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ORIGINAL RESEARCH

Risk of COVID-19 among unvaccinated and vaccinated patients with systemic lupus erythematosus: a general population study

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ABSTRACT

Objective To compare the risk of SARS-CoV-2 infection and its related severe sequelae between patients with systemic lupus erythematosus (SLE) and the general population according to COVID-19 vaccination status.

Methods We performed cohort studies using data from The Health Improvement Network to compare the risks of SARS-CoV-2 infection and severe sequelae between patients with SLE and the general population. Individuals aged 18–90 years with no previously documented SARS-CoV-2 infection were included. We estimated the incidence rates and HRs of SARS-CoV-2 infection and severe sequelae between patients with SLE and the general population according to COVID-19 vaccination status using exposure score overlap weighted Cox proportional hazards model.

Results We identified 3245 patients with SLE and 1 755 034 non-SLE individuals from the unvaccinated cohort. The rates of SARS-CoV-2 infection, COVID-19 hospitalisation, COVID-19 death and combined severe outcomes per 1000 person-months were 10.95, 3.21, 1.16 and 3.86 among patients with SLE, and 8.50, 1.77, 0.53 and 2.18 among general population, respectively. The corresponding adjusted HRs were 1.28 (95% CI: 1.03 to 1.59), 1.82 (95% CI: 1.21 to 2.74), 2.16 (95% CI: 1.00 to 4.79) and 1.78 (95% CI: 1.21 to 2.61). However, no statistically significant differences were observed between vaccinated patients with SLE and vaccinated general population over 9 months of follow-up.

Conclusion While unvaccinated patients with SLE were at higher risk of SARS-CoV-2 infection and its severe sequelae than the general population, no such difference was observed among vaccinated population. The findings indicate that COVID-19 vaccination provides an adequate protection to most patients with SLE from COVID-19 breakthrough infection and its severe sequelae.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Findings on the risks of COVID-19 infection and its severe sequelae in patients with systemic lupus erythematosus (SLE) were controversial.

⇒ COVID-19 vaccination elicited a suboptimal response in patients with SLE compared with heathy controls; however, the real-world effectiveness of COVID-19 vaccination on the risks of breakthrough infection and severe sequalae was unclear.

WHAT THIS STUDY ADDS

⇒ In the population-based retrospective cohort study using data from The Health Improvement Network, we found that patients with SLE are at higher risk of SARS-CoV-2 infection and its severe outcomes when they are unvaccinated.

⇒ After COVID-19 vaccination, no such statistical difference was observed between patients with SLE and the general population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings offer more evidence that COVID-19 vaccination should be recommended to patients with SLE since this could provide an adequate protection to patients with SLE from COVID-19 breakthrough infection and its severe sequelae.

INTRODUCTION

The COVID-19 pandemic has generated an unprecedented impact on global health, with 628 035 553 confirmed cases including 6 572 800 deaths as of 2 November 2022.[1] To date, COVID-19 vaccination has been demonstrated as one of the most effective preventive strategies to control for COVID-19 infection and mitigation of its severe sequelae.[2 3] Compared with the general population, patients with systemic lupus erythematosus (SLE) may be more susceptible to SARS-CoV-2 infection and experience poor outcomes[4 5] due to immune dysfunction,[6] immunosuppressive medication,[7] elevated levels of COVID-19 binding receptor[8] and frequent comorbidities, such as cardiovascular and renal diseases.[9–11] Indeed, several

