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Impact of SARS-CoV-2 Infection on Patients With Systemic Lupus Erythematosus in England Prior to Vaccination: A Retrospective Observational Cohort Study

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ABSTRACT (300/300)

Objectives: Determine the pre-vaccination healthcare impact of COVID-19 in patients with systemic lupus erythematosus (SLE) in England

Design: Retrospective cohort study of adult patients with SLE from May 1–October 31, 2020.

Setting: Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics (HES) databases from general practitioners across England combining primary care and other health-related data.

Participants: Overall, 6145 adults with confirmed SLE diagnosis ≥1 year prior to May 1, 2020 were included. Most patients were female (91.0%), White (67.1%), and diagnosed with SLE at age <50 (70.8%). Patients were excluded if they had a COVID-19 diagnosis before May 1, 2020.

Primary and Secondary Outcome Measures: Demographics and clinical characteristics were compared. COVID-19 severity was determined by patient care required and procedure/diagnosis codes. COVID-19 cumulative incidence, hospitalization rates, lengths of stay, and mortality rates were determined and stratified by SLE and COVID-19 severity.

Results: Of 6145 patients, 3927 had mild, 1288 moderate, and 930 severe SLE at baseline. The majority of patients with moderate to severe SLE were on oral corticosteroids and antimalarial treatments. Overall, 54/6145 (0.88%) patients with SLE acquired COVID-19, with 45 classified as mild, 6 moderate, and 3 severe COVID-19. Cumulative incidence was higher in patients with severe SLE (1.4%) compared with patients classified as mild (0.8%) or moderate (0.8%). Ten COVID-19–specific hospital admissions occurred (n=6 moderate; n=4 severe). Regardless of COVID-19 status, hospital admission rates and length of stay increased with SLE severity. Of 54 patients with SLE diagnosed with COVID-19, 1 (1.9%) COVID-19–related death was recorded in a patient with both severe SLE and severe COVID-19.

Conclusions: There was no clear evidence that SLE severity impacted COVID-19 outcomes in this study. The COVID-19 pandemic is evolving and follow-up studies from different regions are needed to understand the relationship between COVID-19 and SLE.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study provided unique insight into the outcomes of COVID-19 for patients with SLE before the availability of COVID-19 vaccines.
- Due to the nature of a database study, there were limitations in the data captured in the system.
- The number of diagnosed COVID-19 cases was low in patients with SLE and the general population.
- The information about secondary care prescriptions in this population was limited.

INTRODUCTION

Since December 2019, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has caused significant morbidity and mortality worldwide, with over 6.6 million deaths as of December 2022.[1-3] Case fatality rate of SARS-CoV-2 infection is estimated by the World Health Organization, as of December 2022, to be 0.8% in the United Kingdom and 1.0% globally.[1] Case fatality rates can vary substantially according to viral strain and pathogenicity and across countries and patient subgroups,[4-9] with personal health status, including age and underlying diseases, significantly impacting the risk and prognosis of SARS-CoV-2 infection.[8] COVID-19 symptoms and disease state can vary in severity from mild flu-like symptoms to severe life-threatening disease,[10] with critical COVID-19 disease leading to acute respiratory distress syndrome, sepsis and septic shock, cardiac disease, and thromboembolic events such as pulmonary disease and multiple organ failure.[11, 12] Overall, the wide spectrum of symptoms and multi-system nature of this disease continues to make COVID-19 a global threat, especially to high-risk groups.[12]

Systemic lupus erythematosus (SLE) is a heterogenous, chronic, autoimmune disease that presents as a range of clinical manifestations across organ systems, with variable severity, disease course, and prognosis.[13] Both the innate and adaptive immune responses are dysregulated in patients with SLE,[14, 15] leading to the production of pathogenic auto-antibodies that cause inflammation and tissue damage.[16] SLE disease activity is controlled with immunosuppressive therapies;[13] therefore, patients may be more susceptible to infection. Both SLE disease activity and prolonged glucocorticoid use contribute towards progressive organ damage.[17-19]

SLE and COVID-19 are both complex, multi-system diseases, and it has been difficult to determine whether patients with SLE are more susceptible to SARS-CoV-2 infection or severe presentations of COVID-19. Additionally, there is no clear evidence if SLE treatments confer a protective or detrimental effect on SARS-CoV-2 infection in patients with SLE.[20] While standard therapies and organ damage may make patients with SLE more susceptible to severe COVID-19, it is unclear what the full extent of COVID-19 disease complications may be for patients with SLE.[21, 22]

Our study aimed to examine COVID-19 impact on adult patients with SLE in England from May 2020 to October 2020, prior to the start of the COVID-19 vaccination program and the emergence of key SARS-CoV-2 variants of concern, such as the delta variant. Data from the linked Clinical Practice Research Datalink (CPRD) Aurum, Hospital Episode Statistics (HES), and Office for National Statistics (ONS) death registry databases were used to determine the incidence of COVID-19 among patients with SLE, stratified by severity, and the demographic and clinical characteristics of patients with SLE who acquired COVID-19. We also determined hospitalization rate, length of stay, and mortality rate of patients with SLE, with and without COVID-19, stratified by both SLE and COVID-19 severity.

METHODS

Study Design

This was an observational, retrospective cohort study of adult patients with SLE in England between May 1, 2020 and October 31, 2020. This timeframe was selected because SARS-CoV-2 testing capabilities in England were expanded beyond testing critical key workers and patients with COVID-19 in April 2020[23] to allow testing of the broader general population. In early December 2020, vaccination against COVID-19 began in England,[24] and therefore the study cut-off date of October 31, 2020, was selected to avoid capturing the interaction of vaccinations among this high-risk, priority SLE population. A schematic of the study design is shown in **Figure 1**.

Datasets

The study used electronic medical record data from the Clinical Practice Research Datalink (CPRD) Aurum database, which collects de-identified patient data from a network of general practitioners across England and links primary care data to a range of other health-related data, providing a longitudinal health dataset broadly representative of geographical coverage, area-level deprivation, age, and sex in England. The CPRD Aurum database encompasses 60 million patient lives, with approximately 18 million patients currently registered.[25, 26] CPRD Aurum records were linked to the Hospital Episode Statistics (HES) database, which records complete, detailed, and reliable information on all inpatient admissions, outpatient appointments, and accident and emergency attendances in England.[25, 27] Relevant hospital admissions, including admission of patients with SLE who had COVID-19 as the primary diagnosis were identified. CPRD records were also linked to the Office for National Statistics (ONS) database, which

records annual mortality data registered by age, sex, and selected underlying cause of death.[28, 29] Further information regarding these datasets is shown in **Supplemental Table 1**.

Population

A flow chart describing patient selection procedures is shown in **Supplemental Figure 1**. Eligible patients were aged 18 years or older presenting at primary or secondary care with one or more diagnosis codes for SLE, determined by database codes in primary care, or an International Classification of Diseases (ICD-10) code in secondary care. The first recorded diagnosis (the index diagnosis) of SLE was required to be prior to May 1, 2019. SLE was confirmed by inclusion of at least one subsequent diagnosis of SLE following the index diagnosis. Patients were required to have valid data available beyond May 1, 2020.

Patients were excluded if they had drug-induced, cutaneous, or discoid lupus, or if they did not have a "definitive code" anywhere in their CPRD record or HES to confirm diagnosis. Patients were also excluded if a diagnosis of COVID-19 was recorded prior to the beginning of the study observation period on May 1, 2020.

Disease Severity Classifications

The main variables calculated for each patient were SLE severity, determined at the beginning of the observation period, and COVID-19 severity, where applicable.

SLE Disease Severity

SLE disease severity subgroups (severe, moderate, or mild) were determined based on published classification criteria.[30] Specifically, patients were classified as having severe SLE if they had a prescription of cyclophosphamide or rituximab or oral glucocorticoids at a dosage of ≥60 mg/day prednisone equivalent and had ≥1 ICD-10 code for diagnosis of severe renal,

cardiovascular, hepatic, gastrointestinal, neurological, ocular, or other comorbidities. Patients were classified as moderate SLE if they were prescribed immunosuppressants (excluding cyclophosphamide) or oral glucocorticoids at a dosage of 7.5 to <60 mg/day prednisone equivalent, and if they had ≥1 ICD-10 code for diagnosis of moderate renal, cardiovascular, hepatic, gastrointestinal, neurological, ocular, or other comorbidities. Patients whose SLE was not considered moderate or severe were defined as mild. SLE severity was evaluated from 12 months prior to study entry (May 1, 2019 to May 1, 2020), and the highest severity observed within this period was recorded.

COVID-19 Diagnosis and Severity

Diagnosis of COVID-19 was identified using CPRD database codes in primary care and the HES ICD-10 code in secondary care. Patients with a confirmed COVID-19 diagnosis were stratified based upon COVID-19 severity.

COVID-19 severity was determined using the following definitions: COVID-19 was deemed severe if, in the same admission as a new COVID-19 diagnosis or with COVID-19 in the primary diagnosis position, the patient required critical/intensive care in any episode during admission, and/or required mechanical ventilation (Office of Population Censuses and Surveys [OPCS]-4 procedure code), and/or experienced shock or sepsis (ICD-10 diagnosis codes), and/or experienced organ failure not previously coded (heart, lung, kidney, liver) (ICD-10 code). COVID-19 was deemed moderate if the patient was hospitalized with a new COVID-19 diagnosis but did not meet the severe criteria. COVID-19 was deemed mild if the patient had any new COVID-19 diagnoses outside of secondary care.

Study Outcomes

Outcomes were evaluated in all identified patients with SLE overall, and in mild, moderate, and severe SLE subgroups. The total number and cumulative incidence of COVID-19 infections per calendar month from May 1, 2020 to October 31, 2020, were calculated and stratified by COVID-19 severity. Patient demographics and clinical disease characteristics with respect to both SLE severity and COVID-19 severity were also compared.

Among patients with SLE who developed COVID-19, the following clinical outcomes were evaluated for each SLE subgroup and COVID-19 severity group: age at COVID-19 diagnosis, acute case fatality rate of COVID-19 (defined as a patient death within 28 days of an initial COVID-19 diagnosis and reported within the ONS death registry), COVID-19–specific hospitalization rate and length of stay, all-cause hospital admission rate per 1000 patients and lengths of stay (bed days) among COVID-19 severity groups, including those without a COVID-19 diagnosis, and number of patients with respiratory distress, organ failure, or pneumonia, and of patients requiring oxygen therapy or mechanical ventilation.

Statistical Analysis

This was a descriptive study and therefore no comparative statistical analyses were planned or performed. Descriptive statistics for the study population were calculated, including total numbers of patients, clinical and demographic profiles, and length of time patients with SLE were followed since diagnosis and inclusion within the study. Cumulative incidence of COVID-19 infections was determined monthly. Right censoring was used for patients who had no record of outcomes by the end of the 6-month study period. Left censoring was mitigated through record review for at least 10 years prior to the index date of May 1, 2020.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Demographics and Disease Characteristics of Patients With SLE

Overall, 6145 patients were included for analysis, with 3927 defined as having mild SLE, 1288 with moderate SLE, and 930 with severe SLE. Demographics and SLE disease characteristics at the index date, both overall and according to SLE disease severity, are shown in **Table 1**. The majority of patients with moderate to severe SLE were on oral corticosteroids and antimalarial therapy. A total of 4350/6145 (70.8%) patients were diagnosed with SLE at age <50 years, with a mean 42.2 years of age (standard deviation [SD] 14.2) at diagnosis. Mean age (SD) of diagnosis was similar across SLE disease severity subgroups, with 42.0 (13.9) years for mild, 41.7 (14.9) years for moderate, and 43.5 (14.7) years for severe SLE. The majority of patients were female (91.0%), and most patients were White (67.1%), with smaller proportions of patients of Black (11.7%) or Asian (10.2%) race. Overall, 80.0% of patients had a low Charlson comorbidity score (<2). The most prevalent comorbidities were hypertension (19.1%), asthma (17.9%), history of pneumonia (14.7%), and diabetes (12.4%).

Incidence of COVID-19 in Patients With SLE

From May 1, 2020 to October 31, 2020, 54 (0.88%) of the 6145 patients with SLE were diagnosed with COVID-19. Of these COVID-19 cases, 45 (83.3%) were classified as mild, 6 (11.1%) were moderate, and 3 (5.6%) were severe. Overall cumulative incidence of COVID-19 over the 6-month observation period and according SLE severity subgroup is shown in **Figure 2**. Cumulative incidence of total COVID-19 cases rose more steeply in patients with severe SLE compared with patients classified with mild or moderate SLE (**Figure 2**). This difference was driven predominantly by an increase in mild COVID-19 cases in patients with severe SLE.

