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Impact of COVID-19 vaccination in patients with auto-immune diseases – A nationwide survey from 842 autoimmune patients

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ABSTRACT

Objectives: To combat the Coronavirus Disease 2019 (COVID-19) pandemic, the World Health Organization announced the emergency license for the usage of COVID-19 vaccinations. Various literature postulated a few cross-talks between autoimmune disease and COVID-19 vaccination. The molecular mimicry between autoimmune diseases as well as autoimmune antibodies and the antibodies against Severe Acute Respiratory Syndrome Coronavirus-2 S proteins triggers the development of a severe form of autoimmune disease. The causal association between autoimmune disease and COVID-19 vaccinations is still under debate. Hence, in this study, we aim to analyze the impact of COVID-19 vaccination on patients with autoimmune diseases.

Material and Methods: Patients were recruited from a nationwide survey throughout India from October 1, 2021, to December 30, 2021. All patients of autoimmune diseases enrolled in this study had received a diagnosis of COVID-19. A Google form was created in the English language with relevant items, including demographic variables, COVID-19 vaccination-related variables, and its impact on autoimmune disease. Association between the COVID-19 severity, vaccination status, and autoimmune disease status was analyzed.

Results: Eight hundred and forty-two patients with autoimmune disease participated in the study with 86% of vaccination rate. We noted comparable infection rates among vaccinated (37.5%, n = 272) and non-vaccinated (33.3%, n = 39) respondents with autoimmune disease (P = 0.38). Although 22.5% (n = 163) of patients with autoimmune disease demonstrated deterioration following vaccination, 75.3% (n = 546) of patients did not show any change in disease profile. We noted a significant increase in the computed tomography (CT) severity score of COVID-19 infection among non-vaccinated individuals (odds ratio = 1.1,95% confidence interval [0.29, 2.29], P < 0.001). Moreover, we also noted a significant increase in the need (P = 0.01) and length of hospitalization (P < 0.001) among COVID-19 non-vaccinated individuals. We also noted vaccination significantly prevented an acute flare-up of auto-immune disease when infected with COVID-19 (P < 0.001).

Conclusion: Although vaccination did not affect the incidence of disease among patients with auto-immune disease, it did significantly decrease the CT severity score, hospitalization rate, and length of stay following COVID-19 infection. Moreover, vaccination also prevented acute flare-ups of autoimmune disease following COVID-19 infection.

Keywords: COVID-19, Autoimmune, Vaccination, Molecular mimicry

INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic has created a major challenge in identifying the symptoms, signs, management, and complications.[1,2] The pandemic caused by SARS-CoV-2 affects the morbidity, mortality, and quality of life of the population of various groups.[3] Despite being a respiratory pathogen, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) had demonstrated extra-pulmonary manifestations, making the disease an international public health concern.[4] To combat this COVID-19 disease, the World Health Organization (WHO) announced the emergency license for the usage of COVID-19 vaccinations (Covaxin, Covishield, AstraZeneca/Oxford, Johnson and Johnson, Moderna, Pfizer, Sinopharm, Sinovac, Nuvaxovid, and CanSino)[5] Globally, 494 crores (63.3%) population are fully vaccinated whereas 94.6 crores (68.6%) population are completely vaccinated against COVID-19 disease as of September 18, 2022.[6]

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Various literature postulated a few cross-talks between autoimmune disease and COVID-19 vaccination.[7,8] The molecular mimicry between autoimmune diseases as well as autoimmune antibodies and antibodies against SARS-CoV-2 S proteins trigger the development of a severe form of autoimmune disease.[9-11] Due to antibody-dependent enhancement mechanisms, the development of vaccine-induced antibodies was observed in autoimmune disease individuals. These vaccine-induced antibodies facilitate antigen-antibody reaction which results in immune complex deposition and tissue damage.[12,13,14] Literature evidence states the lesser COVID-19 infectivity and severity among autoimmune patients in the post-vaccination phase.[7,13] There is no evidence to support the timing of immunomodulatory therapies for inflammatory disorders concerning COVID-19 vaccine safety and efficacy. However, several guidelines have been provided to give medication to optimize vaccine response.[15,16] A recent meta-analysis demonstrated lower vaccine efficacy (70.4%) in immunocompromised patients with solid organ transplants, inflammatory and autoimmune diseases, and malignancy when compared with controls.[17] The incidence of exacerbation in autoimmune disease after COVID-19 vaccination has not significantly differed by the COVID-19 vaccine manufacturer. COVID-19 vaccines were found to be more immunogenic resulting in spike protein-specific T-cell responses and neutralizing antibody levels.[15] Vaccine-induced autoimmune reaction exacerbations are due to the agonists of toll-like receptors (TLRs) – 7, −8, and −9.[18] The stimulation of innate immunity through TLRs induced by mRNAs triggers autoimmune inflammatory diseases.[19] The spatial and temporal association between autoimmune disease and COVID-19 vaccinations is still under debate. Hence, in this study, we aim to analyze the impact of COVID-19 vaccination in patients with autoimmune diseases.

