Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Short term outcomes of COVID-19 in lupus: Propensity score matched analysis from a nationwide multi-centric research network

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ABSTRACT

Objectives: To determine the severity and outcome of COVID-19 among individuals with lupus as compared to controls. The secondary objective was to identify the risk association of sex, race, presence of nephritis, and use of various immunomodulators with COVID-19 outcomes.

Methods: Retrospective data of individuals with lupus with and without COVID-19 between January 2020 to May 2021 was retrieved from the TriNetX. A one-to-one matched COVID-19 positive control was selected using propensity score(PS) matching. We assessed several outcomes, including all-cause mortality, hospitalisation, intensive care unit (ICU) admission, mechanical ventilation, severe COVID, acute kidney injury (AKI), Haemodialysis, acute respiratory distress syndrome (ARDS), ischemic stroke, venous thromboembolism (VTE) and sepsis were assessed.

Results: We identified 2140 SLE patients with COVID-19, 29,853 SLE without COVID-19 and 732,291controls. Mortality within 30 days of COVID-19 diagnosis was comparable among SLE and controls [RR-1.26; 95%CI-0.85,1.8]. SLE with COVID-19 had a higher risk of hospitalisation [RR-1.28; 95% CI 1.14–1.44], ICU admission [RR-1.35; 95% CI 1.01–1.83], mechanical ventilation [RR- 1.58 95% CI 1.07–2.33], stroke [RR-2.18; 95% CI 1.32,3.60], VTE [RR-2.22; 95% CI 1.57–03.12] and sepsis [RR-1.37; 95% CI 1.06–1.78].Individuals with SLE who contracted COVID-19 had higher mortality, hospitalisation, ICU admission, mechanical ventilation, AKI, VTE and sepsis ($p < 0.001$) compared to SLE without COVID-19. Males with SLE had a higher risk of AKI [RR-2.05; 95% CI 1.27–3.31] than females. Lupus nephritis was associated with higher risk of hospitalisation [RR-1.36; 95% CI 1.05–1.76], AKI [RR-2.32; 95% CI 1.50–3.59] and sepsis [RR-2.07; 95% CI-1.12–3.83].

Conclusion: The mortality of individuals with SLE due to COVID-19 is comparable to the general population but with higher risks of hospitalisation, ICU admission, mechanical ventilation, stroke, VTE and sepsis. The presence of nephritis increases the risk of AKI, thus probably increasing hospitalisation and sepsis

1. Introduction

The Coronavirus Disease 2019 (COVID-19) has affected over 180 million worldwide since its first reporting in December 2019 [1]. The pandemic has resulted in over 3,104,743 human deaths and has tested the limits of the healthcare systems across the world. The overarching theme emerging from data across the globe is that the severity of COVID-19 is worse among several vulnerable groups. Various studies

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have identified factors like older age, male sex, presence of comorbidities like diabetes mellitus and hypertension as important determinants of poor outcomes in the general population [2–4]. Individuals living with rheumatic and musculoskeletal diseases (RMDs) are, however, underrepresented in those studies.

Several studies that have focused on the COVID-19 outcomes in patients with RMD have shown mixed results. While some studies have shown no difference in outcomes of COVID-19 among those with RMDs as compared to the general population [5–7], a few others have shown contradicting results [8,9]. The reasons for such diverse results may be numerous, ranging from the geographical location, the genetic make-up of the study population, prevalence of comorbidities, immunosuppressive agent usage, and, most importantly, the heterogeneity between different RMDs. Hence, evaluating the outcomes of COVID-19 collating all the RMDs in a single group may not be an optimal approach.

Systemic lupus erythematosus (SLE) is a heterogeneous group of autoimmune diseases with manifestations ranging from mild skin rash to life-threatening renal, musculoskeletal, neuropsychiatric or pulmonary disease. The organ involvement, comorbidities and immunosuppressive agents used in SLE may directly bear on the mortality and morbidity of these patients. Treatment of SLE is usually a combination of glucocorticoids and immunosuppressive agents, including cyclophosphamide, mycophenolic acid, azathioprine, methotrexate and calcineurin inhibitors. Several biological agents like rituximab which have shown poor outcomes among those contracting COVID-19 [10] are being increasingly used to treat lupus. Moreover, interferons which are key antiviral cytokines, are elevated in the majority of the individuals with SLE [11], which may have some protective effect against SARS-CoV-2 infection.

