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Original Article

Clinical and immunological responses to COVID-19 vaccination in rheumatoid arthritis patients on disease modifying antirheumatic drugs: a cross-sectional study

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Objective: This study was conducted to investigate the immunological and clinical response to COVID-19 vaccination in rheumatoid arthritis (RA) patients receiving disease modifying antirheumatic drugs (DMARDs).

Methods: A cross-sectional study was conducted among RA patients who received two doses of COVID-19 vaccine within 6 months to one year. Demographic information, comorbidities, vaccination details, and past COVID-19 infection details were collected. Hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) levels were estimated. Disease Activity Score-28 (DAS-28) was calculated for RA patients. Anti-spike antibody (ASA) concentrations were measured, and compared with a healthy control population. Correlations of ASA with age, sex, disease parameters, medication use, and comorbidities were assessed.

Results: A total of 103 RA patients and 185 controls were included in the study. RA patients had higher mean age, lower mean Hb, higher ESR, and elevated IL-6 levels. Both groups showed positive results for anti-spike antibodies, with a higher percentage in controls. Among RA patients majority had low DAS-28 score. The number of DMARDs used showed a negative correlation with antibody levels. There was a slight positive correlation between ASA concentration and DAS-28 score. Comorbidities did not significantly influence antibody concentration. No significant differences were found in antibody levels based on the type of COVID-19 vaccine or previous COVID-19 infection or booster dose vaccination among RA patients.

Conclusion: The study revealed that RA patients showed a reduced antibody response following COVID-19 vaccination compared to the control group and potentially influenced by immunosuppressive treatments and disease-related factors.

Keywords: COVID-19, Vaccination, Rheumatoid arthritis, Anti-spike antibody, Disease-modifying antirheumatic drugs

INTRODUCTION

The coronavirus disease 19 (COVID-19) pandemic caused by the SARS-CoV-2 has had a profound impact on global health and economies. Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a crucial strategy to control the spread of the virus and mitigate its severe outcomes. However, certain populations, such as patients with rheumatoid arthritis (RA), face an inherently heightened susceptibility for developing infections, including COVID-19.

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RA is one of the most prevalent autoimmune diseases characterized by the inflammation of the synovium [1].

It has been reported that COVID-19 causes severe inflammation and induces autoimmune phenomena. Studies have identified the presence of auto-antibodies, anti-cardiolipin, antiβ2-glycoprotein I and antinuclear antibodies, anti-citrullinated protein antibodies in patients with COVID-19 [2]. Additionally, case series have indicated a potential flare-up of RA disease following COVID-19 vaccination [3]. These observations raise concerns about the immunogenicity and efficacy of COVID-19 vaccination in RA patients, particularly those receiving disease modifying antirheumatic drugs (DMARDs).

DMARDs are commonly prescribed drugs to treat RA which modulate the immune system response while reducing inflammation. However, the immune-modulating effects of DMARDs can potentially impact the response to vaccines. Previous studies have shown that methotrexate discontinuation for a period of two weeks after influenza vaccination can enhance immunogenicity, while rituximab treatment reduces immune response to neoantigen and polysaccharide-pneumococcal vaccines [4].

In India, COVID-19 vaccines such as Covishield and Covaxin have played a crucial role in combating the pandemic and there is a lack of data regarding the response to vaccination in RA patients. Immunocompromised patients, including those with RA or on immunosuppressive medications, are typically excluded from vaccine trials. Therefore, it is essential to generate evidence on the immunological response to COVID-19 vaccination in RA patients receiving DMARDs. When our study was proposed, only one study with a small sample size has been conducted in India with regards to the response to vaccination in RA patients. The study found that fewer RA patients had positive IgG antibody titre to the spike protein compared to non-RA patients one month after receiving the second dose of the vaccine. There was a significant difference in antibody production between the two vaccines and 95% of those who received ChAdOx1 and 68.7% of those who received BBV152 had detectable antibodies. Furthermore, the antibody titres were higher in ChAdOx1 recipients compared to BBV152 recipients [5]. No studies were available on the antibody status in RA patients 6 months after the second vaccine. Hence, the present study was planned to evaluate the presence of antibodies specific to the spike protein in RA patients on DMARDs who completed the second dose vaccination and also to compare the response with healthy control population.

