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Risks of mortality and severe coronavirus disease 19 (COVID-19) outcomes in patients with or without systemic lupus erythematosus

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ABSTRACT

Objectives We compared the outcomes of patients with or without systemic lupus erythematosus (SLE) who were diagnosed with coronavirus disease 19 (COVID-19) and evaluated factors within patients with SLE associated with severe outcomes.

Methods This retrospective cohort study used the deidentified Optum COVID-19 electronic health record dataset to identify patients with COVID-19 from 1/1/2020 to 31/12/2020. Cases with SLE were matched with general controls at a ratio of 1:10 by age, sex, race and ethnicity and COVID-19 diagnosis date. Outcomes included 30-day mortality, mechanical ventilation, hospitalisation and intensive care unit admission. We evaluated the relationship between COVID-19-related outcomes and SLE using multivariable logistic regression. In addition, within SLE cases, we examined factors associated with COVID-19 related outcomes, including disease activity and SLE therapy.

Results We included 687 patients matched with 6870 controls. Unadjusted rates of outcomes for patients with SLE were significantly worse than for matched controls including mortality (3.6% vs 1.8%), mechanical ventilation (6% vs 2.5%) and hospitalisation (31% vs 17.7%) (all p<0.001). After multivariable adjustment, patients with SLE had increased risks of mechanical ventilation (OR 1.81, 95% CI 1.16 to 2.82) and hospitalisation (OR 1.32, 95% CI 1.05 to 1.65). Among patients with SLE, severe disease activity was associated with increased risks of mechanical ventilation (OR 5.83, 95% CI 2.60 to 13.07) and hospitalisation (OR 3.97, 95% CI 2.37 to 6.65). Use of glucocorticoids, mycophenolate and tacrolimus before COVID-19 was associated with worse outcomes.

Conclusion Patients with SLE had increased risk of severe COVID-19-related outcomes compared with matched controls. Patients with severe SLE disease activity or prior use of corticosteroids experienced worse outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with systemic lupus erythematosus (SLE) may have an increased risk of morbidity and mortality from coronavirus disease 19 (COVID-19).

WHAT THIS STUDY ADDS

⇒ This is a large retrospective cohort study that shows that in 2020, prior to vaccination availability, patients with SLE had a highly increased risk of severe outcomes that cannot solely be explained by comorbidities.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Practitioners should continue encourage COVID-19 vaccination and discuss early treatment options if diagnosed.

INTRODUCTION

Autoimmune diseases can confer increased risk of worse outcomes in patients who develop coronavirus disease 19 (COVID-19) caused by the SARS-CoV-2 virus.[1–4] Patients with systemic lupus erythematosus (SLE) may have an increased risk of severe COVID-19 outcomes due to their underlying comorbidities, abnormalities in the innate immune system and immunosuppression—though the data on the effects of immunosuppression and COVID-19 have varied. For example, antitumour necrosis factor (anti-TNF) agents have been shown to potentially decrease the risk of hospitalisation whereas glucocorticoids, even at doses less than 10 mg a day, increase the risk.[2 5–8]

The treatment of SLE frequently involves the use of glucocorticoids, which may increase the risk of hospitalisation or mortality from COVID-19. Furthermore, patients with SLE have more comorbidities, including renal and cardiovascular disease, which may also increase the risk of severe outcomes.[9] The objectives of this study were twofold: (1) to compare the outcomes of 30-day mortality, mechanical ventilation, intensive care unit (ICU) admission excluding mechanical ventilation and hospitalisation in patients with or without SLE and (2) to evaluate among patients with SLE the association between COVID-19 outcomes and SLE disease activity and prior therapy among those with SLE.

METHODS

Data source

We queried the Optum deidentified COVID-19 electronic health record (EHR) data set to conduct this study. This includes data from more than 700 hospitals and 7000 clinics across the USA with data specific to patients who were tested for COVID-19 in both inpatient and ambulatory settings. Available data include demographic variables, diagnostic/procedure codes, prescription claims, hospitalisations and mortality. We followed The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[10]

Cohort selection

We identified all patients ≥18 years of age who were tested for COVID-19 by International Classification of Diseases (ICD, both ICD-9 and ICD-10) diagnosis codes, Healthcare Common Procedure Coding system codes (HCPCS), Logical Observation Identifier Names and Codes and laboratory test name with a subsequent positive result from either PCR, antigen test or serological confirmation (online supplemental table A1). We used the earliest specimen collection, test or result data as our COVID-19 diagnosis (index) date. We included patients who had a positive result or diagnostic code (whichever was earliest) for COVID-19 between 1/1/2020 and 31/12/2020 to capture outcomes prior to the COVID-19 vaccinations being widely available.