On the other hand, the interferon response is altered that might have unpredictable effects on the infection. Therefore, it is important to study the impact of COVID-19 on SLE. The studies performed specifically in SLE have been limited by relatively small sample sizes [12,13]. To overcome this limitation which is often encountered in single centre studies, and to control adequately for the variables, we derived the information from a large electronic healthcare database.

We utilised the TriNetX database to determine the severity and outcome of COVID-19 among individuals with SLE as compared to matched controls. The secondary objective was to identify the association of several factors, including sex, race, presence of nephritis, and use of various immunomodulators with poor COVID-19 outcomes.

2. Materials and methods

2.1. Design and participants

In this retrospective population-based comparative study, data of individuals diagnosed with systemic lupus erythematosus with and without COVID-19 between January 2020 and May 2021 was retrieved from the TriNetX (Cambridge, MA) Research Network using International Classification of Diseases tenth revision (ICD-10), Current Procedural Terminology (CPT) codes, or Logical Observation Identifiers Names and Codes (LOINC) (Supplementary material 1). A one-to-one matched COVID-19 positive controls who did not have a diagnosis of RMD was selected using propensity score(PS) (Supplementary material 1).

2.2. Outcomes

We then compared the following outcomes: All-cause mortality, hospitalisation, intensive care unit (ICU) admission, mechanical ventilation, severe COVID, acute kidney injury (AKI), kidney replacement therapy (KRT)/Haemodialysis, acute respiratory distress syndrome (ARDS), ischemic stroke, venous thromboembolism (VTE) and sepsis within 30-day after the COVID-19 diagnosis between individuals with SLE and the matched general population. Severe COVID defined as mortality or those requiring mechanical ventilation was considered as a composite variable. The time window of 30 days was considered for this study because certain states in the United states of America needed additional accreditation for deaths reported beyond 30 days and that information may not have been available in the database at the time of analysis [14]. For SLE without COVID-19, all the outcomes except severe COVID were compared between lupus patients with and without COVID-19 infection.

Following this analysis, we conducted subgroup analyses looking at the difference in the outcomes among the individuals with SLE with COVID-19. The subgroups were based on sex, race, presence of nephritis, use of biological diseases modifying drugs (DMARDS) versus those on conventional synthetic DMARDs.

2.2.1. Variables

Demographic characteristics (age, sex, race, body mass index), presence of comorbidities (hypertension [ICD10 code: I10], chronic lower lung disease [ICD10 codes: J40-J47], diabetes mellitus [ICD10 codes: E08-E13], ischemic heart disease [ICD10 codes: I20–I25], chronic kidney disease (CKD) [ICD10 codes: N18], heart failure [ICD10 codes: I50], cerebrovascular disease [ICD10 codes: I60–I69], nicotine dependence [ICD10 code:F17] and malignancies [ICD were extracted. Records of medication used in the 12 months preceding the diagnosis of COVID-19 were extracted.

Details of glucocorticoid prescription which included Prednisone, Methylprednisolone and Dexamethasone any time in the last 3 months were extracted for analysis. Biological DMARDs considered were B-cell activating factor inhibitors (belimumab), CD20 inhibitors (rituximab, ocrelizumab, ofatumumab), CTLA-4 immunoglobulin (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), IL-23 inhibitors (ustekinumab) and TNF-inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab). CsDMARDs included Azathioprine, Cyclophosphamide, Cyclosporine, Hydroxychloroquine, Leflunomide, Methotrexate, Mycophenolate (MMF)/mycophenolic acid and Sulfasalazine.

2.3. Statistics

Propensity scores (PS) was used to select matching controls using the greedy nearest-neighbour algorithm with a calliper of 0.1 pooled standard deviations. The demographic characteristics and comorbidities mentioned above were used as covariates for the matching. Risk ratios (with 95% confidence intervals) were calculated for the outcomes mentioned above, comparing with both unmatched and matched controls as described in a previous publication [15]. Two-sided tests of significance were used with a p-value of less than 0.05 taken as the cut-off. Any cell counts <11 are obfuscated to protect patient privacy, and any statistical results with these values were not reported.