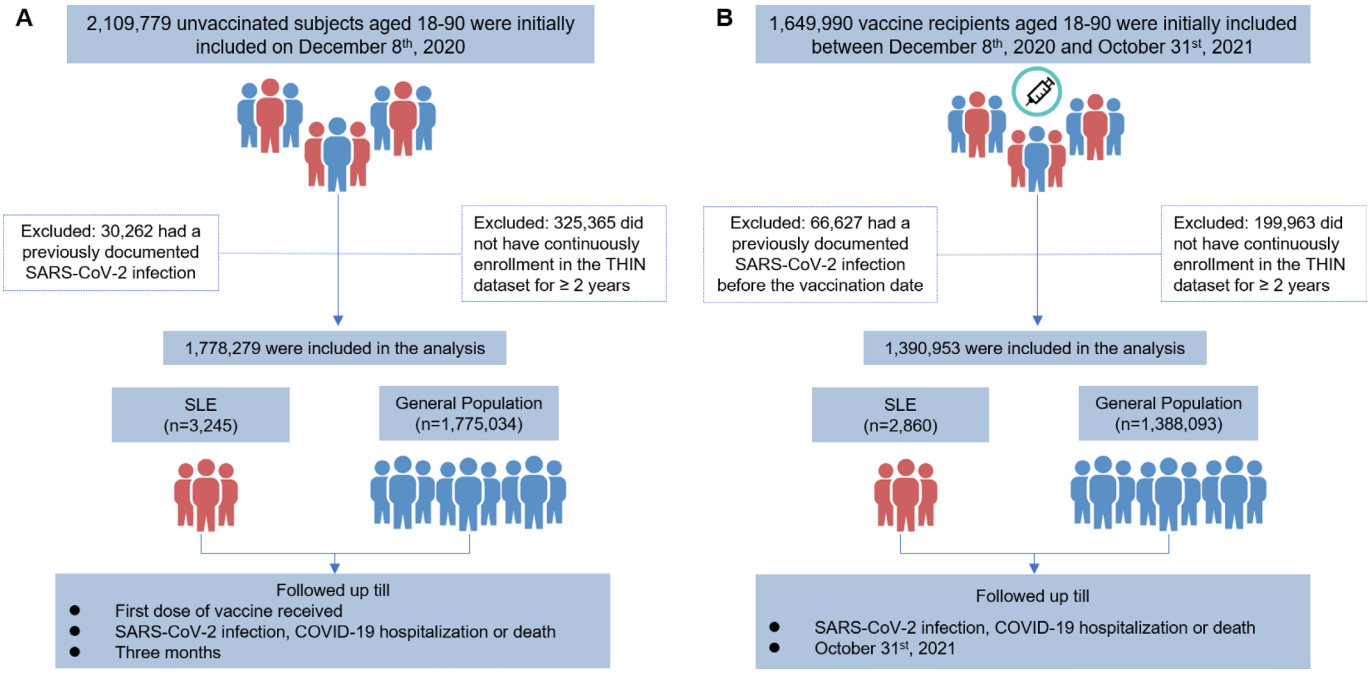

Figure 1 Selection process of included patients with SLE and the general population. (A) Unvaccinated cohort; (B) vaccinated cohort. SLE, systemic lupus erythematosus; THIN, The Health Improvement Network.

studies have assessed the risk of SARS-CoV-2 infection and its severe sequelae in patients with SLE; however, the findings were inconsistent.[12–22] In addition, the majority of these studies were conducted during the prevaccination or early vaccination period. Recently, Saxena *et al* reported a lower rate of COVID-19 breakthrough infection after receiving an additional vaccination dose in patients with SLE; however, the study did not assess the risk of severe sequelae of COVID-19 (eg, hospitalisation and death) and did not include the healthy individuals as a comparison group.[23] Despite the indirect evidence regarding immunogenicity,[24–27] there is still a paucity of data on the effect of COVID-19 vaccination, especially its long-term effect, on the risk of SARS-CoV-2 breakthrough infection and its related sequelae among patients with SLE. Therefore, knowledge gaps exist regarding the efficacy or effectiveness of vaccination in the face of waning immunity, as well as the need for additional vaccination and preventive measures in patients with SLE.

To fill in this knowledge gap, we conducted two retrospective cohort studies to compare the risks of SARS-CoV-2 infection and its two severe sequelae, that is, COVID-19 hospitalisation and death, between patients with SLE and the general population without SLE (hereafter referred to as general population) according to their COVID-19 vaccination status.

METHODS

Data source

We used data from The Health Improvement Network (THIN) database (now called IQVIA Medical Research Database). THIN is an electronic medical record database from general practitioners (GPs) in the UK. It is quite similar to the General Practice Research Database (GPRD),[28] in which approximately 60% of patients are overlapped with those in THIN. Both the GPRD and THIN databases have been validated in several independent studies and could produce comparable estimates of the burden of disease.[29–31] THIN consists of approximately 17 million persons in the UK and represents the UK population regarding patient demographics and the prevalence of medical conditions.[32] During consultation with patients, health information is recorded on site by GP using a computerised system. The computerised information includes sociodemographics, anthropometrics, lifestyle factors and details from visits to GPs (ie, prescriptions, diagnoses from specialist referrals, hospital admissions and results of laboratory tests). The Read classification system is used to code specific diagnoses,[33] whereas a dictionary based on the Multilex classification system is used to code drugs.[34]

Study design

Using the study design and statistical methods as previously described by our research group,[35 36] we conducted two retrospective cohort studies to compare the risks of SARS-CoV-2 infection, COVID-19 hospitalisation and death between patients with SLE and the general population according to their COVID-19 vaccination status. SLE diagnosis was made using Read codes according to our previous study (online supplemental table S1).[37] We did not conduct an external validation because GPs would give a Read code only after hospital specialist's confirmation and positive predictive values of other autoimmune diseases diagnosed by Read codes were >90%.[38] Eligible participants consisted of those who were 18–90 years of

