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Characteristics associated with poor COVID-19 outcomes in individuals with systemic lupus erythematosus: data from the COVID-19 Global Rheumatology Alliance

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ABSTRACT

Aim To determine characteristics associated with more severe outcomes in a global registry of people with systemic lupus erythematosus (SLE) and COVID-19.

Methods People with SLE and COVID-19 reported in the COVID-19 Global Rheumatology Alliance registry from March 2020 to June 2021 were included. The ordinal outcome was defined as: (1) not hospitalised, (2) hospitalised with no oxygenation, (3) hospitalised with any ventilation or oxygenation and (4) death. A multivariable ordinal logistic regression model was constructed to assess the relationship between COVID-19 severity and demographic characteristics, comorbidities, medications and disease activity.

Results A total of 1606 people with SLE were included. In the multivariable model, older age (OR 1.03, 95% CI 1.02 to 1.04), male sex (1.50, 1.01 to 2.23), prednisone dose (1–5 mg/day 1.86, 1.20 to 2.66, 6–9 mg/day 2.47, 1.24 to 4.86 and ≥10 mg/day 1.95, 1.27 to 2.99), no current treatment (1.80, 1.17 to 2.75), comorbidities (eg, kidney disease 3.51, 2.42 to 5.09, cardiovascular disease/hypertension 1.69, 1.25 to 2.29) and moderate or high SLE disease activity (vs remission; 1.61, 1.02 to 2.54 and 3.94, 2.11 to 7.34, respectively) were associated with more severe outcomes. In age-adjusted and sex-adjusted models, mycophenolate, rituximab and cyclophosphamide were associated with worse outcomes compared with hydroxychloroquine; outcomes were more favourable with methotrexate and belimumab.

Conclusions More severe COVID-19 outcomes in individuals with SLE are largely driven by demographic factors, comorbidities and untreated or active SLE. Patients using glucocorticoids also experienced more severe outcomes.

INTRODUCTION

During the COVID-19 pandemic, individuals with systemic lupus erythematosus (SLE) have been of particular concern. SLE disproportionately impacts populations most severely affected by COVID-19, including those from non-white racial and ethnic groups, and those with low socioeconomic status.[1] Moreover, individuals with SLE are often heavily immunosuppressed and have a high comorbidity burden with multiple risk factors for more severe COVID-19. Although previous analyses have evaluated outcomes of infection with SARS-Cov-2 in rheumatic diseases as a group, data on individuals with SLE are limited, and it remains unclear which risk factors are associated with worse COVID-19 outcomes in this population.

Key messages

What is already known about this subject?

- Demographic factors as well as comorbidities have been associated with poorer COVID-19 outcomes in the general population.
- The COVID-19 Global Rheumatology Alliance has reported glucocorticoid dose (≥10 mg/day), some immunosuppressive drugs and disease activity as predictors of poorer COVID-19 outcomes in individuals with different rheumatic diseases.

What does this study add?

- More severe COVID-19 outcomes in individuals with systemic lupus erythematosus (SLE) are mainly driven by demographic factors, comorbidities and untreated or active SLE.
- Individuals using glucocorticoids (even low dose) experienced more severe outcomes.

How might this impact on clinical practice or future developments?

- Individuals with lupus and these characteristics should be prioritised for close monitoring, counselled to receive vaccination, and receive preventive therapies if infected with SARS-CoV2.

Data from the COVID-19 Global Rheumatology Alliance (C19-GRA) registry, a large physician reported registry of individuals with rheumatic diseases and COVID-19, suggest that those with moderate or high disease activity, as well as those receiving specific medications, including moderate or high doses of prednisone, rituximab, immunosuppressive drugs (ie, mycophenolate mofetil/mycophenolic acid (MMF), tacrolimus, azathioprine and cyclophosphamide) compared with a reference group of individuals receiving methotrexate have poorer outcomes.[2] Furthermore, in an analysis of patients in the C19-GRA registry with rheumatoid arthritis (RA), treatment with rituximab or Janus Kinase (JAK) inhibitors was associated with poorer outcomes compared with treatment with tumour necrosis factor inhibitors.[3] However, medications associated with more severe COVID-19 outcomes in SLE have not been extensively examined.