For our SLE cohort, we included patients who had two SLE claims (ICD-10 M32.x (excluding M32.0)) within 1 year before COVID-19 diagnosis and had a prescription or a HCPCS claim of a SLE drug (steroids, biologics, immunosuppressants or antimalarials) within 1 year before or 1 year after the lupus diagnosis date and before the COVID-19 diagnosis date. Our general cohort excluded patients who had one or more claims of SLE within 1 year before the COVID-19 diagnosis.

We exactly matched controls with patients with SLE 10 to 1 by age, sex, race and ethnicity and COVID-19 diagnosis month.

Outcomes

Outcomes included all-cause mortality, mechanical ventilation, hospitalisation and ICU stays excluding ventilation within 30 days of COVID-19 diagnosis. We identified the outcomes using HCPCS or ICD-10 procedure codes and other definitions (online supplemental table A1). All-cause mortality was assessed from health electronic records and the Social Security Administration Death Master File.

Covariates

Demographics

We collected demographic and baseline variables including age at COVID-19 diagnosis, sex, race and ethnicity (White non-Hispanic or White, Black non-Hispanic or Black, Hispanic, Asian non-Hispanic or Asian and unknown), residence according to the U.S. Census region and insurance status. Other variables available included date of COVID-19 diagnosis categorised by quarter, skilled nurse facility stay within 3 months before COVID-19 diagnosis, severe obesity (body mass index ≥40 kg/m^2) and smoking status.

Comorbidities

We used the Charlson's Comorbidity score to identify comorbidities (0, 1, 2+).[11,12] SLE is part of the comorbidity score and was excluded as a variable.

Lupus covariates

We estimated disease activity using the Garris index within 6 months prior to the COVID-19 diagnosis. The Garris index is an algorithm from administrative claims data with a sensitivity of 85.7%, specificity 67.6%, positive predictive value (PPV) 81.8% and negative predictive value (NPV) 73.5% for distinguishing moderate/severe from mild SLE when comparing administrative claims data to the SLE Disease Activity Index-2000.[13]

Among patients with SLE, we collected prescription data including patient-reported medications for average glucocorticoid dose 1 month prior to COVID-19 diagnosis (all corticosteroids were converted to prednisone equivalent doses). We used 1 month prior to COVID-19 diagnosis as opposed to 3 months due to inconsistent reporting of corticosteroids over a 3-month average (eg, tapering doses and dispensing quality were not readily available). We categorised other SLE medications into immunosuppressants (methotrexate, leflunomide, azathioprine, mycophenolate mofetil, tacrolimus, ciclosporine or cyclophosphamide), antimalarials (hydroxychloroquine, quinacrine or chloroquine) and biologics (rituximab or belimumab). For non-steroidal treatment including biologics, immunosuppressants and antimalarials, we used any prescription within 6 months before COVID-19 diagnosis. Drug codes are found in online supplemental table A2.

Statistical analysis

We performed the analysis using SAS software V.9.4 (SAS Institute). We compared the patient characteristics and 30-day outcomes according to group (SLE or controls) using χ^2 tests for categorical measures. Statistical significance was defined as two-sided p≤0.05.

For matched SLE and controls, we performed step-by-step multivariable logistic regression models to examine how each set of variables changed the association of groups (SLE, control) with 30-day outcomes (mortality, mechanical ventilation, hospitalisation and ICU excluding ventilation). Model 1 adjusted for matching variables (age, sex, race and ethnicity, COVID-19 diagnosis month) and other socioeconomical variables (insurance, region). Model 2 added obesity and smoking status. To control for confounding of comorbidities, Model 3 additionally adjusted for the comorbidity score (0, 1, 2+). Model 4 adjusted for the individual comorbidities. Results are expressed as adjusted ORs and 95% CIs. Patients with missing data were grouped as a separate category for the corresponding variable and were included in the analysis.