Table 1 Demographics and disease characteristics at index of patients with SLE according to SLE severity

Characteristics	All patients with SLE, N=6145	SLE severity subgroup		
		Mild, n=3927	Moderate, n=1288	Severe, n=930
Age at SLE diagnosis, years, mean (SD)	42.2 (14.2)	42.0 (13.9)	42.4 (14.9)	43.5 (14.7)
Age group, n (%)				
18–29	1301 (21.2)	804 (20.5)	318 (24.7)	179 (19.2)
30–39	1557 (25.3)	1024 (26.1)	314 (24.4)	219 (23.5)
40–49	1492 (24.3)	984 (25.1)	283 (22.0)	225 (24.2)
50–59	1006 (16.4)	642 (16.3)	197 (15.3)	167 (18.0)
60+	789 (12.8)	473 (12.0)	176 (13.7)	140 (15.1)
Female, n (%)	5593 (91.0)	3598 (91.6)	1150 (89.3)	845 (90.9)
Race, n (%)				
White	4123 (67.1)	2647 (67.4)	856 (66.5)	620 (66.7)
Black	717 (11.7)	389 (9.9)	178 (13.8)	150 (16.1)
Asian	627 (10.2)	372 (9.5)	157 (12.2)	98 (10.5)
Mixed	119 (1.9)	81 (2.1)	18 (1.4)	20 (2.2)
Other	152 (2.5)	98 (2.5)	33 (2.6)	21 (2.3)
Unknown	407 (6.6)	340 (8.7)	46 (3.6)	21 (2.3)
BMI, kg/m², mean (SD)	26.3 (5.9)	26.0 (5.9)	26.4 (6.1)	27.0 (5.7)
Total time in cohort, patient days	1,104,535	706,175	230,998	167,362
Follow-up time, patient months, mean (SD)	5.99 (0.59)	5.99 (0.58)	5.98 (0.62)	6.00 (0.60)
Primary care prescriptions during the baseline period, n (%)[a]				
Oral corticosteroids	1951 (31.7)	449 (11.4)	1055 (81.9)	447 (48.1)
Other corticosteroids	711 (11.6)	399 (10.2)	168 (13.0)	144 (15.5)
Azathioprine	478 (7.8)	201 (5.1)	190 (14.8)	87 (9.4)

Cyclosporin	55 (0.9)	18 (0.5)	11 (0.9)	26 (2.8)
Methotrexate	435 (7.1)	199 (5.1)	108 (8.4)	128 (13.8)
Mycophenolate	449 (7.3)	172 (4.4)	183 (14.2)	94 (10.1)
Hydroxychloroquine/antimalarials	3248 (52.9)	1881 (47.9)	836 (64.9)	531 (57.1)
Charlson comorbidity score distribution, n (%)				
0	3009 (49.0)	2439 (62.1)	432 (33.5)	138 (14.8)
1	1906 (31.0)	1045 (26.6)	485 (37.7)	376 (40.4)
2	679 (11.0)	267 (6.8)	230 (17.9)	182 (19.6)
3	296 (4.8)	120 (3.1)	84 (6.5)	92 (9.9)
4+	255 (4.1)	56 (1.4)	57 (4.4)	142 (15.3)
Comorbidities, n (%)				
Hypertension	1172 (19.1)	514 (13.1)	318 (24.7)	340 (36.6)
Asthma	1101 (17.9)	608 (15.5)	294 (22.8)	199 (21.4)
Pneumonia (history)	902 (14.7)	396 (10.1)	255 (19.8)	251 (27.0)
Diabetes	764 (12.4)	390 (9.9)	201 (15.6)	173 (18.6)
Pleurisy	357 (5.8)	178 (4.5)	104 (8.1)	75 (8.1)
Obesity	356 (5.8)	191 (4.9)	84 (6.5)	81 (8.7)
Stroke (history)	306 (5.0)	153 (3.9)	65 (5.0)	88 (9.5)
Myocardial infarction (history)	219 (3.6)	95 (2.4)	65 (5.0)	59 (6.3)
ESRD or dialysis	89 (1.4)	19 (0.5)	23 (1.8)	47 (5.1)
Arterial/venous thrombosis	53 (0.9)	5 (0.1)	1 (0.1)	47 (5.1)
Nephritis	49 (0.8)	0	21 (1.6)	28 (3.0)
Hypercholesterolemia	44 (0.7)	21 (0.5)	9 (0.7)	14 (1.5)
Hemolytic anemia	21 (0.3)	1 (0.03)	11 (0.9)	9 (1.0)

[a]Secondary care prescribed medications are not reported.

BMI, body mass index; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; SD, standard deviation; SLE, systemic lupus erythematosus.

Demographics and disease characteristics of patients with and without COVID-19 are shown in **Table 2**. Compared with the 6091 patients with SLE without COVID-19, the 54 patients with COVID-19 were slightly older (mean age 45.2 vs 42.1 years), with similar body mass indices (mean 25.9 vs 26.3), and a similar proportion were female (92.6% vs 91.0%). A greater proportion of patients with versus without COVID-19 had a Charlson comorbidity score of ≥2 (33.3% vs 19.9%) and had comorbidities, including diabetes (24.1% vs 12.3%), hypertension (27.8% vs 19.0%), history of pneumonia (25.9% vs 14.6%), asthma (22.2% vs 17.9%), and history of myocardial infarction (11.1% vs 3.5%). Of the 54 patients diagnosed with COVID-19, 31 had mild, 10 had moderate, and 13 had severe SLE (**Table 2**).

There was a trend towards patients with severe SLE also having a severe COVID-19 diagnosis (patients with severe SLE made up 9/45 [20.0%] of mild, 2/6 [33.3%] of moderate, and 2/3 [66.7%] of severe COVID-19 cases); however, there were small numbers of patients who had severe COVID-19 (n=3) (**Supplemental Figure 2**).

Table 2 Demographics and disease characteristics at index of patients with SLE with and without COVID-19 diagnosis

Characteristics	Without COVID-19, n=6091	With COVID-19, n=54
SLE severity, n (%)		
Mild	3896 (64.0)	31 (57.4)
Moderate	1278 (21.0)	10 (18.5)
Severe	917 (15.1)	13 (24.1)
Age at SLE diagnosis, years, mean (SD)	42.1 (14.2)	45.2 (15.8)
Age group, n (%)		
18–29	1295 (21.3)	6 (11.1)
30–39	1540 (25.3)	17 (31.5)
40–49	1478 (24.3)	14 (25.9)
50–59	999 (16.4)	7 (13.0)
60+	779 (12.8)	10 (18.5)
Female, n (%)	5543 (91.0)	50 (92.6)
Race, n (%)		
White	4085 (67.1)	38 (70.4)
Black	710 (11.7)	7 (13.0)
Asian	620 (10.2)	7 (13.0)
Mixed	118 (1.9)	1 (1.9)
Other	152 (2.5)	0
Unknown	406 (6.7)	1 (1.9)
BMI, kg/m^2, mean (SD)	26.3 (5.9)	25.9 (6.1)
Total time in cohort, patient days	1,094,913	9,622
Follow-up time, patient months, mean (SD)	5.99 (0.59)	5.94 (0.84)
Primary care prescriptions during the baseline period, n (%)[a]		
Oral corticosteroids	1930 (31.7)	21 (38.9)

Other corticosteroids	707 (11.6)	4 (7.4)
Azathioprine	474 (7.8)	4 (7.4)
Cyclosporin	54 (0.9)	1 (1.9)
Methotrexate	433 (7.1)	2 (3.7)
Mycophenolate	448 (7.4)	1 (1.9)
Hydroxychloroquine/antimalarials	3224 (52.9)	24 (44.4)
Charlson comorbidity score distribution, n (%)		
0	2998 (49.1)	21 (38.9)
1	1891 (31.0)	15 (27.8)
2	672 (11.0)	7 (13.0)
3	292 (4.8)	4 (7.4)
4+	248 (4.1)	7 (13.0)
Comorbidities, n (%)		
Hypertension	1157 (19.0)	15 (27.8)
Asthma	1089 (17.9)	12 (22.2)
Pneumonia (history)	888 (14.6)	14 (25.9)
Diabetes	751 (12.3)	13 (24.1)
Pleurisy	355 (5.8)	2 (3.7)
Obesity	351 (5.8)	5 (9.3)
Stroke (history)	303 (5.0)	3 (5.6)
Myocardial infarction (history)	213 (3.5)	6 (11.1)
ESRD or dialysis	87 (1.4)	2 (3.7)
Arterial/venous thrombosis	52 (0.9)	1 (1.9)
Nephritis	49 (0.8)	0
Hypercholesterolemia	44 (0.7)	0
Hemolytic anemia	21 (0.3)	0

[a]Secondary care prescribed medications are not reported.

BMI, body mass index; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; SD, standard deviation; SLE, systemic lupus erythematosus.

Clinical Outcomes

A summary of clinical outcomes can be found in **Table 3**. The mean age (SD) at COVID-19 diagnosis was 55.8 (17.8) years overall for all patients with SLE, 53.7 (16.2) years in patients with mild SLE, 69.1 (18.9) years in patients with moderate SLE, and 54.1 (15.2) years in patients with severe SLE.

Hospitalizations

Among the 54 patients with SLE and COVID-19, 10 (18.5%) were recorded as having COVID-19–specific hospitalizations, as defined by diagnostic codes in the primary diagnostic position in the same admission as was documented in the HES database (**Table 3**). Of these hospitalizations, 6 were for moderate COVID-19 and 4 were for severe COVID-19. Of the 6 patients hospitalized with moderate COVID-19, 1 had mild, 3 had moderate, and 2 had severe SLE; the mean (SD) length of stay for these patients was 10.2 (6.2) days. Of the 4 patients hospitalized with severe COVID-19, 3 had severe SLE and 1 had mild SLE; the mean (SD) length of stay was 18.0 (18.0) days. In total, there were 2152 all-cause hospital admissions among the SLE cohort during the observation period, 96 of which occurred in patients diagnosed with COVID-19.

The all-cause hospital admission rate per 1000 patients increased with severity of SLE regardless of COVID-19 status (from 158 for mild SLE to 1125 for severe SLE in patients without COVID-19, and from 194 for mild SLE to 6385 for severe SLE in patients with COVID-19) (**Table 3**). The all-cause mean hospital length of stay also increased with severity of SLE regardless of COVID-19 status (from 3.0 days for mild SLE to 6.4 days for severe SLE in patients without COVID-19, and from 0.3 days for mild SLE to 16.0 days for severe SLE in patients with COVID-19) (**Table 3**).

Table 3 Clinical outcomes in patients with SLE with and without COVID-19 according to SLE severity

COVID-19	Without COVID-19				With COVID-19			
SLE Severity	**Total SLE, n=6091**	**Mild SLE, n=3896**	**Moderate SLE, n=1278**	**Severe SLE, n=917**	**Total SLE, n=54**	**Mild SLE, n=31**	**Moderate SLE, n=10**	**Severe SLE, n=13**
All-cause								
Hospital admissions, n	2056	615	409	1032	96	6	7	83
Admission rate per 1000 patients	338	158	320	1125	1778	194	700	6385
Length of stay, bed days, mean (SD)	4.6 (11.9)	3.0 (8.6)	5.3 (12.7)	6.4 (15.0)	12.8 (10.3)	0.3 (0.6)	17.3 (5.1)	16.0 (10.9)
Total number of deaths	45	14	19	12	2	1	0	1
COVID-19-specific								
Age at COVID-19 diagnosis, mean (SD)	-	-	-	-	55.8 (17.8)	53.7 (15.2)	69.1 (18.9)	54.1 (15.2)
COVID-19 severity, n (%)								
Mild	n/a	n/a	n/a	n/a	45 (83.3)	29 (93.5)	7 (70.0)	9 (69.2)
Moderate					6 (11.1)	1 (3.2)	3 (30.0)	2 (15.4)
Severe					3 (5.6)	1 (3.2)	0 (0)	2 (15.4)
Hospital admissions, n	-	-	-	-	10	2	3	5
Admission rate per 1000 patients	-	-	-	-	185	65	300	385
Length of stay, bed days, mean (SD)								

Overall	-	-	-	-	2.1 (6.4)	0.03 (0.2)	4.4 (7.4)	5.4 (10.7)
Moderate COVID-19[a]	-	-	-	-	10.2 (6.2)	-	-	-
Severe COVID-19[b]	-	-	-	-	18.0 (18.0)	-	-	-
Total number of deaths within 28 days of COVID-19 diagnosis	-	-	-	-	1	0	0	1
COVID-specific deaths (COVID-19 listed as primary cause of death)	1	0	1[c]	0	1	0	0	1
Acute COVID-19 case fatality rate per 1000 patients	-	-	-	-	19	0	0	77
COVID-19 outcomes and directed therapies, n (%)								
Organ failure	-	-	-	-	8 (14.8)	1 (3.2)	2 (20.0)	5 (38.5)
Pneumonia	-	-	-	-	7 (13.0)	1 (3.2)	3 (30.0)	3 (23.1)
Respiratory distress	-	-	-	-	1 (1.9)	0 (0)	1 (10.0)	0 (0)
Oxygen therapy	-	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)
Mechanical ventilation	-	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)

[a]Based on n=6 patients with SLE, diagnosed with moderate COVID-19.
[b]Based on n=1 patient with SLE, diagnosed with severe COVID-19.
[c]Patient did not have a hospital admission with COVID-19, but in the ONS data COVID-19 was listed on the death certificate. The diagnosis for this patient in HES was J18 (pneumonia, organism unspecified).

