

COVID-19 in patients with systemic lupus erythematosus: A systematic review

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Abstract

The objectives of the study were to review the articles to identify (a) the epidemiology of systemic lupus erythematosus (SLE) and coronavirus disease 2019 (COVID-19); (b) the clinical characteristics of SLE patients with COVID-19; (c) the treatment of COVID-19 in SLE patients; and (d) the impact of COVID-19 pandemic on SLE patients. PubMed was systematically reviewed for literature published from December 2019 to June 2021. Our search was limited to human studies, with language restriction of English. Studies were included if they reported COVID-19 in SLE patients. Our systematic review included 52 studies. The prevalence of COVID-19 infection ranged from 0.0% to 18.1% in SLE patients, and the hospitalisation rates ranged from 0.24% to 10.6%. COVID-19 infection is likely to mimic SLE flare. Hydroxychloroquine (HCQ) was ineffective in prevention of COVID-19, and SLE patients with COVID-19 faced difficulty in healthcare access, had financial constraints and suffered from psychological distress during the pandemic. The pandemic had a significant effect on mental and physical health. Adequate healthcare access, along with containment policies, social distancing measures and psychological nursing was required.

Keywords

SLE, COVID-19, SARS-CoV-2, Systematic Review

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic leads to serious illness in a considerable proportion of infected patients.^{1,2} As of 27 July 2021, the pandemic of COVID-19 has been responsible for more than 194 million infections and four million deaths globally.³ Some populations are at greater risk from poor outcomes related to this disease, including the elderly, male, obese people and individuals with any comorbidities, especially those with hypertension, cardiovascular disease or diabetes.⁴

Prognoses of COVID-19 vary widely between individuals. Systemic lupus erythematosus (SLE) patients are prone to COVID-19 infection on account of the aberrant immune responses inherent to the disease and the frequent treatment of immune-suppressants.⁵ Age over 60 years, male sex, Black and Asian ground, steroids, cyclophosphamide or rituximab and high disease activity were related to increased risk of poor consequences of COVID-19 in SLE patients.⁶

The purposes of the systematic review were to evaluate the epidemiology of SLE and COVID-19, to identify the clinical characteristics of SLE patients with COVID-19, to

clarify the treatment of COVID-19 in SLE patients and to assess the impact of COVID-19 pandemic on SLE patients.

Methods

Search strategy

The review followed the Preferred reporting items for systematic reviews guidelines (PRISMA)⁷ for articles that revealed the relationship between COVID-19 and SLE. PubMed was searched to identify relevant articles from December 2019 to June 2021. The following search strategy

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was developed: (coronavirus[Title/Abstract] OR coronavirus[Title/Abstract] OR COVID[Title/Abstract] OR 'COVID-19'[Mesh Terms] OR COVID-19[Title/Abstract] OR COVID-2019[Title/Abstract] OR severe acute respiratory syndrome coronavirus[Title/Abstract] OR severe acute respiratory syndrome coronavirus 2[Title/Abstract] OR 2019-nCoV[Title/Abstract] OR 'SARS-CoV-2'[Mesh Terms] OR SARS-CoV-2[Title/Abstract] OR 2019nCoV[Title/Abstract]) AND ('Lupus Erythematosus, Systemic'[Mesh Terms] OR Lupus Erythematosus, Systemic[Title/Abstract] OR systemic lupus erythematosus[Title/Abstract] OR SLE[Title/Abstract]). Our search was limited to human studies, with language restriction of English. We also assessed the reference lists for eligible studies.

Selection criteria

Studies were eligible if they reported relationship between COVID-19 and SLE. Observational studies (e.g. case reports and series, cross-sectional studies, case-control studies and cohort studies), correspondence with relevant clinical data and randomised controlled trials were included. Comments, animal studies and in vitro studies were excluded. Studies were ineligible if the full texts were not available.

Study selection and data collection

Two independent reviewers conducted the phases of screening, eligibility and inclusion. They reviewed titles and abstracts for potential inclusion. Both reviewers inspected the full text for potential studies. Any discrepancy was resolved through consensus amongst review authors or through adjudication by an additional review author. Two authors tabulated outcome results from the included studies in detail, to examine and evaluate the potential patterns within the data. Quality assessment was performed using criteria adapted from the National Institutes of Health.⁸

Data synthesis

A narrative synthesis was performed within the following categories: (a) the epidemiology of SLE and COVID-19; (b) the clinical characteristics of SLE patients with COVID-19; (c) the treatment of COVID-19 in SLE patients; and (d) the impact of COVID-19 pandemic on SLE patients.

Results

We initially yielded 253 literature, of which 52 met the eligibility criteria (Figure 1).^{9–60} The quality assessment of the 52 articles revealed a high quality in 19/52 (36.5%) studies. Characteristics and outcomes are shown in Table 1.