MATERIALS AND METHODS

This cross-sectional study was conducted at two tertiary care centers, over a period of one year, from May 2022 to April 2023. The study included diagnosed patients of RA, including both seropositive and seronegative individuals who were receiving DMARDs, either as single or combination therapy and completed the second dose of vaccination as test group. The study excluded patients with cancer or other autoimmune/immune suppressant disorders, pregnant or breastfeeding women and patients who had an active SARS-CoV-2 infection. Hospitalized or critically ill patients and RA patients who had not received vaccination were not included in the study. The control group consisted of participants who did not have any underlying diseases and completed the second dose of vaccination. The timeframe for inclusion of these participants was set between 6 months and one year after they had received the second vaccine dose.

Sample size

The sample size for this study was determined using statistics and sample size calculation software. It was calculated based on the comparison of two proportions, aiming for a 5% absolute precision and 80% power. The assumed serologic response rate after two doses of vaccination was 86% in RA [6] patients and 95% [7] in controls. The calculated sample size was 166 participants in each group. Considering the 10% non-response rate, the final sample size was increased to 184 participants in each group and the total sample size for the study was 368.

Data collection

The study was conducted after obtaining approval from the All India Institute of Medical Sciences, Bibinagar Instituional Ethics Committee (IEC) (Approval no.: AIIMS/BBN/IEC/AUG/2021/60-R, date: 05-09-2022 and Ref no: 799/U/IEC/ESICMC/F490/09/2022 dated 31.10.2022). After getting written informed consent from the participants, demographic data, details onco-morbidities (disease type and medication details), past history of COVID-19 infection, vaccination details (including number of doses, date, type, and adverse events), and medication details including DMARDs (dose, duration, and frequency) were collected. Additionally, the Disease Activity Score-28 (DAS-28) was recorded for RA patients as a measure of disease activity. During the study period, 10 mL of blood sample was

collected from each participant to estimate the complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), neutralizing antibodies for COVID-19 (anti-S antibodies-IgG by Coviprotect kits), as well as liver function test and renal function test. The Figure 1 depicts the study participants enrollment and progression.

Anti-spike ab testing

The neutralizing antibodies for COVID-19 were measured using an enzyme immunoassay, specifically a blocking assay, with a kit from J Mitra & Co Pvt Ltd, India. The kit detects SARS-CoV-2 neutralizing antibodies against receptor binding domain (RBD) in human serum/plasma. Results were reported as positive if ≥30% inhibition was noted, while <30% inhibition was reported as negative. The sensitivity and specificity of kit is 96.99% and 100% respectively. The participants who tested positive for antibodies were categorized based on neutralizing antibody titers into three categories. Category 1: neutralizing antibody titer 90% and above, Category 2: neutralizing antibody titer 50%~90%, Category 3: neutralizing antibody titer less than 50%.

