FOE OR FRIEND? SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) PATIENTS AND COVID-19 VACCINATION: A SYSTEMATIC REVIEW

Stella MM[1], Tanadi C[1], Tandarto K[2], Sutanto KW[1], and Oey C[3].
[1]Medical Profession Study Programme, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[2]Doctor of Medicine, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[3]Department of Internal Medicine, St. Carolus Hospital, Jakarta, Indonesia

Correspondence:
Cindy Oey,
Department of Internal Medicine,
St. Carolus Hospital, Jakarta, Indonesia
Email: cindy_oey@yahoo.com

Abstract

Background: In the early year of 2020, SARS-CoV-2 was first diagnosed in Indonesia after an outbreak in Wuhan, China. Later, this disease became a worldwide pandemic. Systemic lupus erythematosus (SLE) patients are more vulnerable to COVID-19. They are also prone to relapse and have lower efficacy for COVID-19 immunization.

Objective: This study aimed to evaluate the antibody seroconversion and disease status after COVID-19 vaccination in SLE patients.

Method: We followed the PRISMA guidelines to systematically search and collect literature in the following databases: ProQuest, PubMed, EBSCOhost, SAGE, JSTOR, and ScienceDirect from 1st January 2019 to 24th April 2023. Titles and abstracts were reviewed for relevance. The inclusion criteria are original articles, written in English, investigated the effects of COVID-19 vaccination in SLE patients. The quality of evidence was evaluated using the Newcastle-Ottawa Scale.

Results and Discussion: From 1,088 studies, we retrieved nine studies for this review. There were cohort studies (n = 5), case-control studies (n = 2), and observational studies (n = 2) published between 2021 and 2022. Vaccines against SARS-CoV-2 are currently widely available and SLE patients should receive vaccination. In a large study involving healthy individuals and healthcare professionals, nearly all of the individuals who received two doses of BNT162b2 developed antibodies to the vaccine. Seroconversion after a first COVID-19 vaccination is delayed in older patients on specific immunosuppressive drugs.

Conclusion: This systematic review found that the overall immunogenicity and safety of COVID-19 vaccines were satisfactory in patients with SLE.

Keywords: SLE, COVID-19 Vaccination, Antibody Response, Disease Status

Introduction

Respiratory tract infections can arise from various types of pathogens, ranging from viruses, bacteria, and fungal infections. Recently, there was an outbreak of coronavirus disease 2019 (COVID-19) that originated in Wuhan, China, and subsequently spread globally. This disease was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belonged to the coronavirus group. Although the general population has been affected by this outbreak, certain populations may be more susceptible to COVID-19 infection and have diverse outcomes in terms of demographics, associated organ damage, and comorbidities. Among these, people with systemic lupus erythematosus (SLE) are a noteworthy population (1).

Studies have shown that the mortality rate of COVID-19 tends to be higher in those receiving immunosuppressive treatments which are frequently administered for SLE patients. In addition, several early studies have also shown that SLE patients have an increased risk for hospitalization, regardless of race, ethnicity, comorbidities, and body mass index (2). These findings highlight the important role of humoral immunity in preventing SARS-CoV-2 infection and thus offer insights into the potential efficacy of active immunization in SLE patients (3).

Despite the benefits of vaccination, individuals with rheumatic diseases, including SLE, are still hesitant to receive vaccination due to concerns regarding potential

relapses (4). To address this issue, several cohort studies that investigated the efficacy of COVID-19 vaccination in SLE patients have been conducted (5). This systematic review aims to assess the immune response and disease status in SLE patients post-COVID-19 vaccination.

Materials and Methods

This systematic review was constructed following the Preferred Reporting Items guidelines for Systematic Reviews and also Meta-analysis (PRISMA) 2020 (6). Figure 1 shows the PRISMA flow diagram.

Literature search

We conducted a comprehensive literature search to evaluate the immune response and disease status in patients with SLE after COVID-19 vaccination in ProQuest, PubMed, EBSCOhost, SAGE, JSTOR, GARUDA, Open Gray. The articles were retrieved from 1st January 2019 to 24th April 2023. The search terms used were: (((((((((“immunology”[MeSH Subheading]) OR (“Immunity, Heterologous”[Mesh])) OR (“Immunity, Humoral”[Mesh])) OR (“Adaptive Immunity”[Mesh])) OR (“Immunity, Active”[Mesh])) OR (immune response)) OR (immunity)) AND ((Disease status) OR (Severity))) AND (((“COVID-19 Vaccines”[Mesh]) OR (COVID-19 vaccine)) OR (SARS-CoV-2 vaccination))) AND ((((“Lupus Erythematosus, Systemic”[Mesh]) OR (SLE)) OR (Systemic Lupus Erythematosus)). The literature search was limited to articles published in English and full-text is available. We also performed a manual search for additional possible studies from references.