The epidemiology of SLE and COVID-19

Thirteen studies reported the epidemiology of SLE and COVID-19. The proportion of SLE patients varied from 7% to 32.9% in rheumatic patients infected with COVID-19.^{25,36,42} Relative to patients with other autoimmune diseases, SLE patients with COVID-19 infection appeared to develop more severe manifestations of COVID-19 infection, with higher rates of hospitalisation, invasive ventilation requirement or death.^{21,25,36,39,53} The prevalence of COVID-19 infection varied between 0.0% and 18.1% in SLE patients,^{13,18,19,41,45,59} and the hospitalisation rates ranged from 0.24% to 10.6%.^{19,45,59} A decline in SLE hospitalisation rate was found during the COVID-19 pandemic, and disease flare (38.9%) and infection (22.2%) were considered as the main reasons for hospitalisation in SLE patients.¹⁵

The clinical characteristics of SLE patients with COVID-19

The clinical characteristics of SLE patients with COVID-19 were reported in 23 studies. COVID-19 infection might mimic SLE flare, and sometimes could occur concurrently with SLE flare.^{14,17,29,30,40,46,51} The main clinical symptoms of COVID-19 infection in SLE patients were fever, cough, shortness of breath, headache, increased respiratory rate, myalgia, rhinorrhoea and diarrhoea.^{13,37,45,46} The clinical presentation described in paediatric SLE population with COVID-19 might be similar to those in adults, characterised by increased work of breathing and low oxygen saturation.⁴⁹ Bozzalla Cassione et al.¹³ also reported that 11 of 12 SLE patients with COVID-19 are likely to have a mild and self-resolving disease course. However, patients with multivisceral SLE damage would be at risk of severe COVID-19.^{52,55} A patient of SLE with COVID-19 could develop COVID-19-related varicelliform rashes, leptomenigeal involvements, thrombotic events and immune thrombocytopenia.^{9,20,28,33,35,48} The infection of COVID-19 could trigger the presentation or exacerbation of SLE.^{12,27,44,57}

The treatment of COVID-19 in SLE patients

Thirteen studies reported the treatment of COVID-19 in SLE patients. Previous use of immunosuppressants did not seem to influence COVID-19 infection or symptoms in SLE patients.^{22,23} Intravenous immunoglobulin treatments and increased dose of corticosteroids might be effective for patients with COVID-19 and SLE.^{23,40} According to the available evidence, hydroxychloroquine (HCQ) did not appear to prevent the occurrence of COVID-19.^{10,23,31,32,37,40,45,47,51,60} Cardiovascular adverse events were frequently reported in patients with SLE under HCQ or chloroquine (CQ) treatment,²⁶ and paediatric SLE patients might develop hyperpigmentation induced by HCQ.³⁴

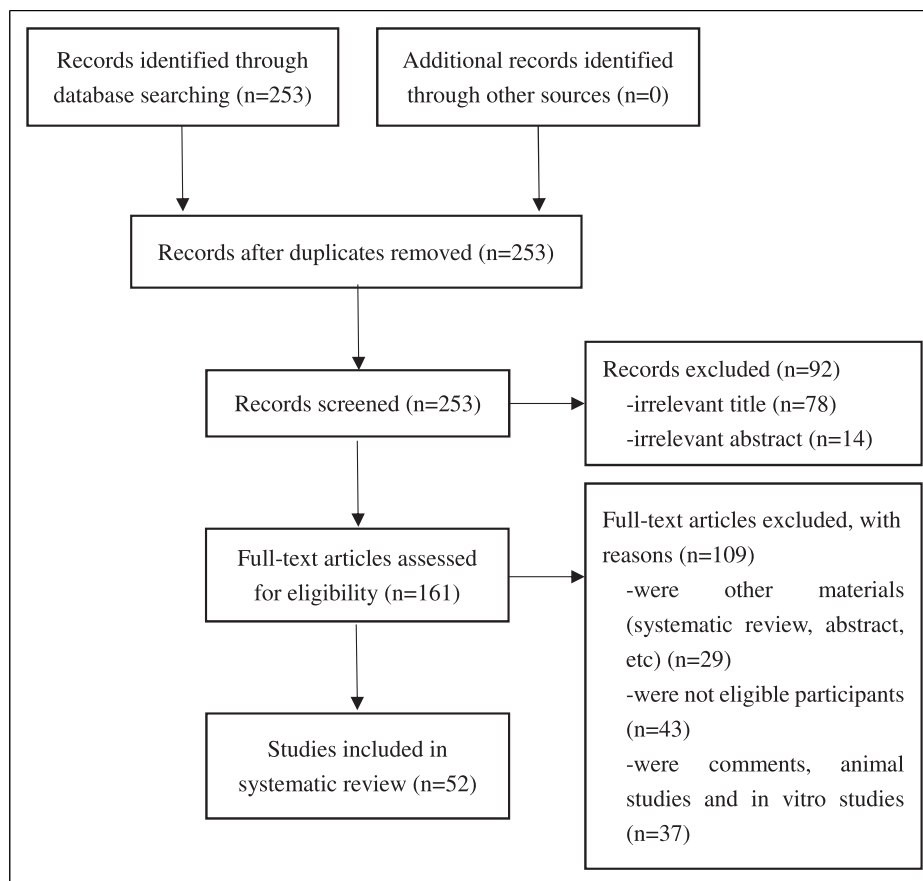


Figure 1.. Flowchart of literature search and study selection.