COVID-19, coronavirus disease 2019; HES, Hospital Episode Statistics; ONS, Office for National Statistics; SD, standard deviation; SLE, systemic lupus erythematosus.

Deaths

There were 45/6091 (0.74%) deaths among patients with SLE without a COVID-19 diagnosis and 2/54 (3.7%) deaths among patients with SLE who were diagnosed with COVID-19 (**Table 3**). Only 1 death was deemed related to COVID-19 and occurred in a 58-year-old female patient diagnosed with SLE at least 16 years prior, who was classified as having severe SLE. She received prescriptions of prednisone, methotrexate, and rituximab throughout her course as captured in the database. She had multiple comorbidities, including hypertension, chronic kidney disease (with a history of dialysis), obesity, depression, diabetes, and poor functional capacity. Her death occurred during an admission for COVID-19, and included critical care admission, mechanical ventilation for respiratory failure, dialysis for renal failure, and a secondary diagnosis of hospital-acquired pneumonia. The second death caused by acute myocardial infarction occurred in a patient classified with mild SLE and mild COVID-19. Overall, the acute COVID-19 case fatality rate was 19 per 1000 patients with SLE.

DISCUSSION

We retrospectively evaluated the incidence and outcomes of COVID-19 among a large SLE cohort in England prior to the advent of vaccination from May 1, 2020 to October 31, 2020. We found few cases of COVID-19 in this cohort over this time period, and among those, a small number were severe. Interestingly, the cumulative incidence of total COVID-19 cases appeared greater in patients with severe SLE as compared with mild or moderate SLE, although this was driven predominantly by mild COVID-19 cases.

The overall incidence of COVID-19 in patients with SLE during the 6-month observation period was low (0.88%), with the large majority (83.3%) of COVID-19 cases being of mild severity. In contrast, COVID-19 incidence in the general population from May 1, 2020 to October 31, 2020 in England was 1.3%.[31, 32] Low incidence of COVID-19 among patients with SLE could have been associated with low testing rates and underestimates during this timeframe[33] in combination with public health precautions used to prevent the spread of SARS-CoV-2. During the height of the COVID-19 pandemic, NHS was required to prioritize treatment of patients with COVID-19 in hospitals, which led to patients with SLE receiving care at home to a greater extent.[34, 35] This shift in SLE management may be reflected in the data here, perhaps leading to fewer SLE-related hospital admissions or more poorly controlled disease activity. Patients with SLE were also identified as high risk,[36] and NHS guidelines recommended patients to "shield" and take more extreme measures to prevent exposure to COVID-19;[34, 37] this may have contributed to the low COVID-19 incidence.

There were some differences between the demographic and clinical characteristics of patients with SLE who acquired COVID-19 and those who did not, including older age and the prevalence of comorbidities, including diabetes, hypertension, history of pneumonia, asthma, and

history of myocardial infarction, many of which are in line with previously identified risk factors in the non-SLE population.[38, 39] Overall, being diagnosed with COVID-19 at any severity was associated with an increased rate of subsequent all-cause hospitalization (1778 vs 338 per 1000 patients) at any time after COVID-19 diagnosis and prolonged length of stay in those subsequent all-cause admissions (mean stay 12.8 vs 4.6 days) compared with not having COVID-19; however, only 10 of the 2152 hospital admissions were deemed COVID-19 related. The mortality rate of COVID-19 in patients with SLE was low, and there was only one COVID-specific death, which occurred in a patient with severe SLE.

Limitations of this study include that it is a database study and, therefore, analyses are limited by the type of data and extent to which said data are captured in the system. For this reason, we likely underestimated the incidence of positive COVID-19 cases in both patients with SLE and the general population. There were significant limitations in capturing secondary care prescriptions in this dataset, resulting in limited numbers of biologic, cyclophosphamide, and glucocorticoid use and a possible underestimation of other SLE prescriptions. Sample size was also low due to the small number of diagnosed COVID-19 cases among these patients with SLE. Overall, the data used in this study represent a “snapshot” of time in the fast-moving landscape of the COVID-19 pandemic. This provided unique insight into this SLE population prior to the availability of COVID-19 vaccines and was both a strength and a limitation of the study.

Treatment recommendations and preventive strategies for COVID-19 have also been evolving quickly, making it challenging to evaluate the risk of SLE and its therapies alone in the absence of vaccination or native infection. The population included in this analysis were vaccine-naïve; however, since the study period (May 2020 to October 2020), a large-scale vaccination scheme has been introduced in the UK.[40] The start date was chosen due to the lack of widespread

community testing in the UK prior to this date. Inclusion of COVID-19 diagnoses prior to this date would capture only the most severe hospitalized cases, underestimating the true incidence and overestimating severity of infections within this time period. Patients with SLE were considered a high-risk group, and were eligible to receive their first COVID-19 vaccination in the UK from February 2021.[36] Findings of this study of vaccine-naïve patients with SLE may not be translatable to vaccinated patients with SLE as vaccines have changed the prognosis of COVID-19 in the UK,[24] but may be of interest in countries with lower vaccination rates and less controlled stages of the COVID-19 pandemic. Although small case numbers were identified, our study does not suggest that SLE disease necessarily increases the risk of severe COVID-19 disease. It does, however, suggest that patients with more severe SLE might be at higher risk for acquiring infection due to either their higher disease activity or therapy regimens[21] and will need further investigation. Additionally, it is known that different SARS-CoV-2 variants have differing virulence characteristics,[5, 41] which could be impacted by SLE-related disease or treatment factors and further influenced by primary immunity acquired from native SARS-CoV-2 infection or prior vaccination.[41, 42] Therefore, studies such as the one presented here provide an important evaluation of COVID-19 in a pre-vaccination population of patients with SLE for future analysis to build upon. Vaccination against COVID-19 is reported to be safe and efficacious in patients with SLE with minimal risk of flares, and continued analysis of COVID-19 vaccination data will be useful in understanding the long-term impact of vaccination in patients with SLE.[22, 43, 44]

CONCLUSIONS

In conclusion, this large retrospective cohort study of 6145 patients with SLE in England provided no clear evidence that SLE impacts SARS-CoV-2 infection, or that SLE severity

impacts COVID-19 outcomes. Results from this study provide a unique snapshot into the outcomes of COVID-19 for patients with SLE in England during the pre-vaccine phase of the pandemic, when government-imposed safety measures were in place. Given the evolving nature of the COVID-19 pandemic, including changes in safety measures, vaccination rates, diagnostic methods, and treatment options, as well as the infectiousness and pathogenicity of new SARS-CoV-2 variants, follow-up studies are needed to fully understand the impact of COVID-19 on patients with SLE in other geographic regions over a longer period of time.

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COMPETING INTERESTS

AR, **RK**, **RT**, and **HS**, are employees of and stockholders in AstraZeneca. **HS** is a stockholder of GlaxoSmithKline (GSK). **KW** has served as a consultant to AbbVie, AstraZeneca, Bristol Myers Squibb (BMS), Eli Lilly & Company, Galapagos, Gilead, GSK, Novartis, Pfizer, Roche, Regeneron, Sanofi, and Union Chimique Belge (UCB); and has received grant/research support from BMS and Pfizer.

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CONTRIBUTIONS

AR, WL, RK, RT, and **HS** designed the research study. **AR, WL** conducted the research. **AR, WL, RK, HS, and JW** performed the analysis. **AR, WL, RK, RT, HS, JW,** and **KW** contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript.

DATA SHARING STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Ethics

This study used data that existed in an anonymized, structured format that contained no personal patient information. The study protocol was reviewed and approved by CPRD's Independent Scientific Advisory Committee (application number 21_000327) on March 9, 2021.[45] Linkage of datasets was performed using anonymized and pseudonymized patient identification codes and was undertaken by NHS Digital, following study protocol approval.

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FIGURE LEGENDS

Figure 1 Schematic of study design and criteria for patient selection

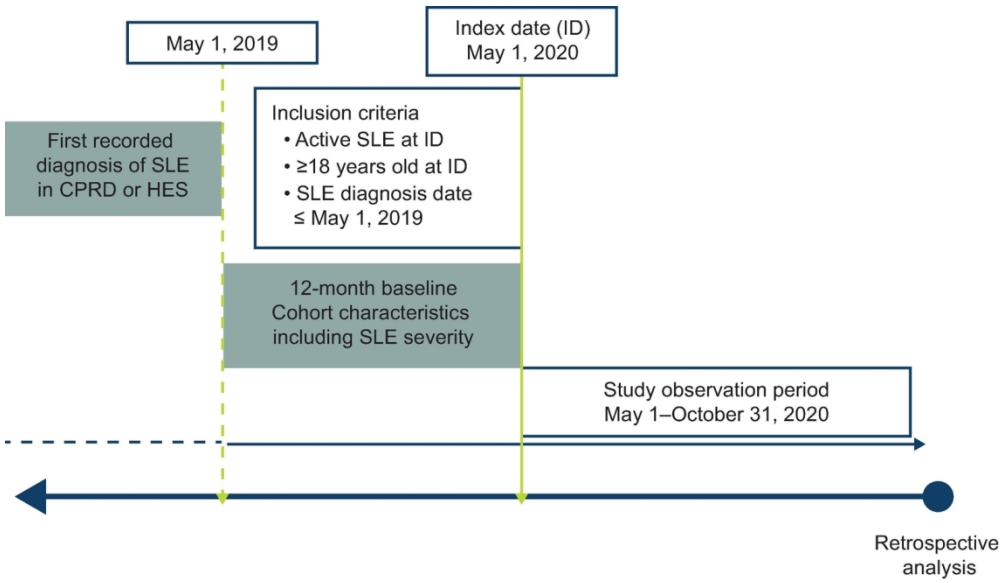
Patients were stratified by SLE severity within the 12-month baseline period (May 2019 to May 2020). All patients were required to have valid data to be considered for evaluation in the follow-up period and to be considered at-risk of COVID-19 within the study.

COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ID, index date; SLE, systemic lupus erythematosus.

Figure 2 Cumulative incidence of COVID-19 diagnoses over the 6-month evaluation period according to SLE severity

No comparative inferential statistical analyses were performed; cumulative incidence of COVID-19 diagnoses across SLE subgroups was evaluated with descriptive statistics only.

COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus.



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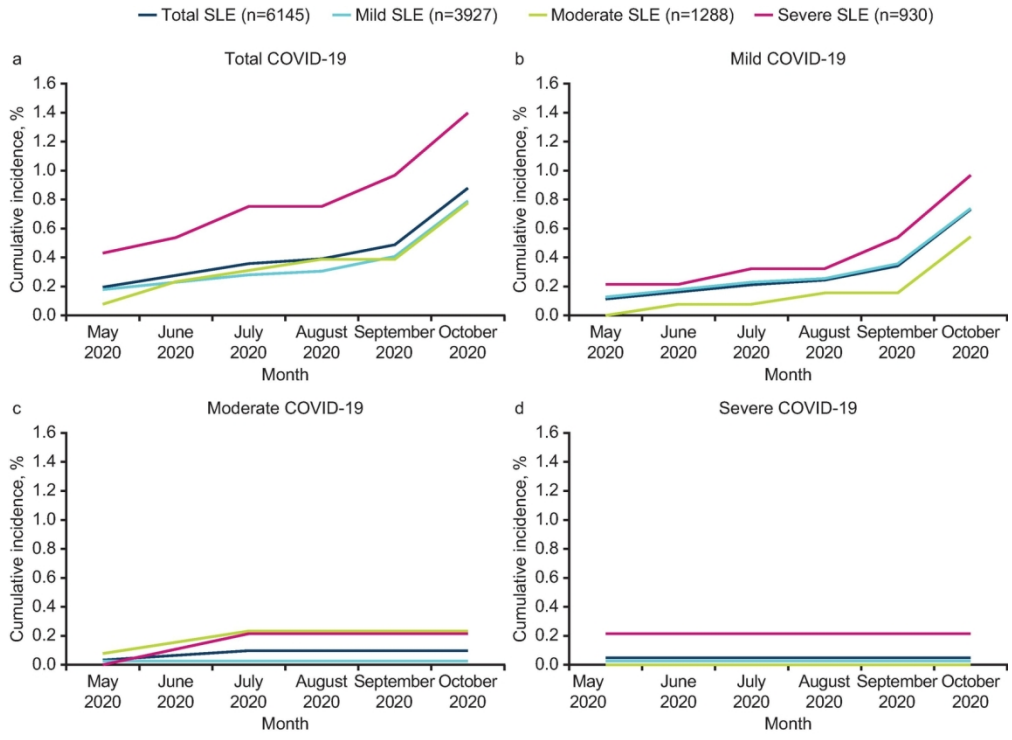
137x79mm (300 x 300 DPI)



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COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus.