Study selection

The inclusion criteria were: 1. Articles published from 1st January 2019 to 24th April 2023; 2. Written in English; 3. Full text is available; 4. Investigated the effects of COVID-19 vaccination in SLE patients and has a clear methodology. The exclusion criteria were: 1. Reviews, letter to editor, case report; 2. Repeated publications; 3. Lack of suitable data.

Data extraction

Four authors extracted the data independently from the included studies. Any differences were resolved by a fifth author. The extracted data were as follows: 1. The name of the first author and publication year; 2. Study design; 3. Country; 4. Participants; 5. Methods; 6. Outcome; 7. Results; 8. Conclusion.

Quality assessment

Four independent reviewers assessed the risk of bias using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. The NOS contains a total of 8 items. For cohort studies, a maximum score of 9 can be given (score 0-3: very high risk of bias; 4-6: high risk of bias; 7-9: high quality). Any disagreements will be resolved through discussion with a fifth reviewer.

Type of outcome measures

Antibody seroconversion rate and disease status (flare and side effects of COVID-19 vaccination) were investigated in this systematic review.

Results

During the initial search, a total of 1,088 articles were obtained. Subsequently, all articles underwent screening, and 72 articles were identified. The full text of each article was then obtained and only nine articles were finally included in this review. The PRISMA 2020 flow chart was used as a guideline for performing the literature search and can be viewed in Figure 1. Due to the limited number of studies and the presence of significant heterogeneity, a formal statistical analysis cannot be performed. Hence, a detailed systematic review was carried out.

Characteristics of eligible studies

The studies included in this systematic review were published from 2021 to 2022 (Table 1). This review included observational studies, cohorts, and case controls (Table 2). In the preliminary search, a total of 1,088 articles were retrieved. Following duplicate removal, 939 articles were identified and subsequently subjected to a second screening. Reviews, letter to editor, case reports, repeated publications, and articles that lacked suitable data were excluded from this review. After the second screening, nine articles were eligible for full-text screening. All nine articles were then evaluated for the risk of bias using NOS. Overall, the risk of bias for the included studies was low. The risk of bias for each study has been shown in Table 1.

Tien et al. (7) stated that in Taiwan, the titers and positive rates of anti-S/RBD-IgG in individuals who received the BNT162b2 or mRNA-1273 vaccine were significantly higher compared to the AZD1222 vaccine. In addition, an augmentation of immunogenicity has been observed after receiving the second-dose vaccination in individuals with immune-mediated inflammatory diseases (IMID). Following the administration of the first dose, Anti-S/RBD-IgG titers were noticeably lower in patients with rheumatoid arthritis (RA) compared to those with primary Sjögren’s syndrome (pSS). However, no significant differences were detected in the titers or positive rate of anti-S/RBD-IgG following the second-dose administration across all five IMID groups.

Pinte et al. (8) showed that there was no discernible distinction in the risk of flare-ups between the vaccinated and non-vaccinated group. The flare-up rates were 1.16 and 1.72 flare-ups per 100 patients-months for the vaccinated and non-vaccinated groups, respectively (P = 0.245). The vaccines used in the study included Comirnaty (BioNTech/Pfizer, Germany, Mainz) (86%), Vaxzevria (Oxford/AstraZeneca, Nijmegen, Netherlands) (9%), Spikevax (Moderna Biotech, Cambridge, USA) (3%), and Janssen vaccine (Johnson & Johnson, Leiden, Netherlands)