2.4. Ethics statement

Use of the TriNetX database is covered under a waiver by the Western Institutional Review Board since it provides only de-identified data such as aggregated counts and statistical summaries.

3. Results

We identified 2140 SLE patients who had COVID-19 and 29,853 individuals with SLE without COVID-19, and 732,291controls with no diagnosis of RMD. The average age of individuals with SLE with COVID-19 was 49.4 $\pm$ 15.6 years and was similar to SLE without COVID (48.4 $\pm$ 16.1 years) and the general population (47.4 $\pm$ 18.6 years). Over 85% of individuals with SLE were females, and just more than half (50.33%) were white. Demographics and prevalence of different comorbidities in SLE and the general population are represented in Table 1. After matching for age, sex, BMI, and comorbidities,2,135individuals with

Table 1
Unmatched and matched features of individuals with lupus and general population with COVID-19 infection in the database.

Parameters		Unmatched SLE	Unmatched General population		Matched SLE	Matched General population	
Total numbers		N = 2140	N = 732,291	S.DIFF	N = 2135	N = 2135	S.DIFF
Age (years)		49.4 ± 15.6	47.4 ± 18.6	0.1187	49.5 ± 15.6	51.5 ± 16.3	0.1308
Body Mass Index (>30)		689 (32.2%)	125,233 (17.1%)	0.3558	687 (32.2%)	730 (34.2%)	0.0428
Female		1867 (87.24%)	400,822 (54.74%)	0.7672	1862 (87.21%)	1855 (86.89%)	0.0098
R	Other Race	1077 (50.33%)	449,291 (61.35%)	0.2234	1077 (50.45%)	1104 (51.71%)	0.0253
A	African Americans	718 (33.55%)	128,707 (17.58%)	0.3725	713 (33.4%)	701 (32.83%)	0.0119
C	Asian	41 (1.92%)	18,051 (2.47%)	0.0375	41 (1.92%)	32 (1.5%)	0.0325
E							
C	Hypertension (%)	1120(52.34%)	178,976 (24.44%)	0.5988	1115 (52.23%)	1156 (54.15%)	0.0385
O	ILD (%)	42 (1.96%)	1938 (0.27%)	0.1623	40 (1.87%)	37 (1.73%)	0.0106
M	CKD (%)	484 (22.62%)	35,774 (4.89%)	0.5328	479 (22.44%)	501 (23.47%)	0.0245
O	Type 2 DM (%)	445 (20.79%)	87,316 (11.92%)	0.2416	445 (20.84%)	475 (22.25%)	0.0342
R	IHD (%)	350 (16.36%)	51,574 (7.04%)	0.2928	346 (16.21%)	357 (16.72%)	0.0139
B	CHF (%)	265 (12.38%)	28,780 (3.93%)	0.3126	262 (12.27%)	275 (12.88%)	0.0184
I	STROKE (%)	261 (12.2%)	31,072 (4.24%)	0.2926	259 (12.13%)	246 (11.52%)	0.0189
D	Nicotine Dependence	323 (15.09%)	51,864 (7.08%)	0.2572	319 (14.941%)	332 (15.55%)	0.0169
I	Neoplasms	676 (31.59%)	125,991 (17.21%)	0.3397	671 (31.43%)	689 (32.27%)	0.0181
T	Alcohol Related Disorder	79 (3.69%)	17,357 (2.37%)	0.0771	77 (3.61%)	86 (4.03%)	0.0220
I	Chronic Lower Respiratory Diseases	670 (31.31%)	102,870 (14.05%)	0.4212	665 (31.15%)	708 (33.16%)	0.0431
E							
S							

S. Diff- Standardized difference, ILD- Interstitial lung diseases, CKD- Chronic kidney disease, DM- Diabetes mellitus, IHD- Ischemic heart disease, CHF- Chronic heart failure.

SLE and controls with COVID-19 were identified with a standardised difference of all matched parameters less than 0.15 (Tables 1 and 2).

