



Systemic lupus erythematosus in the light of the COVID-19 pandemic: infection, vaccination, and impact on disease management

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Abstract

Patients with systemic lupus erythematosus (SLE) form a vulnerable group in terms of the impact of the COVID-19 pandemic on disease management. We conducted this overview by searches through Medline/PubMed, Scopus, and the Directory of Open Access Journals (DOAJ). The prevalence and severity of COVID-19, efficacy of COVID-19 vaccination, impact on the management of SLE, and the attitudes of SLE patients to COVID-19 and vaccination were explored. After screening and due exclusions, 198 studies were included for the final review. Patients with SLE have a greater risk of acquiring COVID-19 (0.6–22%) and related hospitalization (30%), severe disease (13.5%), and death (6.5%) than the general population. Older age, male gender, comorbidities, moderate or high disease activity, and glucocorticoid, rituximab, and cyclophosphamide use are associated with unfavorable outcomes, whereas methotrexate and belimumab use showed no association with outcomes. COVID-19 vaccines are safe in SLE with minimal risk of severe flares (<2%). Vaccine efficacy is negatively associated with glucocorticoids. The overall attitude of patients towards vaccination is positive (54–90%). The pandemic has negatively affected access to medical care, hospitalizations, procurement of drugs, employment, and the mental health of patients which need to be addressed as part of holistic care in SLE.

Key Points

- *Lupus patients are at a greater risk of acquiring COVID-19, related hospitalization, severe disease, and death than the general population.*
- *COVID-19 vaccines are relatively safe for lupus patients with minimal risk of severe flares.*
- *Lupus patients' attitude towards COVID-19 vaccination is predominantly positive.*

Keywords COVID-19 · COVID-19 vaccines · Glucocorticoids · Immunosuppressive agents · Mental health · Pandemics · Rituximab · SARS-CoV-2 · Systemic · Vaccine efficacy

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has ravaged the world with over four billion cases and close to six million deaths (as of April 1, 2022) over the last 2 years [1]. The USA is plagued by the highest number of cases to date with the highest mortality in terms of deaths/million followed closely by Brazil and the UK [1]. These numbers represent only the tip of the iceberg with respect to the adverse impact of the pandemic on other aspects of health-care that have taken a back foot since then.

The characteristics of the novel coronavirus or severe acute respiratory syndrome-coronavirus-2 (SARS-Cov-2) infection include more severe presentation in vulnerable populations with various comorbidities as observed in Wuhan right from the early stages of the pandemic [2]. The

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concern about infections in patients with autoimmune rheumatic diseases (AIRDs) is understandable and springs from various disease- and treatment-related factors. With the emergence of COVID-19, there was a palpable apprehension among physicians about the risk, severity of infection, and post-infective sequelae secondary to the underlying immune dysregulation as well as the immunosuppressant drugs used for their management. These issues represent the imminent problems posed by the COVID-19 pandemic.

The near paralysis of the non-COVID healthcare delivery system with countrywide lockdowns resulted in lack of access to care and follow-up visits, doubts about the initiation and continuation of immunosuppressive therapy, and, above all, the safety and efficacy of vaccination against COVID-19. The recognition of these issues was promptly dealt with by researchers across the globe, and early reports from the Global Rheumatology Alliance (GRA) described a higher rate of hospitalization (46%) and mortality (9%) than the general population [3]. The scientific community has stood up to the challenge, and numerous studies have been undertaken to answer these questions posed by the pandemic [4, 5]. Constraints on resources and manpower during the pandemic have resulted in studies with flaws in design and methodology with multiple biases. Hence, it is difficult to translate the results of individual studies to the clinic.

Systemic lupus erythematosus (SLE) is a prototype AIRD with a wide range of severity and organ involvement. It requires a delicate evaluation and follow-up with management centered around immunosuppressive therapy. There is an added vulnerability of common comorbidities such as diabetes mellitus and arterial hypertension which are commonly associated with SLE and are risk factors for severe COVID-19 [2]. Furthermore, the drugs used for its management may result in further suppression of immunity with a greater risk of severe COVID disease as well as poor vaccine efficacy, especially in patients on glucocorticoids (GC) and rituximab (RTX) therapies [4, 6, 7]. Therefore, a detailed evaluation of the impact of the COVID-19 pandemic on patients with SLE assumes great importance.

Previous reviews have summarized the severity of COVID-19 in SLE and the influence of immunomodulatory drugs; however, the rapid addition of information warrants newer insights into this area [8–11]. There are recent studies on the impact of COVID-19 on SLE as well as various aspects of vaccination in patients with SLE. Thus, this narrative review is undertaken to gain an overall perspective of SLE in the time of the ongoing pandemic.

The aim of this narrative review is to explore the impact of the COVID-19 pandemic on SLE in terms of prevalence and severity of infection, efficacy of COVID-19 vaccination, management of SLE, and the patients' attitudes to the disease and related vaccines.

Search strategy

Searches through Medline/PubMed and Scopus were performed in line with previously published recommendations [12]. Articles published until March 28, 2022, were retrieved and analyzed using the following keywords: (“COVID-19” OR “SARS-CoV-2”) AND (“SLE” OR “lupus”). Of the 360 and 688 articles obtained, respectively, in PubMed/Medline and Scopus, articles in a language other than English were excluded [13] (Fig. 1). Studies including both adults and children were studied, and trials, observational studies, letters, and case reports were included. After an initial screening of titles and abstracts, 198 relevant articles were retained (132 articles and 66 case reports). Those studies reporting general outcomes in rheumatic diseases without detailed data on patients with SLE were excluded. Additionally, information about specific sections was obtained through an individualized search strategy (“COVID-19” AND “lupus” AND “severity,” “COVID-19” AND “lupus” AND “hospitalizations,” “COVID-19” AND “lupus” AND “vaccines”). Relevant articles searchable at the Directory of Open Access Journals (DOAJ) and references of included articles were also processed for eligibility and inclusion for this review.