Table 1 Baseline characteristics of patients with SLE and general cohort without SLE in the vaccinated and unvaccinated cohort

	Unvaccinated cohort						Vaccinated cohort					
	Before overlap weighting			After overlap weighting			Before overlap weighting			After overlap weighting		
Variable list	SLE	General cohort	SMD	SLE	General cohort	SMD	SLE	General cohort	SMD	SLE	General cohort	SMD
Number	3245	1755034		3233	3233		2860	1388093		2848	2848	
Demographics												
Age, mean (SD), years	58.74 (14.76)	50.32 (17.99)	0.512	58.72 (14.76)	58.72 (17.34)	<0.001	59.52 (14.51)	52.66 (17.87)	0.422	59.52 (14.51)	59.52 (16.71)	<0.001
Women (%)	83.9	50.0	0.771	83.8	83.8	<0.001	83.7	51.8	0.727	83.7	83.7	<0.001
Socioeconomic deprivation index score (%)*			0.054			<0.001			0.051			<0.001
Missing	11.5	12.5		11.5	11.5		10.9	11.5		10.9	10.9	
1	14.6	15.1		14.6	14.6		14.4	15.6		14.4	14.4	
2	18.7	17.8		18.7	18.7		19.2	19.1		19.2	19.2	
3	20.7	19.4		20.7	20.7		20.9	19.9		20.9	20.9	
4	18.0	18.9		18.0	18.0		18.4	18.6		18.4	18.4	
5	16.5	16.4		16.5	16.5		16.3	15.3		16.3	16.3	
BMI, mean (SD), kg/m^2	28.04 (6.54)	27.72 (6.12)	0.05	28.03 (6.54)	28.05 (6.50)	0.002	28.12 (6.54)	28.03 (6.15)	0.015	28.12 (6.54)	28.25 (6.68)	0.019
BMI, %			0.384			<0.001			0.351			<0.001
<18.5 kg/m^2	2.1	1.8		2.1	2.1		2.1	1.6		2.1	2.1	
≥18.5 and <25.0 kg/m^2	32.2	27.8		32.2	32.2		31.7	26.9		31.7	31.7	
≥25.0 and <30.0 kg/m^2	28.8	27.8		28.8	28.8		29.4	29.2		29.4	29.4	
≥30.0 kg/m^2	30.6	24.0		30.6	30.6		31.2	26.2		31.2	31.2	
Missing	6.3	18.6		6.4	6.4		5.6	16.1		5.6	5.6	
Region, %			0.094			<0.001			0.126			<0.001
England	18.2	18.4		18.2	18.2		15.9	14.2		15.9	15.9	
Northern Ireland	13.6	13.2		13.6	13.6		14.0	13.6		13.9	13.9	
Scotland	42.9	39.3		42.9	42.9		45.1	41.6		45.1	45.1	
Wales	25.2	29.1		25.3	25.3		25.1	30.6		25.1	25.1	

Continued

Table 1 Continued

Variable list	Unvaccinated cohort						Vaccinated cohort					
	Before overlap weighting			After overlap weighting			Before overlap weighting			After overlap weighting		
	SLE	General cohort	SMD	SLE	General cohort	SMD	SLE	General cohort	SMD	SLE	General cohort	SMD
Type of first dose vaccination (%)	–	–		–	–				0.245			<0.001
Oxford-AZ	–	–		–	–		67.3	55.7		67.3	67.3	
Pfizer	–	–		–	–		31.4	41.9		31.4	31.4	
Moderna or Janssen	–	–		–	–		1.3	2.4		1.3	1.3	
Type of second dose vaccination (%)	–	–		–	–				0.237			0.035
No second dose	–	–		–	–		5.9	6.9		5.9	5.2	
Oxford-AZ	–	–		–	–		63.7	52.9		63.7	64.1	
Pfizer	–	–		–	–		29.9	38.5		29.9	30.0	
Moderna or Janssen	–	–		–	–		0.6	1.7		0.6	0.7	
Number of COVID-19 test, mean (SD)	0.09 (0.28)	0.08 (0.27)	0.03	0.09 (0.28)	0.09 (0.28)	<0.001	0.14 (0.34)	0.14 (0.35)	0.008	0.14 (0.34)	0.14 (0.34)	<0.001
Lifestyle factors												
Drinking (%)			0.429			<0.001			0.402			<0.001
None	24.2	15.9		24.2	24.2		24.0	15.4		23.9	23.9	
Past	4.0	2.5		4.0	4.0		3.9	2.7		3.9	3.9	
Current	65.3	61.9		65.3	65.3		66.2	64.5		66.2	66.2	
Missing	6.5	19.7		6.5	6.5		5.9	17.4		6.0	6.0	
Smoking (%)			0.294			<0.001			0.276			<0.001
None	50.0	55.0		50.0	50.0		50.0	56.3		50.1	50.1	
Past	29.2	22.2		29.2	29.2		29.5	23.6		29.5	29.5	
Current	20.1	18.0		20.1	20.1		19.8	16.3		19.8	19.8	
Missing	0.8	4.8		0.8	0.8		0.6	3.9		0.6	0.6	