DAS-28 score

The clinical response was assessed using the DAS-28 quan-

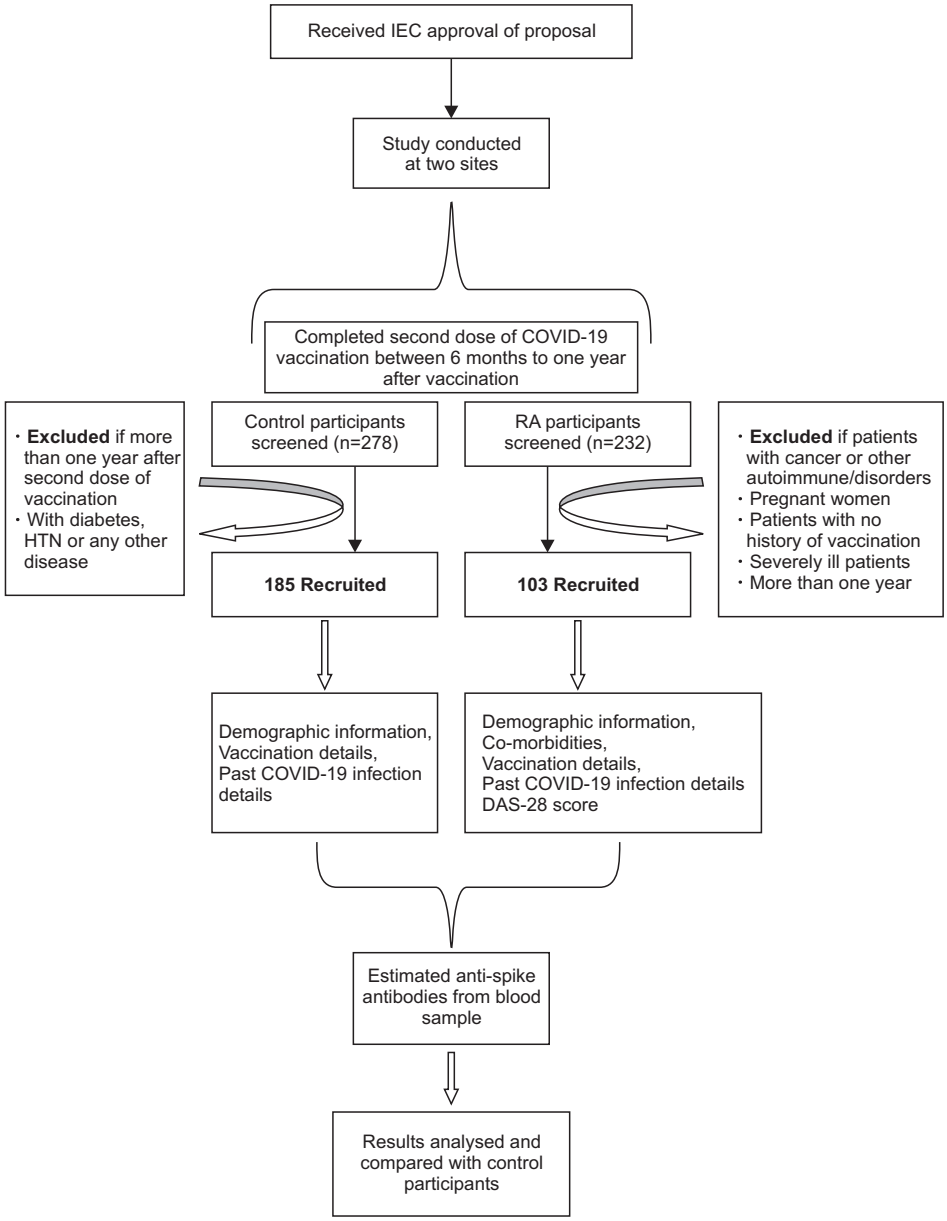

Figure 1. Illustration of study participants enrollment and progression. IEC: Institutional Ethics Committee, RA: rheumatoid arthritis, HTN: hypertension.

titative tool for measuring disease activity in RA patients [8]. The DAS-28 score was calculated online using a formula that considers number of tender joints and swollen joints out of the 28 joints assessed, acute phase reactants such as ESR or CRP and patient's global health. The score ranges from 0 to 10, with higher scores indicating greater disease activity. The DAS-28 score ≤2.6 indicates remission, score between 2.6 and ≤3.2 is low disease activity, 3.2 to ≤5.1 represents moderate disease activity, and score >5.1 indicates high disease activity.

Statistical analysis

The data was expressed as mean±standard (SD) deviation if distribution following normality and median (interquartile range [IQR]) in non-normality of the data distribution. The demographic details, co morbid status, vaccination, previous COVID-19 infection and DMARDs usage were expressed as percentages. The anti-spike antibodies were expressed median (IQR). Correlation of anti-spike antibodies concentration with age, interleukin-6 (IL-6) among RA cases and controls was done by Pearson correlation statistics. Association of anti-spike antibodies with sex, type of vaccine past COVID-19 history and booster dose vaccination among RA cases and controls was done by unpaired student t-test and chi square test respectively. Spearman's rank correlation test was used to assess the relationship between anti-spike antibodies concentration and DAS-28 score and DMARDs among RA cases. One way-ANOVA test was used to assess the relationship between anti-spike antibodies and use of DMARS drugs and comorbidities among RA cases.