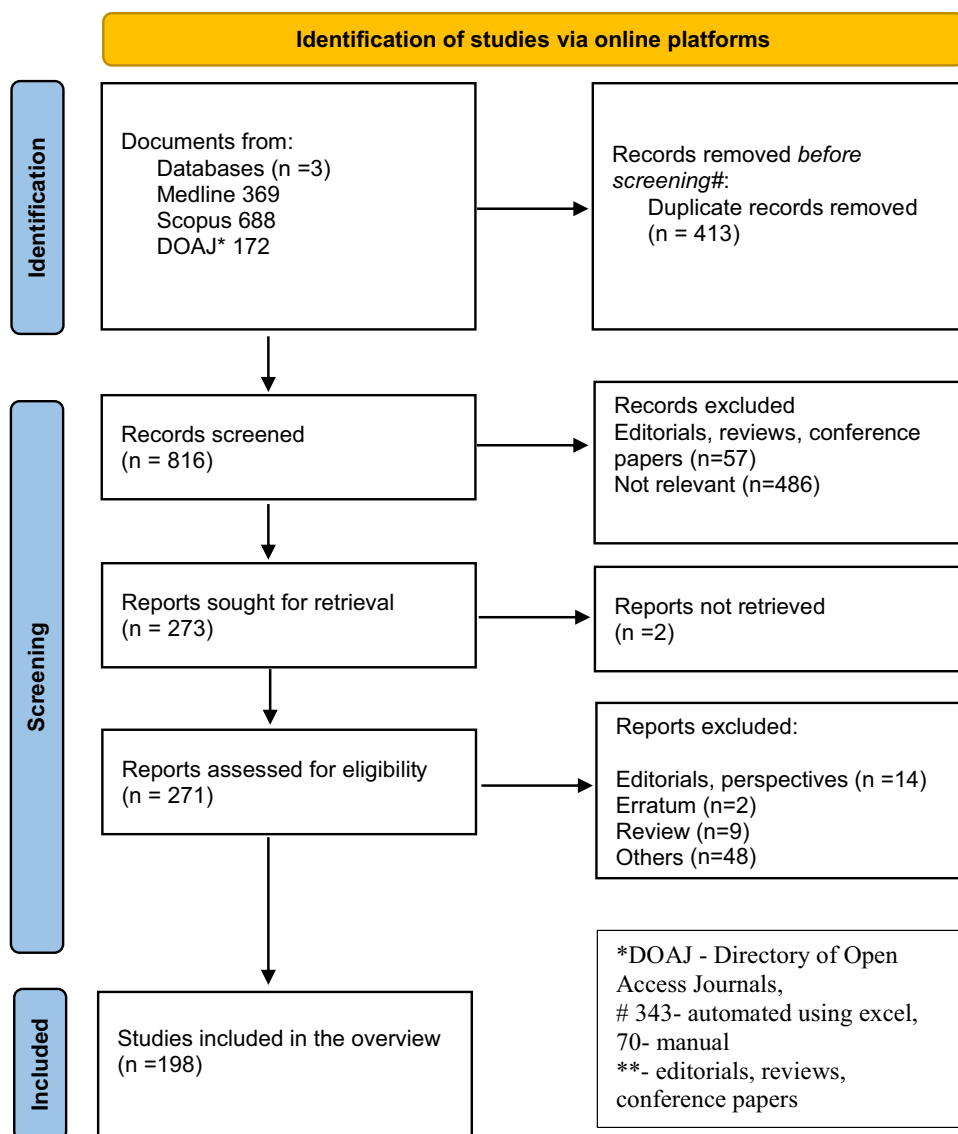
Features of COVID-19 in patients with SLE and effects of drugs

Prevalence

The early reports of features of COVID-19 in SLE from China, Europe, and the USA during the first wave of the pandemic described a similar prevalence of infection as compared to the general population [14] except from France and the USA [15, 16]. The French study was a telephonic survey of presumptive cases where a prevalence of 6.6% (versus 0.11% in the general population) was found [15], whereas the study from New York reported a prevalence of 4% in the Columbia Lupus Cohort (versus 2% in the general population) [16]. Single-center studies from Napoli and Pisa also reported a higher rate of 18–20% in patients with SLE than in other studies; however, the rates in the general population were not reported in parallel [17, 18]. Conclusion on the severity of COVID-19 in SLE patients could not be drawn effectively from these early studies due to small sample sizes and biases involved in the interpretation of hospital-based studies.

Subsequent studies reported a mixed prevalence of 0.6–22% [19–21] with variability likely due to the different timings of subsequent waves of the pandemic across different countries, high prevalence of infection in certain regions, and the different methodologies of the surveys conducted (Table 1).

Fig. 1 Methodology of comprehensive and systematic searches through databases and registers



Hospitalization

The rate for hospitalization was variable ranging from 0.8 to 80% across various countries; results from the Global Rheumatology Alliance (GRA) of 1606 patients with SLE reported a rate of 30% [22]. A wide range for hospitalization was observed due to different time points of conduction of the studies and different methodologies with major differences between surveys and hospital-based studies. Studies from very early phases of the pandemic have a low prevalence of 0.8% likely due to countrywide lockdowns. Subsequently hospitalization rates increased which were predominantly due to severe disease, but a small proportion seemed to be due to anxiety of the comorbid status. However, most studies do not clearly mention the reason for hospitalizations and is a subject for further study. Recent studies report a lower rate possibly due to decline in anxiety associated

with COVID-19 as well as ramping up of the immunization against it. Furthermore, healthcare policies have been modified with better understanding of the disease process in subsequent waves of the pandemic that may have led to fewer hospitalizations, especially of the asymptomatic and mild cases in the later part of the pandemic.

