverse events (ADEs) being reported [4, 5]. However, due to the exclusion of patients with SAIDs from these initial trials, gaps remain in the evidence of short- and long-term safety and efficacy of COVID-19 vaccines in this cohort. Patients as well as rheumatologists have expressed concerns regarding vaccination triggered flares, allergic reactions, thrombogenic events as well as other ADEs and concerns of inefficacy, potentially contributing to vaccine hesitancy [6–9]. Several studies have reported COVID-19 vaccination-related ADEs in patients with SAIDs though considerably fewer included a control group for comparison [10, 11]. However, studies with a large sample size of both patients as well as controls, and heterogeneity of disease types are scarce.

Recently, preliminary analysis from the COVAD study suggested a higher risk of rashes in patients with idiopathic inflammatory myopathies (IIM) as compared to HCs [12]. Early events after vaccination may provide unique insights and baseline data for further trends, including long-term studies. Different vaccine types may be potentially associated with different frequency and type of ADEs in relation to preservatives used, vaccine primary content, and in term of risk for triggered autoimmunity [13]. However most studies in the current literature consider the effects of a single or few vaccine types, and those comparing the ADEs associated with multiple vaccine types are lacking [14].

The COVID-19 Vaccination in Autoimmune Diseases (COVAD) study aims to address this gap in literature regarding the safety of COVID-19 vaccinations in the SAID population [15]. Thus, we compared short-term ADEs between SAIDs and HCs at seven days post-vaccination. Moreover, this study aimed to evaluate vaccine ADEs based on the type of vaccine administered.

Methods

We developed a comprehensive, online, cross-sectional, patient self-reporting survey as part of the COVAD study, consisting of questions to evaluate demographic details, SAID diagnosis and treatment details, COVID-19 vaccination status, 7-day post vaccination adverse effects based on CDC criteria, and patient reported outcome

measures according to the Patient Reported Outcomes Measurement Information System (PROMIS) tool [15–17]. The survey was extensively disseminated by the COVAD study group (Supplementary Data S3, available at *Rheumatology* online). Participants (both patients with SAIDs and HCs) were invited to complete the survey between April and September 2021, irrespective of their vaccination status. Patients with SAIDs were encouraged to have their healthy family relatives complete the survey, and HCs also included respondents on social media. Participants from 94 countries completed the survey. Data was extracted on 30th September 2021. Patients who had not received even a single dose of any COVID-19 vaccine at the time of survey completion and who had not completed the survey in full were excluded from the analysis (Figure 1). Multiple relevant variables were retrieved from the responses of the included participants. ADEs occurring after both the first as well as second primary dose of vaccination were considered and combined as most of the world population had received a single dose of vaccination at the time of survey dissemination.

Descriptive and comparative analysis was performed based on the data distribution and variable type. The variables found significant in univariate analysis, and those expected to be independently significant based on evidence from current literature, which was limited at the time of analysis, as well as the clinical judgement of three rheumatologists (LG, RA and NR), underwent binary logistic regression analysis (BLR) with baseline adjustment for age, gender, ethnicity, immunosuppressants received, and vaccine type. Bonferroni corrected p value <0.0125 was considered significant.

Additional methods have been described in Supplementary Data S1 (available at *Rheumatology* online) and detailed at length in the protocol for the COVAD study previously published [15].

Ethics approval

Ethical approval was obtained from the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli Road, Lucknow, 226014 (IEC Code: 2021-143-IP-EXP-39)