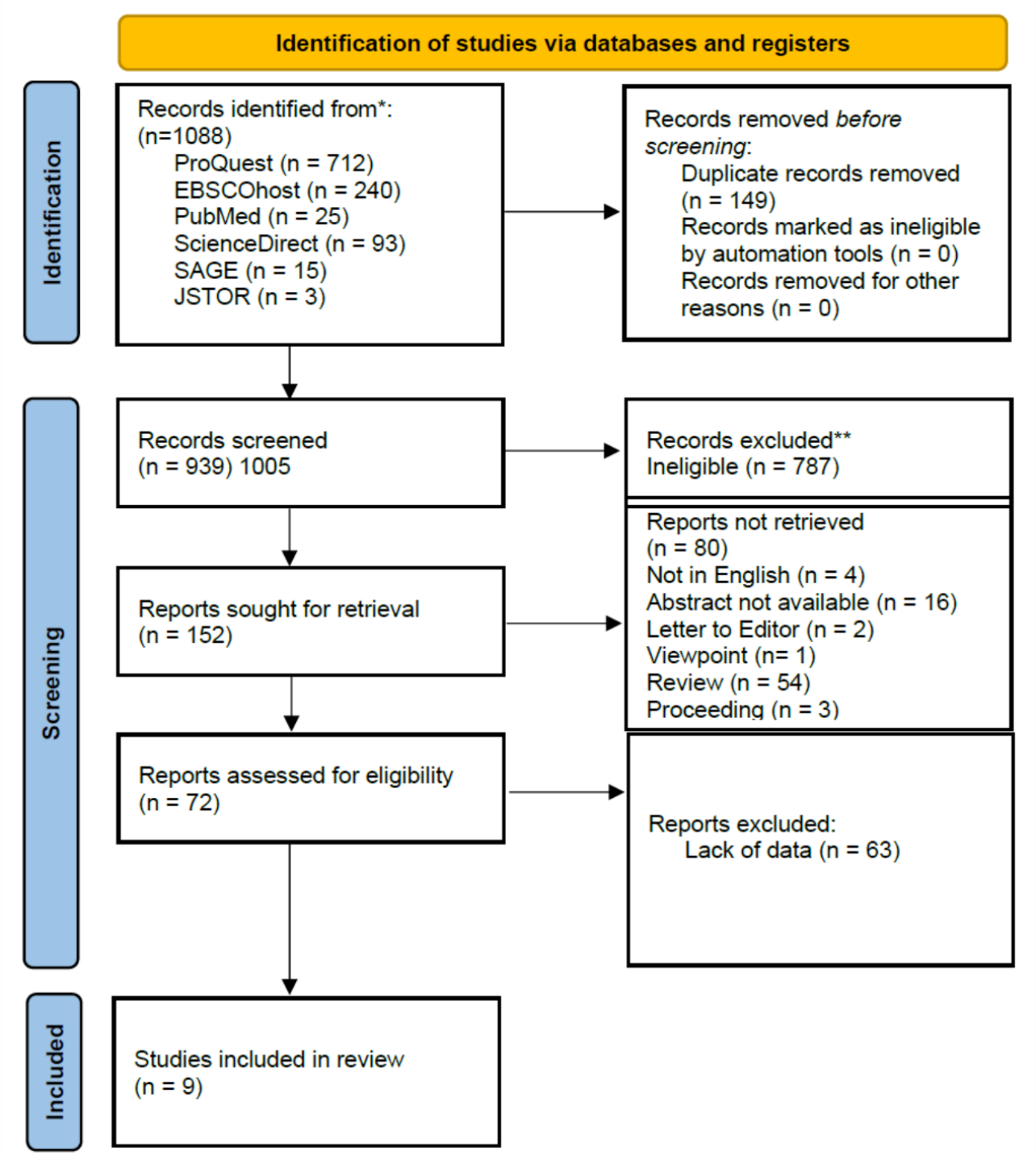

Figure 1: PRISMA flow diagram

Table 1: Newcastle-Ottawa Scale risk of bias tools

	Selection				Comparability	Outcome			Total score (max 9)
Author	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohort on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up cohorts	
Tien et al., 2020 (7)	1	0	1	1	2	0	1	1	7 (high quality)
Pinte et al., 2021 (8)	1	1	1	0	2	0	1	1	7 (high quality)
Ammitzbøll et al., 2021 (9)	1	1	1	1	2	0	1	1	8 (high quality)
Boekel et al., 2021 (10)	1	0	1	1	2	0	1	1	7 (high quality)
Chen et al., 2021 (11)	1	1	1	1	2	0	1	1	8 (high quality)
Furer et al., 2021 (12)	1	0	1	1	2	0	1	1	7 (high quality)
Izmirly et al., 2021 (13)ġ@	1	1	1	1	1	1	1	1	8 (high quality)
So et al., 2022 (14)	1	1	1	1	2	0	1	1	8 (high quality)
Yuki et al., 2022 (15)	1	0	1	1	2	0	1	1	7 (high quality)