OpenSAFELY, a large analysis of primary care records of >17 million adults linked to 10 926 COVID-19-related deaths reported that after adjustment for a wide variety of factors such as demographic characteristics and comorbidities, those with autoimmune disease (SLE, RA or psoriasis as a group) had a higher risk of mortality, but this study did not adjust for medication use, nor did it evaluate SLE as a discrete or separate disease.[4] Several case series or single-centre/country studies suggest that some individuals with SLE can have a severe disease course, but the small size of these studies has precluded a comprehensive analysis of risk factors for poor COVID-19 outcomes.[5–10]

We used the C19-GRA registry to identify sociodemographic and clinical factors associated with more severe COVID-19 outcomes in individuals with SLE.

METHODS

Data source

Subjetcs with rheumatic disease and COVID-19 from the C19-GRA registry and European Alliance of Associations for Rheumatology (EULAR) COVID-19 registry were included in the analyses, which covered the period from 12 March 2020 to 1 June 2021. Data entry portals include one limited to European countries (eular.org/eular_covid19_database.cfm; hosted by The University of Manchester, UK) and a second for all other countries (rheum-covid.org/provider-global/; hosted by the University of California, San Francisco (UCSF), California, USA).[11 12] Cases are entered into these registries by their treating clinicians. This study includes all individuals from these registries with SLE diagnosed with COVID-19 by 1 June 2021. Prior studies using C19-GRA and EULAR databases have included some individuals also reported in this study,[2 13 14] but the number of individuals in this analysis is significantly higher than reported in previous publications.

Data quality was assessed by the data coordinating centres at UCSF and the University of Manchester and included procedures to identify and remove any duplicate cases.

COVID-19 outcomes

We used an ordinal severity outcome in the analyses, with mutually exclusive categories including: (1) not hospitalised, (2) hospitalised with no oxygenation, (3) hospitalised with any ventilation or oxygenation or (4) death. These outcomes were chosen so that the analyses could reflect the full spectrum of disease associated with COVID-19 and are analogous to outcome measures used in many trials evaluating COVID-19 therapeutics. Only the highest severity level of the outcome occurring during the patient's disease course was included, and all individuals were required to have a resolved clinical course.

Covariates, including medication exposure

Covariates included demographic characteristics, including age, sex and region (Europe, the USA and Canada, Latin America and other), as well as clinical characteristics, including number of comorbidities (including lung, liver or neurological diseases, cancer, diabetes, obesity, among others), specific comorbidities (chronic renal insufficiency or end-stage renal disease and hypertension or cardiovascular disease), disease activity (assessed by a physician global assessment categorised as remission, low, moderate or high), dose of glucocorticoids (GCs; entered as daily oral prednisone equivalents) and use of immunosuppressive or immunomodulating medications. Additionally, the date of the case report was analysed in three time periods: 24 March 2020 to 15 June 2020, 16 June 2020 to 30 September 2020 and 1 October 2020 to 1 June 2021. The first period ended at the release of the RECOVERY study, which changed COVID-19 treatment protocols to incorporate GCs.[15] The second cut-off was based on the beginning of the second wave in many countries around the world.

Medications taken by patients prior to COVID-19 were categorised as: conventional synthetic drugs (antimalarials (hydroxychloroquine, chloroquine), conventional disease-modifying monotherapies generally considered to represent less intensive immunosuppression (sulfasalazine, methotrexate and leflunomide), conventional disease-modifying monotherapies with more intense immunosuppressive drugs (MMF, tacrolimus, cyclophosphamide, ciclosporin, azathioprine)); biologics (abatacept, belimumab, rituximab, interleukin (IL)-6 inhibitors, IL-12/IL-23 inhibitors, IL-17 inhibitors, tumour necrosis factor inhibitors (anti-TNF)) and targeted synthetic drugs, specifically JAK inhibitors and GCs. In analyses, we divided medications into five groups: no SLE medications, antimalarial only, conventional disease-modifying monotherapies generally considered to represent less intensive immunosuppression (sulfasalazine, methotrexate and leflunomide), conventional disease-modifying

monotherapies with more intense immunosuppressive drugs (MMF, tacrolimus, cyclophosphamide, ciclosporin, azathioprine), biologic/targeted synthetic drug monotherapy and finally combination therapy with conventional and biologic disease-modifying immunosuppressive drugs. GCs were categorised into four groups by dose: prednisone dose=0 mg/day, between 1 and 5 mg/day, between 6 and 9 mg/day and ≥10 mg/day.