3.1. Outcomes

In comparison, the risk of death due to COVID among SLE was comparable to that in the PS matched general population [RR-1.26; 95% CI-0.85,1.8]. But SLE with COVID had a higher risk of hospitalisation RR-1.28; 95% CI 1.14–1.44], intensive care unit admission [RR-1.35; 95% CI 1.01–1.83], mechanical ventilation [RR- 1.58 95% CI 1.07–2.33], stroke [RR-2.18; 95% CI 1.32,3.60], venous thromboembolism [RR-2.22; 95% CI 1.57–03.12] and sepsis [RR-1.37; 95% CI 1.06–1.78](Table 3).

During the same time frame individuals with SLE who contracted COVID-19 had worse outcomes in the form of higher all-cause mortality [RR-4.91; 95% CI 2.57–9.36], hospitalisation [RR-1.62; 95% CI 1.43–1.85], ICU admission RR-3.73; 95% CI 2.17–4.94], mechanical ventilation [RR-3.82; 95% CI 2.25–6.5], AKI [RR-2.08 95% CI 1.62–2.67], VTE RR-1.49; 95% CI 1.10–2.02] and sepsis RR-4.78; 95% CI 3.17–7.21] compared to SLE without COVID-19 (Table 3).

3.2. sub-group analyses

Individuals with lupus nephritis had a higher risk of hospitalisation [RR-1.36; 95% CI 1.05–1.76], acute kidney injury [RR-2.32; 95% CI 1.50–3.59] and sepsis [RR-2.07; 95% CI-1.12–3.83] as compared to those with SLE without pre-existing nephritis but the risk for mortality was comparable between the two subgroups (Table 4).

When the effect of race was analysed, we found that there was no difference in outcomes between African Americans as compared to the white races(Supplementary Table 4).

On analysis of sex-based outcomes of the patients, males with SLE had a higher risk of AKI [RR-2.05; 95% CI 1.27–3.31] than females. All the other outcomes were similar across both sexes (Supplementary

Table 2
Unmatched and matched features of lupus with and without COVID-19 infection in the database.

Parameters		SLE with COVID	Unmatched SLE without COVID		Matched SLE with COVID	Matched SLE without COVID	
Total numbers		N = 2140	N = 29,853	S.DIFF	N = 2135	N = 2135	S.DIFF
Age (years)		49.4 ± 15.6	48.4 ± 16.1	0.0625	49.4 ± 15.6	49.4 ± 15.5	0.0005
Body Mass Index		31.6 ± 8.41	29.6 ± 7.81	0.2368	31.6 ± 8.42	30.9 ± 8.19	0.0822
Female		1867 (87.24%)	26,366 (88.32%)	0.0329	1864 (87.31%)	1888 (88.43%)	0.0344
R	Other Race	1077 (50.33%)	16,205 (54.28%)	0.0793	1077 (50.45%)	1087 (50.91%)	0.0094
A	African Americans	718 (33.55%)	8139 (27.26%)	0.1370	714 (33.44%)	718 (33.63%)	0.0040
C	Asian	41 (1.92%)	829 (2.78%)	0.0569	41 (1.92%)	52 (2.44%)	0.0353
E							
C	Hypertension (%)	1120 (52.34%)	10,380 (34.77%)	0.3600	1115 (52.23%)	1127 (52.79%)	0.0113
O	ILD (%)	79 (3.69%)	637 (2.13%)	0.0927	76 (3.56%)	72 (3.37%)	0.0102
M	CKD (%)	42 (1.96%)	372 (1.25%)	0.0571	41 (1.92%)	37 (1.73%)	0.0140
O	Type 2 DM (%)	445 (20.79%)	3344 (11.20%)	0.2639	440 (20.61%)	430 (20.14%)	0.0116
R	IHD (%)	350 (16.36%)	2739 (9.18%)	0.2164	347 (16.25%)	311 (14.57%)	0.0467
B	CHF (%)	484 (22.62%)	4324 (14.48%)	0.2104	479 (22.44%)	460 (21.55%)	0.0215
I	STROKE (%)	265 (12.38%)	1864 (6.24%)	0.2124	260 (12.18%)	222 (10.4%)	0.0563
D	Nicotine Dependence	261 (12.2%)	2125 (7.12%)	0.1726	258 (12.08%)	230 (10.77%)	0.0412
I	Neoplasms	323 (15.09%)	3336 (11.18%)	0.1162	322 (15.08%)	310 (14.52%)	0.0158
T	Alcohol Related Disorder	676 (31.59%)	6489 (21.74%)	0.2242	672 (31.48%)	702 (32.88%)	0.0301
I	Chronic Lower Respiratory Diseases	670 (31.31%)	5461 (18.29%)	0.3049	665 (31.15%)	682 (31.94%)	0.0171
E							
S							

S. Diff- Standardized difference, ILD- Interstitial lung diseases, CKD- Chronic kidney disease, DM- Diabetes mellitus, IHD- Ischemic heart disease, CHF- Chronic heart failure.