The risk for hospitalization was three-fold higher than the general population as per a nationwide study in Denmark [23]. There was an increased risk associated with race (odds ratio [OR] 7.78 for non-Whites versus Whites, 95% CI 1.13–53.58), presence of comorbidities (OR 4.66, 95% CI 1.02–21.20), and body mass index (BMI) (1.08 per increase in kg/m², 95% CI 0.99–1.18) as per results from the New York University (NYU) Lupus Cohort [24]. Rituximab use was associated with the risk of hospitalization (OR 12, 95% CI 5.8–28) [21, 25]. Contrasting associations with belimumab and GC use were observed with

Table 1 Studies of frequency of COVID-19 and its severity in lupus patients

Study	Country	Type of study	SLE, <i>n</i>	COVID-19, (PCR, presumptive)	Severe infections, <i>n</i> (%)	Hospitalizations, <i>n</i> (%)	Deaths, <i>n</i> (%)	Prevalence of COVID-19 in SLE, %	Prevalence of COVID-19 in general population, %	Drugs
Ramirez et al. 2020 [87]	Italy (SMILE, Milan Lupus Consortium)	Q (web-based)	417	5, 9	-	1(0.8)	-	3.2	4	No effect of HCQ (I)
Pablos et al. 2020 [88]	Spain	R	2253	-	-	-	-	0.62	0.58	-
Holubar et al. 2020 [16]	France	T	120	-, 8	-	0	-	6.6	0.11	No effect of HCQ (I)
Cordtz et al. 2021 [23]	Denmark	Nationwide cohort study	2533	95	-	18(18.9)	-	3.7	-	No effect of HCQ or GC, 3 times higher risk than general population (H)
Fasano et al. 2020 [17]	Italy (Napoli)	T	268	1, 50	0	0	0	22.6	-	No effect of HCQ (I)
Gendebium et al. 2020 [26]	Belgium	T	225	5, 13	-	2 (11)	0	8	-	No effect of HCQ (H, I). Higher risk with Belimumab and GC (H)
Marques et al. 2020 [36]	Brazil (Reuma-Cov Brasil register)	P	-	110	14 (12.7)	20(18)	11(10)	-	-	No effect of HCQ (I). GC and CYC (unfavorable outcomes)
Walters et al. 2020 [29]	USA	P	262 children	11, 6	0	0	0	-	-	-
Gartsheyn et al. 2020 [15]	USA (Columbia lupus cohort and New York Presbyterian-Columbia database)	Case series	450, 835	10, 8	3 (33)	7(38)	-	4	2	-
Mathain et al. 2020[14]	France	Case series	-	17	11(64.7)	14(82.3)	2(11.7)	-	-	-
Zen et al. 2020[18]	Italy (Padua cohort)	T	397	1, 74	-	-	-	18.8	-	-

Table 1 (continued)

Study	Country	Type of study	SLE, <i>n</i>	COVID-19, (PCR, presumptive)	Severe infections, <i>n</i> (%)	Hospitalizations, <i>n</i> (%)	Deaths, <i>n</i> (%)	Prevalence of COVID-19 in SLE, %	Prevalence of COVID-19 in general population, %	Drugs
Fernandez-Gutierrez et al. 2021 [24]	USA (NYU Lupus Cohort, NYU-Bellevue EPIC reports, WARCOW referrals)	Q (web-based)	-	42, 41	4 of 42(9)	24 of 42(58.9)	4 of 41 (9)	-	-	Non-White race, comorbidity, BMI (H)
Bertoglio et al. 2021[28]	Brazil	Nationwide cohort study	-	319, 63 (all hospitalized)	251(65.7)	382	154 (40)	-	-	-
Mageau et al. 2021[89]	France	Hospital based	-	190 (all hospitalized)	190 (100), only severe cases included	190 (0.2)	62(32.6)	-	-	-
Espinosa et al. 2021[90]	Spain	T	400	4, 26	3(10)	3(10)	0	7.5	1.5	No effect of HCQ (I)
Zucchi et al. 2021[19]	Italy (Pisa)	T	330	5, 1	2 (33)	3(50)	0	1.5	-	No effect of HCQ. GC and biologics may increase risk (I)
Attaoui et al. 2021[91]	Denmark	Population-based cohort study	1159	9	-	-	-	2.14	1.84	Older age, comorbidities, stopping IS (H), GC (severe disease)
Ramirez et al. 2021[27]	Italy	Q (web-based)	334	19, 9	-	-	-	8.3	-	Active disease, GC, AZA, CsA, age (I)
Shobha et al. 2021[92]	India	P	561	4	-	-	-	0.7	0.22	No effect of HCQ, Belimumab
Saadoun et al. 2021[93]	Europe	P	605	28	-	-	-	4.6	-	Lung disease, no effect of HCQ (I)
Clemente et al. 2021[30]	Spain	R	-	8 children	-	1(12.5)	-	-	-	-

Table 1 (continued)