RESULTS

A total of 185 controls and 103 RA patients were recruited for this study. The mean age in the test group was 44 years, while in the control group it was 30.7 years. The majority of participants in the control group were males, whereas there were more females in the test group. Among the participants in the test

Table 1. Demographic and vaccination details of the study participants

Sl. no.	Particular	Control group (n=185)	RA group (n=103)
1.	Age (yr)	30.7±8.6	44.1±9.9
2.	Male	103 (55.6)	11 (10.7)
3.	Female	82 (44.4)	92 (89.3)
4.	Comorbid status	-	
	DM		6 (5.8)
	HTN		10 (9.7)
	DM+HTN		7 (6.8)
	Hypothyroidism		17 (16.5)
	Hyperthyroidism		1 (1.0)
	Poly cystic ovarian		1 (1.0)
	Disease pulmonary tuberculosis		1 (1.0)
	Renal disease		0 (0)
	Ischemic heart disease		1 (1.0)
	CNS disorders		1 (1.0)
	NIL		60 (58.3)
5.	Type of vaccine		
	Covaxin	16 (8.64)	21 (20.4)
	Covishield	169 (91.3)	82 (79.6)
6.	Booster received	-	13 (12.6)
7.	COVID-19 infection history	-	14 (13.6)
8.	RA positive (n)	-	87
9.	RA negative (n)	-	10
10.	DAS-28 score	-	2.9±1.1

Values are presented as mean±standard deviation or number (%). RA: rheumatoid arthritis, DM: diabetes mellitus, HTN: hypertension, CNS: central nervous system, DAS-28: Disease Activity Score-28.

group, 42% had comorbidities, with the highest percentage being those with hypothyroidism (16.5%). Regarding vaccination, 91.3% of the control group and 79.6% of the test group received Covishield. In the test group alone, 12% received a booster dose. No past history of symptomatic COVID-19 infection was reported in the control group, whereas it was 13.6% in the test group. In the RA patient group, there were 87 patients who tested positive for RA factor and DAS-28 was 2.9±1.1, indicating low disease activity. Demographic and vaccination details are shown in Table 1.

The majority of RA patients (64.1%) were receiving a three-drug regimen and methotrexate was the most commonly prescribed single drug accounting for 7.8% of prescriptions, while prednisolone was the lowest prescribed drug. Additionally, some patients in the test group were also taking anti-diabetic drugs, anti-hypertensives, and medications for hypothyroidism. There was no statistically significant difference or association between anti-spike antibody concentration and different comorbidities among RA cases (Table 2 and Figure 2D).

Laboratory investigations showed that, low hemoglobin (Hb) levels and significantly increased ESR levels were found in the RA group compared to the control group. The majority of participants in both groups had negative CRP values. However, a significant increase in the IL-6 above the normal range was observed in the RA group compared to the control population. Details are shown in Table 3.

Both groups were positive for anti-spike antibodies (≥30% inhibition rate). Majority of participants in the control group (97.8%) showed NAT >90% whereas it was 41.7% in the RA group. The anti-spike antibodies levels were 95.9 (95.2~97.69) and 89.5 (87.1~91.7) in control and RA group respectively and the difference was statistically significant (Table 3 and Figure 3).

The results indicated a significant positive correlation between age and anti-spike antibody concentration specifically among

Table 2. Association of DMARDs treatment and comorbidities anti-spike antibodies concentration and among RA patients

Sl. no	Parameter	Frequency	Percentage (%)	Anti-spike antibody concentration (mean±SD)	p-value
DMARD					0.0192
1.	HCQ	6	5.8	95.7±3.2	
2.	Methotrexate	8	7.8	88.4±5.1	
3.	Prednisolone	2	1.9	94.8±4.9	
4.	2 drug regimen	17	16.5	90.6±3.7	
	HCQ & Methotrexate OR				
	HCQ & Sulfasalazine OR				
	Methotrexate & Prednisolone OR				
	Methotrexate & Leflunomide				
5.	3 drug regimen	66	64.1	87.7±6.7	
	HCQ+Methotrexate+Prednisolone OR				
	HCQ+Methotrexate+Leflunomide				
6.	4 drug regime	4	3.9	87.9±3.6	
	HCQ+Methotrexate+Prednisolone+Leflunomide				
Comorbidity					0.7405
7.	DM	6	5.8	89.5±3.6	
	HTN	10	9.7	90.4±3.2	
	DM and HTN	7	6.8	92.7±6.4	
	Hypothyroidism	17	16.5	88.1±5.5	
	Hyperthyroidism	1	1.0	87.9±0.0	
	Poly cystic ovarian disease	1	1.0	90.1±0.0	
	Pulmonary tuberculosis	1	1.0	91.33±0.0	
	NIL	60	58.2	88.2±7.0	

DMARD: disease modifying anti-rheumatic drugs, RA: rheumatoid arthritis, SD: standard deviation, HCQ: hydroxychloroquine, DM: diabetes mellitus, HTN: hypertension. $p<0.05$ considered significant.