Table 2: Characteristics of the eligible studies

Author	Country of origin	Study Design	Subjects				Methods		
			Total	Inclusion Criteria	Diagnosis Criteria	Exclusion Criteria	Vaccine	Procedure	Outcome
Tien et al., 2022 (7)	Taiwan	Cohort study	36 SLE patients and 30 healthy workers	≥20 years old patients with stable disease activity (≥3 months) before the first dose vaccination, without SARS-CoV-2 infection.	1997 revised criteria for SLE	The lack of inclusion criteria or existence of SARS-CoV-2 infection, which was shown by a positive outcome of a PCR test on samples from the nasal or pharynx.	Three types of vaccines: AZD1222, mRNA-1273, and BNT162b2	Plasma levels of IgG-antibody against SARS-CoV-2 targeting the receptor-binding domain of spike protein (anti-S/RBD-IgG) were determined by chemiluminescent immunoassay 3–4 weeks after the first-dose and second- dose vaccination.	Plasma levels of IgG-antibody against SARS-CoV-2 targeting the receptor-binding domain of spike protein (anti-S/RBD-IgG)
Pinte et al., 2021 (8)	Europe	Cohort study	623 AID-IMD patients (416 vaccine, 207 non-vaccine)	AID-IMD patients	N/A	N/A	Comirnaty (BioNTech/ Pfizer, Germany, Mainz) (86%), Vaxzevria (Oxford/ Astra-Zeneca, Nijmegen, Nether-lands) (9%), Spikevax (Moderna Biotech, Cam-bridge, USA) (3%), and Janssen vaccine (Johnson & Johnson, Leiden, Nether-lands) (2%).	Enrolling the patients with AID-IMD who voluntarily completed our questionnaire, both online and during hospital evaluation. Based on their decision to receive the vaccine, the patients were divided into two groups (vaccinated and non-vaccinated) Participants who chose not to receive the vaccine served as a control group in terms of flare-ups.	The primary outcome measure was the time to first flare, while secondary outcome included incidence of flare-ups between the two groups (vaccine and non-vaccine) as well as vaccine-related adverse effects.
Ammitzbøll et al., 2021 (9)	Denmark	Cohort study	Patients with SLE (n = 61) and RA (n = 73) with median age of 70 (69-74) years and 60 (46-67) years	Patients with SLE or RA. All patients resided in the same geo-graphical region of Denmark (Central and North Region)	ACR 1982 revised	N/A	BNT162b2 vaccine	Patients received the BNT162b2 vaccine, with 21 days (interquartile range, 21-24) between the two vaccinations. (December 2020 and April 2021). All patients had total antibodies against SARS-CoV-2 measured before vaccination and 1 week after the second vaccination.	Total anti-bodies against SARS-CoV-2
Boekel et al., 2021 (10)	Netherlands	Cohort study	Adult patients (aged ≥18 years) with CID from the ARC Patients with auto-immune disease and healthy controls	Patients aged ≥18 years with CID or MS	N/A	N/A	Covid-19 vaccine based on vaccination program (Dutch national vaccination program) included four COVID-19 vaccine types: ChAdOx1 nCoV-19 (Astra-Zeneca), BNT162b2 (tozinameran; Pfizer-BioNtech), CX-024414 (elasomeran; Moderna), and Ad.26.COV2.S (Janssen).	Demo-graphic and clinical data were collected via online questionnaires that were distributed by email. Questionnaires were sent at baseline and up to three times during follow-up.	SC rates and IgG antibody titers against the receptor-binding domain of the SARS-CoV-2 spike protein

Table 2: Characteristics of the eligible studies (continued)

Author	Country of origin	Study Design	Subjects				Methods		
			Total	Inclusion Criteria	Diagnosis Criteria	Exclusion Criteria	Vaccine	Procedure	Outcome
Chen et al., 2021 (11)	China	Cohort study	Patients with CID	Patients with CID treated with chronic immune-suppressive drug mono-therapy	N/A	N/A	BNT162b2m-RNA vaccine	77 CID treated as mono-therapy with chronic immune-suppressive drugs for antibody responses in serum against historical and variant SARS-CoV-2 viruses after immunization with BNT162b2 mRNA vaccine.	Antibody titers
Furer et al., 2021 (12)	Israel	Observational study	Patients with AIIRD	Patients aged ≥ 18 years with AIIRD	SLE/1997 ACR or 2012 SLICC criteria	Pregnancy, history of past vaccination allergy, and previous COVID-19 infection	BNT162b2 mRNA vaccine	Multicenter observational study evaluated the immunogenicity and safety of the two-dose regimen BNT162b2 mRNA vaccine in adult patients with AIIRD (n=686) compared with the general population (n=121). Serum IgG antibody levels against SARS-CoV-2 spike S1/ S2 proteins were measured 2–6 weeks after the second vaccine dose. Seropositivity was defined as IgG ≥15 binding antibody units (BAU)/ mL. Vaccination efficacy, safety, and disease activity were assessed within 6 weeks after the second vaccine dose	Antibody titer, vaccine efficacy and safety
Izmirly et al., 2021 (13)	USA (New York)	Case control	90 SLE patients and 20 healthy controls	SLE patients aged ≥ 18 years who are to receive COVID-19 vaccine	Meets at least one of the following: (1) ACR revised classification criteria; (2) SLICC classification criteria; (3) EULAR/ ACR classification criteria	Not willing to provide blood after the second dose of the vaccine, incomplete vaccination schedule, and speaking a language other than English, Spanish, or Mandarin	COVID-19 vaccine	90 SLE patients and 20 healthy controls receiving a complete COVID-19 vaccine regimen were included. IgG seroreactivity to the SARS-CoV-2 spike receptor-binding domain (RBD) and SARS-CoV-2 micro-neutralization were used to evaluate B cell responses; IFN-γ production to assess T cell responses was measured by ELISpot. Disease activity was measured by the hybrid SLE disease activity index (SLEDAI) and flares were assigned by the SELENA/ SLEDAI flare index	Seroreactivity and disease flares after COVID-19 vaccination