Study	Country	Type of study	SLE, <i>n</i>	COVID-19, presumptive (PCR, presumptive)	Severe infections, <i>n</i> (%)	Hospitalizations, <i>n</i> (%)	Deaths, <i>n</i> (%)	Prevalence of COVID-19 in SLE, %	Prevalence of COVID-19 in general population, %	Drugs
Schioppo et al. 2021[94]	Italy	R	830	51	3 (5)	3(5)	-	6.1	-	GC and major organ disease were risk factors for symptomatic COVID-19
Bachiller-Corral et al. 2021 [25]	Spain	R	-	254	-	4(1.5)	2(0.75)	-	-	RTX (H)
Assar et al. 2022[95]	Iran	P	260	58	-	-	-	22.3	-	GC > 20 mg (I)
Ugarte-Gill et al. 2022, [22]	Global	Registry based	-	1606	213(13.5%)	488(30.1%)	105(6.5%)	-	-	Older age, male, not on treatment, GC, high disease activity and comorbidities (severe outcomes). RTX, MMF and CYC (poor outcomes) Belimumab and MTX showed no association

Studies that have included cases of COVID-19 confirmed with RT-PCR and presumptive cases with symptoms suggestive of COVID-19 without confirmation by RT-PCR

Q questionnaire, *T* telephonic, *R* retrospective, *P* prospective, *I* infection, *H* hospitalization, *GC* glucocorticoid, *AZA* azathioprine, *CsA* cyclosporine, *HCQ* hydroxychloroquine, *MTX* methotrexate, *PCR* polymerase chain reaction

regard to the risk of hospitalization [23, 24, 26]. There was no effect of hydroxychloroquine (HCQ) on the risk of COVID-19 and hospitalization across all studies [17, 19, 27].

Severity and outcomes

The rates of severe COVID-19 and related deaths were variable across studies owing to the different time-frames of recruitment, study designs, and country-wise prevalence of COVID-19 [17, 19, 27] (Table 1). As per the GRA report [22], severe disease (13.5%) and death (6.5%) were higher in the SLE than the general population and were associated with older age of SLE patients (OR 1.03, 95% CI 1.02–1.04), male gender (OR 1.5, 95% CI 1.01–2.23), no current treatment (OR 1.8, 95% CI 1.17–2.75), comorbidities (kidney disease OR 3.51, 95% CI 2.42–5.09; cardiovascular disease/arterial hypertension OR 1.69, 95% CI 1.25–2.29), and moderate or high SLE disease activity (versus remission; OR 1.61, 95% CI 1.02–2.54 and OR 3.94, 95% CI 2.11–7.34, respectively). A study from Brazil reported twice the frequency of unfavorable outcomes in SLE as compared with the general population without comorbidities, but the risk was similar when compared to the general population with comorbidities (Table 1) (Fig. 2) [28].

Two studies in pediatric SLE reported favorable outcomes, with a prevalence of 2.6% and none requiring hospitalization in the study from the USA [29], whereas the Spanish study reported eight cases with one requiring hospitalization [30].

Influence of immunosuppressants

HCQ was widely prescribed for the prevention of COVID-19 in the early phases of the pandemic based on observational studies, but no influence of HCQ on the prevention was

proven subsequently [31]. Likewise, across all observational studies in SLE, no effect of HCQ was observed in the prevention of symptomatic COVID-19 (Table 1). The absence of evidence supporting the positive role of HCQ in COVID-19 as well as the risk of arrhythmias when used in combination with azithromycin resulted in phasing out the over-prescription of HCQ during the pandemic [32–34]. Furthermore, no QTc prolongation was observed with the standard doses used in SLE in a study from the Colombia Lupus Cohort [35].

Concerns regarding GC use during the pandemic stem from the pan immunosuppressive effect and increased risk of infections as well as severity observed with them. GC are irreplaceable for the management of SLE, and hence the impact of GC on the risk and severity of COVID-19 infection was of concern. A nationwide cohort study in Denmark [23] and a telephonic survey in Belgium [26] found no impact of GC on the risk of COVID-19 infections [23, 26]. Most other studies have observed an increased association of GC use with the risk of COVID-19 infection, hospitalizations, and unfavorable outcomes even in SLE patients with low disease activity or remission; and use of low dose GC (<7.5 mg/day) [19, 26, 27, 36]. The initial report from the GRA observed twice the odds for hospitalizations with GC doses above 10 mg/day [3], whereas the latest report observed an increased association of GC with unfavorable outcomes in COVID-19 with GC doses less than 5 mg/day (1–5 mg/day OR 1.86, 95% CI 1.2–2.66; 6–9 mg/day OR 2.47, 95% CI 1.24–4.86; and ≥ 10 mg/day OR 1.95, 95% CI 1.27–2.99) [22]. Furthermore, data from the ReumaCov registry from Brazil showed recent pulse methylprednisolone (MPS) therapy in addition to oral GC had twice the odds for hospitalization and intensive care unit admission, with pulse MPS alone associated with death [36]. Despite the risks associated with GC use, control of disease activity in SLE is of prime importance and is an additional factor for unfavorable COVID-19 outcomes. Hence, most guidelines recommend appropriate GC use without abrupt discontinuation [37].

Fig. 2 Factors associated with severity of COVID-19 in lupus patients. CYC, cyclophosphamide; MMF, mycophenolate mofetil; AZA, azathioprine

- Younger age
- Female
- Disease in remission
- Methotrexate
- Belimumab



- Older age
- Male
- Non-White race
- Comorbidity
- Glucocorticoid use
- CYC, MMF or AZA
- Rituximab
- Active disease
- Stopping of medications

Patients of SLE with COVID-19 were 2.3 times and 7.7 times more likely to be on azathioprine (AZA) and cyclosporine (CsA), respectively, as per an Italian web-based survey [27]. Mycophenolate mofetil (MMF) (OR 1.2, 95% CI 0.93–1.55) and CYC (OR 1.92, 95% CI 0.95–3.91) use were not associated with unfavorable outcomes across multiple studies including the GRA [22, 27, 36]. Also, no association was found between methotrexate (OR 0.71, 95% CI 0.5–1.01) and unfavorable outcomes of COVID-19 in SLE [22]. Other studies have shown no associations of the risk of infection and severity with conventional immunosuppressants such as AZA, CsA, MTX, MMF, and CYC (Table 1) [26, 38].