143x104mm (300 x 300 DPI)

SUPPLEMENTARY MATERIAL FOR:

Impact of SARS-CoV-2 Infection on Patients With Systemic Lupus Erythematosus in England Prior to Vaccination: A Retrospective Observational Cohort Study

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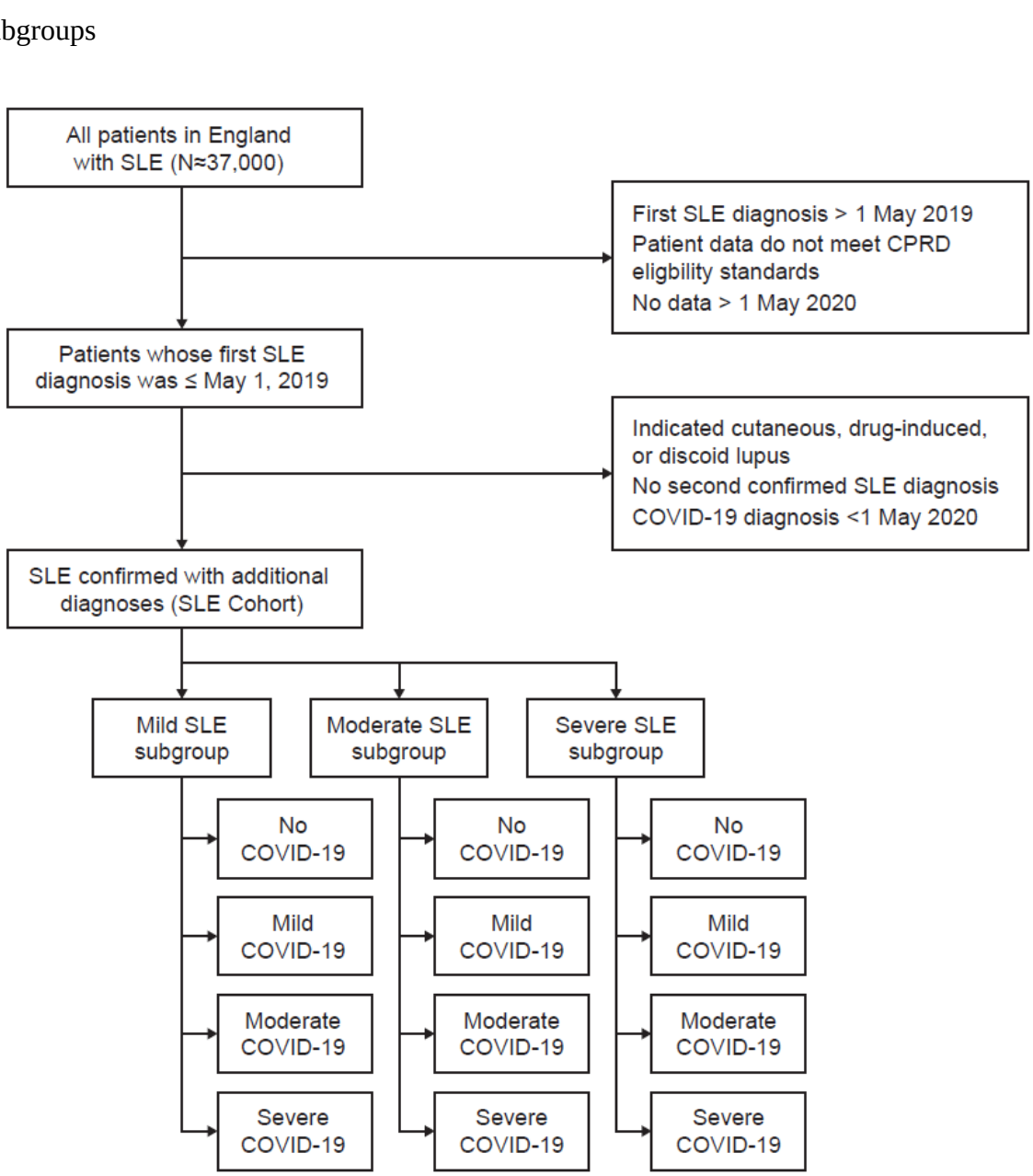
Supplemental Table 1 Summary table of the datasets used in the analysis

Dataset	Data Provider	Data
Hospital Episode Statistics (HES)	NHS Digital	Diagnoses, comorbidities, and complications
		Inpatient activity (admissions, procedures, bed days, readmissions, tariffs, specialities including CC)
		Outpatient activity (appointments, procedures, tariffs)
		A&E activity (attendances, interventions, tariffs)
		Healthcare Provider of Treatment and other interventions
		Geography of CCG
Clinical Practice Research Datalink Aurum Database (CPRD)	MHRA	Diagnoses, comorbidities, and complications
		Symptoms
		Diagnostic tests
		GP attendances
		Nursing visits and attendances
		Prescriptions, component medications (including brands where feasible)
		Pathway mapping in primary care
		Costs through PSSRU
Office of National Statistics	ONS	Cause of death
		Reported date of death

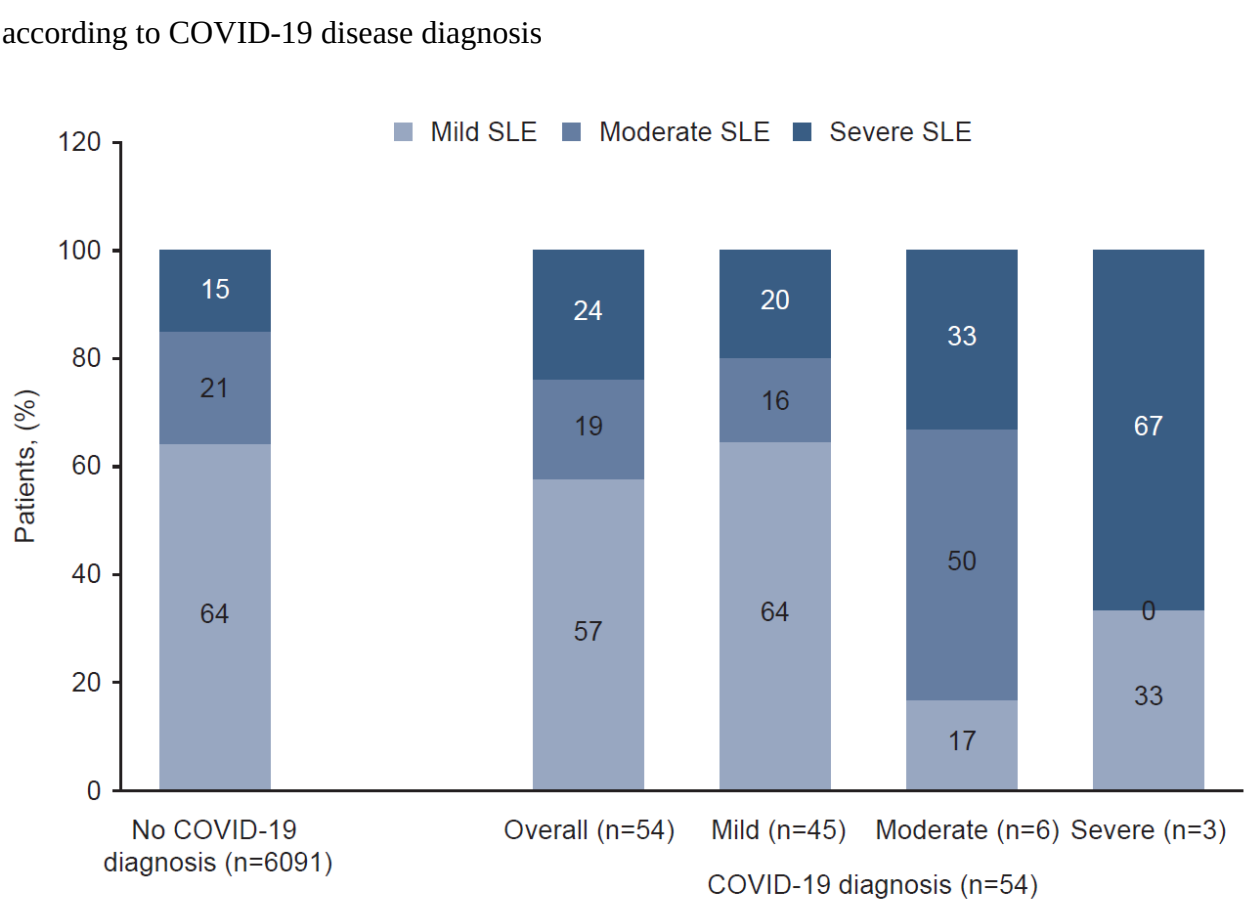
A&E, accident and emergency; CC, critical care; CCG, clinical commission groups; CPRD, Clinical Practice Research Database; HES, Hospital Episode Statistics; GP, general practitioner; MHRA, Medicines and Health Products Regulatory Agency; NHS, National Health Service; ONS, Office for National Statistics; PSSRU, Personal Social Security Services Research Unit.

Supplemental Figure 1 Flow diagram of patient identification for the final SLE cohort and subgroups



COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Database; SLE, systemic lupus erythematosus.

Supplemental Figure 2 Proportions of patients with mild, moderate, or severe SLE according to COVID-19 disease diagnosis



No comparative inferential statistical analyses were performed.

COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported (Page #)	RECORD items	Location in manuscript where items are reported (Page #)
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 2, 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	2 2 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6		
Objectives	3	State specific objectives, including any prespecified hypotheses	6		

Methods					
Study Design	4	Present key elements of study design early in the paper	7		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed	8 N/A	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	8 N/A 30 and Figure 1

		Case-control study - For matched studies, give matching criteria and the number of controls per case			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	8–10	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	8–10
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7–10		
Bias	9	Describe any efforts to address potential sources of bias	17, 18		
Study size	10	Explain how the study size was arrived at	N/A		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7–10		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10		

		(b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	7–10 17 N/A N/A		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	7 N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage	30

				and methods of linkage quality evaluation should be provided	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	12 N/A N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	12
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	12 N/A N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time	12–15		

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12–15 12–15 N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
Discussion					
Key results	18	Summarise key results with reference to study objectives	16, 17		
Limitations	19	Discuss limitations of the study, taking into account	17, 18	RECORD 19.1: Discuss the implications of using data that were	17, 18

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		sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19		
Generalisability	21	Discuss the generalisability (external validity) of the study results	18		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	20

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Impact of SARS-CoV-2 Infection on Patients With Systemic Lupus Erythematosus in England Prior to Vaccination: A Retrospective Observational Cohort Study

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Impact of SARS-CoV-2 Infection on Patients With Systemic Lupus Erythematosus in England Prior to Vaccination: A Retrospective Observational Cohort Study

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ABSTRACT (299/300)

Objectives: Determine the pre-vaccination healthcare impact of COVID-19 in patients with systemic lupus erythematosus (SLE) in England.

Design: Retrospective cohort study of adult patients with SLE from May 1–October 31, 2020.

Setting: Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics (HES) databases from general practitioners across England combining primary care and other health-related data.

Participants: Overall, 6145 adults with confirmed SLE diagnosis ≥1 year prior to May 1, 2020 were included. Most patients were female (91.0%), White (67.1%), and diagnosed with SLE at age <50 (70.8%). Patients were excluded if they had a COVID-19 diagnosis before May 1, 2020.

Primary and Secondary Outcome Measures: Demographics and clinical characteristics were compared. COVID-19 severity was determined by patient care required and procedure/diagnosis codes. COVID-19 cumulative incidence, hospitalization rates, lengths of stay, and mortality rates were determined and stratified by SLE and COVID-19 severity.

Results: Of 6145 patients, 3927 had mild, 1288 moderate, and 930 severe SLE at baseline. The majority of patients with moderate to severe SLE were on oral corticosteroids and antimalarial treatments. Overall, 54/6145 (0.88%) patients with SLE acquired and were diagnosed with COVID-19, with 45 classified as mild, 6 moderate, and 3 severe COVID-19. Cumulative incidence was higher in patients with severe SLE (1.4%) compared with patients classified as mild (0.8%) or moderate (0.8%). Ten COVID-19–specific hospital admissions occurred (n=6 moderate; n=4 severe). Regardless of COVID-19 status, hospital admission rates and length of stay increased with SLE severity. Of 54 patients with SLE diagnosed with COVID-19, 1 (1.9%) COVID-19–related death was recorded in a patient with both severe SLE and severe COVID-19.