Table 3
Risk of adverse COVID outcomes between propensity matched individuals with SLE and general population and over all-cause outcomes between SLE with and without COVID-19 infection.

Parameters	Matched SLE with COVID-19	Matched General population with COVID-19			Matched SLE with COVID-19	Matched SLE without COVID-19		
Outcome	N = 2135	N = 2135	Risk Ratio [95%CI]	*p*-value	N = 2135	N = 2135	Risk Ratio [95%CI]	*P*-value
Mortality	54 (2.53%)	43 (2.01%)	1.26 [0.85,1.87]	0.26	54 (2.53%)	11 (0.52%)	4.91 [2.57,9.36]	<0.001
Hospitalisation	498 (23.33%)	390 (18.27%)	1.28 [1.14,1.44]	<0.001	498 (23.33%)	307 (14.38%)	1.62 [1.43,1.85]	<0.001
ICU admission	96 (4.5%)	71 (3.33%)	1.35 [1.01,1.83]	0.048	95 (4.45%)	29 (1.36%)	3.73 [2.17,4.94]	<0.001
Mechanical Ventilation	63 (2.98%)	40 (1.89%)	1.58 [1.07,2.33]	0.022	65 (3.04%)	17 (0.8%)	3.82 [2.25,6.5]	<0.001
AKI	180 (8.43%)	147 (6.89%)	1.22 [0.99,1.51]	0.058	179 (8.38%)	86 (4.03%)	2.08 [1.62,2.67]	<0.001
KRT	17 (0.86%)	11 (0.54%)	1.59 [0.75,3.39]	0.223	17 (0.86%)	20 (0.99%)	0.87 [0.46,1.66]	0.68
ARDS	41 (1.92%)	29 (1.36%)	1.41 [0.88,2.27]	0.148	41 (1.92%)	10*	NA	NA
STROKE	48 (2.25%)	22 (1.03%)	2.18 [1.32,3.60]	0.002	47 (2.20%)	51 (2.39%)	0.92 [0.62,1.36]	0.683
VTE	102 (4.78%)	46 (2.16%)	2.22 [1.57,3.12]	<0.001	100 (4.68%)	67 (3.14%)	1.49 [1.10,2.02]	0.009
Sepsis	129 (6.04%)	94 (4.40%)	1.37 [1.06,1.78]	0.016	129 (6.04%)	27 (1.27%)	4.78 [3.17,7.21]	<0.001

AKI- Acute kidney injury, ARDS- acute respiratory distress syndrome, ICU- intensive care unit, KRT- Kidney replacement therapy, NA- Not applicable, VTE-venous thromboembolism, * < 11 events (number was hidden by TriNetX for privacy reasons).

Table 4
Comparison of adverse COVID-19 outcomes between individuals with and without lupus nephritis.

Outcome	Before Propensity Matching		Risk Ratio [CI]	*P*-value	After Propensity Matching		Risk Ratio	*P*-value
	SLE-Nephritis	SLE-Non nephritis			SLE Nephritis	SLE Non nephritis		
	N = 326	N = 1814			N = 251	N = 251		
Mortality	10*	46 (2.54%)	NA	NA	10*	10*	NA	NA
Hospitalisation	113 (34.66%)	388 (21.4%)	1.621 [1.36,1.93]	<0.001	94 (37.45%)	69 (27.49%)	1.36 [1.05,1.76]	0.017
ICU admission	24 (7.36%)	72 (3.97%)	1.855 [1.19,2.90]	0.006	19 (7.57%)	10*	NA	NA
Mechanical Ventilation	15 (4.60%)	51 (2.81%)	1.637 [0.93,2.88]	0.085	12 (4.78%)	10*	NA	NA
Severe COVID[#]	18 5.52%	75 4.14%	1.34 [0.81,2.20]	0.001	15 (5.98%)	12 (4.78%)	1.25 [0.6,2.62]	0.553
AKI	65 (19.94%)	117 (6.45%)	3.09 [2.34,4.09]	<0.001	58 (23%)	25 (10%)	2.32 [1.50,3.59]	<0.001
KRT	10*	10*	NA	NA	10*	10*	NA	NA
ARDS	14 (4.29%)	27 (1.49%)	2.89 [1.53,5.44]	<0.001	13 (5.2%)	10*	NA	NA
STROKE	10*	43 (2.37%)	NA	NA	10*	13 (5.18%)	NA	NA
VTE	24 (7.36%)	78 (4.3%)	1.712 [1.1,2.66]	0.017	19 (7.57%)	17 (6.77%)	1.12 [0.6,2.1]	0.729
Sepsis	32 (9.82%)	97 (5.35%)	1.836 [1.25,2.77]	0.002	29 (11.6%)	14 (5.58%)	2.07 [1.12,3.83]	0.017