Rituximab and belimumab are the most frequent biologics used in SLE [39]. Rituximab directly targets B cells, whereas the latter inhibits soluble B lymphocyte stimulator BLyS and prevents its interaction with its receptors on B cells, decreasing their survival. RTX therapy has been associated with increased hospitalization and unfavorable outcomes with OR 1.62 in the GRA study [22]. A study in Belgium reported a higher risk of hospitalization with belimumab [26]. However, the sample size was small with only two hospital admissions, thus making it difficult to interpret the findings [26]. Other studies reported no effect of belimumab on outcomes of COVID-19 [22, 27].

COVID-19 vaccination in SLE

Vaccine safety

Multiple studies evaluating various COVID-19 vaccines have reported safety of these in adolescent and adult patients with SLE [40–42]. An online survey in Denmark explored the safety of BNT162b2 (Pfizer/BioNTech) vaccine and compared it to the original vaccine trial in patients with SLE ($n = 182$) and rheumatoid arthritis (RA) ($n = 103$). An increased frequency of local side effects in the form of pain (74% versus 66%) and swelling (26% versus 7%) was reported, and the majority of the effects were mild. Fatigue (69% versus 51%) and headache (52% versus 39%) were the most common systemic side effects. Five of 285 patients (1.8%) reported adverse events requiring emergency hospitalization [43]. Other studies from India [44], Mexico [45], the EU [41, 46, 47], and the USA [48, 49] reported similar results with local pain, headache, and fatigue being the most common adverse effects of different COVID-19 vaccines (Table 2). Severe reactions were noted in 0–1.8% across various studies [43, 44, 51]. The EULAR Coronavirus Vaccine (COVAX) physician-reported registry has examined vaccine-related adverse events in 5121 patients, including 369 with SLE. Vaccine-related adverse events were reported in 37%

overall; mRNA-1273 (Moderna) had the highest risk of local adverse events (40%) compared with others (12%) [41]. AZD1222 had the highest risk for systemic adverse events in the form of fever (12%) compared with others (6%) [41]. Arrhythmia, myocarditis, liver injury, arthritis, and rash were observed in SLE as adverse events without major consequences [41].

In a single-center study evaluating the safety of COVID-19 vaccination in pediatric SLE, adverse events were noted in 4 of 16 patients (25%), and none were severe [40]. The adverse events were more frequent with the BNT162b2/Pfizer BioNTech vaccine than CoronaVac inactivated SARS-CoV-2. Post vaccination lupus flares were seen in two patients, and both were mild [40].

Vaccine-induced lupus flares

Vaccines can trigger and flare autoimmunity due to both the viral proteins and adjuvants used in the manufacturing process [50]. Studies from the NYU Lupus Cohort as well as the GRA reported a flare rate of 11% and 13%, respectively, of which 1.3% were severe in the former study and 4.6% required a change of medication in the latter study [42, 48]. The EULAR COVAX registry reported a flare rate of 3% with severe flares being infrequent (<1%) [41]. Most other studies also reported a similar flare rate and severity irrespective of the vaccine type [42, 46, 48]. These differences are likely due to the higher adverse effects reported by patients in questionnaire-based studies, whereas lower rates were observed with physician-reported events (Table 2). Thus, vaccine-induced lupus flares are infrequent, mild, and only about 5% require a change in medications.

Vaccine-induced SLE

The reports of new-onset SLE following COVID-19 vaccination are summarized in Table 3. These cases were seen irrespective of age and gender bias, with known autoimmune disease or family history of the same being risk factors. Lupus symptoms were seen predominantly with B162b2/PfizerBioNTech (8 of 10) after either of the doses. Most patients were treated with GC along with steroid-sparing drugs, and all patients improved in the short term (Table 3) [51–60].

COVID-19 vaccine efficacy in SLE

SLE is characterized by immune dysregulation due to the disease itself compounded by the use of immunosuppressants. Most live vaccines are contraindicated in SLE,

Table 2 Studies of COVID-19 vaccination in lupus patients

Study	Country	Vaccine	SLE, N	Local adverse events	Systemic adverse events	Severe adverse events	Flare	Positive humoral	Negative humoral
Bartels et al. 2021[43]	Denmark, web-based Q	BNT162b2	182	78%, pain most common	81%, headache and fatigue most common, greater than HC	1.8%	-	-	-
Machado et al. 2021 [41]	Europe, EULAR COVAX, physician-reported registry	BNT162b2, AZD1222, mRNA-1273	369	Pain (20%)	Fatigue (12%), headache (6%)	0.5%	3%, severe < 1%	-	-
Moyon et al. 2022[46]	France, P	BNT162b2	136	Pain (67.5%)	Fatigue (39.7%), Headache 25%	-	0.02% (mild)	Baseline Ig levels, B lymphocyte %	MMF, MTX
Izmirly et al. 2021[48]	USA, NYU lupus cohort, P	BNT162b/mRNA-1273, Ad26, COV2.S	90 vs 20 HC	-	-	-	11%, 1.3% severe	-	IS, normal dsDNA, 28% IgG response < 100U/l, lower antibody response in SLE
Ferri et al. 2021[47]	Italy, P	BNT162b2, mRNA-1273	38	Headache	-	-	0.05%	-	MMF, RTX, GC
Zavala Flores et al., 2021 BNT162b2[96]	Peru, prospective P	BNT162b2	100	Pain (90%)	-	-	27%, severe 2%	-	-
Esquivel-Valerio et al., 2021[45]	Mexico, cross-sectional observational study	AZD1222, Ad5-nCoV2, Ad26, COV2.S, mRNA-1273, BNT162b2, and CoronaVac	25	Pain (70%)	Fatigue (78%), headache (30%)	none	-	-	-
Sattui et al., Liew et al., 2021[42] [97]	Global Rheumatology Alliance	AZD1222, Ad5-nCoV2, Ad26, COV2.S, mRNA-1273, BNT162b2, and CoronaVac	391	-	Fatigue (33%), headache (27%)	0.2%	13%, 4.6% required change in drugs	-	Breakthrough infections in 2.5%
Conolly et al. 2021 [98]	USA, web-based Q	BNT162b2, mRNA-1273	91	Pain (89%)	Fatigue (58%), headache (50%)	-	-	-	-
So et al. [62]	Hong Kong	Comirnaty, CoronaVac	68	70	66%	0	0	Comirnaty	GC, MMF 92% had neutralizing antibodies (versus 100% controls)