Conclusions: SLE severity did not appear to impact COVID-19 outcomes in this study. The COVID-19 pandemic is evolving and follow-up studies are needed to understand the relationship between COVID-19 and SLE.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study provided unique insight into the outcomes of COVID-19 for patients with SLE before the availability of COVID-19 vaccines.
- Due to the nature of a database study, there were limitations in the data captured in the system.
- The number of diagnosed COVID-19 cases was low in patients with SLE.
- The information about secondary care prescriptions in this population was limited.

INTRODUCTION

Since December 2019, infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has caused significant morbidity and mortality worldwide, with over 6.6 million deaths as of December 2022.[1, 2] Case fatality rate of SARS-CoV-2 infection was estimated from data published by the World Health Organization, as of December 2022, to be 0.8% in the United Kingdom and 1.0% globally.[1] Case fatality rates can vary substantially according to viral strain and pathogenicity and across countries and patient subgroups,[3-8] with personal health status, including age and underlying diseases, significantly impacting the risk and prognosis of SARS-CoV-2 infection.[7] COVID-19 symptoms and disease state can vary in severity from mild flu-like symptoms to severe life-threatening disease,[9] with critical COVID-19 disease leading to acute respiratory distress syndrome, sepsis and septic shock, cardiac disease, and thromboembolic events such as pulmonary disease and multiple organ failure.[10, 11] Overall, the wide spectrum of symptoms and multi-system nature of this disease continues to make COVID-19 a global threat, especially to high-risk groups.[11, 12]

Systemic lupus erythematosus (SLE) is a heterogenous, chronic, autoimmune disease that presents as a range of clinical manifestations across organ systems, with variable severity, disease course, and prognosis.[13, 14] Both the innate and adaptive immune responses are dysregulated in patients with SLE,[14, 15] leading to the production of pathogenic auto-antibodies that cause inflammation and tissue damage.[16] SLE disease activity is commonly controlled with immunosuppressive therapies; therefore, patients may be more susceptible to infection.[13] Both SLE disease activity and prolonged glucocorticoid use contribute towards progressive organ damage.[17-19]

SLE and COVID-19 are both complex, multi-system diseases. During the early stages of the pandemic, the British Society for Rheumatology (BSR) classified SLE patients as at normal, moderate, or high risk of severe illness from COVID-19 depending on their disease symptoms and treatment;[20] however, it has been difficult to determine whether patients with SLE are more susceptible to SARS-CoV-2 infection or severe presentations of COVID-19. Additionally, there is limited evidence if SLE treatments confer a protective or detrimental effect on SARS-CoV-2 infection in patients with SLE.[21] While standard therapies and organ damage may make patients with SLE more susceptible to severe COVID-19, it is unclear what the full extent of COVID-19 disease complications may be for patients with SLE.[22, 23]

Our study aimed to examine COVID-19 impact on adult patients with SLE in England from May 2020 to October 2020, prior to the start of the COVID-19 vaccination program and the emergence of key SARS-CoV-2 variants of concern, such as the delta variant. Data from the linked Clinical Practice Research Datalink (CPRD) Aurum, Hospital Episode Statistics (HES), and Office for National Statistics (ONS) death registry databases were used to determine the incidence of COVID-19 among patients with SLE, stratified by severity, and the demographic and clinical characteristics of patients with SLE who were diagnosed with COVID-19. We also determined hospitalization rate, length of stay, and mortality rate of patients with SLE, with and without COVID-19, stratified by both SLE and COVID-19 severity.

METHODS

Study Design

This was an observational, retrospective cohort study of adult patients with SLE in England between May 1, 2020 and October 31, 2020. This timeframe was selected because SARS-CoV-2 testing capabilities in England were expanded beyond pilot testing of critical key workers and patients with COVID-19 in April 2020.[24] In early December 2020,[25] vaccination against COVID-19 began in England, and therefore the study cut-off date of October 31, 2020 was selected to avoid capturing the interaction of COVID-19 vaccinations with COVID-19 disease among the SLE population. A schematic of the study design is shown in **Figure 1**.

Datasets

The study used electronic medical record data from the CPRD Aurum database, which collects de-identified patient data from a network of general practitioners across England and links primary care data to a range of other health-related data, providing a longitudinal health dataset broadly representative of geographical coverage, area-level deprivation, age, and sex in England.[26] The CPRD Aurum database encompasses 60 million patient lives, with approximately 18 million patients currently registered.[27] CPRD Aurum records were linked to the HES database, which records information on inpatient admissions, outpatient appointments, and accident and emergency attendances in England.[26] Relevant hospital admissions, including admission of patients with SLE who had COVID-19 as the primary diagnosis were identified. CPRD records were also linked to the ONS database, which records annual mortality data registered by age, sex, and selected underlying cause of death.[28, 29] Consent for sharing patient data with CPRD Aurum was provided by clinical practices, with individual-level opt-out

choice offered and implemented upon request.[26] Further information regarding these datasets is shown in **Supplemental Table 1**.

Population

A flow chart describing patient selection procedures is shown in **Supplemental Figure 1**. Eligible patients were aged 18 years or older presenting at primary or secondary care with one or more diagnosis codes for SLE, determined by database codes in primary care, or an International Classification of Diseases (ICD-10) code in secondary care. The first recorded diagnosis (the index diagnosis) of SLE was required to be prior to May 1, 2019. SLE was confirmed by inclusion of at least one subsequent diagnosis of SLE following the index diagnosis. Patients were required to have valid data available beyond May 1, 2020.

Patients were excluded if they had drug-induced, cutaneous, or discoid lupus, or if they did not have a "definitive code" anywhere in their CPRD record or HES to confirm diagnosis. Patients were also excluded if a diagnosis of COVID-19 was recorded prior to the beginning of the study observation period on May 1, 2020.

Disease Severity Classifications

The main variables calculated for each patient were SLE severity, determined at the beginning of the observation period, and COVID-19 severity, where applicable.

SLE Disease Severity

SLE disease severity subgroups (severe, moderate, or mild) were determined based on published classification criteria,[30] previously used in a retrospective cohort analysis study in the UK.[31] Specifically, patients were classified as having severe SLE if they had a prescription of cyclophosphamide or rituximab or oral glucocorticoids at a dosage of ≥60 mg/day prednisone

equivalent and had ≥1 ICD-10 code for diagnosis of severe renal, cardiovascular, hepatic, gastrointestinal, neurological, ocular, or other comorbidities. Patients were classified as having moderate SLE if they were prescribed immunosuppressants (excluding cyclophosphamide) or oral glucocorticoids at a dosage of 7.5 to <60 mg/day prednisone equivalent, and if they had ≥1 ICD-10 code for diagnosis of moderate renal, cardiovascular, hepatic, gastrointestinal, neurological, ocular, or other comorbidities. Patients whose SLE was not considered moderate or severe were defined as mild. SLE severity was evaluated from 12 months prior to study entry (May 1, 2019 to May 1, 2020), and the highest severity observed within this period was recorded.

COVID-19 Diagnosis and Severity

Diagnosis of COVID-19 was identified using CPRD database codes in primary care and the HES ICD-10 code in secondary care. Patients with a confirmed COVID-19 diagnosis were stratified based upon COVID-19 severity.

COVID-19 severity was determined using the following definitions: COVID-19 was deemed severe if, in the same admission as a new COVID-19 diagnosis or with COVID-19 in the primary diagnosis position, the patient required critical/intensive care in any episode during admission, and/or required mechanical ventilation (Office of Population Censuses and Surveys [OPCS]-4 procedure code), and/or experienced shock or sepsis (ICD-10 diagnosis codes), and/or experienced organ failure not previously coded (heart, lung, kidney, liver) (ICD-10 code). COVID-19 was deemed moderate if the patient was hospitalized with a new COVID-19 diagnosis but did not meet the severe criteria. COVID-19 was deemed mild if the patient had any new COVID-19 diagnoses outside of secondary care.

Study Outcomes

Outcomes were evaluated in all identified patients with SLE overall, and in mild, moderate, and severe SLE subgroups. The total number and cumulative incidence of COVID-19 infections per calendar month from May 1, 2020 to October 31, 2020, were calculated and stratified by COVID-19 severity. Patient demographics and clinical disease characteristics with respect to both SLE severity and COVID-19 severity were also compared.

Among patients with SLE who developed COVID-19, the following clinical outcomes were evaluated for each SLE subgroup and COVID-19 severity group: age at COVID-19 diagnosis, acute case fatality rate of COVID-19 (defined as a patient death within 28 days of an initial COVID-19 diagnosis and reported within the ONS death registry over the total number of COVID-19 cases in the target population), COVID-19–specific hospitalization rate and length of stay, all-cause hospital admission rate per 1000 patients and lengths of stay (bed days) among COVID-19 severity groups, including those without a COVID-19 diagnosis, and number of patients with respiratory distress, organ failure, or pneumonia, and of patients requiring oxygen therapy or mechanical ventilation.

Statistical Analysis

This was a descriptive study and therefore no comparative statistical analyses were planned or performed. Descriptive statistics for the study population were calculated, including total numbers of patients, clinical and demographic profiles, and length of time patients with SLE were followed since diagnosis and inclusion within the study. Cumulative incidence of COVID-19 infections was determined monthly. Right censoring was used for patients who had no record of outcomes by the end of the 6-month study period. Left censoring was mitigated through record review for at least 10 years prior to the index date of May 1, 2020.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination of this research.

RESULTS

Demographics and Disease Characteristics of Patients With SLE

Overall, 6145 patients were included for analysis, with 3927 defined as having mild SLE, 1288 with moderate SLE, and 930 with severe SLE. Demographics and SLE disease characteristics at the index date, both overall and according to SLE disease severity, are shown in **Table 1**. The majority of patients with moderate to severe SLE were on oral corticosteroids and antimalarial therapy, according to primary care prescription data. A total of 4350/6145 (70.8%) patients were diagnosed with SLE at age <50 years, with a mean 42.2 years of age (standard deviation [SD] 14.2) at diagnosis. Mean age (SD) of diagnosis was similar across SLE disease severity subgroups, with 42.0 (13.9) years for mild, 41.7 (14.9) years for moderate, and 43.5 (14.7) years for severe SLE. The majority of patients were female (91.0%), and most patients were White (67.1%), with smaller proportions of patients of Black (11.7%) or Asian (10.2%) race. Overall, 80.0% of patients had a low Charlson comorbidity score (<2). The most prevalent comorbidities were hypertension (19.1%), asthma (17.9%), history of pneumonia (14.7%), and diabetes (12.4%).

Incidence of COVID-19 in Patients With SLE

From May 1, 2020 to October 31, 2020, 54 (0.88%) of the 6145 patients with SLE were diagnosed with COVID-19. Of these 54 cases, 45 (83.3%) were classified as mild COVID-19, 6 (11.1%) were moderate, and 3 (5.6%) were severe. Overall cumulative incidence of COVID-19 over the 6-month observation period and according to SLE severity subgroup is shown in **Figure 2**. Cumulative incidence of total COVID-19 cases rose more steeply in patients with severe SLE compared with patients classified with mild or moderate SLE (**Figure 2**). This difference was driven predominantly by an increase in mild COVID-19 cases in patients with severe SLE.