The impact of COVID-19 pandemic on SLE patients

Fifteen studies reported the impact of COVID-19 pandemic on SLE patients. During this lockdown period, SLE patients experienced supply shortages, missed the doses of drugs, underwent financial constraints and spent more money on healthcare.^{38,45,46} Many patients faced problems of reduced care access, such as missing their scheduled follow-up visits and being unable to get their investigations.^{14,24,46} A few patients discontinued previous treatments, which might result in worse SLE clinical outcomes.^{11,45,55,58,59} Besides possible clinical effects, treatment discontinuation might cause psychological consequences including anxiety, concern and probably a sense of uncertainty about the future.^{16,24,43,56} Patients also displayed a high adherence to social distancing measures,^{18,56,58} but it often came at the cost of physical activity, increased pain, disease activity, anxiety, depression and sleep disorders.^{11,50,54,56}

Discussion

This systematic review found that there was variation in infection rates and hospitalisation rates in SLE patients across the included studies. HCQ lacked preventive effect

on COVID-19, and SLE patients with COVID-19 experienced supply shortages, missed the doses of drugs, underwent financial constraints and suffered from psychological distress during the pandemic.

The COVID-19 infection rates in SLE patients ranged from 0.0% to 18.1%. This wide variation might be attributed to prevention of contagion adopted by SLE patients. The strict implements of the precaution in public could greatly contain the outbreak.⁶¹ Social distancing measures along with handwashing and mask-wearing could play important roles in tackling COVID-19.⁶² SLE patients were found to have higher overall attack rates of COVID-19 relative to the general population.^{45,55} This is possibly because of immune dysfunction, use of immunosuppressant agents, impairment from prior disease activity, presence of comorbidities and over-expression of angiotensin-converting enzyme two receptor.⁶

Disease flare was the main cause of hospitalisation in SLE patients.¹⁵ Treatment discontinuation was likely to result in SLE flare.^{59,63} The reasons for poor adherence in medications included concern about adverse effects, being distracted, life getting in the way, uncertainty or disagreement about the important role of medications and having personal reasons.⁶⁴ Furthermore, HCQ shortage was frequently

Table 1. Characteristics and outcomes of included studies.

Author	Study details	Results and conclusions	Strengths and limitations
Aguirre-Alastuey et al., 2021	Case study	A 22-year-old-woman with SLE and aPL antibodies suffered from pulmonary thromboembolism during the COVID-19 infection. The authors made the hypothesis that COVID-19 could trigger the antiphospholipid syndrome	Small sample size
Ammitzbøll et al., 2021	Patients with RA or SLE ($n=405$) and blood donors ($n=513$)	206 SLE patients (91.3% females. Median age, 49.0 years [IQR, 38.3–60.1]. Median disease duration, 11.9 years [IQR, 6.0–24.0]), 199 RA patients (71.4% females. Median age, 62.5 years [IQR, 51.6–70.5]. Median disease duration, 14.0 years [IQR, 8.0–21.0]) and 513 blood donors (49.1% females. Median age, 47 years [IQR, 33–57 years]). Isolation was related to significant protection against COVID-19, but it often came at the cost of physical activity, increased pain, disease activity and depressive symptoms	
Cornet et al., 2021	SLE patients using HCQ	51.8% of patients experienced supply problems. 56.1% of patients underwent high anxiety due to the unavailability of HCQ. Even if normal supply resumed, 27.4% remained anxious	
Favalli et al., 2021	62 SLE patients between 25 Feb and 10 Apr	91% were females. Mean age, 44.1 years. No cases had confirmed COVID-19, while 8 cases (including 5 on HCQ) had symptoms similar to COVID-19, rapidly recovering without additional therapy. Three patients contacted with COVID-19 cases and none developed symptoms of COVID-19 infection. No patients changed the medication and 93.5% had stable diseases. 95% of patients adopted strict preventive measures. The authors hypothesised that SLE did not increase the risk of COVID-19	
Freeman-Beman et al., 2021	Case study	An SLE patient with COVID-19 experienced a thrombotic event with concurrent recurrence of positive antiphospholipid antibodies	Small sample size
Goldman et al., 2021	Non-COVID-19 patients received HCQ/CQ treatment (07/2014-9/2019)	HCQ/CQ was frequently used by patients with RA ($n = 1,655$, [51%]), SLE ($n = 758$, [24%]), SjS ($n = 99$, [3%]), arthritis or arthralgia ($n = 93$, [3%]) and cutaneous lupus erythematosus ($n = 80$, [2.5%]). CVAEs frequently occurred in patients with SLE (34% vs 22%, $p < 0.01$)	
Gracia-Ramos et al., 2021	Case study	COVID-19 infection triggered the presentation or exacerbation of the autoimmune disease in SLE patients	Small sample size
Jung et al., 2021	Patients with RA or SLE tested for SARS-CoV-2 ($n = 2066$) until 15 May 2020	90.9% of patients had RA and 14.5% had SLE. 31.4% (649/2066) used HCQ. 93.7% of HCQ users received 200–400 mg/day. 98.0% of HCQ users received HCQ over 3 months before the test. The infection rate in the HCQ users (2.3%, 15/649) was similar to that in the HCQ non-users (2.2%, 31/1417) ($p = 0.860$). After the attack, one HCQ non-users needed ICU admission, required ventilator treatment and died The authors hypothesised that prophylactic intake of HCQ at a standard dose was not effective in COVID-19 prevention	
Marques et al., 2021	IMRD patients with COVID-19 ($n = 334$) between 20 May 2020 and 24 Jul 2020	SLE (32.9%) and RA (28.4%) were the most common rheumatic disease diagnoses. 28 patients died (11 had SLE, 4 had RA, 2 had axial spondyloarthritis, 5 had SSc and 6 had other diseases). SLE played a protective role for ICU admission (PR = 1.72, 95%CI 1.04 to 2.88, $p = 0.036$)	An observational multicentre prospective cohort
Mendel et al., 2021	Experience of physicians from SLE referral centres	31 responses (rate 74%) were received. 55% reported HCQ shortages in SLE patients during the pandemic, and 65% were contacted regarding this problem. The estimated proportion of SLE patients affected was 15% (IQR 5%–35%). The reasons for HCQ shortages were off-label prescribing and clinical trials of HCQ	Physician estimates from single tertiary centres