Table 2: Characteristics of the eligible studies (continued)

Author	Country of origin	Study Design	Subjects				Methods		
			Total	Inclusion Criteria	Diagnosis Criteria	Exclusion Criteria	Vaccine	Procedure	Outcome
So et al., 2022 (14)	Hong Kong	Observational study	Patients with SLE and healthy control	SLE patients aged 18-65 years who plan to undergo COVID-19 immunization	2019 EULAR/ ACR classification criteria	History of allergic reaction to vaccine component, history of severe allergic reactions to any allergen, history of allergic reaction to multiple classes of drugs, severe neurological conditions (e.g. transverse myelitis, Guillain-Barre syndrome), patients with uncontrolled severe chronic diseases (including active SLE), previous COVID-19 infection, pregnant and lactating women	Comirnaty (Pfizer) and Coronavac	Patients with SLE planning to receive COVID-19 vaccines were recruited and matched 1:1 with healthy controls. The immun0genicity of the COVID-19 vaccines was assessed by a surrogate neutralization assay at 28 days after the second dose.	The main outcome was the antibody response comparing SLE patients and controls. Other outcome included reactogenicity, disease activity and predictor of antibody response in SLE.
Yuki et al., 2022 (15)	Brazil	Clinical trial	SARS-CoV-2-naive SLE patients and SARS-CoV-2-naive controls	SLE patients aged ≥ 18 years old	SLICC classification criteria for SLE	Acute fever or manifestations suggestive of COVID-19, history of anaphylactic response to vaccine components, received blood transfusion ≤ 6 months before study entry, received inactivated virus vaccine ≤ 14 days prior to entry, prior SARS-CoV-2 vaccination, positive COVID-19 serology and/ or NAb prior to immunization	Sinovac-CoronaVac	232 SARS-CoV-2-naive SLE patients and 58 SARS-CoV-2-naive controls who were vaccinated with 2 doses of Sinovac-CoronaVac with a 28-day interval (day 0/ day 28 [D0/D28]). Immunogenicity analysis at D0/D28 and D69 included anti-SARS-CoV-2 S1/S2 IgG SC and NAb positivity. The influence of individual drugs on immune response and safety was assessed.	The immunogenicity of an inactivated SARS-CoV-2 vaccine (Sinovac-CoronaVac) and the influence of different medications in SLE.

ACR: American college of rheumatology; AID-IMD: Autoimmune and immune-mediated diseases; AIIRD: Autoimmune inflammatory rheumatic diseases; ARC: Amsterdam rheumatology and immunology center; CID: Chronic inflammatory disease; COVID-19: Coronavirus disease 2019; EULAR: European alliance of associations for rheumatology; MS: Multiple sclerosis; N/A: Not available; Nab: Neutralizing antibodies; PCR: Polymerase chain reaction; RA: Rheumatoid arthritis; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SC: Seroconversion; SELENA: Safety of estrogens in lupus national assessment; SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; SLICC: Systemic lupus international collaborating clinics.

(2%). Another research conducted by Ammitzbøll et al. (9) reported that there was no significant difference between SLE and RA patients. Furthermore, no correlation was detected for age and antibody levels (r = -0.12; P = 0.18).

Boekel et al. (10) found that compared to the control group, SLE patients had significantly lower seroconversion rates after the first vaccination, with an odds ratio of 0.33 (95% CI 0.23-0.48; P < 0.0001). This was primarily due to lower seroconversion rates in patients who received anti-CD20 or methotrexate. Chen et al. (11) observed that within five months of vaccination, TNFi-treated individuals had serum-neutralizing titers below the threshold required for antibody-mediated protection. Furer et al. (12) discovered that patients with autoimmune inflammatory rheumatic diseases (AIIRD) had significantly lower seropositivity rates and S1/S2 IgG levels compared to control (86% vs 100%, P < 0.0001; 132.9±91.7 vs 218.6±82.06 BAU/mL, P < 0.0001, respectively).

Izmirly et al. (13) found that SLE patients who completed the COVID-19 vaccination have significantly lower levels of IgG antibodies compared to control. Furthermore, around 28.8% of SLE patients exhibited IgG levels lower than the minimum level observed in control. So et al. (14) reported that 92% of the patients had positive neutralizing antibodies at day 28 after the second vaccine dose, with a higher percentage in the Comirnaty group compared to CoronaVac (100% vs. 82%, P = 0.01). Adverse reactions in lupus patients were common but mild. Yuki et al. (15) found that although SLE patients had lower IgG seroconversion and neutralizing antibody positive rate when compared to

the control group, it was still moderate (IgG seroconversion 70.2% vs. 98.1%, P < 0.001; Neutralizing antibody positivity 61.5% vs. 84.6%, P = 0.002).