SLE systemic lupus erythematosus, MMF mycophenolate mofetil, RTX rituximab, GC glucocorticoids, IS immunosuppressant, Ig immunoglobulin, MTX methotrexate, USA United States of America, NYU New York University, RNA ribonucleic acid

Table 3 Cases of new-onset SLE after COVID-19 vaccination

Study	Age/sex	Nationality/race	Vaccine	Timing	Organ involvement	Serology	Treatment	Outcome
Kaur et al. [51]	54/M	Asian	BNT162b2	2 weeks post the second dose	ACLE, hematologic, ?lupus nephritis, NPSLE	ANA, anti-dsDNA, SSA, SSB, Smith, RNP, Histone low C3, C4	GC, MMF	Improved
Raviv et al. [52]	24/M	Israeli	BNT162b2	2 days post first dose	ACLE	ANA, anti- nucleosome, ribosomal P	HCQ, topical steroids	Improved
Hidaka et al. [53]	53/F, VKH, Hashimoto and BA	Japanese	BNT162b2	2 weeks post the second dose	Evans	ANA, Lupus anticoagulant, low C3, C4	GC	Improved
Baez-Nigrón and Vila [54]	27/F, T1DM, family history of SLE		mRNA 1273	2 weeks post the 2nd dose	MSK, Lupus Nephritis	ANA, anti-dsDNA, SSA, SSB, low C3, C4	GC, MMF	Improved
Zavala Miranda et al. [55]	23/F		AZD1222	1 week post the first dose	Lupus nephritis	ANA, low C3, C4	GC, MMF, HCQ	Improved
Zengarini et al. [56]	30/F	Italian	BNT162b2	10 days post the second dose	SCLE, hematologic	ANA, anti-dsDNA, SSA, smith, RNP, nucleosome, histone, low C3, C4	GC	Improved
Patil et al. [60]	22/F, family history of Hashimoto	Indian	AZD1222	2 weeks post the second dose	MSK, hematologic, MC, lupus nephritis	ANA, anti-dsDNA, nucleosome, histone, low C3, C4	GC, MMF	Improved
Alrashdi et al. [57]	22/F	Saudi	BNT162b2	1 week post the first dose	ACLE, pancreatitis, hematologic	ANA, anti-dsDNA, low C3, C4	GC, Azathioprine	
Nune et al. [59]	24/M	Caucasian	BNT162b2	2 weeks post the second dose	MSK, MC, hematologic	ANA, anti-dsDNA, low C3, C4	GC, MTX	Improved
Molina-Rios et al. [58]	42/F			2 weeks post the first dose	MSK, PE	ANA, anti-dsDNA, b2GPI, Lupus anticoagulant	GC, Azathioprine, anticoagulation	Improved

C complement, dsDNA double-stranded deoxyribonucleic acid, ANA anti-nuclear antibody, SS Sjogren's syndrome, RNP ribonucleoprotein, GPI glycoprotein I, GC glucocorticoid, MMF mycophenolate mofetil, MTX methotrexate, HCQ hydroxychloroquine, ACLE acute cutaneous lupus erythematosus, SCLE subacute cutaneous lupus erythematosus, SLE systemic cutaneous lupus erythematosus, NP neuropsychiatric, MSK musculoskeletal, MC mucocutaneous, PE pulmonary embolism

and inactivated vaccines need to be given before starting immunosuppression [61]. The humoral immune response examined in a prospective observational study from the NYU Lupus Cohort (90 lupus patients and 20 healthy controls [HC]) was found to be lower in SLE than in HC with 28% having anti-receptor binding domain (RBD) antibodies below 100 IU/ml which was the lowest level observed in controls [48]. Positive predictors of anti-RBD antibodies were baseline immunoglobulin levels, B lymphocyte percentage, and young age, whereas negative predictors included the use of MMF, MTX, GC, and RTX [47, 48]. A moderate correlation ($R=0.57$, $P=0.0135$) was observed between anti-RBD antibodies and cell-mediated response with 57% having T cell responses among those with good neutralizing antibodies compared to only 10% in those without neutralizing antibodies [46, 48]. No association was observed between SLE disease activity, GC, HCQ, belimumab, baseline interferon-alpha levels, and total lymphocyte count with anti-RBD antibodies [46, 48]. Another study in Hong Kong also reported lower neutralizing antibodies in patients with SLE ($n=65$) as compared to healthy controls ($n=65$) [62]. In the EULAR COVAX registry, breakthrough COVID-19 infections were seen in 0.7% of the fully vaccinated SLE patients [41].

Thus, COVID-19 vaccines appear to be safe in SLE patients with more local reactions with mRNA vaccines. The side effects included mild local pain, fatigue, and headache. The risk of severe lupus flares is minimal. The efficacy of COVID-19 vaccination is lower than in the general population, especially for those on MMF, RTX, GC, and inactivated vaccines.