Table 1 Demographics and disease characteristics at index of patients with SLE according to SLE severity

Characteristics	All patients with SLE, N=6145	SLE severity subgroup		
		Mild, n=3927	Moderate, n=1288	Severe, n=930
Age at SLE diagnosis, years, mean (SD)	42.2 (14.2)	42.0 (13.9)	42.4 (14.9)	43.5 (14.7)
Age group, n (%)				
18–29	1301 (21.2)	804 (20.5)	318 (24.7)	179 (19.2)
30–39	1557 (25.3)	1024 (26.1)	314 (24.4)	219 (23.5)
40–49	1492 (24.3)	984 (25.1)	283 (22.0)	225 (24.2)
50–59	1006 (16.4)	642 (16.3)	197 (15.3)	167 (18.0)
60+	789 (12.8)	473 (12.0)	176 (13.7)	140 (15.1)
Female, n (%)	5593 (91.0)	3598 (91.6)	1150 (89.3)	845 (90.9)
Race, n (%)				
White	4123 (67.1)	2647 (67.4)	856 (66.5)	620 (66.7)
Black	717 (11.7)	389 (9.9)	178 (13.8)	150 (16.1)
Asian	627 (10.2)	372 (9.5)	157 (12.2)	98 (10.5)
Mixed	119 (1.9)	81 (2.1)	18 (1.4)	20 (2.2)
Other	152 (2.5)	98 (2.5)	33 (2.6)	21 (2.3)
Unknown	407 (6.6)	340 (8.7)	46 (3.6)	21 (2.3)
BMI, kg/m², mean (SD)	26.3 (5.9)	26.0 (5.9)	26.4 (6.1)	27.0 (5.7)
Total time in cohort, patient days	1,104,535	706,175	230,998	167,362
Follow-up time, patient months, mean (SD)	5.99 (0.59)	5.99 (0.58)	5.98 (0.62)	6.00 (0.60)
Primary care prescriptions during the baseline period, n (%)[a]				
Oral corticosteroids	1951 (31.7)	449 (11.4)	1055 (81.9)	447 (48.1)
Other corticosteroids	711 (11.6)	399 (10.2)	168 (13.0)	144 (15.5)
Azathioprine	478 (7.8)	201 (5.1)	190 (14.8)	87 (9.4)

Cyclosporin	55 (0.9)	18 (0.5)	11 (0.9)	26 (2.8)
Methotrexate	435 (7.1)	199 (5.1)	108 (8.4)	128 (13.8)
Mycophenolate	449 (7.3)	172 (4.4)	183 (14.2)	94 (10.1)
Hydroxychloroquine/antimalarials	3248 (52.9)	1881 (47.9)	836 (64.9)	531 (57.1)
Charlson comorbidity score distribution, n (%)				
0	3009 (49.0)	2439 (62.1)	432 (33.5)	138 (14.8)
1	1906 (31.0)	1045 (26.6)	485 (37.7)	376 (40.4)
2	679 (11.0)	267 (6.8)	230 (17.9)	182 (19.6)
3	296 (4.8)	120 (3.1)	84 (6.5)	92 (9.9)
4+	255 (4.1)	56 (1.4)	57 (4.4)	142 (15.3)
Comorbidities, n (%)				
Hypertension	1172 (19.1)	514 (13.1)	318 (24.7)	340 (36.6)
Asthma	1101 (17.9)	608 (15.5)	294 (22.8)	199 (21.4)
Pneumonia (history)	902 (14.7)	396 (10.1)	255 (19.8)	251 (27.0)
Diabetes	764 (12.4)	390 (9.9)	201 (15.6)	173 (18.6)
Pleurisy	357 (5.8)	178 (4.5)	104 (8.1)	75 (8.1)
Obesity	356 (5.8)	191 (4.9)	84 (6.5)	81 (8.7)
Stroke (history)	306 (5.0)	153 (3.9)	65 (5.0)	88 (9.5)
Myocardial infarction (history)	219 (3.6)	95 (2.4)	65 (5.0)	59 (6.3)
ESRD or dialysis	89 (1.4)	19 (0.5)	23 (1.8)	47 (5.1)
Arterial/venous thrombosis	53 (0.9)	5 (0.1)	1 (0.1)	47 (5.1)
Nephritis	49 (0.8)	0	21 (1.6)	28 (3.0)
Hypercholesterolemia	44 (0.7)	21 (0.5)	9 (0.7)	14 (1.5)
Hemolytic anemia	21 (0.3)	1 (0.03)	11 (0.9)	9 (1.0)

[a]Secondary care prescribed medications are not reported.

BMI, body mass index; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; SD, standard deviation; SLE, systemic lupus erythematosus.

Demographics and disease characteristics of patients with and without COVID-19 are shown in **Table 2**. Compared with the 6091 patients with SLE without COVID-19, the 54 patients with COVID-19 were slightly older (mean age 45.2 vs 42.1 years), with similar body mass indices (mean 25.9 vs 26.3), and a similar proportion were female (92.6% vs 91.0%). A greater proportion of patients with versus without COVID-19 had a Charlson comorbidity score of ≥2 (33.3% vs 19.9%) and had comorbidities, including diabetes (24.1% vs 12.3%), hypertension (27.8% vs 19.0%), history of pneumonia (25.9% vs 14.6%), asthma (22.2% vs 17.9%), and history of myocardial infarction (11.1% vs 3.5%). Of the 54 patients diagnosed with COVID-19, 31 had mild, 10 had moderate, and 13 had severe SLE (**Table 2**).

There was a trend towards patients with severe SLE also having a severe COVID-19 diagnosis (patients with severe SLE made up 9/45 [20.0%] of mild, 2/6 [33.3%] of moderate, and 2/3 [66.7%] of severe COVID-19 cases); however, there were small numbers of patients who had severe COVID-19 (n=3) (**Supplemental Figure 2**).

Table 2 Demographics and disease characteristics at index of patients with SLE with and without COVID-19 diagnosis

Characteristics	Without COVID-19, n=6091	With COVID-19, n=54
SLE severity, n (%)		
Mild	3896 (64.0)	31 (57.4)
Moderate	1278 (21.0)	10 (18.5)
Severe	917 (15.1)	13 (24.1)
Age at SLE diagnosis, years, mean (SD)	42.1 (14.2)	45.2 (15.8)
Age group, n (%)		
18–29	1295 (21.3)	6 (11.1)
30–39	1540 (25.3)	17 (31.5)
40–49	1478 (24.3)	14 (25.9)
50–59	999 (16.4)	7 (13.0)
60+	779 (12.8)	10 (18.5)
Female, n (%)	5543 (91.0)	50 (92.6)
Race, n (%)		
White	4085 (67.1)	38 (70.4)
Black	710 (11.7)	7 (13.0)
Asian	620 (10.2)	7 (13.0)
Mixed	118 (1.9)	1 (1.9)
Other	152 (2.5)	0
Unknown	406 (6.7)	1 (1.9)
BMI, kg/m^2, mean (SD)	26.3 (5.9)	25.9 (6.1)
Total time in cohort, patient days	1,094,913	9,622
Follow-up time, patient months, mean (SD)	5.99 (0.59)	5.94 (0.84)
Primary care prescriptions during the baseline period, n (%)[a]		
Oral corticosteroids	1930 (31.7)	21 (38.9)

Other corticosteroids	707 (11.6)	4 (7.4)
Azathioprine	474 (7.8)	4 (7.4)
Cyclosporin	54 (0.9)	1 (1.9)
Methotrexate	433 (7.1)	2 (3.7)
Mycophenolate	448 (7.4)	1 (1.9)
Hydroxychloroquine/antimalarials	3224 (52.9)	24 (44.4)
Charlson comorbidity score distribution, n (%)		
0	2998 (49.1)	21 (38.9)
1	1891 (31.0)	15 (27.8)
2	672 (11.0)	7 (13.0)
3	292 (4.8)	4 (7.4)
4+	248 (4.1)	7 (13.0)
Comorbidities, n (%)		
Hypertension	1157 (19.0)	15 (27.8)
Asthma	1089 (17.9)	12 (22.2)
Pneumonia (history)	888 (14.6)	14 (25.9)
Diabetes	751 (12.3)	13 (24.1)
Pleurisy	355 (5.8)	2 (3.7)
Obesity	351 (5.8)	5 (9.3)
Stroke (history)	303 (5.0)	3 (5.6)
Myocardial infarction (history)	213 (3.5)	6 (11.1)
ESRD or dialysis	87 (1.4)	2 (3.7)
Arterial/venous thrombosis	52 (0.9)	1 (1.9)
Nephritis	49 (0.8)	0
Hypercholesterolemia	44 (0.7)	0
Hemolytic anemia	21 (0.3)	0

[a]Secondary care prescribed medications are not reported.

BMI, body mass index; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease; SD, standard deviation; SLE, systemic lupus erythematosus.

Clinical Outcomes

A summary of clinical outcomes can be found in **Table 3**. The mean age (SD) at COVID-19 diagnosis was 55.8 (17.8) years overall for all patients with SLE, 53.7 (16.2) years in patients with mild SLE, 69.1 (18.9) years in patients with moderate SLE, and 54.1 (15.2) years in patients with severe SLE.

Hospitalizations

Among the 54 patients with SLE and COVID-19, there were 10 recorded COVID-19–specific hospitalizations, as defined by diagnostic codes in the primary diagnostic position in the same admission as was documented in the HES database (**Table 3**). Note that one patient can be hospitalized multiple times. Of these hospitalizations, 6 were for moderate COVID-19 (6 patients) and 4 were for severe COVID-19 (3 patients). Of the 6 patients hospitalized with moderate COVID-19, 1 had mild, 3 had moderate, and 2 had severe SLE; the mean (SD) length of stay for these patients was 10.2 (6.2) days. Of the 3 patients hospitalized with severe COVID-19, one patient with severe SLE was hospitalized once, one patient with severe SLE was hospitalized twice, and one patient with mild SLE was hospitalized once;; the mean (SD) length of stay was 18.0 (18.0) days. In total, there were 2152 all-cause hospital admissions among the SLE cohort during the observation period, 96 of which occurred in patients diagnosed with COVID-19.

The all-cause hospital admission rate per 1000 patients increased with severity of SLE regardless of COVID-19 status (from 158 for mild SLE to 1125 for severe SLE in patients without COVID-19, and from 194 for mild SLE to 6385 for severe SLE in patients with COVID-19) (**Table 3**). The all-cause mean hospital length of stay also increased with severity of SLE regardless of COVID-19 status (from 3.0 days for mild SLE to 6.4 days for severe SLE in patients without

COVID-19, and from 0.3 days for mild SLE to 16.0 days for severe SLE in patients with COVID-19) (**Table 3**).

Table 3 Clinical outcomes in patients with SLE with and without COVID-19 according to SLE severity

COVID-19	Without COVID-19				With COVID-19			
SLE Severity	**Total SLE, n=6091**	**Mild SLE, n=3896**	**Moderate SLE, n=1278**	**Severe SLE, n=917**	**Total SLE, n=54**	**Mild SLE, n=31**	**Moderate SLE, n=10**	**Severe SLE, n=13**
All-cause								
Hospital admissions, n	2056	615	409	1032	96	6	7	83
Admission rate per 1000 patients	338	158	320	1125	1778	194	700	6385
Length of stay, bed days, mean (SD)	4.6 (11.9)	3.0 (8.6)	5.3 (12.7)	6.4 (15.0)	12.8 (10.3)	0.3 (0.6)	17.3 (5.1)	16.0 (10.9)
Total number of deaths	45	14	19	12	2	1	0	1
COVID-19-specific								
Age at COVID-19 diagnosis, mean (SD)	-	-	-	-	55.8 (17.8)	53.7 (15.2)	69.1 (18.9)	54.1 (15.2)
COVID-19 severity, n (%)								
Mild	n/a	n/a	n/a	n/a	45 (83.3)	29 (93.5)	7 (70.0)	9 (69.2)
Moderate					6 (11.1)	1 (3.2)	3 (30.0)	2 (15.4)
Severe					3 (5.6)	1 (3.2)	0 (0)	2 (15.4)
Hospital admissions, n	-	-	-	-	10	2	3	5
Admission rate per 1000 patients	-	-	-	-	185	65	300	385
Length of stay, bed days, mean (SD)								

Overall	-	-	-	-	2.1 (6.4)	0.03 (0.2)	4.4 (7.4)	5.4 (10.7)
Moderate COVID-19[a]	-	-	-	-	10.2 (6.2)	-	-	-
Severe COVID-19[b]	-	-	-	-	18.0 (18.0)	-	-	-
Total number of deaths within 28 days of COVID-19 diagnosis	-	-	-	-	1	0	0	1
COVID-specific deaths (COVID-19 listed as primary cause of death)	1	0	1[c]	0	1	0	0	1
Acute COVID-19 case fatality rate per 1000 patients	-	-	-	-	19	0	0	77
COVID-19 outcomes and directed therapies, n (%)								
Organ failure	-	-	-	-	8 (14.8)	1 (3.2)	2 (20.0)	5 (38.5)
Pneumonia	-	-	-	-	7 (13.0)	1 (3.2)	3 (30.0)	3 (23.1)
Respiratory distress	-	-	-	-	1 (1.9)	0 (0)	1 (10.0)	0 (0)
Oxygen therapy	-	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)
Mechanical ventilation	-	-	-	-	0 (0)	0 (0)	0 (0)	0 (0)

[a]Based on n=6 patients with SLE, diagnosed with moderate COVID-19.
[b]Based on n=1 patient with SLE, diagnosed with severe COVID-19.
[c]Patient did not have a hospital admission with COVID-19, but in the ONS data COVID-19 was listed on the death certificate. The diagnosis for this patient in HES was J18 (pneumonia, organism unspecified).

COVID-19, coronavirus disease 2019; HES, Hospital Episode Statistics; ONS, Office for National Statistics; SD, standard deviation; SLE, systemic lupus erythematosus.