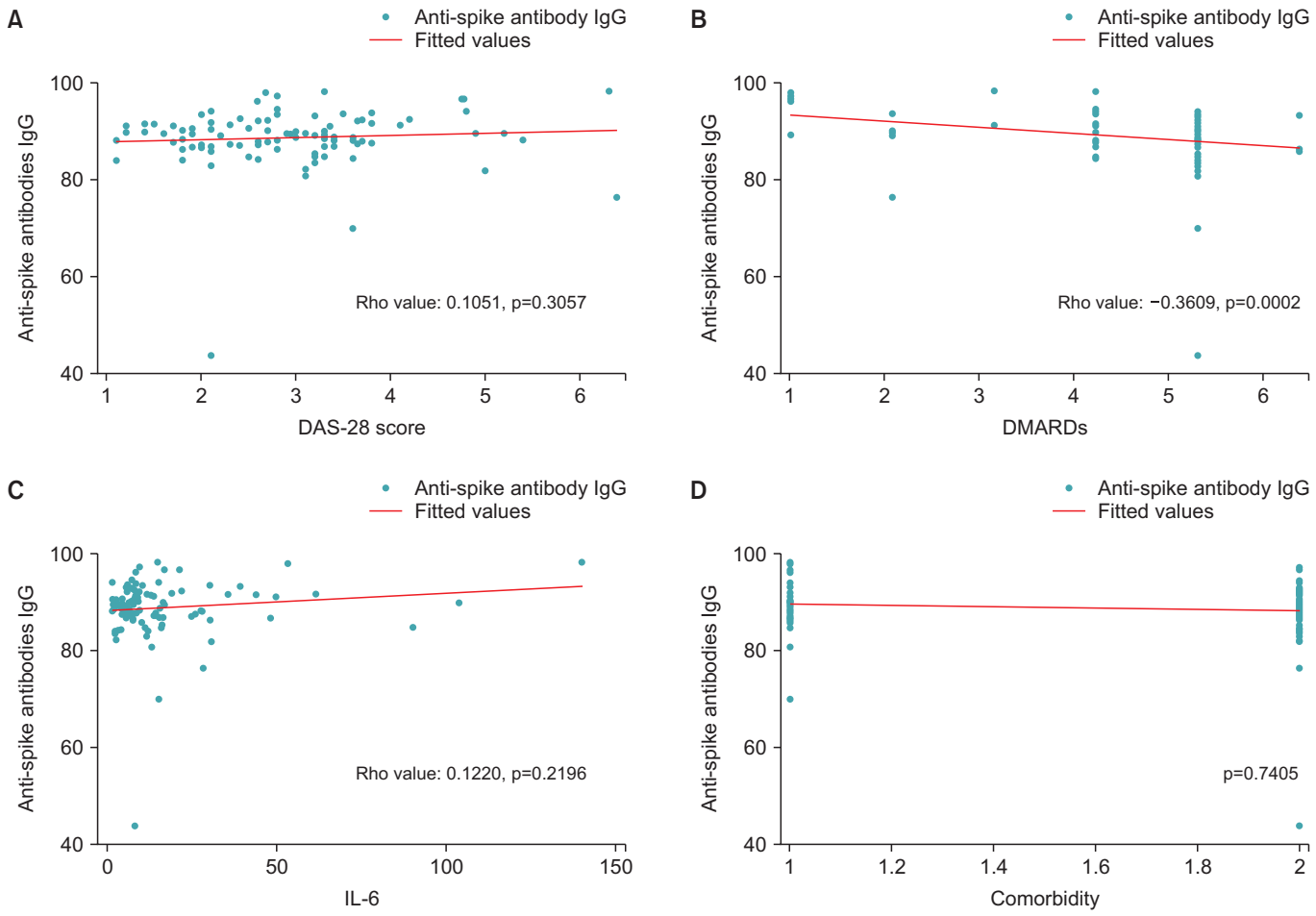

Figure 2. Correlation of anti-spike antibodies concentration with DAS-28 score (A), DMARDs (B), IL-6 (C), and association of comorbidities (D) among RA cases (n=103). DAS-28: Disease Activity Score-28, DMARDs: disease modifying anti-rheumatic drugs, IL-6: interleukin-6, RA: rheumatoid arthritis. p<0.05 is considered statistically significant.