Discussion

The SARS-CoV-2 vaccines are widely available and recommended for patients with SLE (Table 3). A study conducted by Polack et al. (16) involving a large group of healthy reported nearly 100% efficacy in preventing COVID-19 infection after two doses of BNT162b2 vaccine. However, the study conducted by Ammitzbøll et al. (9) reported significantly fewer responders, with only 77 individuals showing detectable antibodies. The presence of antibodies is closely connected with cell-mediated immunity, and is thus crucial for vaccine efficacy against SARS-CoV-2 (17). Consequently, individuals who do not exhibit antibody response are presumed to lack immunity against SARS-CoV-2 (18).

Table 3: Summary of the included studies

Authors	Adverse Event	Results	Conclusion
Tien et al., 2022 (7)	The most common AE reported after first dose vaccination in all types of vaccine were injection site pain with/ without skin rash, followed by grade 1 to 2 non-specific systemic reactions (fever, headache, myalgia, fatigue). There is a greater incidence of high-grade systemic or constitutional AEs after the first dose of AZD1222. After the second dose, there is a decrease in AEs. For mRNA-based vaccines, administration of the second dose could cause increased reactogenicity.	The positive rate and titers of anti-S/RBD-IgG were significantly higher in mRNA-1273 or BNT162b2 than in the AZD1222 vaccine. Immunogenicity was augmented after the second dose of any vaccine type in all IMID patients, suggesting that these patients should complete the vaccination series. Anti-S/RBD-IgG titers after first-dose vaccination were significantly lower in RA patients than pSS patients, but there was no significant difference after second-dose vaccination among five groups of IMID patients. The positive rate and titers of anti-S/RBD-IgG were significantly lower in patients receiving abatacept/rituximab therapy than in those receiving other DMARDs. All three SARS-CoV-2 vaccines showed acceptable safety profiles, and the common AEs were injection site reactions.	SLE as a significant predictor of increased autoimmunity and would like to promote awareness of the possibility of autoimmunity following vaccination.
Pinte et al., 2021 (8)	Most common symptoms were discomfort at injection site, weariness, headache, chills, joint pain, and myalgia. There was no meaningful difference in adverse events between AIRD and non-AIRD patients. Incidence-densities of flare-ups were 1.16 and 1.72/100 patients-months in those who received vaccination and those who did not, respectively (P = 0.245, Log Rank test). There was no significant difference between the types of COVID-19 vaccines and incidence of flare-ups: Comirnaty (BioNTech/Pfizer) (19/359, 5%), Vaxzevria (Oxford/AstraZeneca) (4/37, 11%), or Spikevax (Moderna Biotech) (2/12, 17%) [P = 0.43].	A total of 623 patients, 416 vaccinated and 207 non-vaccinated, were included in the study during hospital evaluations (222/623) and after online (401/623) enrolment. There was no difference concerning the risk of flare-up between vaccinated and non-vaccinated patients (1.16, versus 1.72 flare-ups/100 patients-months, P = 0.245). The flare-ups were associated with having more than one immune disease, and with a previous flare-up during the past year.	We did not find an increased risk of flare-up following COVID-19 vaccination in patients with autoimmune-/immune-mediated diseases, after a median follow-up of 5.9 months. According to our results, there should not be an obvious reason for vaccine hesitancy among this category of patients.

Table 3: Summary of the included studies (continued)