Deaths

There were 45/6091 (0.74%) deaths among patients with SLE without a COVID-19 diagnosis and 2/54 (3.7%) deaths among patients with SLE who were diagnosed with COVID-19 (**Table 3**). Only 1 death was deemed related to COVID-19 and occurred in a patient diagnosed with SLE more than 10 years prior to this study, who was classified as having severe SLE and had multiple additional comorbidities. During this period, the patient received prescriptions of prednisone, methotrexate, and rituximab. Death occurred during an admission for COVID-19. The second death caused by acute myocardial infarction occurred in a patient classified with mild SLE and mild COVID-19. Overall, the acute COVID-19 case fatality rate was 19 per 1000 patients with SLE.

DISCUSSION

We retrospectively evaluated the incidence and outcomes of COVID-19 among a large SLE cohort in England prior to the advent of vaccination from May 1, 2020 to October 31, 2020. We found few cases of COVID-19 in this cohort over this time period, and among those, a small number were severe. Interestingly, the cumulative incidence of total COVID-19 cases appeared greater in patients with severe SLE as compared with mild or moderate SLE, although this was driven predominantly by mild COVID-19 cases.

The overall incidence of COVID-19 in patients with SLE during the 6-month observation period was low (0.9%). In the general population, COVID-19 incidence from May 1, 2020 to October 31, 2020 in England was approximately 1.3%.[32, 33]. Low incidence of COVID-19 among patients with SLE could have been due to low testing rates leading to underestimates of infection rates during this timeframe in combination with public health precautions used to prevent the spread of SARS-CoV-2.[34, 35]

Our study identified some differences between the demographic and clinical characteristics of patients with SLE who were diagnosed with COVID-19 and those who were not, including older age and the prevalence of comorbidities (diabetes, hypertension, history of pneumonia, asthma, and history of myocardial infarction). The demographic and clinical differences were in line with previously identified risk factors for severe COVID-19 disease outcomes in the non-SLE population.[12, 36] Although, to our knowledge, studies linking SLE disease activity and susceptibility for being infected with SARS-CoV-2 have not yet been published, previous studies have shown an association between SLE severity and developing severe COVID-19.[23] Furthermore, SLE disease activity has been previously identified as a risk factor for serious non-

SARS-CoV-2 infections (eg, urinary tract infection, lower respiratory tract infection) and, conversely, attainment of low disease activity state was protective against serious infections.[37]

The BSR consider patients with SLE as at high risk of developing severe COVID-19 disease if they have poorly controlled disease/recent flares, are receiving high dosages of glucocorticoids or are receiving certain immunosuppressive drugs.[20] Patients classified as having severe SLE in this study would have been categorized as high risk during the pandemic, and therefore would have been advised by the NHS to "shield" and be less exposed to COVID-19 infection.[20, 38] Our findings suggest that this shielding did not completely circumvent the potentially increased COVID-19 infection risk for some SLE patients. Notably, testing was not available for the general population in England until 2021.[39] It would be difficult to extrapolate on the prioritization of SLE patients in terms of COVID-19 testing. However, for patients to receive care in hospitals, a test would have been required.[40] Thus, in line with the objective of this study to examine the healthcare impact of COVID-19 in patients with SLE, COVID-19 testing would have been an assumed step for hospitalized patients based on NHS guidance at the time,[40] and was captured in our dataset.

During the height of the COVID-19 pandemic, the NHS prioritized treatment of patients with COVID-19 in hospitals, which led to patients with SLE receiving more care at home through phone consultations.[41, 42] This shift in SLE management may have led to prioritized hospital admissions for patients with SLE following a COVID-19 diagnosis. In this study, being diagnosed with COVID-19 at any severity was associated with an increased rate of subsequent all-cause hospitalization at any time after COVID-19 diagnosis and prolonged length of stay in those admissions compared with not having COVID-19; however, only 10 of the 2152 hospital admissions were deemed COVID-19 related. The mortality rate of COVID-19 in patients with

SLE was low, and there was only one COVID-specific death, which occurred in a patient with severe SLE.

Study limitations include that this is a database study and, therefore, analyses are limited by the type of data and extent to which said data are captured in the system. As such, we likely underestimated the incidence of positive COVID-19 cases in patients with SLE. There may have been a selection bias for patients who had valid data available beyond May 1, 2020, as individuals who acquired COVID-19 prior to this date and died were not included. Deaths, hospitalizations, and diagnosis outside of England were also not captured in our dataset. These limitations are partially alleviated by the inclusion of a large number of patients with SLE in this study who were previously deemed to be representative of the UK population (>6100 patients out of an eligible >7700 patients).[43, 44] Although the CPRD Aurum database covers 16.45% of practices in the UK,[45] SLE is usually diagnosed by a rheumatologist or other specialists rather than in primary care.[46] Furthermore, only 2.7% of all patients opted-out from sharing their clinical data for research purposes by September 2020.[47] The use of HES to search for SLE diagnosis likely also provided a reliable picture of SLE incidence in hospitalized patients in England.

Additional limitations include that SLE severity classification criteria used in this study did not include detailed SLE severity classification, and was instead based on patients' prescribed medication and recorded ICD-10 codes for various comorbidities, which are challenging to capture completely in healthcare databases. There were significant limitations in capturing secondary care prescriptions in this dataset, resulting in limited numbers of biologic, cyclophosphamide, and glucocorticoid use and a possible underestimation of other SLE prescriptions. Patients were classified as having mild, moderate, or severe SLE; however, a

dichotomous classification comparing mild to moderate/severe disease may better capture clinically relevant disease activity in this heterogenous condition.[48] Furthermore, SLE severity was classified based on the highest severity status within the 12-month timeframe prior to study entry, and disease activity/treatment could change during this period. However, the highest severity was considered in order to look at the "worst case scenario" in assessing SLE patients for the objectives in the study. Sample size was also low due to the small number of diagnosed COVID-19 cases among these patients with SLE. Overall, the data used in this study represent a "snapshot" of time in the fast-moving landscape of the COVID-19 pandemic. This provided unique insight into this SLE population prior to the availability of COVID-19 vaccines and was both a strength and a limitation of the study.

Treatment recommendations and preventive strategies for COVID-19 have been evolving quickly, making it challenging to evaluate the risk of SLE and its therapies alone in the absence of vaccination or native infection. The population included in this analysis were vaccine-naïve; however, since the study period (May 2020 to October 2020), a large-scale vaccination scheme has been introduced in the UK.[49] The start date was chosen due to the lack of widespread community testing in the UK prior to this date. Inclusion of COVID-19 diagnoses prior to this date would capture only the most severe hospitalized cases, underestimating the true incidence and overestimating severity of infections within this time period. Some patients with SLE were considered a high-risk group, and were eligible to receive their first COVID-19 vaccination in the UK from February 2021.[50] Findings of this study of vaccine-naïve patients with SLE may not be translatable to vaccinated patients with SLE as vaccines have changed the prognosis of COVID-19 in the UK,[51] but may be of interest in countries with lower vaccination rates and less controlled stages of the COVID-19 pandemic. Additionally, it is known that different SARS-

CoV-2 variants have differing virulence characteristics,[4, 23, 52] which could be impacted by SLE-related disease or treatment factors and further influenced by primary immunity acquired from native SARS-CoV-2 infection or prior vaccination.[52, 53] Therefore, studies such as the one presented here provide an important evaluation of COVID-19 in a pre-vaccination population of patients with SLE for future analysis to build upon. Vaccination against COVID-19 is reported to be safe and efficacious in patients with SLE with minimal risk of flares, and continued analysis of COVID-19 vaccination data will be useful in understanding the long-term impact of vaccination in patients with SLE.[23, 54, 55]

CONCLUSIONS

In conclusion, analysis of this large retrospective cohort study of 6145 patients with SLE in England suggested that SARS-CoV-2 infection was more prevalent in patients with severe versus mild or moderate SLE; despite small group sizes, SLE severity did not appear to impact COVID-19 outcomes. Results from this study provide a unique snapshot into the outcomes of COVID-19 for patients with SLE in England during the pre-vaccine phase of the pandemic, when government-imposed safety measures were in place. Given the evolving nature of the COVID-19 pandemic, including changes in safety measures, vaccination rates, diagnostic methods, and treatment options, as well as the infectiousness and pathogenicity of new SARS-CoV-2 variants, follow-up studies are needed to fully understand the impact of COVID-19 on patients with SLE in other geographic regions over a longer period of time.

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COMPETING INTERESTS

AR, **RK**, **RT**, and **HS**, are employees of and stockholders in AstraZeneca. **HS** is a stockholder of GlaxoSmithKline (GSK). **KW** has served as a consultant to AbbVie, AstraZeneca, Bristol Myers Squibb (BMS), Eli Lilly & Company, Galapagos, Gilead, GSK, Novartis, Pfizer, Roche, Regeneron, Sanofi, and Union Chimique Belge (UCB); and has received grant/research support from BMS and Pfizer.

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CONTRIBUTIONS

AR, WL, RK, RT, and **HS** designed the research study. **AR, WL** conducted the research. **AR, WL, RK, HS, and JW** performed the analysis. **AR, WL, RK, RT, HS, JW,** and **KW** contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript.

DATA SHARING STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

Ethics

This study used data that existed in an anonymized, structured format that contained no personal patient information. The study protocol was reviewed and approved by CPRD's Independent Scientific Advisory Committee (application number 21_000327) on March 9, 2021.[56] Linkage of datasets was performed using anonymized and pseudonymized patient identification codes and was undertaken by NHS Digital, following study protocol approval. The CPRD obtains research ethics approval annually for receiving and supplying patient data for public health research from the UK's Health Research Authority Research Ethics Committee; no additional ethics approval is required for observational studies in public health research using CPRD Aurum data.[26]

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FIGURE LEGENDS

Figure 1 Schematic of study design and criteria for patient selection

Patients were stratified by SLE severity within the 12-month baseline period (May 2019 to May 2020). All patients were required to have valid data to be considered for evaluation in the follow-up period and to be considered at-risk of COVID-19 within the study.

COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ID, index date; SLE, systemic lupus erythematosus.

Figure 2 Cumulative incidence of COVID-19 diagnoses over the 6-month evaluation period according to SLE severity

No comparative inferential statistical analyses were performed; cumulative incidence of COVID-19 diagnoses across SLE subgroups was evaluated with descriptive statistics only.

COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus.

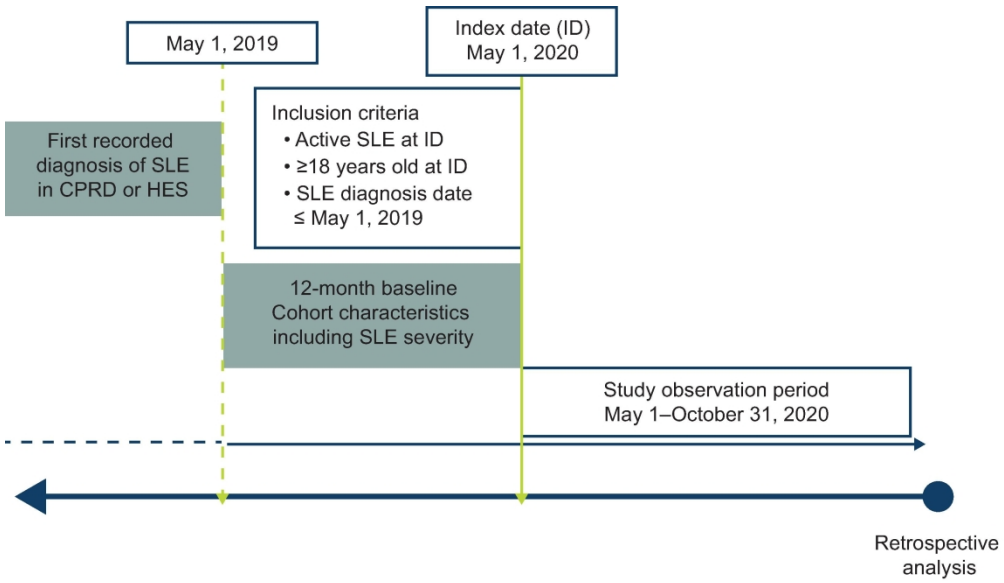

Figure 1 Schematic of study design and criteria for patient selection
Patients were stratified by SLE severity within the 12-month baseline period (May 2019 to May 2020). All patients were required to have valid data to be considered for evaluation in the follow-up period and to be considered at-risk of COVID-19 within the study.
COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ID, index date; SLE, systemic lupus erythematosus.