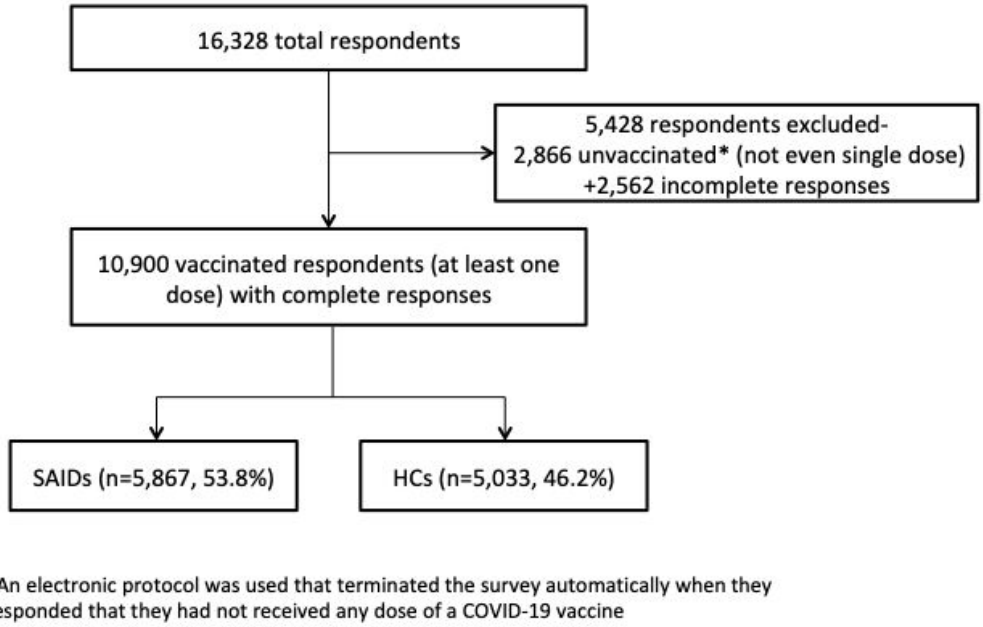

Figure 1. Data Extraction

Results

Population characteristics

10,900 vaccinated respondents (74% female, aged 42 (30-55) years, 46% Caucasian) primarily from Turkey (n=1,517), Mexico (n=1,255), India (n=1,136), UK (n=1,161) and the USA (n=980) were included in the analysis (Figure 1). The cohort comprised of two groups, patients with SAIDs (5867, 53.8%) and the HCs (5033, 46.2%) (Table 1).

The predominant SAID reported in the cohort was rheumatoid arthritis (13%, n=1,459), followed by IIM (11%, n=1,227), and hyper/hypothyroidism (9%, n=1,051), All patients had received at least a single dose of the COVID-19 vaccine and 69% had received both primary doses. The largest number of respondents received the Pfizer-BioNTech vaccine (39.8%, n=4,333), followed by the Sinopharm (17%, n=1,821) and Oxford/AstraZeneca (13.4%, n=1,456) vaccines. The population characteristics of the study cohort are given in Table 1.

Baseline demographics differed by an older SAID population [49 (38-61) years] compared to HCs [33 (25-46) years], as well as a slightly greater predominance of females in SAIDs (M:F 1:4.7 in SAID vs 1:1.8 in HC).

Variable	Total (n=10900)	SAIDs (n=5867)	HC (N=5033)
Median Age in years (IQR)	42 (30-55)	49 (38-61)	33 (25-46)
Gender (Male: Female)	1:2.9	1:4.7	1:1.8
Ethnicity			
Caucasian	4972 (45)	3185 (54)	1787 (35)
African American or of African origin	83 (0.7)	56 (1)	27 (0.5)
Asian	2018 (18)	852 (14)	1166 (23)
Hispanic	1193 (11)	448 (7)	745 (15)
Native American/ Indigenous/ Pacific Islander	342 (3)	19 (0.3)	23 (0.5)
Do not wish to disclose	449 (4)	204 (3)	323 (6)
Other	865 (8)	148 (2.5)	245 (5)
Unanswered	1672 (15)	955 (16)	717 (14)
Vaccine taken			
Pfizer-BioNTech (BNT162b2)	4333 (39)	2687 (45.8)	1443 (28.7)
Oxford/Astra Zeneca (ChAdOx1 nCoV-19)	1456 (13)	969 (16.5)	487 (9.7)
Johnson & Johnson (J&J) (JNJ-78436735)	95 (1)	57 (1)	38 (0.8)
Moderna (mRNA-1273)	910 (8)	747 (12.7)	163 (3.2)
Novavax (NVX-CoV2373)	14 (0.1)	10 (0.2)	4 (0.1)
Covishield (ChAdOx1 nCoV-19)	1194 (11)	473 (8)	721 (14)
Covaxin (BBV152)	248 (2)	126 (2.1)	122 (2.4)
Sputnik (Gam-COVID-Vac)	204 (2)	68 (1.2)	136 (2.7)
Sinopharm (BBIBP-CorV)	1821 (17)	378 (6.4)	1443 (28.7)
I am not sure	62 (0.5)	27 (0.5)	35 (0.7)
Others	563 (5)	325 (5.5)	238 (4.7)
Diagnosis			
No autoimmune disease	5033 (46)	-	5033 (100)
Rheumatoid arthritis	1459 (13)	1459 (25)	
Idiopathic inflammatory myopathies	1227 (11)	1227 (20)	
Systemic lupus erythematosus	600 (6)	600 (10)	
Systemic sclerosis	493 (4)	493 (8)	
Ankylosing spondylitis or psoriatic arthritis	394 (4)	394 (7)	
Sjögren's syndrome	294 (3)	294 (5)	
Mixed connective tissue disorder (MCTD)	106 (1)	106 (2)	
Vasculitis	142 (1)	142 (2)	
Crohn's disease or ulcerative colitis (IBD)	239 (2)	239 (4)	
Thyroid (hypothyroid or hyperthyroid)	1051 (9)	1051 (18)	
Type 1 Diabetes	141 (1)	141 (2)	
Multiple sclerosis	46 (0.5)	46 (0.7)	
Myasthenia gravis	46 (0.5)	46 (0.7)	
Pernicious anaemia	24 (0.2)	24 (0.4)	
Hemolytic anemia / idiopathic thrombocytopenic purpura (ITP)	32 (0.2)	32 (0.5)	
Polymyalgia rheumatica	43 (0.3)	43 (0.7)	
Others	1192 (10)	1192 (20)	