Authors	Adverse Event	Results	Conclusion
Ammitzbøll et al., 2021 (9)	N/A	77% of 134 patients showed a detectable serological response to the vaccination. No significant difference was observed between patients with RA or SLE when adjusting for treatment. There was also no correlation between antibody levels and age was detected (r = -0.12; P = 0.18).	Antibody measurements against SARS-CoV-2 in patients with RA and SLE after two doses of the BNT162b2 vaccine demonstrated that 23% of patients could not mount a detectable serological response to the vaccine.
Boekel et al., 2021 (10)	N/A	Seroconversion after first vaccination were significantly lower in patients than in controls (210 [49%] of 432 patients *vs* 154 [73%] of 210 controls; adjusted odds ratio 0·33 [95% CI 0·23–0·48]; P < 0·0001), mainly due to lower seroconversion in patients treated with methotrexate or anti-CD20 therapies.	Seroconversion after a first COVID-19 vaccination is delayed in older patients on specific immunosuppressive drugs.
Chen et al., 2021 (11)	N/A	Within 5 months of vaccination, serum neutralizing titers of all TNFi-treated individuals tested fell below the presumed threshold for antibody-mediated protection. However, TNFi-treated individuals receiving a third mRNA vaccine dose boosted their serum neutralizing antibody titers by more than 16-fold.	Vaccine boosting or administration of long-acting prophylaxis (e.g. monoclonal antibodies) will likely be required to prevent SARS-CoV-2 infection in this susceptible population.
Furer et al., 2021 (12)	Notable AEs include uveitis (n = 2), herpes labialis (n = 1), pericarditis (n = 1), and non-disseminated herpes zoster (HZ) in five individuals after the first vaccine dose and in one patient. There was no difference in the prevalence of moderate adverse events between AIIRD patients and controls.	Following vaccination, the seropositivity rate and S1/S2 IgG levels were significantly lower among patients with AIIRD versus controls (86% (n=590) vs 100%, P < 0.0001 and 132.9±91.7 vs 218.6±82.06 BAU/mL, P < 0.0001, respectively).	mRNA BNTb262 vaccine was immunogenic in the majority of patients with AIIRD, with an acceptable safety profile. Treatment with glucocorticoids, rituximab, mycophenolate mofetil, and abatacept was associated with a significantly reduced BNT162b2-induced immunogenicity**.**
Izmirly et al., 2021 (13)	Postvaccination flare occurs in 9 out of 79 patients (11.4%). All but one were mild or moderate (2 in new organ systems: arthritis untreated and pericarditis treated with naproxen).	Overall, fully vaccinated SLE patients produced significantly lower IgG antibodies against SARS-CoV-2 spike RBD than controls. Twenty-six SLE patients (28.8%) generated an IgG response below that of the lowest control (<100 units/ml). In logistic regression analyses, the use of any immunosuppressant or prednisone and a normal anti-dsDNA level prior to vaccination is associated with decreased vaccine responses. IgG seroreactivity to the SARS-CoV-2 Spike RBD strongly correlated with the SARS-CoV-2 microneutralization titers and antigen-specific IFN-γ production determined by ELISpot. In a subset of patients with poor antibody responses, IFN-γ production was likewise diminished.	In a multi-ethnic/racial study of SLE patients 29% had a low response to the COVID-19 vaccine which was associated with being on immunosuppression. Reassuringly, disease flares were rare. While minimal protective levels remain unknown, these data suggest protocol development is needed to assess efficacy of booster vaccination.

Table 3: Summary of the included studies (continued)

Authors	Adverse Event	Results	Conclusion
So et al., 2022 (14)	Compared to CoronaVac, Comirnaty produced significantly higher local reactions after two doses (95% vs 37%, P = 0.001; 90% vs 33%, P = 0.001) and systemic side effects (82% vs 44%, P = 0.002). Patients' SLEDAI-2k, anti-dsDNA level, and proteinuria all increased numerically rather than declining (49% vs. 39%, 43% vs. 26%, and 19% vs. 16%, respectively). There was no meaningful change in SLE disease activity measures.	At day 28 after the second dose of vaccines, 92% (Comirnaty: 100% vs CoronaVac: 82%, P = 0.01) of the patients had positive neutralizing antibody. However, compared to the age, gender, vaccine type matched controls, the level of neutralizing antibody was significantly lower (P < 0.001). The self-reported adverse reactions after vaccines in lupus patients were common but mild, and were more frequent in the Comirnaty group. There was no significant change in lupus disease activity up to 28 days after vaccination.	COVID-19 vaccines produced satisfactory but impaired humoral response in SLE patients compared to controls which was dependent on the immunosuppressive medications use and type of vaccines received. There was no new short-term safety signal noted. Booster dose is encouraged.
Yuki et al., 2022 (15)	After the first dose, patients with SLE experienced arthralgia more frequently (14.7% compared 3.4%; P = 0.024) and less myalgia compared to control (6.5% versus 15.5%; P = 0.025). By the end of the immunization, 4.7% of SLE patients experienced disease exacerbation. There was no worsening of the SLEDAI-2K score 3 months after receiving the entire immunization in 118 SLE patients (2.0 versus 2.0; P = 0.07). There were no reports of moderate or severe AEs.	Patients and controls were well balanced for age (P = 0.771). SLE patients showed a moderate IgG seroconversion (70.2% versus 98.1%; P < 0.001) and moderate frequency of neutralizing antibody positivity (61.5% versus 84.6%; P = 0.002), although both frequencies were lower than in controls.	Sinovac-CoronaVac has a moderate immunogenicity in SARS-CoV-2-naive SLE patients with an excellent safety profile.

AEs: Adverse events; AIIRD: Autoimmune inflammatory rheumatic diseases; COVID-19: Coronavirus disease 2019; DMARDs: Disease-modifying antirheumatic drugs; N/A: Not available; RA: Rheumatoid arthritis; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SLE: Systemic lupus erythematosus; SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000.

RA or SLE patients exhibit a significantly lower immunogenicity compared to healthy subjects. Around 77% of these patients could demonstrate a discernible serological response to the vaccine. Notably, only 23% of patients receiving rituximab, a drug used to treat various autoimmune diseases, were able to produce detectable anti-SARS-CoV-2 antibodies post-vaccination (19).