Surveys of patients' attitudes to COVID-19 vaccines

Concerns about COVID-19 vaccination in patients with AIRDs stem from the exclusion of these patients from vaccine trials with reservations about potential adverse effects, flares, and interaction with drugs. These are compounded further by misinformation most commonly from social media [63].

In a questionnaire-based study from the SMILE cohort in Italy ($n=317$), 76% of patients had a positive attitude towards vaccination, with the remaining having concerns about the potential risk of flare and side effects [27]. Likewise, in a nationwide survey of 908 participants with AIRDs in Brazil, including 188 patients with SLE, the vaccine acceptance rate was 80% with the most frequent reasons for vaccine hesitancy being short vaccine trials followed by concerns of side effects and flares [64]. Those treated with HCQ, belimumab, pulse MPS, and having kidney disease, cancer, and fibromyalgia were more likely to be vaccine hesitant [64].

An early report from the GRA of 900 patients, including 397 patients with SLE, revealed that the majority (80%) discussed this issue with their physicians and received positive feedback from them [42]. About two-thirds of all patients were willing to withhold immunosuppression temporarily during vaccination; the remaining had concerns about plausible lupus flares [42]. In contrast, a study from Egypt exploring rheumatology faculty opinion on this topic found that only 70% of surveyees were willing to recommend COVID-19 vaccination to patients with AIRDs, of which SLE was the disease with the highest priority for vaccination [65]. A survey (VAXICOV study) with respondents predominantly from South America and Europe reported willingness to receive vaccine in 54%, and uncertainty in 30% in patients with AIRDs, including 492 patients with SLE. This figure increased to 62% when the vaccination was recommended by a physician [66]. A similar observation was noted in a Chinese survey where only 30% of patients with SLE showed willingness for vaccination which improved to 90% after recommendation by a physician [67].

Thus, a majority of lupus patients have a positive attitude towards vaccination, especially after receiving physicians' recommendation. Concerns are mainly due to short-term follow-ups and fear for adverse events and flares.

Impact of the COVID-19 pandemic on patients with SLE

Patients with chronic diseases are prone to more severe COVID-19 and unfavorable outcomes [68]. Psychological stress due to lockdowns and social distancing has resulted in a rise in anxiety and depression among patients with SLE [69]. Irregular supply of medications, difficulty in scheduling hospital appointments, and inaccessibility of medical care have further complicated the issue [69]. Similar themes emerged from a social media-based study providing real-time data on concerns of patients with AIRDs during the pandemic [70].

Thus, the pandemic has posed multiple issues concerning COVID-19, management of SLE, and repercussions on patients' mental health. Having said that, most lupus patients have a positive attitude towards social distancing, masks, and alcohol-based hand rubs for the prevention of infection [69, 71].

Impact on disease

In a questionnaire-based study from the SMILE Lupus Cohort in Italy, the median overall health reported as per Numerical Rating Scale was 7 (6–8) during 2020, with 30% requiring treatment escalation (62% GC, 51% new immunosuppressant, 7% addition of belimumab) predominantly for

joint and skin disease [27]. Thirty-four percent of patients reported adequately controlled disease allowing tapering of GC (68%) and/or immunosuppressants (35%). About two-thirds reported missed appointments secondary to healthcare delivery disruption. Overall, 54% reported no significant effect of the pandemic on their disease, while the remaining reported worsening (17%) and improvement (4%). Twenty-five percent were uncertain about the same [27].

An online survey from the INSPIRE Lupus Cohort in India reported difficulty in procuring medications and scheduling hospital visits due to the lockdown restrictions [72]. Worsening of disease during the pandemic was noted in 25%, and the mean patient global assessment value was 6.69 (1.26) [72]. Interestingly, 61% felt confident of the correct management of disease during the lockdown by being associated with the cohort [72]. Another survey from the Philippines with 405 lupus patients reported similar findings, with two-thirds reporting their health status as good [73]. An irregular supply of HCQ resulted in increased frequency of myalgia and rash [73, 74]. Similar results from Egypt, Poland, Saudi Arabia, and the GRA were observed (Table 4) [75, 76].

When 97 patients with lupus nephritis from Brazil were analyzed, fear for COVID-19 was rated to be 8 of 10, for flare 7 of 10, with >90% compliance to the use of masks and drugs for SLE, and fear for the use of immunosuppressants was zero [10]. Another study from Egypt also reported a greater likelihood of patients with SLE for drug adherence and social distancing [71]. Hence, the attitude of patients towards COVID-19 and medications also depends on SLE severity. Those on biologics were also more likely to follow social distancing norms as per an American study [77].

From the Padua Lupus Cohort, 3% of patients discontinued medications during the first wave of the COVID-19 pandemic [18]; a study from Pisa reported a discontinuation rate of 11% either by physician recommendation or patient choice with a significant association with flares [19].

In a retrospective study in Malaysia, the frequency of hospitalization of patients with lupus was reduced by 65% but required more intensive treatment due to higher severity of symptoms [78, 79]. Elective admissions for renal biopsies and hemodialysis training in them also reduced significantly [78, 79].

Thus, worsening disease activity was noted in 8–50% of patients with SLE across multiple studies based on patient-reported questionnaires. Up to 75% of patients with lupus encountered difficulties with medical care access, and 70% of them had difficulty procuring drugs (Table 4).

Impact on psychosocial health

A questionnaire-based study of 361 patients with rheumatic diseases, including 125 patients with lupus, revealed overall frequencies of 9% for depression and 7% for anxiety [76,

80–83]. The rates have been reported to be as high as 40% in studies from France and the Philippines [74, 84]. However, an Italian study concluded that these rates were comparable with the general population [85]. Poor access to medical care rather than the risk of COVID-19 stirred anxiety in a large survey in the UK [69]. Female gender, rural residency, and GC use were all positively associated with anxiety and depression. Anxiety and depression were negatively associated with satisfaction with available health information and wearing of face masks [83].