Discontinued medicines (DMARDs/Immunosuppressants) before vaccination	773 (7)	773 (13)	-
Duration of discontinuing medicines (days)	13 (7-21)	13 (7-21)	-
SAID: Systemic autoimmune and inflammatory disorders, HC: helathy controls			

Table 1. Population characteristics

Comparison of vaccine ADEs between SAIDs and HC

Overall, the incidence of minor vaccine ADEs was comparable between SAIDs and HCs, with SAIDs only at a slightly higher risk of experiencing any minor ADE than HCs [80% vs 77%, OR=1.2 (1.18-1.4), P<0.001], the absolute risk difference being only 3%. In the uncontrolled univariate analysis, injection site pain was reported more frequently in the SAID cohort compared to the HC, albeit the absolute risk being somewhat comparable [65% vs 62%, OR=1.1(1.04-1.2), P=0.002]. However, these minor difference in overall minor ADEs and injection site pain, were not significantly different after adjustment for baseline variables (age, gender, ethnicity, vaccine type, and stratified for country of origin).

Minor systemic vaccine ADE specifically myalgia, body ache, fever, chills, headache and fatigue were very frequent (10-70%), however, did not differ significantly between SAIDs and HCs in adjusted analysis except headache, which was found to be higher in SAIDs than HCs [26% vs 22%, OR 1.1 (1.03-1.3), p 0.014] after adjustment for baseline variables (age, gender, ethnicity, vaccine type, and stratified for country of origin. Among less frequency minor ADEs, abdominal pain [2.6% vs 1.4%, OR 1.5 (1.1-2), P 0.021], dizziness [5.9% vs 4.4%, OR=1.3 (1.07-1.6), P 0.011], fatigue [31% vs 27%, OR 1.1 (1.02-1.2), p 0.021], diarrhea [3.5% vs 2.4%, OR 1.5 (1.1-2.3), p 0.011], palpitations [3.3% vs 2.5%, OR 1.3 (1-1.7), P 0.046] and others [9% vs 5%, OR 1.6 (1.3-1.9), p<0.001] were statistically significantly greater in SAIDs than HCs, after adjustment for baseline variables, with small absolute risk difference (2-4%) (Table 2).

Similarly, the overall absolute risk of major vaccine ADEs was very small in both the SAID (4%) as well as the HC (2%) cohorts, however, was significantly increased in SAIDs as compared to HC [OR=1.9 (1.6-2.2), P<0.001] after controlling for baseline variables, with the absolute risk difference of 2%. Specifically, the risk of throat closure was higher in SAIDs than HCs [0.5% vs 0.3%, OR=5.7 (2.9-11), P 0.010] after adjusted analysis, though the absolute risk was less than 1% in both SAIDs and HCs, with small numbers potentially limiting our ability to draw firm conclusions. Hospitalizations due to vaccine ADEs were infrequent (0.5% in SAIDs and 0.2% in HCs), and notably there was no statistically significant difference between SAIDs and HCs after adjustment for baseline variables (Table 2).

These differences in vaccine ADEs between SAIDs and HCs remained consistent across different vaccine types.

N (%)	SAIDs (n=5867)	HCs (n=5033)	Univariate		Multivariate	
			OR (CI)	P value (Bonferroni P value of <0.0125 is significant)	OR (CI)	Adjusted P value#
Injection site pain	**3820 (65)**	**3138 (62)**	1.1 (1.04-1.2)	0.003	-	0.636
Minor ADEs to vaccine						
Any minor ADEs	**4721 (80)**	**3853 (77)**	1.2 (1.18-1.4)	<0.001	-	0.518
Myalgia	**921 (15.7)**	**778 (15.5)**	-	0.731	-	-
Body ache	1300 (22)	1082 (21)	-	0.406	-	-
Fever	**1014 (17)**	**960 (19)**	0.88 (0.8-0.97)	0.015	-	0.083
Chills	**890 (15)**	**631 (12.5)**	1.2 (1.1-1.4)	<0.001	-	0.534
Nausea and vomiting	**385 (6.6)**	**222 (4.4)**	1.5 (1.2-1..8)	<0.001	-	0.089
Headache	**1561 (26.6)**	**1125 (22.4)**	1.2 (1.1-1.3)	<0.001	1.1 (1.03-1.3)	0.014
Rashes	**125 (2.1)**	**48 (1)**	2.2 (1.6-3.1)	<0.001	-	0.165
Fatigue	**1859 (31.7)**	**1359 (27)**	1.2 (1.1-1.4)	<0.001	1.1 (1.02-1.2)	0.021
Diarrhoea	**203 (3.5)**	**120 (2.4)**	1.4 (1.1-1.8)	0.001	1.5 (1.15-2)	0.003
Abdominal pain	**153 (2.6)**	**72 (1.4)**	1.8 (1.3-2.4)	<0.001	1.5 (1.1-2.3)	0.011
High pulse rate or palpitations	**193 (3.3)**	**125 (2.5)**	1.3 (1.06-1.6)	0.013	1.3 (1-1.7)	0.046
Rise in blood pressure	73 (1.2)	47 (0.9)	-	0.122	-	-
Fainting	27 (0.5)	16 (0.3)	-	0.237	-	-
Difficulty in breathing	69 (1.2)	50 (1)	-	0.360	-	-
Dizziness	**349 (5.9)**	**229 (4.4)**	1.3 (1.1-1.5)	<0.001	1.3 (1.07-1.6)	0.011
Chest pain	98 (1.7)	60 (1.2)	-	0.051	-	-
Others	**506 (9)**	**270 (5)**	1.6 (1.4-1.9)	<0.001	1.6 (1.3-1.9)	<0.001
Major ADEs to vaccine						
Any major ADEs	**261 (4)**	**90 (2)**	2.5 (2-3.2)	<0.001	1.9 (1.6-2.2)	<0.001
Anaphylaxis	11 (0.2)	5 (0.4)	-	0.129	-	-
Marked difficulty in breathing	36 (0.6)	27 (0.5)	-	0.596	-	-
Throat closure	**27 (0.5)**	**4 (0.3)**	5.8 (2-16)	0.003	5.7 (2.9-11)	0.010
Severe rashes	41 (0.7)	15 (0.3)	2.3 (1.3-4.2)	0.004	2.3 (1.1-5)	0.025
Others	**187 (3)**	**56 (1)**	2.9 (2.1-3.9)	<0.001	2.3 (1.6-3.4)	<0.001
Hospitalization	**27 (0.5)**	**11 (0.2)**	3.2 (1.6-6.2)	0.033	-	0.452