(continued)

Table 1. (continued)

Author	Study details	Results and conclusions	Strengths and limitations
Rathi et al., 2021	SLE patients ($n = 1040$) from an Indian inception cohort	90% females. Mean age, 27.5 (SD, 19.1) years. Mean disease duration 1.25 years. Twenty-Four (2.3%) patients developed fever, but none had COVID-19. 262 patients (25.2%) had difficulty in finance, with an average excess expenditure of more than \$30 per month on healthcare. 378 patients (36%) complained that they were unable to get prescribed medicines because of lockdown, and of these, 40% of patients required to change the drug schedule. Nearly 54% of patients missed the follow-up visits and 37% reported problems in getting their investigations done because of lockdown. During the pandemic, 266 patients (25.5%) complained about worsening of symptoms SLE like joint pain, malar rash or oral ulcers	
Rentsch et al., 2021	Adults first diagnosed with RA or SLE ($n = 194\ 637$) at least 6 months before 1 March 2020	30 569 (15.7%) patients received two or more prescriptions of HCQ (median number of prescriptions 5). HCQ users were younger and most were females. There were 547 deaths due to COVID-19, 70 were HCQ users. HCQ users had a standardised cumulative COVID-19 mortality of 0.23% (95% CI 0.18–0.29), while the standardised cumulative mortality among non-users was 0.22% (0.20–0.25). There was no relationship between HCQ use and COVID-19 mortality (HR = 1.03, 95% CI 0.80–1.33)	Large sample size
Slimani et al., 2021	Case study	A case of SLE with APS developed a COVID-19-related varicelliform rash	Small sample size
Sukhdeo et al., 2021	Case study	An SLE child with COVID-19 presented with increased work of breathing and low oxygen saturation. The authors suggested that the clinical presentation described in paediatric SLE population with COVID-19 might be similar to those in adults	Small sample size
Zamani et al., 2021	Case study	A 39-year-old with COVID-19 infection produced autoantibodies or developed the clinical characteristics of SLE	Small sample size
Zucchi et al., 2021	SLE patients ($n = 332$) from a single Italian centre between Feb and Jul 2020	91.3% females. Median age, 47 years. Median duration of the disease, 17 years. 6 patients (1.8%) had confirmed COVID-19 infection, 3 of them (50.0%) needed hospitalisation, but none were sent to the ICU. There was a significant relationship between bDMARDs and COVID-19 (OR = 7.35, 95% CI 1.42 to 37.87, $p = 0.02$). 36 patients (11.0%) discontinued medication for SLE due to physician's suggestions or personal choice, and disease flare occurred in 8.1% ($n = 27$) of cases during the COVID-19 pandemic, all of which were not severe. There was a relationship between disease flare and treatment discontinuation. The authors hypothesised that treatment discontinuation might result in disease flare	A single Italian centre
Alharthy et al., 2020	Case study	A patient with SLE and end-stage kidney disease was admitted to ICU because of COVID-19. She was infected with COVID-19 despite the administration of HCQ.	Small sample size
Bonometti et al., 2020	Case study	An 85-year-old woman with COVID-19 infection developed autoimmune antibodies, and she was diagnosed with SLE. The authors hypothesised that SLE was probably one of the possible chronic rheumatologic diseases triggered by COVID-19	Small sample size

(continued)

Table 1. (continued)