MATERIAL AND METHODS

As a cross-sectional study, we recruited the patients through a nationwide survey throughout India from October, 2021, to December 30, 2021, after obtaining institutional ethical clearance from JJM Medical College (JJMMC/IEC/2021/00142) on September 20, 2021. All patients with autoimmune diseases enrolled in this study had received a diagnosis of COVID-19 according to the diagnostic criteria from the fifth edition of the Guidelines on the Diagnosis and Treatment of COVID-19 by the National Health Commission of China. The Institutional Ethics Committee, approval was obtained, and written informed consent was received from all the participants. The respondents with autoimmune disease were approached through the snowball technique.

A Google form was created in the English language with relevant items, including demographic variables, COVID-19 vaccination-related variables, COVID-19 severity, and status of autoimmune disease. Comorbidities such as presence of diabetes and hypertension were assessed among the participants. The Google form included a basic description of the purpose for which this survey was conducted. The Google form link, as well as the study's description and objective, were sent to potential volunteers by mail or social media platforms and the respondents were given a choice to not take part in the study after detailing the study objectives.

Descriptive statistics were reported as mean (standard deviation) for continuous variables, and frequencies (percentage) for categorical variables. Chi-square at a 5% level of significance was used to find statistical significance. Fischer's exact test is used when the expected cell count is <5. Logistic regression was subjected to find the relationship between the dependent variable and one or more independent variables. Logistic regression was applied on Co-RADS, computed tomography (CT) severity score, hopsitalization, length of hospitalization, and autoimmune ailment during COVID-19 infection with COVID-19 vaccination status. Data were statistically evaluated with IBM SPSS Statistics for Windows, Version 25.0., IBM Corp., Chicago, IL.

RESULTS

There were about 907 total responses of which 899 agreed to take part in the study. Among them, 842 had autoimmune disease, and of them, only 725 were vaccinated. Among them, only 311 had COVID-19 infection [Figure 1].

The majority of them were in the age group of 35–44 years (28.6%) followed by 45–54 years (23.2%), 25–34 years (18.7%), 55–64 years (11.3%), 18–24 years (18.7%), and 65 years and above (3.9%). The majority of them were females (52.7%). Around 32.6% had a bachelor's degree followed by 25.4% being high school graduates, 24.1% uneducated, 15.1% master's degree, and 2.8% with doctorate degrees. The majority of the respondents were from South India (47.5%), followed by North India (17.7%) and Central India (11.9%) as shown in [Table 1].

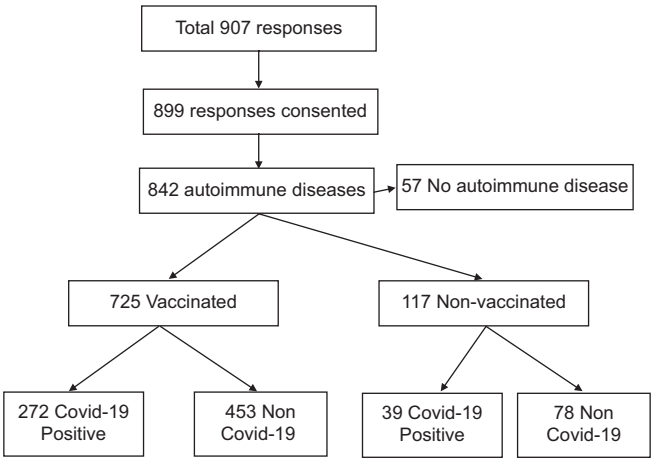

Figure 1: Flow diagram of the total responses (*n*=899).

Table 1: Distribution of demographic characteristics among the study participants (*n*=899).

Variable	Frequency	Percentage
Age		
18–24	128	14.2
25–34	168	18.7
35–44	257	28.6
45–54	209	23.2
55–64	102	11.3
65 and above	35	3.9
Gender		
Male	425	47.3
Female	474	52.7
Education		
Bachelor's degree	293	32.6
Doctorate degree	25	2.8
High school graduate	228	25.4
Master's degree	136	15.1
None of the above	217	24.1
Region		
Central India	107	11.9
East India	73	8.1
North India	159	17.7
Northeast India	77	8.6
Others	9	1.0
South India	427	47.5
Western India	47	5.2

Table 2: Distribution of variables related to autoimmune disease among the study participants (*n*=842).