Among patients with SLE, we examined the 30-day outcomes using multivariable logistic regression models adjusting for (age, skilled nursing facility admission within 3 months before COVID-19 diagnosis, smoking and region) and the SLE severity via the Garris index. We included the Belimumab in 6 months before COVID-19 diagnosis for adjustment because it was not included in the Garris index (as a potential variable for severe disease). In addition, we compared the outcomes according to use of SLE drugs prior to COVID-19 diagnosis using χ^2 or Fisher's exact test as appropriate.

Sensitivity analyses

We performed a sensitivity analysis on an expanded cohort by defining patients with SLE as those with two or more lupus diagnosis codes that were at least 30 days apart but without requirement for treatment of SLE within 1 year of the COVID-19 diagnosis.

This study used deidentified data and was exempted by our institutional review board at the University of Texas MD Anderson Cancer Center.

RESULTS

Baseline characteristics

We identified 687 SLE cases matched with 6870 controls (table 1). Baseline characteristics of unmatched cohorts are shown in online supplemental table A3. The median age was 52 (IQR 40–64 years) and patients were predominantly female (92%). Forty-five per cent of the patients were White, and 34% were Black. After matching, patients with SLE were more likely to have smoked, have more comorbidities, have an admission to a skilled nursing facility within 3 months before COVID-19 diagnosis and be Medicare beneficiaries. The sensitivity analysis using a less stringent SLE definition matched 1209 patients with SLE with 12 090 controls with similar baseline characteristics (online supplemental table A4).

Unadjusted rates of outcomes

After matching, patients with SLE fared worse than matched controls for all outcomes examined (table 2). Patients with SLE had higher unadjusted rates of 30-day mortality (3.6% vs 1.8%), mechanical ventilation (6% vs 2.5%), hospitalisation (31% vs 17.7%) and ICU admission excluding ventilation (7.1% vs 3.9%) (all p<0.001). The sensitivity analysis (in which we defined patients with SLE as requiring two or more lupus diagnosis codes that were at least 30 days apart but without requirement for treatment of SLE) showed similar results (online supplemental table A5).

Multivariable model

Results from the multivariable logistic regression models are shown in table 3. Before adjustment for comorbidities,

Table 1 Baseline characteristics for matched SLE and controls among patient diagnosed with COVID-19

	SLE N (%)	Control N (%)	P value
Total (N)	687	6870	
Age, years			
18–39	167 (24.3)	1670 (24.3)	1
40–49	137 (19.9)	1370 (19.9)	
50–54	72 (10.5)	723 (10.5)	
55–59	69 (10)	684 (10)	
60–64	89 (13)	893 (13)	
65–69	58 (8.4)	569 (8.3)	
70–74	42 (6.1)	422 (6.1)	
75–79	27 (3.9)	279 (4.1)	
80–84	18 (2.6)	180 (2.6)	
85+	8 (1.2)	80 (1.2)	
Gender			
Female	631 (91.8)	6310 (91.8)	1
Male	56 (8.2)	560 (8.2)	
Race and ethnicity			
Hispanic	93 (13.5)	930 (13.5)	1
NH Asian	11 (1.6)	110 (1.6)	
NH Black	232 (33.8)	2320 (33.8)	
NH White	310 (45.1)	3100 (45.1)	
Other/Unknown	41 (6)	410 (6)	
COVID-19 diagnosis quarter*			
1	66 (9.6)	660 (9.6)	1
2	242 (35.2)	2420 (35.2)	
3	214 (31.1)	2140 (31.1)	
4	165 (24)	1650 (24)	
Severe obesity (BMI≥40)			
No	581 (84.6)	5945 (86.5)	0.15
Yes	106 (15.4)	925 (13.5)	
Smoking status			
Never	400 (58.2)	4764 (69.3)	<0.001
Current	137 (19.9)	892 (13)	
Former	150 (21.8)	1214 (17.7)	
Comorbidities			
0	92 (13.4)	4055 (59)	<0.001
1	97 (14.1)	1241 (18.1)	
2+	498 (72.5)	1574 (22.9)	
Skilled nurse facility in 3 months before COVID-19 diagnosis			
No	671 (97.7)	6811 (99.1)	<0.001
Yes	16 (2.3)	59 (0.9)	
Insurance			
Commercial	338 (49.2)	3941 (57.4)	<0.001
Medicare	170 (24.7)	950 (13.8)	