Statistical analyses

We used proportional odds logistic regression with severity as dependent variable, and covariates as described in the next paragraphs. This is similar to using binary logistic regression for each of the three possible dichotomisations of the four-category dependent variable, with the assumption that the OR is the same for each cut-off. The parallel lines test for proportional odds ordinal logistic regression confirmed that this assumption was not violated.

Models included demographic variables and clinical characteristics as well as the time period in the pandemic during which the case was reported. Random effects were included for country and time. These variables were applied to capture the significant variability in regulations enforcing personal protective equipment, hospital resource allocation and quarantine procedures between countries and over the course of the pandemic.

We assumed that missing data were 'missing at random' and missing data were handled using multiple imputation, with 50 imputed data sets.

In all models, we included sex, age, region, GCs as a categorical variable (0, 1–5, 6–9, ≥10 mg/day), immunosuppressive medication category, time period and random effects of country and time. To assess the additional impact of comorbidities, we constructed an additional model that included the number of comorbidities and, separately, that included key comorbidities in SLE, including renal disease and hypertension/cardiovascular disease. Finally, we constructed a model that included the above variables but additionally included SLE disease activity.

We conducted several additional analyses to examine associations of six medications of interest in SLE with COVID-19 outcomes: methotrexate (n=173), azathioprine (n=235), MMF (n=332), cyclophosphamide (n=29), rituximab (n=68) and belimumab (n=104). In these analyses, the drug of interest was excluded from the medication category of monotherapies with immunosuppressive drugs or from the biologics/targeted synthetic only category, and their effects were estimated separately. Four models were constructed for each medication: (1) unadjusted, (2) age-adjusted and sex-adjusted, (3) adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region, time period and (4) confirmed cases (diagnosis made by PCR, antibody or antigen) adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region and time period. Additionally, to evaluate the interaction between GC therapy and disease activity, an additional analysis was done adding this multiplicative interaction term.

A sensitivity analysis combining mechanical ventilation or death in the highest category was also performed.

Results were considered statistically significant using a two-sided p<0.05. Analyses were conducted in R V.4.0.2 (R Core Team, 2020).

RESULTS

As of 1 June 2021, 1922 subjects with SLE and COVID-19 were reported in the C19-GRA and EULAR registries. Baseline demographic and clinical characteristics are shown in table 1. Individuals were predominantly female (90.4%) and the mean age was 44.4 years (SD=14.1). Of the 1922 cases, 555 (28.9%) were reported from the USA and Canada, 543 (28.3%) from Europe, 643 (33.5%) from Latin America and 181 (9.4%) from other regions. The majority were non-white (57.3%).

Antimalarials were used as monotherapy by 665 individuals (34.6%), more intense immunosuppressive monotherapies (MMF, tacrolimus, cyclophosphamide, ciclosporin, azathioprine, with or without antimalarials) were used by 630 individuals

Table 1 Characteristics of patients with SLE at the time of COVID-19 diagnosis (n=1922)