Variable	Frequency	Percentage
Rheumatoid arthritis	141	16.7
Psoriasis	132	15.7
Antiphospholipid syndrome	80	9.5
Vitiligo	64	7.6
Polymyositis	46	5.5
Myasthenia gravis	45	5.3
Alopecia areata	40	4.8
Psoriatic arthritis	23	2.7
Ankylosing spondylitis	21	2.5
Reactive arthritis	21	2.5
Inflammatory bowel disease	20	2.4
Systemic lupus erythematosus	18	2.1
Pemphigus vulgaris	16	1.9
Sarcoidosis	15	1.8
Others	160	19.0
More than one autoimmune disease	10	1.2
Severity		
Mild	316	37.5
Moderate	434	51.5
Severe	88	10.5
Very severe	4	0.5
Current phase of disease		
Active phase	452	53.7
Flare following remission	26	3.1
Inactive phase	240	28.5
Remission phase	124	14.7
Comorbidities		
Present	324	38.5
Absent	518	61.5
History of allergic reaction to any licensed or unlicensed vaccine?		
Present	8	1.0
Absent	834	99.0
History of immunoglobulin therapy or blood products transfusion within the past month?		
Present	9	1.1
Absent	832	98.9
Vaccinated		
Yes	725	86.1
No	117	13.9

[Table 2] gives the distribution of the spectrum of autoimmune diseases included in the study. Rheumatoid arthritis (16.7%) and psoriasis (15.7%) were the major contributors. Around 1.2% of the respondents with the autoimmune disease had more than one autoimmune disease. Around 37.5% of the respondents with the autoimmune disease had mild severity, 51.5% moderate severity, 10.5% severe, and 0.5% very severe autoimmune disease. Around 53.7% of the respondents with the autoimmune disease were in an active phase of illness, 28.5% inactive phase, 14.7% were in the remission phase, and 3.1% were in a disease flare-up following remission. Around 38.5% of the respondents with the autoimmune disease had comorbidities, 1% had a history of an allergic reaction, and 1.1% had a history of immunoglobulin therapy or blood product transfusion. Among the respondents with autoimmune disease, 86.1% had been vaccinated for COVID-19.

Among the autoimmune vaccinated respondents (n = 725), around 43.6% had CoviShield and 41.9% Covaxin [Table 3]. About 73.7% of them were fully vaccinated. Around 46.9% had an interval of 4–6 weeks between the two doses of the vaccine while 18.1% had an interval of 6–8 weeks between two doses, 7% had an interval of 8–12 weeks and 1.7% had an interval of more than 12 weeks between the vaccine doses. Although 75.3% of the patient did not note any change in their disease status following vaccination, 22.5% had sudden deterioration due to flare-up of autoimmune disease post-vaccnation, 1.2% had deterioration requiring hospitalization, and 1.0% had deterioration requiring intensive care unit care. Moreover, 6.3% reported adverse events following the vaccination with musculoskeletal symptoms.

Among vaccinated respondents with autoimmune disease, 37.5% were COVID-19 positive. Similarly, 33.3% of non-vaccinated respondents with autoimmune disease were also infected with COVID-19 infection. Among the autoimmune vaccinated respondents, 30.9% had a mild COVID-19

Table 3: Distribution of variables among autoimmune COVID-19 vaccinated individuals (*n*=725).

Variable	Frequency	Percentage
Type of vaccine		
Covaxin	353	41.9
CoviShield	367	43.6
Others	4	0.5
None	1	0.1
History of any other vaccine intake prior to any dose of COVID-19 vaccine (either 2 weeks prior or until 30 days)		
Present	31	4.27
Absent	694	95.73
Fully vaccinated		
Yes	534	73.7
No	191	26.3
Interval between two doses of vaccine		
4–6 weeks	340	46.9
6–8 weeks	131	18.1
8–12 weeks	51	7.0
More than 12 weeks	12	1.7
Any change in autoimmune disease post vaccination		
Deterioration requiring hospitalization	9	1.2
Deterioration requiring intensive care unit care	7	1.0
Sudden deterioration	163	22.5
No change	546	75.3
Reported any adverse event following vaccine		
Yes	46	6.3
No	679	93.7
Severity		
Mild	96	30.9
Moderate	188	60.5
Severe	27	8.7

infection, 60.5% had a moderate COVID-19 infection, and only 8.7% had a severe COVID-19 infection as shown in [Table 4]. However, a significant proportion of the population in both groups was not aware of their clinical severity.