Continued

Table 1 Continued

	SLE N (%)	Control N (%)	P value
Medicaid	77 (11.2)	549 (8)	
Other insurance	23 (3.3)	337 (4.9)	
Uninsured	0 (0)	103 (1.5)	
Unknown	79 (11.5)	990 (14.4)	
Region			
Midwest	318 (46.3)	3538 (51.5)	<0.001
Northeast	200 (29.1)	1496 (21.8)	
South	103 (15)	1217 (17.7)	
West	31 (4.5)	342 (5)	
Other	35 (5.1)	277 (4)	

*Quarter 1 is January–March, Quarter 2 is April–May, Quarter 3 is June–August, Quarter 4 is September–December in 2020.
BMI, body mass index; COVID-19, coronavirus disease 19; NH, non-Hispanic; SLE, systemic lupus erythematosus.

patients with SLE had increased risks of mortality (OR 2.09, 95% CI 1.31 to 3.32), mechanical ventilation (OR 2.43, 95% CI 1.67 to 3.54), hospitalisation (OR 2.06, 95% CI 1.71 to 2.49) and ICU admission (OR 1.82, 95% CI 1.31 to 2.53) . However, after adjusting for the number of comorbidities (0, 1 or ≥2), the association attenuated and lost significance for mortality, mechanical ventilation and ICU admission without ventilation. The association remained significant for hospitalisation (OR 1.32, 95% CI 1.08 to 1.61) but the magnitude of the estimate decreased substantially. After adjusting for individual comorbidities (as opposed to the number of comorbidities), a decrease in effect size was observed, and the associations between SLE and mechanical ventilation (OR 1.81, 95% CI 1.16 to 2.82) and hospitalisation (OR 1.32, 95% CI 1.05 to 1.65) remained statistically significant.

Table 2 Unadjusted rates of COVID-19-related outcomes for patients with SLE vs matched controls

	SLE (N=687) N (%)	Control (N=6870) N (%)	P value
30-day mortality			
Yes	25 (3.6)	123 (1.8)	<0.001
30-day hospitalisation			
Yes	213 (31.0)	1217 (17.7)	<0.001
30-day mechanical ventilation			
Yes	41 (6.0)	172 (2.5)	<0.001
30-day ICU without ventilation			
Yes	49 (7.1)	269 (3.9)	<0.001

COVID-19, coronavirus disease 19; ICU, Intensive care unit; SLE, systemic lupus erythematosus.

Results from the sensitivity analysis (requirement of two SLE codes without drug treatment) are presented in online supplemental table A6 and showed similar patterns, except when adjusting for the individual comorbidities with the OR being non-significant for all outcomes except hospitalisation.

COVID-19-related outcomes in patients with SLE according to disease severity and prior SLE treatment

COVID-19-related outcomes among patients with SLE according to baseline characteristics including disease activity (Garris index) are shown in online supplemental table A7. Moderate or severe SLE disease activity accounted for 30.9% and 15.1% of patients, respectively. After multivariable adjustment for significant patient and clinical characteristics (and belimumab as it is not included in Garris index), patients with severe disease activity, when compared with those with mild disease activity, had increased odds of 30-day mechanical ventilation (OR 5.83, 95% CI 2.60 to 13.07) and hospitalisation (OR 3.97, 95% CI 2.37 to 6.65), but not mortality (OR 2.38, 95% CI 0.85 to 6.66) or ICU admission (OR 0.90, 95% CI 0.38 to 2.12) (table 4). Finally, we compared the composite of 30-day adverse outcome (mortality, mechanical ventilation, hospitalisation or ICU) according to SLE medications, as we did not have adequate sample size to evaluate each outcome individually by each drug (table 5). Individual outcomes are shown in online supplemental table A8. In addition, we did not have a sample size sufficiently large to conduct multivariate analyses comparing all drugs. In total, 241 (35.1%) patients had the composite 30-day adverse outcome. Use of several drugs was significantly associated with more severe outcomes. The unadjusted rates of composite outcome were 50.8% vs 29.1% (p<0.001) for corticosteroids use versus no use in the 3 months before COVID-19, and 48.6% vs 32.6% (p=0.002) for mycophenolate. Negative effects were also seen with methotrexate, leflunomide, ciclosporine and tacrolimus. Belimumab had protective effects for severe outcomes (18.8% vs 35.9%, p=0.047) though the sample size was small (only six patients on belimumab had a severe outcome). No statistically significant differences were observed for azathioprine, cyclophosphamide, rituximab or antimalarials. The sensitivity analysis on the expanded cohort showed that those on corticosteroids, methotrexate, tacrolimus and rituximab had more severe outcomes (online supplemental table A9). Those who had received antimalarial therapy had less severe outcomes (26.7% vs 32.2%, p=0.04).