RA patients (p=0.0015) but not in the control group (r=0.0479, p=0.5153). The proportions of anti-spike antibody concentration were not found to be significantly different between males and females in both the RA group and controls. There was a small positive correlation between anti-spike antibodies concentration and DAS-28 score among RA patients which was statistically insignificant (rho=0.1051, p>0.05) (Figure 2A).

Statistically significant difference in antibody status among different DMARDs usage groups (p=0.0192) was observed by ANOVA test and post-hoc tests indicated a significant difference in the mean levels of anti-spike antibodies between group 5 (users of a three-drug regimen) and group 1 (users of hydroxychloroquine alone). Additionally, a Spearman correlation analysis (Table 2 and Figure 2B) demonstrated a statistically significant negative correlation. As the number of DMARDs increased, there was a decrease in the antibody levels (rho=–0.3609), A small positive correlation with anti-spike antibodies concentration and IL-6 levels among RA patients was observed which was not statistically significant (r=0.1220, p=0.2196) (Figure 2C).

The concentration of anti-spike antibodies was not significantly different between Covishield and Covaxin vaccine users and also there was no association between vaccine type and anti-spike antibody levels in both RA cases and controls. There was no significant difference in the mean levels of percentage of serum anti-spike antibodies between RA group who had a past COVID infection or received a booster dose of COVID vaccine and those who did not. However, a significant association was observed between the three categories of RA cases (p=0.039). No significant association between 3 antibody categories and booster dose among RA patients was observed (p=0.885). Details shown in Table 4.

Table 3. Lab investigations of control and RA group

Sl. no	Investigation	Control group (n=185)	RA group (n=103)	p-value
1.	Hb (g/dL)	14.0±2.3	11.6±1.3	0.000
2.	RBC count (×10^6/μL)	5.2±4.2	3.4±1.0	0.000
3.	WBC (×10^3/μL)	8.7±10.1	8.5±3.3	0.868
4.	ESR	19.2±12.2	26.0±15.9 21 (15~35)	0.0004
5.	CRP			
	Positive (n)	17	20	
	Negative (n)	168	83	
6.	Serum creatinine (mg/dL)	0.87±1.0	0.66±0.18	0.0464
7.	Urea (mg/dL)	19.4±6.6	20.7±6.5	0.1191
8.	Total bilirubin (mg/dL)	0.7±0.5	0.46±0.22	0.000
9.	Direct bilirubin (mg/dL)	0.3±0.2	0.21±0.12	0.0034
10.	Indirect bilirubin (mg/dL)	0.4±0.3	0.25±0.14	0.000
11.	Total proteins (g/dL)	7.6±0.4		
12.	SGOT (U/L)	23.8±18.6 19 (14~27)	22.2±16.6 19.5 (14~25)	0.4944
13.	SGPT (U/L)	28.5±36.6 24 (21~29)	21.9±12.1 20 (15~25)	0.0838
14.	ALP (U/L)	83.6±30.7	90.8±34.7	0.0877
15.	IL-6 (pg/mL)	3.7±2.9	15.8±20.7	0.000
		3.2 (1.53~5.29)	8.56 (5.86~16.46)	
16.	Anti-spike antibody	95.9 (95.2~97.69)	89.5 (87.1~91.7)	0.000

Values are presented as mean±standard deviation or median (interquartile range). RA: rheumatoid arthritis, Hb: hemoglobin, RBC: red blood cell, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, ALP: alkaline phosphatase, IL-6: interleukin-6. p<0.05 considered significant.