ADE: Adverse Drug Event, SAID: Systemic Autoimmune and Inflammatory Disorders, HC: Healthy Control, OR: Odd's Ratio, CI: Confidence interval

Since all of the chi-squares are 2X2, the desired cut off of Bonferroni corrected p value is <0.0125 to be considered significant

Factors adjusted were age, gender, ethnicity, vaccine type

Table 2. Comparison of vaccine ADEs between SAIDs and HC

Comparison of different COVID-19 vaccine related ADEs Among SAIDs

The most common vaccine received by patients with SAID was the Pfizer-BioNTech (n=2687), followed by Oxford/AstraZeneca (n=969), Moderna vaccines (n=747), and others.

The overall risk of any post vaccination ADEs was lower in SAID patients who had received the Covishield (73%, P<0.001), Covaxin (66%, P<0.001) and Sinopharm vaccines (73%, P<0.001) and greater in Moderna (89%, P<0.001), and Oxford/AstraZeneca (83%, P<0.05) when each vaccine is compared to the rest of the vaccines. Interestingly, these overall differences in uncontrolled univariate analysis did not attain significance after adjustment for baseline variables. However, a few statistically significant differences in specific vaccine ADEs between different vaccines were observed (Table 3, Table 4).

In the adjusted analysis, injection site pain was found to be higher in the Moderna (80%, P<0.001) and Pfizer (71%, P<0.001) vaccines, and significantly lower among Oxford/AstraZeneca (59%, P<0.001), Covishield (46%, P<0.001), Covaxin (49%, P<0.001) and Sinopharm (55%, P<0.001) recipients (Table 3, Table 4).

SAID patients receiving the Moderna, Oxford/AstraZeneca, and Covishield vaccines were at an increased risk of most systemic vaccine ADEs in the adjusted analysis [Oxford/ AstraZeneca- fever myalgia (22%), body ache (35%), fever (27%), chills (29%), headache (39%), fatigue (40%) all P<0.001; Moderna- body ache (26%, P<0.05), fever (21%, P<0.005), chills (22%, P<0.001), and fatigue (38%, P<0.001); Covishield- body ache (29%), fever (37%) both P<0.001], while Pfizer-BioNTech, Sinopharm, and Covaxin recipients with SAIDs has lower frequency of these ADEs [Pfizer-BioNTech- myalgia (14%), body ache (16%), fever (11%), chills (12%) all P<0.001, headache (25%, P<0.005); Sinopharm- fever (7%), chills (3%), fatigue (21%) all P<0.001, headache (19%, P<0.005); Covaxin- chills (5%, P<0.005)] (Table 3, Table 4).

Minor gastrointestinal vaccine ADEs (nausea and vomiting, diarrhoea, and abdominal pain) were overall less frequent. Oxford/AstraZeneca recipients were at a higher risk of nausea and vomiting (11%, P<0.001) and abdominal pain (4.5%, P<0.001), while Pfizer-BioNTech recipients were relatively protected from both these ADEs [nausea and vomiting (6%, P<0.005) and abdominal pain (2%, P<0.05)]. The number of patients experiencing diarrhoea was too small to draw firm conclusions (0-5%) (Table 3, Table 4).

Following a similar pattern, patients receiving Oxford/AstraZeneca were at a higher risk of dizziness (87%, P<0.001) while Pfizer-BioNTech vaccine recipients were at a lower risk (5%, P<0.001). SAID patients receiving the Oxford/AstraZeneca vaccine were also at a higher risk of tachycardia (5%, P<0.001) though the absolute risk was small across vaccines (0-7%). While SAID patients receiving Moderna were at a higher risk of rashes (6%, P<0.001),

Pfizer-BioNTech recipients were relatively protected (1.5%, P<0.005) as compared to the rest; the absolute risk was again small (0-6%) across vaccines (Table 3, Table 4).