AKI- Acute kidney injury, ARDS- acute respiratory distress syndrome, ICU- intensive care unit, KRT- Kidney replacement therapy, VTE-venous thromboembolism, * < 11 events (number was hidden by TriNetX for privacy reasons), [#] Severe COVID= Mortality or Mechanical ventilation.

Table 3). Use of glucocorticoids (Supplementary Table 5) was associated with higher hospitalisation [RR-3.03; 95% CI 2.47, 3.71], ICU admission [RR-3.56; 95% CI 2.07,6.15], severe COVID which is a composite measure of mortality and mechanical ventilation [RR-4.84; 95% CI -2.69,8.73], AKI. [RR- 3.01; 95% CI 2.08,4.33], VTE [RR-3.39; 95% CI 2.02,5.67] and sepsis [RR-2.85 95% CI 1.86,4.37] ($p < 0.001$).

All the mentioned outcomes were similar among those receiving biological DMARDs and csDMARDs. Drug specific subgroup analysis could not be performed as only 0.5% of SLE patients had received cyclophosphamide, and 8% received MMF in the past year(Supplementary Table 6).

4. Discussion

This was an analysis of 2140 individuals with SLE who got COVID-19. Their outcomes upon comparison with a propensity-matched general population showed a higher risk of hospitalisation, ICU admission, mechanical ventilation, stroke, venous thromboembolism and sepsis though a comparable risk of death as the general population. Among individuals with SLE, those contracting COVID-19 infection had an exaggerated risk of all-cause mortality, hospitalisation, ICU admission, mechanical ventilation, ARDS, AKI, VTE and sepsis when compared to those without COVID-19.

A recent Danish population-based study on immune-mediated inflammatory (IMID) diseases suggested a significantly higher COVID-19-related hospitalisation and mortality risk. On multivariate analysis, age older than 65 years, comorbidities, and higher glucocorticoid doses were identified as predictors of mortality [16]. The above study included various inflammatory diseases though the number of SLE patients with COVID-19 was limited to nine cases, ruling out meaningful conclusions. In an English population-based study, COVID-19-related death was associated with having an autoimmune disease (SLE, rheumatoid arthritis or psoriasis). That study results were not specific to SLE as three heterogeneous autoimmune diseases were collated in a group [17]. Our findings, assessing SLE individually rather than combining with other RMDs, suggest a heightened risk for most of the outcomes examined,

including hospitalisation, ICU admission, mechanical ventilation, stroke, venous thromboembolism, and sepsis. Notably, the risk of mortality when matched for age, sex, race, and comorbidities was similar to the general population.