Author	Study details	Results and conclusions	Strengths and limitations
Bozzalla Cassione et al., 2020	A telemedicine project of SLE patients ($n = 165$) from Lombardy and Emilia-Romagna since 15 Feb 2020	84% females. Median age, 52.5 years. Median disease duration, 13 years. Fever and cough were common symptoms. 12 cases (7.2%) developed COVID-19, and 4 had confirmed infection, of which one was admitted to ICU. She had severe SLE and was on MMF, HCQ and oral prednisone before COVID-19. She was successfully discharged from ICU after initiation of methylprednisolone and non-invasive ventilation. All 11 remaining patients had mild disease courses and fully recovered. The authors concluded that the disease course was more likely to be mild and self-resolving	
Cho et al., 2020	Case study	Case 1 with stable SLE and COVID-19 infection developed severe thrombocytopenia. Case 2 with active lupus nephritis died from COVID-19 pneumonia. Case 3 with SLE, hypertensive heart disease and chronic kidney disease, and developed active lupus nephritis. All 3 cases had active SLE that required escalation of therapy	Small sample size
Chuah et al., 2020	Patients with SLE during the peak of the pandemic (from 18 Mar 2020 to 9 Jun 2020)	18 cases with SLE required hospitalisation during the lockdown period and 6 were newly diagnosed with SLE. SLE hospitalisation rate fell by 65.4% during the pandemic relative to the same period in 2019, but hospitalised patients were likely to have more severe symptoms. Disease flare (38.9%) and infection (22.2%) were important causes of admission in SLE patients	Small sample size
El Aoud et al., 2020	Case study	A COVID-19 patient presented with multiorgan involvement mimicking SLE and was successfully treated with glucocorticoids and tocilizumab	Small sample size
Fernandez-Ruiz et al., 2020	Patients with SLE ($n = 226$) from a New York University lupus cohort, query of 2 hospital systems and referrals from rheumatologists	41 SLE patients with COVID-19 (24 [58.5%] needed hospitalisation, 4 were admitted to ICU and 4 passed away), 42 had symptoms of COVID-19 (RT-PCR not performed) and 124 were asymptomatic (RT-PCR not performed). An exploratory logistic regression analysis identified nonwhite (OR = 7.78, 95%CI 1.13–53.58, $p = 0.037$) and presence of comorbidities (OR = 4.66, 95% CI 1.02–21.20, $p = 0.047$) as independent predictors of hospitalisation	A large and multi-racial/ethnic cohort
Freites Nuñez et al., 2020	Patients with AIRD and symptomatic COVID-19 ($n = 123$) from Madrid, Spain (1 Mar 2020 to 24 Apr)	Of 8 SLE cases, 6 were non-admitted patients and 2 were admitted patients. SLE was not associated with hospital admission (OR = 0.4, 95%CI 0.07–2.08, $p = 0.27$)	A single centre research
Gartshteyn et al., 2020	Case study	18 SLE patients had confirmed ($n = 10$) or suspected COVID-19 ($n = 8$) infection. 89% females. Mean age, 41 years (SD 11). 50% Hispanic patients and 39% black patients. 61% had lupus nephritis. 15 received immunosuppressants, 7 received steroids and 13 received HCQ or CQ. Previous use of immunosuppressants before hospitalisation was not different between cases with mild and severe disease. 11 outpatients and 4 hospitalised patients improved without requiring supplemental oxygen. One patient with hypoxemic respiratory failure gradually improved while two patients remained critically ill	Small sample size
Gendebien et al., 2020	225 SLE patient	92.9% female. Mean age of 51.7 (SD, 14.9) years. Infection was confirmed or suspected in 18 (8.0%) patients. There was no correlation between immunosuppressive drugs and COVID-19 infection or symptoms, but glucocorticoid dose was positively related to infection (OR = 1.57, $p = 0.025$), hospitalisation (OR = 4.39, $p = 0.030$), anosmia and ageusia (OR = 1.57, $p = 0.025$) and diarrhoea (OR = 1.75, $p = 0.018$). HCQ was ineffective in prevention of COVID-19 infection or suspicion (7.9% for HCQ users, 8.2% for HCQ non-users, $p = 0.93$)	

(continued)

Table 1. (continued)