The number of patients experiencing rise in blood pressure, fainting, and chest pain was too small to draw any firm conclusions however, from the observed results, the absolute risk was very small across vaccine types (Table 3, Table 4).

The number of patients experiencing major ADEs and hospitalizations was too small to draw any firm conclusions. However, from the observed results, the absolute risk of major ADEs and hospitalizations was reassuringly small (0-3.5%, and less than 1% in most cases) and remained fairly consistent across vaccine types except for the minorly increased risk of marked difficulty in breathing in Johnson and Johnson (3.5%, P<0.05) (Table 3, Table 4).

The number of SAID patients who had received the Johnson and Johnson (n=57), Novavax (n=10), and Sputnik (n=68) was too small to draw any meaningful conclusions (Table 3, Table 4).

Since Pfizer vaccine recipients with SAID formed the largest cohort of patients (n=2687), ADEs of the other major vaccines (Oxford/AstraZeneca, Moderna, Covishield, and Sinopharm) were individually compared to Pfizer-BioNTech (Supplementary Data S2, available at *Rheumatology* online).

N (%)	Pfizer-BioNTech (BNT162b2) (n=2687)	Oxford/Astra Zeneca (ChAdOx1 nCoV-19) (n=969)	Johnson & Johnson (J&J) (JNJ-78436735) (n=57)	Moderna (mRNA-1273) (n=747)	Novavax (NVX-CoV2373) (n=10)	Covishield (Serum Institute India) (ChAdOx1 nCoV-19) (n=473)	Covaxin (Bharat Biotech) (BBV152) (n=126)	Sputnik (Gam-COVID-Vac) (n=68)	Sinopharm (BBIBP-CorV) (n=378)
Any adverse effect	2189 (82)	**807 (83)***	51 (89)	**666 (89)*****	7 (70)	**348 (73)*****	**83 (66)*****	53 (78)	**278 (73)*****
Injection site pain	**1910 (71)***#**	**578 (59)***#**	39 (68)	**597 (80)***#**	5 (50)	**218 (46)***#**	**62 (49)*****	39 (57)	**209 (55)***#**
Minor ADEs to vaccine									
Myalgia	**368 (14)***#**	**216 (22)***#**	**16 (28)***	117 (16)	1 (10)	77 (16)	12 (9)	10 (15)	56 (15)
Body ache	**435 (16)***#**	**334 (35)***#**	17 (29)	**194 (26)*#**	0 (0)	**139 (29)***#**	30 (23)	12 (18)	**68 (18)***
Fever	**298 (11)***#**	**267 (27)***#**	**17 (29)***	**158 (21)**#**	0 (0)	**175 (37)***#**	17 (3)	14 (20)	**28 (7)***#**
Chills	**320 (12)***#**	**286 (29)***#**	10 (17)	**169 (22)***#**	0 (0)	**47 (10)****	**7 (5)**#**	13 (19)	**10 (3)***#**
Nausea and	**150**	**106**							

vomiting	**(6)**#**	**(11)***#**	**9 (16)***	70 (9)	0 (0)	**12 (2)*****	5 (4)	5 (7)	**14 (4)*#**
Headache	**664 (25)**#**	**382 (39)***#**	**25 (44)****	220 (29)	3 (30)	**89 (18)*****	**14 (11)*****	18 (26)	**74 (19)**#**
Rashes	**40 (1.5)**#**	19 (2)	1 (2)	**43 (6)***#**	0 (0)	**4 (0.8)***	2 (2)	2 (3)	4 (1)
Fatigue	867 (32)	**385 (40)***#**	**28 (49)****	**289 (38)***#**	3 (30)	**82 (17)*****	**21 (16)*****	15 (22)	**80 (21)***#**
Diarrhoea	103 (4)	**49 (5)****	3 (5)	24 (3)	0 (0)	**3 (0.6)*****	1 (1)	3 (4)	7 (2)
Abdominal pain	**58 (2)*#**	**44 (4.5)***#**	**4 (7)***	23 (3)	1 (10)	7 (1.5)	0 (0)	3 (4)	4 (1)
High pulse rate	88 (3)	**50 (5)***#**	3 (5)	26 (3.5)	0 (0)	**8 (2)***	2 (1.6)	5 (7)	6 (2)
Rise in blood pressure	38 (1.4)	15 (1.5)	1 (2)	3 (0.4)	0 (0)	**1 (0.2)***	3 (2)	2 (3)	5 (1)
Fainting	12 (0.4)	7 (0.7)	0 (0)	4 (0.5)	0 (0)	1 (0.2)	0 (0)	0 (0)	1 (0.3)
Difficulty in breathing	33 (1)	16 (2)	**3 (5)**#**	9 (1)	0 (0)	3 (0.6)	0 (0)	0 (0)	2 (0.5)
Dizziness	**128 (5)*****	**87 (9)***#**	**7 (12)***	51 (7)	1 (10)	23 (5)	4 (3)	4 (6)	22 (6)
Chest pain	46 (2)	22 (2)	1 (2)	11 (1.5)	1 (10)	5 (1)	5 (4)	1 (1.5)	1 (0.3)
Others	232 (8)	78 (8)	7 (12)	77 (10)	2 (20)	28 (6)	6 (5)	6 (9)	26 (7)
Major ADEs									
Anaphylaxis	5 (0.2)	3 (0.3)	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
Marked difficulty in breathing	16 (0.6)	3 (0.3)	**2 (3.5)***	6 (0.8)	**2 (20)*****	1 (0.2)	1 (1)	0 (0)	3 (1)
Throat closure	10 (0.4)	4 (0.4)	1 (2)	2 (0.3)	0 (0)	4 (0.8)	1 (1)	1 (1.5)	0 (0)
Severe rashes	17 (0.6)	8 (0.8)	1 (2)	4 (0.5)	0 (0)	0 (0)	1 (1)	1 (1.5)	3 (1)
Others	81 (3)	29 (3)	4 (7)	36 (5)	1 (10)	18 (4)	5 (4)	4 (6)	9 (2)
Hospitalization	9 (0.3)	4 (0.4)	0 (0)	6 (0.8)	**1 (10)*****	3 (0.6)	2 (1.6)	1 (1.5)	0 (0)