In an analysis of 225 lupus patients, with 8% having suspected COVID-19, it was observed that the use of hydroxychloroquine did not prevent infection. However, the investigators identified that the use of Belimumab was associated with hospitalisation and that the dose of glucocorticoid was positively associated with positive PCR (OR 1.57, p = 0.025) and hospitalisation (OR 4.39, p = 0.030) [18]. COVID-19 may have worse outcomes in SLE even when the lupus diseases activity was low [12,13]. These studies did not have data on healthy controls to account for the confounders. A study of relatively larger (n = 226) SLE patients with 41 confirmed COVID-19 found that the variables predictive of hospitalisation were similar to those identified in the general population [19]. Rituximab and Belimumab are the most common biologics used in the treatment of SLE. The use of rituximab in RA was associated with severe COVID infection [10]. A similar trend of higher COVID mortality has been reported among those with myasthenia gravis on RTX [20]. We did not find any difference in outcomes among those who were on bDMARDs when compared to those on csDMARDs, but the number of events in bDMARDs was low (<11), limiting robust conclusions. We however found in the limited data on the use of glucocorticoids available that use of steroids was associated with poorer COVID outcomes. A similar finding was also observed by us among individuals with rheumatoid arthritis on glucocorticoids from the same database [21]. It is possible that individuals on glucocorticoids also had higher disease activity, details of which were not available in the database thus limiting our ability to make definitive conclusions.

Lupus nephritis is a severe form of SLE which needs upfront aggressive treatment followed by long term continued care. A compromised renal function due to lupus may be an important predictor of AKI during acute infections like that seen in the current study. Moreover, the use of higher steroid doses along with several immunosuppressive agents for lupus nephritis may be the reason for higher risk of sepsis. Hence, the COVID preventive and vaccination strategies should also consider individuals with lupus nephritis as a susceptible group and allow early access to vaccination. Hospitalisation has enormous economic [22] and mental health impacts, which might be amplified manifold among individuals with lupus and especially those with lupus nephritis [23].

Besides nephritis, a higher risk of hospitalisation among SLE could be due to a flare of lupus disease activity. One of the main challenges faced by individuals with RMDs during the pandemic was the inability to access routine health care [24,25] and the lack of information about continuing immunosuppressive agents [26]. This resulted in drug discontinuation in a substantial proportion of patients [27–29], which predisposes to a flare of the underlying RMD. A second hit in the form of COVID-19 infection may potentially portend poorer prognosis in those with uncontrolled RMD and may have resulted in higher hospitalisation. Since the database provides aggregate information, it was not possible to assess lupus disease status in our study.

Another potential area of concern seems to be venous thromboembolism, reportedly manifold higher in patients with SLE with COVID. Higher VTE in COVID-19 could be contributed by disruption of one or all the components of Virchow's triad [30], which are accentuated and dysfunctional in individuals with SLE. The presence of antiphospholipid antibodies (aPLA), a factor common to both lupus and severe COVID [31], could potentially contribute to VTE, although causation remains unproven. The potential for transient aPLA in COVID-19 to accentuate NETosis and, consequently, inflammatory thrombosis is being investigated by researchers [32]. Finally, a prolonged hospital stay and immobilisation may be the reason for high VTE.

The limitations of our study include unavailability of important information about the socioeconomic status, diseases activity, lupus damage index and duration of illness, all of which could confound the results of the study. The use of aggregate data is another limitation that did not allow for in-depth statistical analyses. Many important outcomes in the subgroup analyses could not be performed due to non-availability of data when number of events were <11. This is an important short coming which can be overcome by a prospectively collected database designed to collect even the rare events. Another shortcoming in the data was the information on the dosage of glucocorticoids. As the data was incomplete for the majority of samples assessment of the effect of steroid dosage on outcomes could not be done. However, we have used a large database of patients comparing against propensity-matched controls. This approach has allowed us to identify the risk of worse COVID outcomes in SLE after adjusting for the sex, age and comorbidities.

In conclusion, even though the mortality of individuals with SLE due to COVID is comparable to the general population, higher risks of hospitalisation, ICU admission, mechanical ventilation, stroke, VTE and sepsis are essential factors. Male sex and lupus nephritis increase the risk of AKI, thus probably increasing hospitalisation and sepsis. Therefore, it is crucial to identify the high-risk group among SLE and ensure early vaccination and continuity of lupus care.

Contributors

CK, RR and HP designed the study with inputs from LG, SA and SK. RR, HP and CD performed statistical analyses. KC drafted the manuscript. All authors reviewed the study design and contributed to data interpretation and critical revision of the article. All authors approved the version of the article to be published. RR, and HP verified the underlying data.

Declaration of competing interest

SA has received an honorarium as a speaker for Pfizer (unrelated to the current study) and has no other potential conflicts of interest. SK has received congress travel, accommodation, and participation fee support (12th Anatolian Rheumatology Days) from Abbvie. All other authors declare no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2021.102730.

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