Characteristics	Mean (SD) or number (percentage)
Age, years, mean (SD)	44.4 (14.1)
Female, n (%)	1734 (90.4%)
Race/Ethnicity, n (%)	
White	639 (33.3%)
Non-white	1102 (57.3%)
Missing	181 (9.4%)
Region, n (%)	
Europe	543 (28.3%)
USA and Canada	555 (28.9%)
Latin America	643 (33.5%)
Other	181 (9.4%)
Time period, n (%)	
<15 June 2020	733 (38.1%)
16 June–30 September 2020	444 (23.1%)
1 October 2020–12 April 2021	745 (38.8%)
Comorbidities, n (%)	
0	1098 (57.1%)
1	511 (26.6%)
≥2	313 (16.3%)
Specific comorbidities, n (%)	
Chronic renal insufficiency or ESRD	223 (11.8%)
Hypertension or cardiovascular disease	597 (31.1%)
Disease activity, n (%)	
Remission	587 (30.5%)
Minimal or low	700 (36.4%)
Moderate	229 (11.9%)
Severe or high	77 (4.0%)
Missing	329 (17.1%)
Prednisone dose*, n (%)	
0 mg/day	846 (44.0%)
1–5 mg/day	467 (24.3%)
6–9 mg/day	78 (4.1%)
≥10 mg/day	280 (14.6%)
Missing	251 (13.1%)
Medication category, n (%)	
Antimalarials only	665 (34.6%)
No SLE therapy	230 (12.0%)
Oral synthetic drug monotherapy with methotrexate, leflunomide or sulfasalazine only†	175 (9.1%)
Oral synthetic drug monotherapy with (mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, ciclosporin or azathioprine)†	630 (32.8%)
Biologic/Targeted synthetic monotherapy	45 (2.3%)
Biologic/Targeted and immunosuppressive drug combination therapy†	177 (9.2%)

*All glucocorticoids were converted to prednisone-equivalent doses.
†These patients could be also on antimalarials.
ESRD, end-stage renal disease; SLE, systemic lupus erythematosus.

Table 2 Ordinal COVID-19 severity outcome as a function of medication class in individuals with SLE (n=1606)

	Total (n=1606)	Antimalarial only (n=532)	No DMARD (n=182)	Monotherapy with methotrexate, leflunomide or sulfasalazine only* (n=152)	Monotherapy with mycophenolate/ mycophenolic acid, tacrolimus, cyclophosphamide, ciclosporin or azathioprine* (n=539)	Biologic/Targeted monotherapy* (n=40)	Biologic/Targeted+ immunosuppressive drug combination therapy* (n=161)
Not hospitalised	1118 (69.6%)	401 (75.4%)	102 (56.0%)	117 (77.0%)	358 (66.4%)	27 (67.5%)	113 (70.2%)
Hospitalised with no oxygenation	169 (10.5%)	50 (9.4%)	26 (14.3%)	14 (9.2%)	62 (11.5%)	4 (10.0%)	13 (8.1%)
Hospitalised with any ventilation/oxygenation	214 (13.3%)	53 (10.0%)	34 (18.7%)	14 (9.2%)	84 (15.6%)	6 (15.0%)	23 (14.3%)
Death	105 (6.5%)	28 (5.3%)	20 (11.0%)	7 (4.6%)	35 (6.5%)	3 (7.5%)	12 (7.5%)

*These patients could be also on antimalarials.
DMARD, disease-modifying antirheumatic drug; SLE, systemic lupus erythematosus.

(32.8%) at the time of COVID-19 onset. Two hundred and thirty (12.0%) individuals did not take immunosuppressive drugs or antimalarials. Eight hundred and forty-six (44.0%) individuals did not take prednisone, 467 (24.3%) individuals took between 1 and 5 mg/day, 78 (4.1%) individuals took between 6 and 9 mg/day and 280 (14.6%) individuals took a dose ≥10 mg/day.

Clinical outcomes, as well as outcomes as a function of treatment, for 1606 individuals were captured and are shown in table 2. The majority of individuals (69.6%) were not hospitalised. In the model including demographics, clinical characteristics, medications and disease activity, there were significant associations between demographic factors (older age, male sex, geographic location (being from outside of Europe, USA and Canada and Latin America), time period of the pandemic) and the ordinal severity outcome. Among comorbidities, chronic renal insufficiency or end-stage renal disease, hypertension/cardiovascular disease and the number of other comorbidities were associated with more severe outcomes. GC use was also associated with more severe outcomes compared with those without GCs. Those who were not being treated for their SLE, or had moderate or high SLE disease activity also experienced more severe outcomes compared with those on remission (table 3). These findings were consistent across various sensitivity analysis models (online supplemental table 1).