On analyzing the severity scores of the two groups, the CT severity score was 1.10 times more among COVID-19 non-vaccinated individuals ($P < 0.001$) [Table 5]. Moreover, we noted a significant proportion of non-vaccinated patients required hospitalization following COVID-19 infection ($P = 0.01$) and we also noted that the length of hospitalization was significantly longer among COVID-19 non-vaccinated individuals compared to vaccinated individuals ($P < 0.001$). We also noted vaccination significantly prevented an acute flare-up of auto-immune disease when infected with COVID-19 ($P < 0.001$).

Table 4: Distribution of variables among individuals with autoimmune diseases (*n*=842).

Variable	COVID-19 vaccinated (*n*=725)	Non-vaccinated (*n*=117)	χ^2 (df), *P*
COVID-19-positive			
Yes	272 (37.5)	39 (33.3)	0.76 (1), 0.38
No	453 (62.5)	78 (66.7)	
Severity			
Mild	80 (11)	16 (13.7)	
Moderate	171 (23.6)	17 (14.5)	
Severe	21 (2.9)	6 (5.1)	6.161 (3), 0.10
Not aware	453 (62.5)	78 (66.7)	

DISCUSSION

Even if only adults are vaccinated, a vaccine with a 95% efficacy against disease could significantly reduce future attack rates, hospitalizations, and deaths. Even as vaccines become more widely available over time, non-pharmaceutical interventions continue to play an important role in containing outbreaks. Hospitalization and mortality rates from COVID-19 are significantly higher among adults under 65 who have not been vaccinated than among adults who have received the primary series of the vaccine and who are up to date with subsequent doses.[20] Tens of millions of lives have been saved around the world thanks to the vaccination against COVID-19. However, the impact in low-income settings has been limited due to a lack of access to vaccines, highlighting the importance of global vaccine equity and coverage.

There are those who, due to illness or its treatment, have an impaired immune system and are therefore considered immunocompromised. Patients undergoing chemotherapy for cancer treatment or those who have received a solid organ transplant such as a kidney or heart and are taking medications to maintain their new organ are examples. Some people have to take medicines, such as corticosteroids, that suppress the immune system for an extended period. Such extended use raises the risk of developing secondary or acquired immunodeficiency.

Some individuals who are moderately or severely immunocompromised should receive an additional primary dose and a booster dose after completing the primary vaccination series.[21] Specific recommendations have been crafted because the immune response to the COVID-19 vaccine may vary between people with moderate and severe immunosuppression. Newer COVID-19 vaccines offer better protection against emerging strains, and the centers for disease control and prevention (CDC) recommends that everyone 12 and older get a booster shot. In addition to the original SARS-CoV-2 strain, the most recent Omicron

Table 5: Distribution of variables among COVID-19-positive autoimmune individuals (*n*=311).

Variable	Non vaccinated (*n*=39)	COVID-19 vaccinated (*n*=272)	χ^2 (df), *P*	OR (95% CI)
CO-RADS				
CO-RADS 1	1 (2.6)	2 (0.7)	8.164 (6),	-
CO-RADS 2	3 (7.7)	7 (2.6)	0.22	
CO-RADS 3	3 (7.7)	33 (12.1)		
CO-RADS 4	3 (7.7)	16 (5.9)		
CO-RADS 5	1 (2.6)	35 (12.9)		
CO-RADS 6	23 (59)	142 (52.2)		
Not aware	5 (12.8)	37 (13.6)		
CT severity score				
<8 (Mild)	7 (17.9)	35 (12.9)	24.26 (3),	0.49 (0.17–1.38)
9–15 (Moderate)	11 (28.2)	181 (66.5)	<0.001	0.15 (0.06–0.36)
>15 (Severe)	8 (20.5)	24 (8.8)		1.10 (0.29–2.29)
Not aware	13 (33.3)	32 (11.8)		1
Hospitalization				
Required	30 (76.9)	206 (75.7)	6.511 (1),	1.07 (0.48–2.36)
Not Required	9 (23.1)	66 (24.3)	0.01	1
Length of hospitalization				
<1 week	6 (15.4)	11 (4)	25.40 (5),	2.14 (0.68–6.74)
>6 weeks	0	1 (0.4)	<0.001	-
1–2 weeks	10 (25.6)	125 (46)		0.31 (0.13–0.74)
2–4 weeks	6 (15.4)	75 (27.6)		0.31 (0.11–0.86)
4–6 weeks	2 (5.1)	1 (0.4)		7.86 (0.67–92.67)
Not aware	15 (38.5)	59 (21.7)		1
Autoimmune ailment during COVID-19 infection				
Decreases in symptoms	0	95 (34.9)	24.523 (3),	-
Gradual increase in symptoms	4 (10.3)	49 (18.7)	<0.001	0.44 (0.19–1.02)
Sudden increase in symptoms	8 (20.5)	6 (2.2)		2.76 (0.72–10.48)
No Change	27 (69.2)	122 (44.2)		1