DISCUSSION

To our knowledge, this is the first study using national EHR data in the USA to describe COVID-19 outcomes among patients with SLE compared with matched controls. Patients with SLE had a statistically significant increase in rates of mortality, mechanical ventilation, hospitalisation and ICU admissions without ventilation from COVID-19

Table 3 Multivariable logistic regression models for COVID-19 outcomes comparing patients with SLE vs matched controls

	Model 1* OR (95% CI)	Model 2† OR (95% CI)	Model 3‡ OR (95% CI)	Model 4§ OR (95% CI)
30-day mortality				
Control	1	1	1	1
SLE	2.21 (1.40 to 3.49)	2.09 (1.31 to 3.32)	1.48 (0.92 to 2.38)	1.39 (0.79 to 2.44)
30-day mechanical ventilation				
Control	1	1	1	1
SLE	2.54 (1.76 to 3.67)	2.43 (1.67 to 3.54)	1.40 (0.95 to 2.07)	1.81 (1.16 to 2.82)
30-day hospitalisation				
Control	1	1	1	1
SLE	2.16 (1.79 to 2.59)	2.06 (1.71 to 2.49)	1.32 (1.08 to 1.61)	1.32 (1.05 to 1.65)
30-day ICU without mechanical ventilation				
Control	1	1	1	1
SLE	1.95 (1.41 to 2.70)	1.82 (1.31 to 2.53)	1.12 (0.80 to 1.58)	0.94 (0.62 to 1.41)

*Model 1 included adjustments for age, gender, race and ethnicity, COVID-19 quarter diagnosis, insurance and region.
†Model 2 included adjustments from model 1 and obesity, smoking status, skilled nursing facility admission within 3 months before COVID-19 diagnosis.
‡Model 3 included adjustments from Model 2 and for number of comorbidities (0, 1 or 2+) excluding SLE.
§Model 4 included adjustments for model 2 and for individual comorbidities.
COVID-19, coronavirus disease 19; ICU, intensive care unit; SLE, systemic lupus erythematosus.

from 1 January 2020 to 31 December 2020. These results were especially concerning as despite having a relatively young population (median age 52 years) and predominantly female (92%), we observed high rates of hospitalisation and death within 30 days of SARS-Cov-2 diagnosis among patients with SLE.

After adjusting for demographics, severe obesity, smoking status and skilled nursing facility admissions, the ORs remained elevated for mortality, mechanical ventilation, hospitalisation and ICU without mechanical ventilation. However, after additional adjustment for individual comorbidity from the Charlson comorbidity index (excluding SLE), the associations attenuated for all outcomes but remained elevated for hospitalisation and mechanical ventilation. This suggests that although comorbidities have a significant role in adverse outcomes in patients with SLE with COVID-19, they do not fully explain the excess morbidity seen with COVID-19.

One study using retrospective data from the TriNetX database used propensity scores to match SLE cases with the general population according to age, gender, race, and multiple comorbidities to investigate COVID-19 outcomes.[14] Their analysis including 2135 SLE cases matched to 2135 controls. Similarly, they observed an increased risk of all-cause hospitalisation, ICU admission and mechanical ventilation. The differences between

Table 4 Multivariable logistic regression models of COVID-19 outcomes in patients with SLE

	Mortality OR (95% CI)	Mechanical ventilation OR (95% CI)	Hospitalisation OR (95% CI)	ICU excluding mechanical ventilation OR (95% CI)
SLE Disease Activity				
Mild (reference value)	1	1	1	1
Moderate	1.76 (0.66 to 4.69) p=0.26	1.59 (0.68 to 3.74) p=0.29	2.01 (1.31 to 3.07) p=0.001	1.02 (0.50 to 2.08) p=0.95
Severe	2.38 (0.85 to 6.66) p=0.10	5.83 (2.60 to 13.07) p<0.001	3.97 (2.37 to 6.65) p<0.001	0.90 (0.38 to 2.12) p=0.85

All models were adjusted for Belimumab in 6 months before positive COVID-19. Additionally, model for 30-day mortality was additionally adjusted for age, race and insurance type. Model for 30-day mechanical ventilation was adjusted for age, COVID-19 diagnosis quarter, skilled nurse facility in 3 months before positive COVID-19 and severe obesity. Model for 30-day hospitalisation was adjusted for age, COVID-19 diagnosis quarter, smoking status, insurance type and region. Model for 30-day ICU excluding ventilation was adjusted for age, severe obesity and region. Association with Garris index levels of severity.
COVID-19, coronavirus disease 19; ICU, intensive care unit; SLE, systemic lupus erythematosus.