Finally, additional analyses were performed to assess the associations of methotrexate, azathioprine, MMF, cyclophosphamide, rituximab and belimumab separately with the ordinal severity outcome, demonstrating that there was no independent association of these drugs with the ordinal severity outcome in the fully adjusted model; however, rituximab was associated with poorer outcomes and belimumab with better outcomes in the unadjusted as well as the age-adjusted and sex-adjusted model, and MMF and cyclophosphamide were associated with poorer outcomes and methotrexate was associated with better outcomes only in the age-adjusted and sex-adjusted model (table 4). There was no statistically significant interaction between GC dose and disease activity or between DMARD use and disease activity (data not shown).

The results were nearly identical (online supplemental tables 2 and 3) in the alternative model in which mechanical ventilation and death were combined to constitute the highest category.

DISCUSSION

During the COVID-19 pandemic, rheumatologists have been particularly concerned about individuals with SLE. These individuals are often significantly immunosuppressed, commonly use moderate or high doses of GCs and have a high comorbidity burden. Moreover, many types of immune dysregulation occur in SLE, including in the interferon pathway, which is critical to the innate immune response during SARS-CoV-2 infection.[16] However, SLE is a relatively uncommon disease and it has been difficult to accumulate a sufficient number of cases to examine risk factors for poor COVID-19 outcomes in this

Table 3 Multivariable ordinal regression model examining characteristics associated with more severe COVID-19 outcomes in individuals with SLE

Covariate	OR (95% CI)	P value
Age (years)	1.03 (1.02 to 1.04)	<0.001**
Sex		
Male	1.50 (1.01 to 2.23)	0.042*
Region		
Europe	Reference	
USA and Canada	0.82 (0.22 to 3.02)	0.76
Latin America	1.97 (0.87 to 4.48)	0.11
Other	4.79 (2.21 to 10.37)	<0.001**
Time period		
≤15 June 2020	Reference	
16 June–30 September 2020	0.50 (0.35 to 0.72)	<0.001**
1 October 2020–12 April 2021	0.40 (0.29 to 0.57)	<0.001**
GC dose		
0 mg/day	Reference	
1–5 mg/day	1.86 (1.30 to 2.66)	<0.001**
6–9 mg/day	2.47 (1.25 to 4.86)	0.009**
≥10 mg/day	1.95 (1.27 to 2.99)	0.002**
Medication category		
Antimalarial only	Reference	
No SLE therapy	1.80 (1.17 to 2.75)	0.007**
Monotherapy with methotrexate, leflunomide or sulfasalazine only†	0.74 (0.44 to 1.24)	0.25
Monotherapy with mycophenolate/mycophenolic acid, tacrolimus, cyclophosphamide, ciclosporin or azathioprine†	1.01 (0.71 to 1.43)	0.95
Biologic/Targeted synthetic drug monotherapy	1.38 (0.58 to 3.26)	0.47
Biologic/Targeted synthetic drug and immunosuppressive drug combination therapy†	1.17 (0.72 to 1.91)	0.52
Number of comorbidities (excluding renal and cardiovascular disease/hypertension)	1.60 (1.24 to 2.07)	<0.001**
Chronic renal insufficiency or end-stage renal disease	3.51 (2.42 to 5.09)	<0.001**
Cardiovascular/Hypertension	1.69 (1.25 to 2.29)	<0.001**
Disease activity		
Remission	Reference	
Minimal or low	0.86 (0.61 to 1.21)	0.38
Moderate	1.61 (1.02 to 2.54)	0.041*
Severe or high	3.94 (2.11 to 7.34)	<0.001**

Each model adjusted for all variables listed, and random effects for country and time.
*P<0.05; **p<0.01.
†These patients could be also on antimalarials.
GC, glucocorticoids; SLE, systemic lupus erythematosus.