OR: Odds ratio, CI: Confidence interval

subvariants, BA.4 and BA.5 are the targets of updated boosters, also known as bivalent boosters.[22]

Among 842 participants with autoimmune disease, only 725 were vaccinated. Of which only 311 suffered COVID-19 infection. The occurrence of COVID-19 infection and severity were similar among vaccinated and non-vaccinated respondents with autoimmune disease. Autoimmune diseases are diverse conditions that are connected to an immune system that is not functioning properly. The majority of patients who suffer from autoimmune diseases have either been treated in the past with immunomodulatory medications or biological agents or are currently being treated with such treatments. Patients with autoimmune diseases reduced the number of times that they went to the doctor during the pandemic of COVID-19 because they were worried about the immunosuppressive effects of medications and the contagious nature of SARS-CoV-2. On the other hand, rheumatologic disease flares and worsened disease activity are associated with disruptions in the continuity of medical care as well as non-adherence to prescribed medications. Building a dependable telemedicine platform and providing education on the importance of taking medications as prescribed are therefore highly recommended. The sudden deterioration in the disease status following vaccination noted in 22.5% of the vaccinated population might be explained due to the prior exposure to COVID-19 infection which might have resulted in a robust immune response following the first dose of vaccination along with an increased exacerbation of the autoimmune disease.[15,23]

Since the beginning of this pandemic, infection risk in patients with autoimmune diseases has been a subject of interest.[24-26] Association between autoimmune diseases and COVID-19 as assessed in both a test-negative case–control and population case–control design. Patients suffering from autoimmune diseases had a rate of COVID-19 infection that was comparable to that of the general population, according to the findings of a cross-sectional study that was carried out in the northeastern region of Italy.[25] Another study carried out in Italy, this time in Milan, confirmed that having an autoimmune disease does not increase one's likelihood of testing positive for COVID-19.[24] We also noted in our study

that vaccination did not affect the susceptibility to infection disregarding their vaccination status.

On the other hand, the findings of a retrospective multicentric study that was carried out in Hubei, China, indicated that patients with autoimmune diseases might be more susceptible to COVID-19 infection when compared with controls.[27] In addition to that, this research looked at the patients' relatives who lived in the same area during the outbreak and used them as a control group to investigate.[24] An interesting finding from a study conducted in Milan was that patients suffering from autoimmune diseases did not have a worse prognosis compared to individuals who did not suffer from autoimmune diseases. On the other hand, the findings of a study conducted in Spain showed that patients hospitalized with autoimmune diseases had a more severe course of COVID-19.[28] Based on the results of our study, we could demonstrate that patients with autoimmune diseases who were vaccinated did not demonstrate a severe course of disease or hospitalization compared to non-vaccinated individuals.

One interesting finding from our study is that 34.9% of vaccinated patients noted a decrease in the symptoms of auto-immune disease with COVID-19 infection which needs further exploration. One possible explanation is that the severity of the COVID-19 infection might have masked the patient from perceiving the severity of the autoimmune disease. We also demonstrated that vaccination prevented these patients from getting an acute flare in their disease status following COVID-19 infection.

Our study has certain limitations. Recall bias is an intrinsic limitation of any cross-sectional study and our study is not an exception as noted in the results with some sections recording "unaware" as the patient response. The snowball technique could be useful for studying very rare diseases, but its main drawback is the high level of sampling bias. There might also be a temporal correlation between the disease flares to the COVID-19 vaccine which might have been purely coincidental and the vaccine might not have been an autoimmune trigger. Due to the design of the study, the most severe cases of COVID-19, those that died, could not have been accessed and could not have responded to the questionnaire. Therefore, the most solid data, regarding the effect of the vaccines on rheumatic disease patient survival cannot be addressed. Study focuses on patient's perception of the effects of the vaccine not to the nocebo effect, which is well-known to prevail among patients with autoimmune conditions. The study was conducted in India and recognized the importance of considering the geographical and cultural context when interpreting the results.

CONCLUSION

Although vaccination did not affect the incidence of disease among patients with auto-immune disease, it did significantly decrease the CT severity score, hospitalization rate, and length of stay following COVID-19 infection. Moreover, vaccination also prevented acute flare-ups of autoimmune disease following COVID-19 infection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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