Table 5 Unadjusted rates of COVID-19 outcomes according to SLE treatment received prior to COVID-19

	Total (N=687) N (% over column)	No 30-day outcome (N=446) N (% over row)	Any 30-day outcome (death, mechanical ventilation, ICU, hospitalisation) (N=241) N (% over row)	P value
Steroids average dose* (1 month before COVID-19 diagnosis)				
None	600 (87.3)	402 (67)	198 (33)	0.006
Low (>0 mg and <7.5 mg)	71 (10.3)	34 (47.9)	37 (52.1)	
Medium-High (≥7.5 mg)	16 (2.3)	10 (62.5)	6 (37.5)	
Any steroid use (3 months before COVID-19 diagnosis)				
No	498 (72.5)	353 (70.9)	145 (29.1)	<0.001
Yes	189 (27.5)	93 (49.2)	96 (50.8)	
Azathioprine				
No	638 (92.9)	415 (65)	223 (35)	0.8
Yes	49 (7.1)	31 (63.3)	18 (36.7)	
Cyclophosphamide				
No	673 (98)	437 (64.9)	236 (35.1)	1.0*
Yes	14 (2)	9 (64.3)	5 (35.7)	
Methotrexate				
No	630 (91.7)	401 (63.7)	229 (36.3)	0.02
Yes	57 (8.3)	45 (78.9)	12 (21.1)	
Mycophenolate				
No	582 (84.7)	392 (67.4)	190 (32.6)	0.002
Yes	105 (15.3)	54 (51.4)	51 (48.6)	
Leflunomide				
No	666 (96.9)	437 (65.6)	229 (34.4)	0.03
Yes	21 (3.1)	9 (42.9)	12 (57.1)	
Tacrolimus				
No	648 (94.3)	429 (66.2)	219 (33.8)	0.004
Yes	39 (5.7)	17 (43.6)	22 (56.4)	
Cyclosporine				
No	659 (95.9)	432 (65.6)	227 (34.4)	0.09
Yes	28 (4.1)	14 (50)	14 (50)	
Rituximab				
No	663 (96.5)	434 (97.3)	229 (95)	0.12
Yes	24 (3.5)	12 (2.7)	12 (5)	
Belimumab				
No	655 (95.3)	420 (64.1)	235 (35.9)	0.047
Yes	32 (4.7)	26 (81.3)	6 (18.8)	
Antimalarials				
No	379 (55.2)	244 (64.4)	135 (35.6)	0.74
Yes	308 (44.8)	202 (65.6)	106 (34.4)	

Except for steroid, other treatment drugs were evaluated in 6 months before COVID-19 diagnosis.
*Medium and high dose corticosteroid doses were grouped together due to small sample size.
COVID-19, coronavirus disease 19; ICU, intensive care unit; SLE, systemic lupus erythematosus.

our studies include our use of a more stringent criteria for SLE, COVID-19 diagnosis and also that our control for confounding was more stringent as we performed exact matching, rather than propensity score methods, for important variables with a ratio of 1–10. We also examined more comorbidities individually and we examined the impact of disease activity on COVID-19 outcomes in patients with SLE. A separate study cross-sectional study found that among all patients hospitalised with acute respiratory distress syndrome with COVID-19, those with SLE had the highest risk of poor outcomes even after adjusting for comorbidities.[15] These studies, along with ours, find that SLE is an independent risk factor for severe outcomes in COVID-19.