AID Autoimmune disease, ADE Adverse events

*P<0.05, ** P<0.005, ***P<0.001, **Since all of the chi-squares are 2X2, the desired cut off of Bonferroni corrected p value is <0.0125 to be considered significant. Those with ** and *** are significant after Bonferroni correction**

Chi square for categorical variables and Mann Whitney test for Scale variables

Comparisons are between one vaccine type versus rest, **BOLD** have increased OR when compared to rest, **BOLD Underlined** have decreased OR when compared to rest

Significant in binary logistic regression adjusted for age, gender, ethnicity, immunosuppression received and stratified by the country

Table 3. Vaccine ADEs based on the COVID-19 vaccine received among SAIDs

Factors significant in multivariate regression analysis between different vaccine types for vaccine ADE among SAIDs					
Pfizer-BioNTech vs rest of vaccine recipients			**Oxford/Astra Zeneca vs rest of vaccine recipients**		
Injection site pain	1.6 (1.4-1.8)	<0.001	Injection site pain	0.6 (0.5-0.7)	<0.001
Myalgia	0.7 (0.59-0.83)	<0.001	Myalgia	1.7 (1.4-2)	<0.001
Body ache	0.53 (0.45-0.62)	<0.001	Body ache	2.1 (1.7-2.5)	<0.001
Fever	0.44 (0.38-0.53)	<0.001	Fever	2.3 (1.9-2.7)	<0.001
Chills	0.48 (0.4-0.56)	<0.001	Chills	2.7 (2.2-3.2)	<0.001
Nausea/Vomiting	0.54 (0.42-0.68)	<0.001	Nausea/Vomiting	1.9 (1.4-2.4)	<0.001
Headache	0.67 (0.58-0.77)	<0.001	Headache	2 (1.7-2.3)	<0.001
Rashes	0.45 (0.3-0.7)	<0.001	Fatigue	1.4 (1.2-1.6)	<0.001
Abdominal pain	0.49 (0.34-0.72)	<0.001	Abdominal pain	2.2 (1.5-3.2)	<0.001
J&J vs rest of vaccine recipients			High pulse rate	1.6 (1.2-2.3)	0.005
Difficulty in breathing	4 (1.1-14)	0.032	Dizziness	1.6 (1.2-2.2)	<0.001
Moderna vs rest of vaccine recipients			**Covishield (Serum Institute India) vs rest of vaccine recipients**		
Any minor ADE	2.4 (1.9-3.2)	<0.001	Injection site pain	0.52 (0.4-0.7)	<0.001
Injection site pain	2.5 (2-3.2)	<0.001	Body ache	1.6 (1.2-2.2)	0.001
Body ache	1.5 (1.2-1.8)	<0.001	Fever	3.5 (2.6-4.8)	<0.001
Fever	1.8 (1.4-2.3)	<0.001	**Covaxin (Bharat Biotech) vs rest of vaccine recipients**		
Chills	2 (1.6-2.55)	<0.001	Any minor ADE	0.5 (0.3-0.9)	0.023
Rash	3.7 (2.3-5.8)	<0.001	Chills	3.3 (1.02-10.7)	0.049
Fatigue	1.3 (1.12-1.6)	0.001	-	-	-
Sinopharm vs rest of vaccine recipients			**Sinopharm vs rest of vaccine recipients**		
Any minor ADE	0.48 (0.3-0.6)	<0.001	Chills	9 (4.4-19)	<0.001
Injection site pain	1.9 (1.5-2.6)	<0.001	Nausea/vomiting	1.9 (1.04-3.5)	0.037
Body ache	1.8 (1.3-2.4)	<0.001	Headache	1.8 (1.3-2.4)	<0.001
Fever	4.4 (2.7-6.9)	<0.001	Fatigue	2.2 (1.6-3)	<0.001