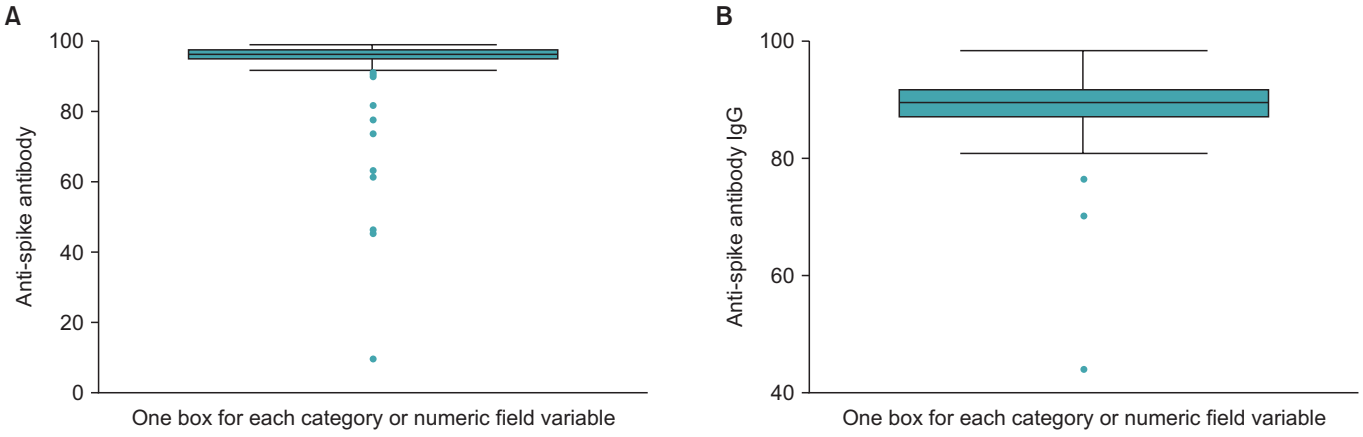

Figure 3. Box-Whisker plot for serum levels of anti-spike antibodies among control (A) and RA group (B). RA: rheumatoid arthritis. p-value <0.001 is considered as statistically highly significant. Refer to Table 1.

DISCUSSION

The present study aimed to investigate the immunological response in RA patients after receiving the second dose of the COVID-19 vaccine, specifically between 6 months to one year after vaccination. A total of 103 RA patients and 185 controls were included in the study. The mean age of the RA patients was significantly higher than that of the control group (44 years vs. 30.7 years), which is expected as RA typically affects old or middle-aged individuals.

Table 4. Association of serum anti-spike antibody levels with type of vaccine, past history of COVID-19 infection, and booster dose vaccination

Parameter	Anti-spike antibody among RA cases	Anti-spike antibody among control
Type of vaccine		
Covishield	88.9±6.7 (n=82)	94.7±8.6 (n=169)
Covaxin	88.7±3.9 (n=21)	91.7±13.5 (n=14)
p-value*	0.9282	0.2343
p-value†	0.803	0.207
Past COVID infection		
RA cases having h/o	86.2±12.6 (n=14)	
RA cases with no h/o	89.3±4.4 (n=89)	
p-value*	0.376	
p-value†	0.039	
Booster dose of COVID vaccine		
RA cases with h/o	89.6±4.4 (n=13)	
RA cases with no h/o	88.7±6.4 (n=90)	
p-value*	0.6534	
p-value†	0.885	

Values are presented as mean±standard deviation. RA: rheumatoid arthritis. $p<0.05$ considered significant. *Unpaired t-test; †by chi-squared test.

We specifically included RA patients who had received two doses of the vaccine and had a time interval between 6~12 months, allowing us to assess the long-term effectiveness and durability of the vaccine-induced immune response as well as to know the potential need for booster doses.

It is well known that RA is more prevalent in women than men, and our study reflected this trend as higher number of female RA patients got enrolled. Similar findings with respect to gender distribution and comorbidities were observed in a study conducted by Cherian et al. [9]. The disparity in RA prevalence between genders may be attributed to the influence of sex hormones, which play a significant role in regulating immune responses. Androgens and progesterone are generally considered natural immunosuppressants, while estrogen is known to enhance immune function [10].

Our study also observed a higher occurrence of hypothyroidism among RA patients. Previous research has reported a higher risk of developing hypothyroidism, mainly due to Hashimoto's thyroiditis, in RA patients. This association may be attributed to the use of drugs for RA treatment (e.g., glucocorticoids, leflunomide), genetic susceptibility, environmental factors, or autoimmunity [11].

The majority of the participants in both the control group and the RA group (80%) received the Covishield vaccine, likely due to its availability at the study sites. Additionally, a small proportion of the RA patients (12%) received a booster dose, highlighting the importance of optimizing immune responses in this vulnerable population.