138x79mm (600 x 600 DPI)

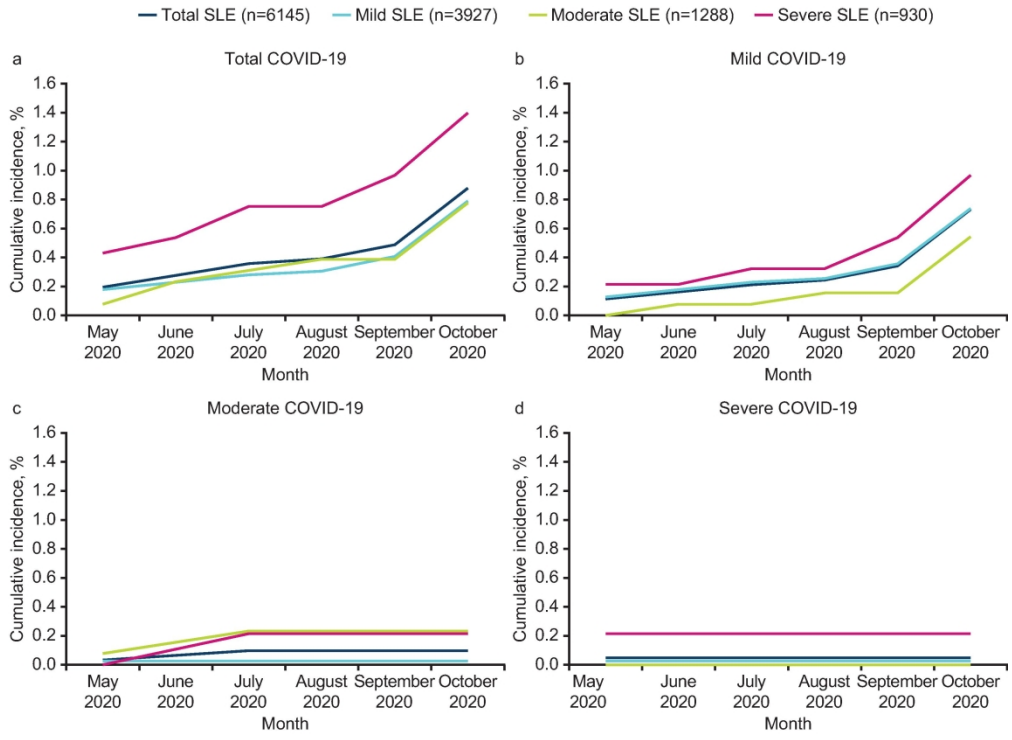

Figure 2 Cumulative incidence of COVID-19 diagnoses over the 6-month evaluation period according to SLE severity
No comparative inferential statistical analyses were performed; cumulative incidence of COVID-19 diagnoses across SLE subgroups was evaluated with descriptive statistics only.
COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus.

143x104mm (600 x 600 DPI)

SUPPLEMENTARY MATERIAL FOR:

Impact of SARS-CoV-2 Infection on Patients With Systemic Lupus Erythematosus in England Prior to Vaccination: A Retrospective Observational Cohort Study

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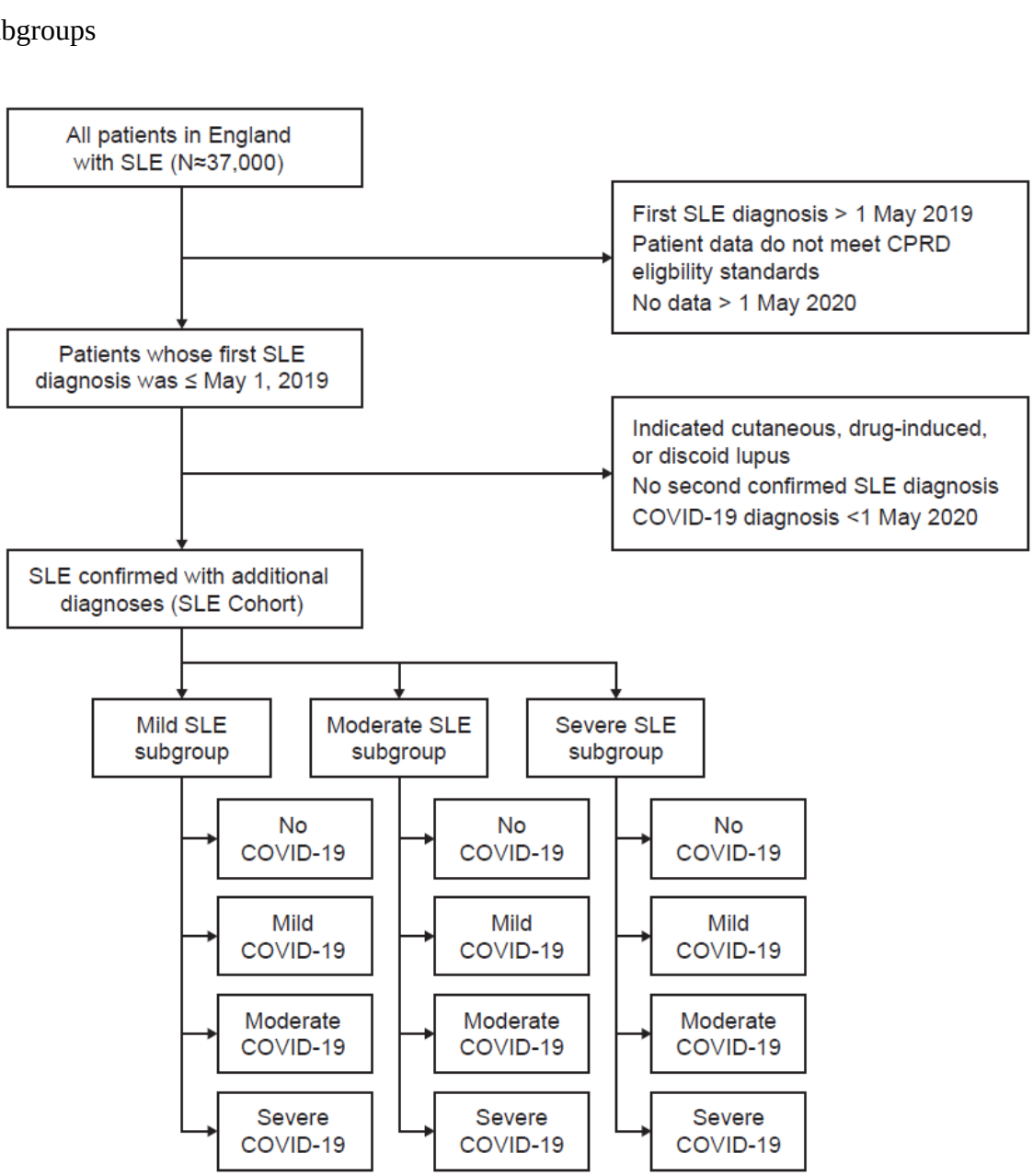
Supplemental Table 1 Summary table of the datasets used in the analysis

Dataset	Data Provider	Data
Hospital Episode Statistics (HES)	NHS Digital	Diagnoses, comorbidities, and complications
		Inpatient activity (admissions, procedures, bed days, readmissions, tariffs, specialities including CC)
		Outpatient activity (appointments, procedures, tariffs)
		A&E activity (attendances, interventions, tariffs)
		Healthcare Provider of Treatment and other interventions
		Geography of CCG
Clinical Practice Research Datalink Aurum Database (CPRD)	MHRA	Diagnoses, comorbidities, and complications
		Symptoms
		Diagnostic tests
		GP attendances
		Nursing visits and attendances
		Prescriptions, component medications (including brands where feasible)
		Pathway mapping in primary care
		Costs through PSSRU
Office of National Statistics	ONS	Cause of death
		Reported date of death

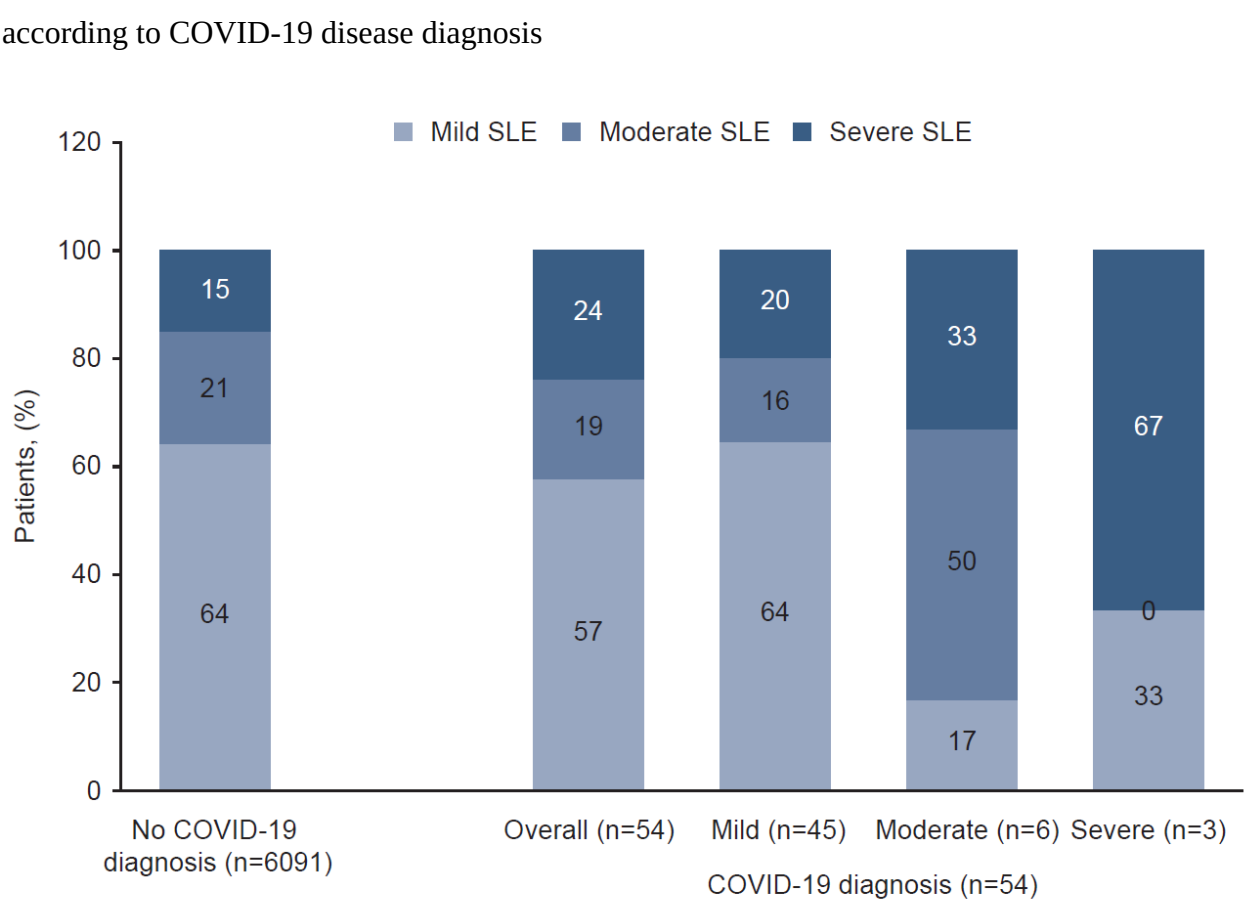
A&E, accident and emergency; CC, critical care; CCG, clinical commission groups; CPRD, Clinical Practice Research Database; HES, Hospital Episode Statistics; GP, general practitioner; MHRA, Medicines and Health Products Regulatory Agency; NHS, National Health Service; ONS, Office for National Statistics; PSSRU, Personal Social Security Services Research Unit.

Supplemental Figure 1 Flow diagram of patient identification for the final SLE cohort and subgroups



COVID-19, coronavirus disease 2019; CPRD, Clinical Practice Research Database; SLE, systemic lupus erythematosus.

Supplemental Figure 2 Proportions of patients with mild, moderate, or severe SLE according to COVID-19 disease diagnosis



No comparative inferential statistical analyses were performed.

COVID-19, coronavirus disease 2019; SLE, systemic lupus erythematosus.

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported (Page #)	RECORD items	Location in manuscript where items are reported (Page #)
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 2, 3	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	2 1, 2 2
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6		
Objectives	3	State specific objectives, including any prespecified hypotheses	6		

Methods					
Study Design	4	Present key elements of study design early in the paper	7		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed	8 N/A	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	8 N/A 38 (Figure 1)

		Case-control study - For matched studies, give matching criteria and the number of controls per case	N/A		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	8–10	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	8–10
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7–10		
Bias	9	Describe any efforts to address potential sources of bias	10, 28, 29		
Study size	10	Explain how the study size was arrived at	N/A		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	10		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	10		

		(b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	7–10 28 N/A N/A		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	7 N/A
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage	7, 8, 11

				and methods of linkage quality evaluation should be provided	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	12, 38 (Figure 1) N/A N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	12, 38 (Figure 1)
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	12 N/A N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events	12–25		

		or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	12–25 12–25 N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	N/A		
Discussion					
Key results	18	Summarise key results with reference to study objectives	26		

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	28, 29	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	28, 29
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26, 27, 30		
Generalisability	21	Discuss the generalisability (external validity) of the study results	29, 30		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	31		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	31

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.