Author	Study details	Results and conclusions	Strengths and limitations
George et al., 2020	Adults from the US with RA, PsA, AS and SLE (n = 1517)	925 had RA, 299 had PsA, 185 had AS and 108 had SLE. Mean age (SD), 55.1 (11.7) years. 88.3% females. 89.5% White. Levels of COVID-19 concerns were high. Avoiding of physician's office visits, laboratory testing and other testing were reported by 56.6%, 42.3% and 36.0% of participants, respectively, with higher rates in participants with SLE (all $p < 0.05$)	
Gianfrancesco et al., 2020	Patients with COVID-19 and rheumatic disease (n = 600): 24 Mar 2020 to 20 Apr 2020	Median age, 56 years (IQR, 45–67 years). 71% females. 38% had RA, 14% had SLE and 12% had PsA. In unadjusted analyses, patients who were hospitalised had SLE (17%) were more than those who were not hospitalised (11%). Compared with RA, SLE was not related to COVID-19 hospitalisation status in unadjusted (OR = 1.51, 95%CI 0.91–2.49) and adjusted (OR = 1.80, 95%CI 0.99–3.29) logistic regression models	Large descriptive studies
Guyen et al., 2020	Case study	A case with SLE with COVID-19 suffered from leptomenigeal involvement	Small sample size
Han et al., 2020	Case study	SLE patients with the long-term intake of prednisone led to atypical infections, prolonged incubation periods and additional transmission of COVID-19	Small sample size
He et al., 2020	Case study	SLE patients with COVID-19 experienced a window period of asymptomatic infection after discharge	Small sample size
Holubar et al., 2020	All adult patients with SLE (n = 120) from Montpellier University Hospital between 1 Feb and 24 Apr	Thirty-six (30.0%) had symptoms of COVID-19. The rate of SLE patients with symptoms of infection was similar in HCQ users (6.9%) and HCQ non-users (6.3%)	
Kondo et al., 2020	Case study	A 58-year-old woman with SLE developed exacerbation of ITP triggered by COVID-19	Small sample size
Leung et al., 2020	Case study	A girl with SLE developed hyperpigmentation induced by HCQ	Small sample size
Mantovani Cardoso et al., 2020	Case study	An SLE female with COVID-19 developed antiphospholipid antibodies and multiple deep venous thrombosis	Small sample size
Mathian et al., 2020	COVID-19 patients with SLE under treatment with HCQ (n = 17): 29 Mar and 6 Apr	Median duration of HCQ therapy before COVID-19, 7.5 years (range, 0.5–29.8 years). Obesity (59%) and chronic kidney disease (47%) were frequently reported. 16 cases had quiescent SLE. 12 cases received prednisone and 7 received an immunosuppressant. The main symptoms were fever (100%), cough (82%), shortness of breath (82%), headache (59%), respiratory rate over 24 breaths per minute (53%), myalgia (47%) and diarrhoea (41%). Viral pneumonia occurred in 13 patients, of which 11 had respiratory failure and 5 had acute respiratory distress syndrome. Three cases had acute renal failure, with 2 cases needing haemodialysis. Median HCQ blood concentration in 8 cases was 648 ng/mL (range: 254–2095 ng/mL). Of 14 hospitalised cases, 7 were admitted to the ICU. 11 cases received oxygen therapy (5 nasal cannula, 1 high-flow nasal cannula and 5 invasive mechanical ventilation). One case required extracorporeal membrane oxygenation. 5 (36%) cases were discharged, 7 (50%) remained hospitalised and 2 (14%) died. HCQ lacked preventive effect on COVID-19 in SLE patients, at least serious COVID-19	Small sample size

(continued)

Table 1. (continued)

Author	Study details	Results and conclusions	Strengths and limitations
Montero et al., 2020	Patients with COVID-19 and underlying RMDs ($n = 62$): 4 Mar and 24 April 2020	Mean age, 60.9 years. 42% men. 32% had RA, 26% had SpA/PsA, 6% had other inflammatory, 15% had SLE and 21% had other CTD. Patients who died were older, most were males and had more comorbidities, mainly DM and hypertension. 10 (16%) patients died, 9 required hospitalisation: 3 had RA, 2 had SLE, 1 had SpA and 4 had other rheumatic diseases. No relationship was found between SLE and more serious infection requiring hospitalisation (OR = 0.94, 95%CI 0.21–4.24). 10 (16%) patients died: 3 with RA, 2 with SLE, 1 with SpA and 4 with other rheumatic diseases	Small number from a single centre
Ning et al., 2020	Case study	An SLE patient who took HCQ and prednisone was found to develop COVID-19 at the second visit, and was recovered from COVID-19 through intravenous immunoglobulin treatments and increased dose of corticosteroids	Small sample size
Pablos et al., 2020	Observational matched cohort study with hospital confirmed COVID-19 rheumatic patients with chronic IA or CTDs ($n = 228$) from 5 centres	65 (28.5%) patients had RA; 35 (15.4%) had PsA; 36 (15.8%) had SpA; 16 (7.0%) had SLE (Mean disease duration, 14.34 years [SD, 10.38]. 43.8% of the patients reported active rheumatic disease)	
Pablos et al., 2020	A retrospective study with patients from rheumatology departments in Spain	SLE patients ($n = 2253$; 77% females; median age of cases, 51 years [IQR, 42–66 years]) had a prevalence of 0.62% (95%CI 0.34%–1.04%)	Large sample size
Plüß et al., 2020	The current situation in SLE patients under the treatment of HCQ in Germany	369 responses were included. 94% women. Almost all (95.8%) of respondents believed HCQ essential for the disease management. 70% complained about the unavailability of medications; 8.8% reduced their daily dose. 86.6% believed no benefit regarding COVID-19, and half of the patients realised increased vulnerability due to SLE. About 45% had supply problems, 44.4% had no problems and 10% stockpiled HCQ beforehand	
Raghavan et al., 2020	Case study	A patient with COVID-19 triggered SLE flare	Small sample size
Ramirez et al., 2020	SLE patients ($n = 545$) from three referral centres. Data from the survey were in comparison with those from general population	A total of 417 (77%) responders. 91% females. Over 60% of patients complained of symptoms of COVID-19 (myalgia [31%], rhinorrhoea [25%], fever [17%] and dry cough [16%]). 1.20% of SLE patients had confirmed COVID-19, in contrast to a 0.73% prevalence in the general population. The hospitalisation rate of infected patients was 0.24%, while the general population had a rate of 0.43%. New-onset fever, anosmia, cough, a history of neuropsychiatric SLE and contacting with COVID-19 patients were related to COVID-19 infection, as well as symptoms and lower compliance to protection. HCQ was ineffective in prevention of COVID-19. 40 responders (10%) reduced or discontinued their drugs. The main cause was doctor's suggestions. Medication shortage was complained by 36% and 17% of patients who reduced or discontinued HCQ or immunosuppressants, with 75% of these patients attributing this event to the COVID-19 pandemic	Descriptive report from questionnaire findings