Table 4 Ordinal regression models examining the association between individual medications and more severe COVID-19 outcomes in individuals with SLE

	Number of individuals taking medication prior to COVID-19 diagnosis with observed outcome	Unadjusted n=1606		Age-adjusted and sex- adjusted n=1606		Fully adjusted model† n=1606		Fully adjusted model +confirmed COVID-19‡ n=1283	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Methotrexate	173	0.71 (0.50 to 1.01)	0.06	0.67 (0.47 to 0.97)	0.032*	0.71 (0.43 to 1.16)	0.17	0.71 (0.40 to 1.25)	0.23
Azathioprine	235	0.88 (0.66 to 1.19)	0.42	0.95 (0.70 to 1.29)	0.75	0.87 (0.57 to 1.34)	0.53	0.89 (0.54 to 1.47)	0.65
Mycophenolate/Mycophenolic acid	332	1.20 (0.93 to 1.55)	0.15	1.36 (1.05 to 1.76)	0.021*	1.08 (0.73 to 1.59)	0.72	1.27 (0.82 to 1.98)	0.29
Cyclophosphamide	29	1.92 (0.95 to 3.91)	0.07	2.55 (1.23 to 5.28)	0.012*	–	–	–	–
Rituximab	68	1.62 (1.00 to 2.63)	0.049*	1.69 (1.04 to 2.75)	0.036*	1.56 (0.84 to 2.90)	0.16	1.91 (0.97 to 3.79)	0.063
Belimumab	104	0.52 (0.32 to 0.86)	0.011*	0.51 (0.31 to 0.85)	<0.001**	0.66 (0.34 to 1.28)	0.22	0.65 (0.31 to 1.34)	0.24

*P<0.05; **p<0.01.
†Model adjusted for age, sex, renal disease, hypertension/cardiovascular disease, comorbidity count, disease activity, region, time period, glucocorticoid and and other DMARD medication categories; random effects applied for country and time. Reference group=antimalarial only.
‡Confirmed cases were defined as having a diagnosis made by PCR, antibody or antigen test or a CT scan.
DMARD, disease-modifying antirheumatic drug; SLE, systemic lupus erythematosus.

vulnerable population. Here, we report the largest study of SLE and COVID-19 to date. In our analyses of over 1600 cases, we found that the use of GCs, having untreated or active SLE, or using rituximab was associated with more severe COVID-19 outcomes. In addition to these factors specific to SLE, our findings also highlight that many factors associated with more severe COVID-19 outcomes in the general population are important in SLE, including male gender,[15 17 18] age[17–20] and comorbidity burden.[17–19]

Prednisone use, even at relatively low doses of <5 mg/day, was associated with poorer outcomes in our analysis. In the C19-GRA registry, which included a wide array of rheumatic diseases, only prednisone at doses ≥10 mg/day was associated with hospitalisation or mortality.[4 13] Interestingly, in additional analyses of the registry we found that in the absence of disease activity, the relationship between GC and mortality diminished.[21] However, in SLE, even low doses of GCs were associated with more severe COVID-19 outcomes, including in those with low disease activity. Like our results, in a small study from Belgium, glucocorticoid dose was positively associated with a higher risk of hospitalisation in patients with SLE.[22] These findings suggest that GCs are of special concern during the pandemic for people with SLE.

Our analyses also demonstrated that individuals not receiving treatment for their SLE at the time of COVID-19 diagnosis had poorer outcomes. The poor outcomes seen in this group may be multifactorial, and it is plausible that social risk factors play a role, such as lack of access to SLE care or treatment, or poor adherence with medications. Consistent with these results, individuals outside Europe, the USA and Canada had a poorer outcome, possibly related to healthcare access, but it was not statistically significant for Latin American individuals. Poverty and inequality have been associated with a higher risk and severity of COVID-19 globally,[14 23] and it is likely that health disparities in SLE may be exacerbated by the pandemic.