ADE: Adverse Drug Event, SAID: Systemic Autoimmune and Inflammatory Disorders, HC: Healthy control

P<0.05 significant

Binary logistic regression was adjusted for age, gender, ethnicity, immunosuppressant drugs and stratified for country of origin

Table 4. Factors significant in multivariate analysis between different vaccine types for vaccine ADE among SAIDs

Discussion

The findings of this international patient self reported survey highlight that following administration of COVID-19 vaccination, patients with SAIDs may be at an increased risk of certain specific minor ADEs including abdominal pain and dizziness and at a reduced risk of headache as compared to HCs. However, these ADEs are easily manageable and should not deter vaccination. Major ADEs overall were higher in SAIDs than HCs, and an increased risk of certain specific ADEs such as throat closure, were also observed to be more frequent in patients with SAIDs, albeit were rare with a very small absolute risk, and did not result in increased hospitalisations. The risk of hospitalisation due to vaccination was negligible and was similar in SAIDs and HCs. Overall, our findings indicate that COVID-19 vaccination is safe in both patients with SAIDs and HCs, and align with recent publications that reaffirm that the risk benefit ratio is favourable in patients with SAID [10, 18].

Among patients with SAID, those receiving the Moderna, Oxford/AstraZeneca, and Covishield vaccines were at a higher risk of most minor vaccine ADEs, particularly systemic ADEs, while Pfizer-BioNTech, Covaxin and Sinopharm vaccine recipients had lower frequencies of these minor ADEs. However, there were no significant differences in major vaccine ADEs and hospitalisations between different vaccine groups, and the absolute risk was very small.

Safety in SAID

The safety of COVID-19 vaccines, as a whole, was reported on by Agha *et al*. Despite the patient cohort not being diagnosed with SAIDs, the results are comparable to the findings of our study, specifically regarding the overall safety profile [19]. 'Negative' reports, including rare adverse effects such as the rare but severe cases of thrombosis associated with the AstraZeneca vaccine often make more sensational news preferred by the media, occasionally to the detriment of overshadowing other noteworthy news such as the overall population benefits of COVID-19 vaccination, leading to vaccine hesitancy and lower vaccine uptake in both SAIDs and HCs [8, 9, 20]. We did not gather specific data on thrombosis given the self-reporting and global nature of the survey but our observations affirm that the risk benefit ratio is largely in favour of vaccination, and that whilst some major ADEs appeared to be more common in those with SAIDs, the rates encountered were generally low, with a overall 2% higher absolute risk over HCs. Not only patients but even practicing rheumatologists should take comfort in the fact that the current evidence indicates that COVID-19 vaccination is safe in patients in SAIDs, and the benefits of vaccination in reducing disease severity and poor clinical outcomes due to COVID-19 outweigh the risk of ADEs and disease flares.

Comparison between vaccine groups

Given the differences in vaccine compositions, differences in vaccine ADEs are to be expected. Both the Pfizer-BioNTech and the Moderna vaccines use mRNA technology, with the published trials reporting efficacy of 94-95% after two doses, with a low risk of ADEs [4, 21]. However, the uncertainty concerning the potential long-term ADEs and limited enrolment of patients with chronic autoimmune diseases in vaccine trials has resulted in hesitation regarding mRNA vaccines [22].

The Oxford/AstraZeneca vaccine utilises AAV technology to administer the COVID-19 vaccination. Rare side effects of AAV vectors include monophasic demyelinating events, including acute disseminated encephalomyelitis, optic neuritis, and transverse myelitis [23](23). Both the AstraZeneca and Johnson and Johnson COVID-19 vaccinations have also been linked to vaccine inducted prothrombotic immune thrombocytopenia [25]. Although these severe adverse events were not apparent in our findings, further studies are warranted to determine the incidence of these effects in both the general population and patients with underlying SAIDs.

Agha et al. demonstrated that the Sinopharm vaccine resulted in the lowest incidence of both minor and major vaccine ADEs compared to the Pfizer-BioNTech and Oxford/AstraZeneca vaccines [19]. This is consistent with our study, which found the risk of any adverse effect to COVID-19 vaccination to be lower among patients with SAID receiving the Sinopharm, Covishield, Covaxin, and Pfizer-BioNTech vaccines, as compared to Oxford/AstraZeneca and Moderna recipients, though after adjusted analysis, no significant difference was found between the risk of overall vaccine ADE between different vaccines.