(continued)

Table 1. (continued)

Author	Study details	Results and conclusions	Strengths and limitations
Tee et al., 2020	Patients with RA ($n = 107$) and SLE ($n = 405$) from May 19 to 26, 2020	95.5% females. Around 20% underwent moderate or severe impacts of COVID-19 outbreak. The mean IES-R score was higher in SLE compared with RA respondents. Stress, anxiety and depression were moderate to severe in 12.3% (mean stress subscale score, 10.11 [SD = 7.95]), 38.7% (mean anxiety subscale score, 6.79 [SD = 6.57]) and 27.7% (mean depression subscale score, 9.03 [SD = 8.77]) of patients. The risk factors for poor mental health included the comorbidities of hypertension and asthma; becoming a healthcare professional; and the specific symptoms, while the protective factors involved satisfaction with existing health information and wearing a mask	
Teh et al., 2020	SLE patients with COVID-19 in Malaysia	There were five cases of SLE. Five were women. Mean age, 52.80 years (SD, 4.46). Mean disease duration, 13.20 years (SD, 3.92). All 5 cases received long-term treatment of HCQ. All patients had moderate to severe infection but were recovered well except one died patient. The authors concluded that background HCQ treatment for SLE patients was not effective for COVID-19 prevention. COVID-19 infection is likely to mimic SLE flare	Small sample size
Tiendrébéogo et al., 2020	Case study	Case 1 was diagnosed with SLE for 3 years. She was infected with COVID-19 in a consultation for headaches and arthromyalgia. Case 2 was an SLE patient with chronic renal failure and nephrotic syndrome. She had confirmed COVID-19 and was admitted to ICU. The authors concluded that SLE patients would be at risk of serious illness from infection, especially those with multivisceral SLE damage	Small sample size
Wallace et al., 2020	31 COVID-19 patients from University of Michigan rheumatology clinics between 1 Mar and 20 Apr 2020	Five had SLE, four of whom received HCQ with a median duration of 7 (rang, 6–8) years. SLE patients might develop more severe manifestations of COVID-19 infection	
Wańkiewicz et al., 2020	723 COVID-19 patients from 6 hospitals from 3 May 2020 to 17 May 2020	134 with SLE (88.81% females. Mean age, 38.34 [5.62] years old), 589 without SLE (46.69% females. Mean age, 39.71 [7.07] years old). COVID-19 patients with SLE had elevated symptoms of anxiety (OR = 3.683, 95%CI 2.271–5.974, $p < 0.001$), depression (OR = 4.183, 95%CI, 2.544–6.878, $p < 0.001$) and sleep disorders (OR = 6.781, 95%CI 2.968–15.492, $p < 0.001$)	
Wen et al., 2020	LE patients and RA patients from Wuhan Union Hospital between 22nd Mar and 25 Mar 2020	Of 338 patients diagnosed with LE/RA, 3 patients had severe COVID-19. Two SLE patients used HCQ were in a critical condition with COVID-19 and one RA patient without HCQ had severe pneumonia. One patient with SLE, concurrent with nephritis, died of respiratory failure due to infection. The attack rate in this study (3/338; 0.89%) appears to be higher than Wuhan's overall infection rate (50,340/10,000,000; 0.46%). The COVID-19 infection rate in the immunosuppressive medications users was similar to that in the immunosuppressive medication non-users ($p > 0.05$). Thirty-two RA/LE patients discontinued previous treatments and 46.9% of them suspended treatment because of city lockdown for COVID-19. Medication withdrawal positively correlated with worse LE or RA clinical outcomes (outcome score in discontinuation due to COVID-19 group vs. continuation group: 2.86 ± 1.12 vs 1.82 ± 0.96 ; $p < 0.001$). In the COVID-19 group, treatment was interrupted after 4 weeks to several months, and the authors speculated that long-term interruption of immunosuppressive therapy would worsen their clinical outcomes	Small sample size

(continued)

Table 1. (continued)