Rituximab has been associated with poorer outcomes in patients with RA.[2] We also found this association in SLE in our analysis, but it was present only in the unadjusted and age-adjusted and sex-adjusted models; this may be due to the smaller number of individuals on rituximab in our study and resultantly low power in statistical analyses (n=68). In fully adjusted models (including confirmed cases and those diagnosed based on symptoms and epidemiological criteria), there was a trend for an association between rituximab and poorer outcomes. It is important to point out that in the age-adjusted and sex-adjusted models MMF, cyclophosphamide was associated with poorer outcomes. Cyclophosphamide was not evaluated in a fully adjusted model due to a small sample size. These findings are similar to what has been reported in other studies. For example, in a recent meta-regression including several rheumatic diseases, GC use and immunosuppressive drugs use in monotherapy or combination were associated with hospitalisation and death from COVID-19.[24] Patients using belimumab generally had more favourable outcomes in our study; it is unclear if this may partly reflect confounding by healthcare access or socioeconomic status, as this drug is more commonly used in high-income nations. The association between methotrexate and better outcomes in the age-adjusted and sex-adjusted model could be related to a better disease activity control, as it did not remain significantly associated in the fully adjusted model. Because there were multiple comparisons, significance should be interpreted with caution. Given that there were six statistical comparisons made, one approach is to adjust the p value to a 0.01 level of significance. Using this more conservative approach, belimumab still remains statistically associated with less severe COVID-19 outcomes in the age-adjusted and sex-adjusted model.

Previous investigators have found an association between SLE disease activity and serious infections.[25] It is likely that both underlying immune dysfunction and the use of immunosuppressive therapies increase the risk of infection in SLE, which would explain the association between SLE disease activity and the severity of SARS-CoV-2 infection reported here.

The prognosis of patients with COVID-19 has improved over the course of the pandemic, which may be the result of many factors, including more widespread testing (leading to diagnosis of milder cases), improved pharmacological therapy and a better understanding of the timing, method of ventilatory support in critically ill patients and vaccination status for the most recent cases. Our findings suggest that patients with SLE diagnosed in later periods of the pandemic had better outcomes relative to the first part of the pandemic, which is consistent with the overall trends in the general population.[26]

It is important to note that chronic kidney disease, a common and serious complication of SLE, has one of the strongest associations with poor COVID-19 outcomes. Chronic kidney disease is also an important risk factor for severe COVID-19 in the general population and may even pose a greater risk than the presence of diabetes.[27] In addition to renal disease, our findings indicate that other comorbidities also increase the risk of severe outcomes, which is consistent with numerous previous studies.[4 19 21] In SLE, medications, particularly GCs, can impact important comorbidities such as hypertension,

diabetes or obesity,[28] which likely increases vulnerability to severe COVID-19 outcomes.

Several limitations of this study should be noted. First, the C19-GRA is a registry that is predicated on physician reporting of COVID-19 in patients with rheumatic disease, and as such, may be skewed to include more severe COVID-19 cases. Patients with more severe COVID-19 are more likely to come to the attention of their rheumatology provider. Second, even though we were able to examine the relationship of several factors with more severe outcomes, we cannot exclude other confounders like access to healthcare or socioeconomic status. Third, although the physician global assessment is a valid, responsive and feasible instrument, given its less than optimal reliability it is not ideal to just assess it to the exclusion of the patient's assessment or other measures of disease activity; this is a limitation of our study. Finally, we were underpowered to look at some important treatments for SLE, such as cyclophosphamide, in our fully adjusted models; data on voclosporin and anifrolumab, two newly approved therapies for SLE, were not available in the registry at the time of our analyses.

In conclusion, we found that in addition to age, male sex and comorbidities, the use of GCs and having untreated or active disease were associated with more severe COVID-19 outcomes in individuals with SLE. Individuals with these characteristics should be prioritised for close monitoring, counselled to receive vaccination and receive preventive therapies such as monoclonal antibodies (when available) if exposed to SARS-CoV-2.

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Ethics approval This study involves human participants but the UK Health Research Authority and the University of Manchester, as well as the University of California, San Francisco Institutional Review Board exempted this study. The C19-GRA physician-reported registry was defined as 'not human subjects research' by the UK Health Research Authority and the University of Manchester, as well as under US Federal Guidelines assessed by the University of California, San Francisco Institutional Review Board. Due to the de-identified and non-interventional nature of the study, it was determined to be exempt by each institutional review board.

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