The incidence of ADEs in the Moderna vaccine recipients was significantly increased compared to the Pfizer vaccine recipients in our study, although this was mitigated in an adjusted analysis accounting for patient profile and numbers available for comparison. Although limited studies report on these outcomes in SAID patients, the current literature corroborates these findings in the general population. Meo et al. compared the adverse effects of both the Pfizer-BioNTech and Moderna vaccines, concluding that the ADEs were less frequent in the Pfizer-BioNTech vaccine than the Moderna vaccine [26]. Furthermore, the minor ADEs experienced within our cohort were validated in a systematic review by Kaur et al. that noted the most common overall systemic ADEs as fever (46%), fatigue (44%), headache (39%), and muscle pain (17%) in vaccine trials [27].

A report by Vogel et al. detailed the possibility that the mRNA technologies present within the COVID-19 vaccinations results in an exacerbation of inflammation and existing autoimmune diseases. In Canada, the National Advisory Committee on Immunization reported two cases of major ADEs linked to the Moderna vaccination in

patients with AIDs, specifically hypothyroidism [28]. Hence, the current literature supports the need to define a proficient strategy for administering COVID-19 vaccines in the SAID population, utilizing previous research regarding the safety of other vaccinations in this cohort [29]. The COVAD study group hopes to address these questions in future surveys analysing long-term functional outcomes after vaccination. However, for now, the current evidence strongly indicates that the benefits of COVID-19 vaccination in patients with SAID outweigh the risk of potential vaccine ADEs [18, 30, 31].

Strengths

With over 16,327 responses accrued from 94 countries, the COVAD study database is one of the largest databases of COVID-19 vaccination associated data in patients with autoimmune diseases. The large as well as ethnically and geographically diverse sample population of respondents, with a large heterogeneity of disease types, in our e-survey is an overall strength of this study, giving our findings both generalizability and reliability within the local SAID population. The inclusion of several different vaccine types further adds to the strength of the study. The large sample size of both patients and controls has allowed for reliable conclusions to be made regarding more rare but serious adverse events. While the format of the study is a self-reporting survey, questions that require specific data regarding verification by a healthcare professional lend credibility to the data, reducing the problems encountered by reporting bias [15]. Furthermore, utilising an e-survey for data collection purposes ensured cost effectiveness across the study as there were limited expenses in disseminating this survey.

Limitations

The key limitation of our study is that it was a self-reporting e-survey to be completed by self-selecting participants. Responses were not validated and those completing the survey may not have been representative of the general population. As with any survey of this kind, there is a risk of recall and reporting bias within the sample [32]. There is also a risk of selection bias as younger and healthier patients are more prone to use the internet and social media, and the deceased were completely excluded. Online surveys are also susceptible to manipulation (multiple responses from individuals, automated “bot” responses, sharing amongst selected groups with specific aims). Whilst we made efforts to reduce the risk of such factors influencing the data collection, particularly through the wide-ranging channels of distribution, and pre-analysis data cleaning and checks, it is not possible to exclude completely. It is also of note that the prevalence of IIM in our cohort was overrepresented, with this diagnosis

accounting for more than 20% of our SAID population, possibly as this survey was shared by myositis support groups more widely than groups for other SAIDs. Furthermore, retrospective inclusion may have resulted in serious adverse effects being missed, such as hospitalisation and death, as these patients may have not been included in the study. For very rare ADEs, potential associations could have been missed despite the large sample size of this study. In addition to this, the questionnaire did not have any specific questions exploring if the respondents were pregnant or breast-feeding, therefore the effect of these factors on post vaccination ADEs could not be evaluated. Data on co-morbidities was also not collected. The control group, being younger than the SAID group may have less co-morbidities, and thus be less predisposed to severe outcomes.

Future directions

Given the novel nature of COVID-19 vaccines, there is currently limited data regarding the long-term adverse effects; therefore, further studies must focus on evaluating the long-term impact of these vaccinations on SAID patients, especially in high risk groups such as pregnant women and patients with AID in whom immune modulation can adversely affect the efficacy and safety profile of COVID-19 vaccination leading to unexpected outcomes, especially as these groups were excluded from the vaccine trials [33]. Future studies should also explore the effect of co-morbidities. Favourable results of safety and efficacy from these studies would be instrumental in discouraging vaccine hesitancy and combating the spread of misinformation, that though based on erroneous hypotheses, have permeated into all parts of society and healthcare, and are becoming increasingly and dangerously popular [34].

The way forward is to study individual patient groups, in well-stratified subsets by region and vaccine type. We also need data on functional status before and after vaccination, which we hope to address by future surveys from the COVAD study.

Conclusion

Vaccination against COVID-19 is relatively safe and tolerable in SAID patients with a small absolute increased risk of 2% in major ADEs as compared to HCs. This is one of the first studies to report short-term COVID-19 vaccination-related adverse events among SAID patients with a comparison group of HC. In this patient reported survey, despite small but significant increased risk of major post COVID-19 vaccination ADEs in those with SAIDs, the rates of hospitalization for ADEs relating to COVID-19 vaccination were similar between the two groups. There is

clearly an unmet need for further research in studying the long-term effects of COVID-19 vaccination in patients with systemic autoimmune and inflammatory disorders.

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Data Availability Statement

Data underlying the article are available in the article and its supplementary material. Additional data will be shared on reasonable request to the corresponding author.

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