Author	Study details	Results and conclusions	Strengths and limitations
Widhani et al., 2020	Patients diagnosed with autoimmune disease ($n = 685$) from Apr to May 2020	Median age, 37 years old (IQR 29–45 years old). 93% females. Most of them had SLE (40.4%). Nearly all patients had great knowledge and practices about COVID-19. Adequacy of information (OR = 0.09, 95% CI 0.01–0.72) and steroid (OR = 0.29, 95% CI 0.11–0.76) or MMF/MPA use (OR = 15.68, 95% CI 1.93–127.31) were associated with cognition of the impact of pandemic on health. Visiting private clinic (OR = 0.45, 95% CI 0.26–0.78) and receiving HCQ/CQ sulfate (OR = 1.85, 95% CI 1.02–3.36) or sulfasalazine (OR = 8.94, 95% CI 1.07–74.87) were associated with concern that autoimmune conditions might make them more vulnerable to COVID-19. Work from home (OR = 2.61, 95% CI 1.06–6.45) was associated with concern that the symptoms would be more serious if infected with COVID-19. Living in Sumatra region (OR = 4.40, 95% CI 1.29–14.94) and getting HCQ/CQ sulfate (OR = 7.22, 95% CI 2.23–23.38) or MMF/MPA (OR = 5.66, 95% CI 1.86–17.23) were associated with perception that autoimmune drugs could prevent COVID-19. Adequate information (OR = 0.22, 95% CI 0.10–0.44), university education (OR = 0.60, 95% CI 0.38–0.95), private clinic visit (OR = 0.52, 95% CI 0.31–0.88) and HCQ/CQ sulfate use (OR = 1.99, 95% CI 1.32–3.01) were linked to perception of unavailability of medications during the pandemic	An online survey
Zen et al., 2020	Patients with ARD ($n = 916$) from Italy: Apr 9th and Apr 25th	397 had SLE (Mean age, 47.8 years [SD, 13.4]. 85.6% females. 84.8% remission. Prednisone > 7.5 mg/day [10.9%], mycophenolate [31.3%], antimalarial drugs [77%] and anti-BLYSS [11.8%] were mainly used. 18.9% has symptom compatible with COVID-19. The main signs and symptoms were fever > 37.5°C [10.1%], cough [10.8%] and sore throat [10.3%], 182 had AAV, 176 had SSc, 111 had RA and 50 had IIM. 65 (7.1%) received SARS-CoV-2 testing, 2 (0.21%) were positive: One had SLE and one had SSc. Drug discontinuation occurred in 13 (3.3%) SLE patients, and of 5 unremitted patients, 3 patients had nephritis	A telephone survey
Zurita et al., 2020	Case study	This case series reported 5 cases with COVID-19 who had used HCQ for SLE prior to infection, which suggested that HCQ lacked preventive effect on COVID-19 in SLE patients	Small sample size

SLE: Systemic lupus erythematosus; aPL: Antiphospholipid antibodies; COVID-19: Coronavirus disease 2019; RA: Rheumatoid arthritis; HCQ: Hydroxychloroquine; CQ: Chloroquine; SjS: Sjogren's syndrome; CVAEs: Cardiovascular adverse events; ICU: Intensive care unit; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; IMRD: Immune-mediated rheumatic disease; SSc: Systemic sclerosis; PR: Prevalence ratio; HR: Hazard ratio; APS, Antiphospholipid syndrome; bDMARDs, biological disease-modifying anti-rheumatic drugs; OR: Odds ratio; MMF: Mycophenolate mofetil; AIRD: autoimmune inflammatory rheumatic diseases; PsA: Psoriatic arthritis; AS: Ankylosing spondylitis; ITP: Immune thrombocytopenia; RMDs: Rheumatic and musculoskeletal diseases; SpA: Spondyloarthritis; DM: Diabetes mellitus; IA: Inflammatory arthritis; CTDs: Connective tissue diseases; IES-R: Impact of Events Scale-Revised; LE: Lupus erythematosus; MPA: Mycophenolic acid; ARD: autoimmune rheumatic diseases; Anti-BLYSS: anti-B lymphocytes stimulating factor; AAV: ANCA-associated vasculitis; IIM: Idiopathic inflammatory myopathies.

reported by SLE patients in our study. HCQ discontinuation or long-term dose reduction was always linked to increased risk of flare in SLE patients.^{65–67} Therefore, abrupt medication withdrawal must be assessed with caution based on infection risk and comorbidities of SLE patients.⁵⁹

In our study, HCQ was not effective in COVID-19 prevention in SLE patients. Similarly, data from completed studies and randomised controlled trials suggest that HCQ does not work.⁶⁸ Previous meta-analysis has proved that although HCQ treatment is safe, it could not decrease mortality or promote clinical/virological recovery in COVID-19 patients.⁶⁹ Whereas

the evidence supporting the HCQ treatment for COVID-19 is not clear, HCQ has shown great efficacy against immune-mediated diseases. Therefore, physicians and individuals should avoid misuse of HCQ for the prophylaxis of COVID-19.⁷⁰

SLE is related to high health-care costs and great loss of productivity.⁷¹ Patients with SLE have an average excess expenditure of more than \$30 per month on healthcare during the outbreak. Mental health problem was a concurrent epidemic of the pandemic.⁷² Mental problems were frequently reported during this period.⁷³ While anxiety, depression and economic stressors are common phenomena around the

world, specific behavioural responses are heavily influenced by government stances, misinformation, conspiratorialism and competing demands of resource scarcity.⁷⁴

Our systematic review has several limitations. First, assumptions on the COVID-19 in SLE patients were mostly based on small sample sizes and thus should be treated with reserve. Second, studies not published in English and not reporting clinical information were excluded, so some studies on the subject may not have been identified.

In conclusion, SLE patients experience a great physical toll and emotional distress during the COVID-19 pandemic. Adequate medical services, containment policies and social distancing measures were essential to limit the effect of COVID-19 on SLE patients. Psychological approaches were also required during this period.

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