Another study observed delayed seroconversion in older patients on specific immunosuppressive medications after the first COVID-19 vaccination. However, continued exposure to SARS-CoV-2, whether by infection or additional vaccinations, led to stronger humoral immunity in patients receiving immunosuppressive treatment. The seroconversion rate following the initial vaccination was significantly lower in the autoimmune group compared to the control group. In the autoimmune group, 210 out of 432 individuals (49%) achieved seroconversion, whereas among the control group, 154 out of 210 individuals (73%) achieved seroconversion. The lower seroconversion rates in autoimmune patients (OR 0.33; 95% CI 0.23-0.48; P < 0.0001) might be attributed to the patients receiving treatment with anti-CD20 agents or methotrexate (10).

Previous studies have demonstrated that discontinuing methotrexate for up to 2 weeks after influenza vaccination resulted in improved IgG antibody titers while minimizing the risk of disease relapse (20). However, it is important to note that both humoral immunity (mediated by antibodies) and cell-mediated immunity serve as a defense mechanism against SARS-CoV-2. Therefore, predicting the extent of IgG antibody titer reduction after vaccination in individuals undergoing anti-CD20 or methotrexate treatment remains a challenge (21).

Although SLE patients managed to exhibit antibody-mediated response six weeks after receiving the second dose of Sinovac-CoronaVac vaccination (D69), the response rate was lower compared to control. These results were consistent with earlier reports on small samples of SLE

patients who received mRNA vaccines as well as larger studies involving SLE patients (22). The results of another study reported that nearly 25% of SLE patients who had never been exposed to SARS-CoV-2 failed to demonstrate seroconversion post-vaccination. The immunogenic response observed in this study using inactivated vaccines was comparable to the results reported in SLE patients who received mRNA or adenovirus vaccines (13).

So et al. (14) observed compromised antibody response in SLE patients compared to the general healthy population. Although side effects following vaccination were common, they were all mild and temporary. Lower antibody responses correlated with higher disease activity. A multivariate analysis showed that the antibody response was independent of immunosuppressive drug use, particularly systemic glucocorticoids and mycophenolic acid. This study also revealed that mRNA vaccines elicited a more robust humoral response and greater responsiveness compared to inactivated vaccines among SLE patients.

Immunogenicity of mRNA COVID-19 vaccines was evaluated in 123 patients with rheumatic diseases, 20% of whom had SLE. Following the first dose, 74% of the patients displayed a measurable antibody response. However, patients receiving mycophenolate or rituximab had statistically significant differences (P = 0.001 and P = 0.04, respectively) in their likelihood of developing an antibody response. Notably, detectable antibodies were present in only 27.3% of mycophenolate-treated individuals. The seroconversion rates following the first dose of mRNA or adenoviral vector COVID-19 vaccines were considerably lower in autoimmune patients compared to controls in a case-control study encompassing 632 patients with SLE making 5% of the group (23).

In a separate large-scale study involving 2,860 patients with autoimmune rheumatic diseases, 14% of whom had SLE, the observed side effects post-vaccination were comparable to those reported in the general population. About 4.6% of patients required a change in dosing due to these side effects. Two meta-analyses have reported consistent findings regarding the immunogenicity and safety of COVID-19 vaccination. However, there is limited data available on the use of inactivated vaccines in SLE patients (24).

In summary, our systematic review provides a comprehensive overview of the immunogenicity of SARS-CoV-2 vaccination, adverse events, and outcome assessment in clinical studies. Although clinical trials have shown significant positive effects of COVID-19 vaccinations, the data are heterogenous. Thus, we could not draw a general conclusion. The limitations of this systematic review are the heterogeneity in the study designs, population, research aims, outcome parameters, type of vaccines, and outcomes. Such a high heterogeneity may also be the cause of inconsistencies in the seroconversion rates among the included studies.

Given the constraints and uncertainties, a narrative synthesis or qualitative analysis may be more suitable in this study for summarizing and discussing the available data. The presence of significant heterogeneity in our study made it unsuitable for conducting a meta-analysis. Through this study, it is hoped that COVID-19 vaccination may be considered for SLE patients in clinical practice.

Conclusion

We have concluded that the overall immunogenicity and safety of COVID-19 vaccinations in SLE patients were sufficiently beneficial, despite the reduced response compared to control. No new safety concerns were identified in this study. Furthermore, there appears to be a discernible difference in the overall response and side effects of the two vaccine platforms. Systemic glucocorticoid dosage, mycophenolic acid use, and vaccine type were significant predictors of antibody activity following vaccination in SLE patients. While booster shots may prove to be beneficial, formal investigations are warranted.

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Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

This research did not involve human subjects and therefore was exempt from the ethical clearance.

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