RA patients exhibited lower Hb levels and higher erythrocyte ESR, indicating anemia and increased inflammation, respectively. It has been reported that 30%~70% of RA patients develop anemia, which could be attributed to changes in iron metabolism, gastrointestinal mucous membrane lesions, or the use of methotrexate and steroid drugs. Elevated ESR indicates the presence of an inflammatory process in the body [12].

Furthermore, the RA group showed a significant increase in IL-6 levels compared to the control group. Elevated IL-6 levels are associated with inflammation and have been implicated in the pathogenesis of RA. IL-6 locally induces joint destruction by promoting the production of IL-8 by endothelial cells. Blockade of IL-6 is a therapeutic strategy for the treatment of RA, and Tocilizumab is one such IL-6 inhibitor [13].

Anti-spike antibody estimation revealed that both the RA group and the control group exhibited positive anti-spike antibodies, indicating a robust immune response following COVID-19 vaccination. However, the RA patient group had a lower proportion of participants with high antibody levels (NAT >90%) compared to the control group. A study conducted by Christensen et al. [14] demonstrated a considerable decline in antibody levels within four months of the second vaccine

dose in 41% of patients with immune-mediated inflammatory diseases, with a greater decline observed in patients receiving tumor necrosis factor (TNF)-alpha inhibitors, either as monotherapy or combination [15]. In our study, RA patients receiving a combination of three drugs showed low mean levels of anti-spike antibodies.

Interestingly, there was a positive correlation between age and anti-spike antibody concentration specifically among RA patients alone, contrary to the findings of study conducted in Hungary [15].

The severity of the disease in RA patients was measured using the DAS-28, and most of them had low disease activity. A meta-analysis of observational studies revealed that the rate of disease flares after COVID-19 vaccination was found to be 7% (95% confidence interval, 5%~9%; p=0.000) [16]. A survey conducted in India reported breakthrough infections in autoimmune patients who received the Covishield vaccine, with infection rates of 4.68% and 0.8% after partial and full vaccination (2 doses), respectively. For the Covaxin, the infection rates were 3.94% and 1.79%, respectively for single and double doses with no statistically significant difference [17].

An observational cohort study (COVIDSER) based on Spanish registry data showed that COVID-19 vaccination did not induce disease flares in RA patients treated with targeted therapies. However, increased disease activity was observed in patients treated with Janus Kinase inhibitors, IL-6 inhibitors, and IL-12/23 inhibitors [18].

Both vaccines, Covishield and Covaxin, induced a good immune response in both the groups, with antibody response rates of 98% and 80%, respectively [19]. A phase 4 trial demonstrated reduced but acceptable short-term immunogenicity in patients with autoimmune rheumatic diseases after receiving the CoronaVac vaccine [20].

In our study, prior exposure to the virus and booster dose vaccination did not significantly impact the antibody response in RA patients. It has been reported that a booster dose with the mRNA-1273 vaccine led to a 1.7-fold increase in neutralizing antibody titers at 1 month post-vaccination [21]. During pregnancy, a booster dose vaccination induced a robust spike-specific humoral immune response [22]. The immune response to vaccination depends on various factors, including the type of vaccine.

Limitations

In our study we were able to recruit 103 participants only in the test group and age-matched control were not able to recruit because most of the middle age persons were already vaccinated before the start of the study. Recruiting sex-matched controls for RA patients was not feasible due to several factors. Firstly, RA has a well-documented predilection for females, resulting in a higher proportion of female RA patients in our study population.

Correlation of duration after second dose vaccination with anti-spike antibody levels was not done, as majority of the participants recruited were within a narrow range of 11~12 months after the second dose of vaccination.

CONCLUSION

This study showed that RA patients had low disease activity and a reduced antibody response following COVID-19 vaccination, probably influenced by DMARDs and disease-related factors. In our study, the concentration of anti-spike antibodies was not significantly different between Covishield and Covaxin vaccines. Prior exposure to the virus or booster dose vaccination also did not significantly impact the antibody response in RA patients. The findings from our study highlight the need to consider the unique characteristics of RA patients in vaccination strategies and emphasize the importance of conducting further research in these patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception and design of study: M.E. Acquisition of data:

V.P.P., R.S., V.S., A.B.P., B.S., N.T.R. Analysis and/or interpretation of data: A.P., M.E. Drafting the manuscript: M.E., V.P.P. Revising the manuscript critically for important intellectual content: R.P., P.P.P. All authors read and approved the final manuscript.

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