The way forward

The management of SLE in times of COVID-19 should include appropriate counseling and healthcare delivery to ensure compliance with COVID protective measures, medications, and promote vaccine willingness. The use of telemedicine to monitor lupus activity and disseminate evidence-based information holds prime importance at the time of COVID-19 waves and lockdowns. Additionally, telemedicine can be employed to follow up lupus patients with stable disease to reduce strain on hospitals. In a large American survey of 3000 patients, although drug compliance is better with physical visits, it is still higher with telemedicine than with no visits [77]. It is also an opportunity to reinforce the importance of vaccination and boosters as per the local recommendations [77].

Although the use of GC and immunosuppressants are associated with severe COVID-19, these drugs should not be abruptly stopped as active disease itself is a risk factor for unfavorable COVID-19 outcomes. GC should be used in the lowest possible doses. The preference of belimumab over rituximab for the management of SLE needs to be explored further. Minor organ manifestations can be treated with HCQ, MTX, or AZA, reserving MMF, CYC, and RTX for major organ disease.

Adequate control of arterial hypertension, diabetes mellitus, and other comorbidities is of prime importance. COVID-19 vaccination should be reinforced in patients with SLE as adverse events are few. Breakthrough infections are uncommon and are usually mild. This should be coupled with appropriate COVID protective measures like the use of face masks and social distancing. More studies are warranted to explore the impact of stopping immunosuppressants at the time of vaccination on the overall vaccine efficacy in SLE. Home-based exercise programs along with the dissemination of appropriate health information should be carried out for reducing anxiety and depression [86].

Although there is significant amount of data on the prevalence and severity of COVID-19, there are definite lacunas in various aspects. More active research is needed in the areas of safety and efficacy of vaccination. Recommendations on

Table 4 Studies of the impact of the COVID-19 pandemic on lupus patients

Study	Country	Type	N	Hospital visits	Hospitalizations	Disease activity-same	Disease activity-increase	Disease activity-decrease	Drug supply	Others
Ramirez et al. 2021[27]	Italy	Q (web-based)	326	Missed appointments (68%)	-	54%	17%	4%	-	-
Salido et al. 2021[73]	Philippines	Q (web-based)	405	-	-	66%	-	-	40% suffered from irregular HCQ supply with resultant myalgias, rashes	-
Zucchi et al. 2021[19]	Italy	T	330	-	-	-	8% (mild-mod)	-	11% discontinued drugs	-
Hausmann et al. 2021[99]	Global	Q (web-based)	2882	-	-	-	-	-	18% discontinued drugs	COVID protective behavior (100%), 13% decrease in employment
Rathi et al. 2020[72]	India, INSPIRE cohort	Q (web-based)	1040	Missed appointments (54%), difficulty in getting investigations (37%)	32%	-	25%	-	Difficulty in procuring drugs (36%)	Financial difficulties in 25%
Tharwat et al. 2021 [71]	Egypt	Q (web-based)	200	71% faced difficulty in hospitalization	-	-	50%	-	Procuring drugs (70%)	-
Plantinga et al. 2022 [100]	USA (GOAL cohort)	Q (web-based)	245	Difficulty in access to medical care (42%)	-	-	-	-	Procuring drugs (21%)	Less physically active (55%) Less sleep (54%)
Scherlinger. 2022 [84]	France	Nationwide Q (web-based)	536	Difficulty in access to medical care (25%)	-	-	31%	-	-	Sleep disorders (54%), anxiety 47%, depression (42%), PTSD (39%) associated with financial issues, access to medical care, Unemployment (25%)
Sloan et al. 2021[69]	UK	Q (web-based)	87	Difficulty in access to medical care (70%)	-	-	-	-	-	-

Table 4 (continued)

Study	Country	Type	N	Hospital visits	Hospitalizations	Disease activity-same	Disease activity-increase	Disease activity-decrease	Drug supply	Others
Ammitzbol et al. 2021 [101]	Denmark	Q (web-based)	405	-	-	-	24%	-	10% discontinued drugs	Depression (19%), reduction in exercise capacity (60%)
Garrido-Cumbrera et al. 2021 [102]	Spain (REUMA-VID)	Q (web-based)	97	Difficulty in access to medical care (> 50%)	-	-	-	-	-	Anxiety (32%), depression (21%)

Q questionnaire, T telephonic, PTSD post-traumatic stress disorder

the use of drugs during COVID-19 vaccination are largely based on older studies of influenza vaccination. Most studies are questionnaire-based; thus, prospective cohort studies and controlled trails are the need of the hour specially to study vaccine effectiveness in SLE. Innovative strategies to manage SLE in the light of COVID-19 need to be devised and assessed objectively.

We acknowledge inherent limitations related to the design of the narrative review with a subjective assessment of the retrieved studies. Most current studies are medical records review or questionnaire-based studies with heterogeneity of results across countries.

In conclusion, patients with SLE seem to have a greater risk of COVID-19 infection and hospitalization than the general population. Older age, male gender, associated comorbidities, GC, CYC, MMF, and RTX use are associated unfavorable outcomes. COVID-19 vaccines are safe and efficacious in SLE with minimal risk for severe flares. The overall attitude of patients towards vaccination is positive, with an influence of physician recommendation on the same. The pandemic has significantly affected access to medical care, hospitalizations, access to drugs, employment, and the mental health of patients which need to be addressed as a part of holistic care in SLE.

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Declarations

Disclosures None.

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