Immunosuppression prior to acquiring COVID-19 may explain the worse outcomes seen in patients with SLE compared with controls, as in patients with SLE, prior use of steroids and other drugs were associated with increased morbidity from COVID-19. This has been suggested by others.[1 3 16] A recent study used data from the COVID-19 Global Rheumatology Alliance registry in which cases are entered into registries by treating clinicians.[3] A total of 1606 SLE cases were included in analysis; corticosteroids, no SLE treatment, active SLE disease and comorbidities were associated with worse outcomes. Our findings show similar results, except that in our sensitivity analysis on the cohort that included patients with SLE without treatment we did not observe worse outcomes with no SLE treatment. Our study included mostly patients with private health insurance, unlike the Global Rheumatology Alliance registry which also likely includes uninsured patients, which could explain worse COVID-19 outcomes in untreated patients with SLE—patients with private insurance and no treatment may be more likely to have mild disease activity compared with uninsured patients were lack of treatment may reflect lack of access and not only mild disease. Finally, a study using claims data in France has also shown that patients with SLE may have worse outcomes after testing positive for COVID-19, although outcomes were ascertained from 30 to 90 days after the initial COVID-19 diagnosis.[17] It is also possible that infection with SARS-CoV-2 may potentially cause hospitalisations for others reasons (eg, SLE flares from holding medications) or due to increased concern on the part of providers.

The strengths of our study include a large national sample of patients with SLE that had a confirmed diagnosis of COVID-19. We were able to exactly match with controls by confounding factors including age, sex, race and ethnicity and date within quarters of COVID-19 diagnosis. Furthermore, Optum also provides the advantage of being able to ascertain mortality, which other databases do not. However, there are limitations that should also be considered. First, there may be ascertainment bias as patients with SLE may have been more likely to undergo COVID-19 testing than their counterparts, nevertheless this would conceivably lead to diagnosis of more mild cases and potentially bias results towards the null hypothesis. Second, our primary analysis included patients with SLE who had been receiving SLE therapy to increase specificity, and therefore our results may not be generalisable to untreated patients with SLE, although our sensitivity analysis did not find major differences. It should also be noted that written prescriptions do not necessarily mean patients are adherent. Third, cases with SLE were mostly insured; however, some matched controls were uninsured. Our data therefore do not broadly apply to uninsured patient populations, but should also be noted that low socioeconomic status is associated with more severe COVID-19 outcomes and that this bias should work towards neutral results yet we will saw significantly more severe outcomes among SLE cases.[18–20] Fourth, we cannot specifically ascertain if our outcomes (hospitalisation, mortality and so on) are directly attributable to SLE versus COVID-19, especially in patients with a high Garris Index. Finally, our analysis of drug use was limited, as we could only ascertain prescriptions, and not whether patients took drugs as prescribed, or for instance, any tapering for corticosteroids. It should also be noted that the although there have been different SARS-Cov2-virus with different disease outcomes, this study is still relevant as (1) similar strains may appear in the future and (2) given the impact, the COVID-19 pandemic had on the world any study on outcomes in a susceptible population, especially that of a rarer disease such as SLE, is needed.

In summary, our study shows that patients with SLE had increased risks of adverse COVID-19 outcomes. This was largely driven, but not fully explained, by the presence of other associated comorbidities. We also found that patients receiving glucocorticoids, mycophenolate and cyclosporine prior to developing COVID-19 had increased incidence of severe outcomes. Further research is needed to determine whether these medications are directly responsible for increased risk of severe COVID-19 outcomes. Clinicians should have increased vigilance in patients with SLE who are diagnosed with COVID-19 and should strongly consider early therapy to prevent severe disease.

Contributors Study conception and design: SB, XL, HZ, JY, MC-M, SHG, MES-A. Data collection: SB, XL, ZH, MSA. Analysis and interpretation of results: SB, XL, HZ, JY, MC-M, SHG, MES-A. Draft manuscript preparation: SB, ZL, ZH, YJ, MC-M, SHG, MES-A. All authors reviewed the results and approved the final version of the manuscript. The guarantor of this study is MES-A and accepts full responsibility for the work and conduct of the study, had access to the data, and the decision to publish.

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Competing interests MES-A has received consultant fees from participation on advisory boards for Gilead, Avenue Therapeutics, ChemoCentryx, is a current member of advisory board for Celgene and all activities are unrelated to this work. JY has research grants from Astra Zeneca, Gilead and the Bristol Myers Squibb Foundation. She has performed consulting for Aurinia, Astra Zeneca and Pfizer, unrelated to this work.

Patient consent for publication Not applicable.

Ethics approval This study used deidentified data and was exempted by our institutional review board at the University of Texas MD Anderson Cancer Center.

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

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