Continued

Table 1 Continued

Variable list	Unvaccinated cohort						Vaccinated cohort					
	Before overlap weighting			After overlap weighting			Before overlap weighting			After overlap weighting		
	SLE	General cohort	SMD	SLE	General cohort	SMD	SLE	General cohort	SMD	SLE	General cohort	SMD
Healthcare utilisation within previous year, mean (SD)												
Hospitalisations†	0.44 (1.43)	0.21 (0.78)	0.203	0.44 (1.42)	0.44 (2.20)	<0.001	0.43 (1.28)	0.22 (0.80)	0.194	0.42 (1.27)	0.42 (1.73)	<0.001
General practice visits†	4.41 (5.97)	2.03 (3.62)	0.483	4.40 (5.93)	4.40 (14.20)	<0.001	4.04 (5.47)	1.94 (3.62)	0.452	4.03 (5.45)	5.11 (12.96)	<0.001
Specialist referrals†	0.44 (0.97)	0.22 (0.64)	0.274	0.44 (0.96)	0.44 (1.19)	<0.001	0.41 (0.92)	0.22 (0.64)	0.248	0.41 (0.92)	0.41 (1.10)	<0.001

*The socioeconomic deprivation index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).
†Frequency during the past year.
SLE, systemic lupus erythematosus; SMD, standardised mean difference; BMI, body mass index; AZ, AstraZeneca.

age between 8 December 2020 (ie, when first COVID-19 vaccination open to public in the UK) and 31 October 2021, had no previously documented SARS-CoV-2 infection and had at least 2 years of continuous enrolment with a general practice.

Cohort definition

For each eligible individual in the unvaccinated cohort, follow-up started on 8 December 2020 (ie, index date) and ended on the day of first dose of vaccine received, developing the outcomes of the interest (ie, SARS-CoV-2 infection, COVID-19 hospitalisation and death) or the end of the study period (31 October 2021), whichever occurred first.

For each eligible individual in the vaccinated cohort, follow-up started on the day when the first dose of vaccine was received (ie, index date) and ended on the day of developing the outcomes of the interest (ie, SARS-CoV-2 infection, COVID-19 hospitalisation and death), or the end of the study period (31 October 2021), whichever occurred first.

Assessment of outcomes

The primary outcome was a documented diagnosis of SARS-CoV-2 infection,[39] and the secondary outcomes were hospitalisation for COVID-19 and death from COVID-19. Confirmed SARS-CoV-2 infection diagnosis was made based on Read codes (online supplemental table S1) according to a previous study using UK general population-based data.[39] Hospitalisation for COVID-19 was defined as a hospitalisation record in THIN within 30 days after documentation of SARS-CoV-2 infection, and death from COVID-19 was defined as a death within 30 days of SARS-CoV-2 infection.[40] Combined severe outcomes defined as either COVID-19 hospitalisation or COVID-19 death were considered as a composite variable.

Assessment of covariates

Among unvaccinated cohort, the covariates included sociodemographic factors (age, sex, Townsend Deprivation Index), geographic location, body mass index (BMI), lifestyle factors (alcohol drinking and smoking status), previous COVID-19 test performed and healthcare utilisation (hospitalisations, general practice visits and specialist referrals) during the past 1 year before the index date. THIN only contained medications prescribed by GPs, but not by the specialists; thus, the data on immunosuppressive agents and biologics, which were often prescribed by the specialists, were not available in THIN. As a result, we were unable to adjust for the immunosuppressive agents and biologics in the analysis. Since SLE is a risk factor for many comorbidities and we are interested in the relation of SLE and its comorbidities as a whole to the risk of SARS-CoV-2 infection and severe sequelae, we did not adjust for comorbidities in the analyses. Missing values were treated as a separate missing category for each

variable. Among the vaccinated cohort, we also collected information on the vaccine type received as the first dose.

Statistical analysis

For both cohorts, we used exposure score (analogous to propensity score) overlap weighting to balance baseline characteristics between the comparison groups. Specifically, the exposure score for SLE was calculated using the logistic regression model with the covariates described previously. Patients with SLE were weighted by the probability of not being SLE, that is, 1−exposure score, and non-SLE individuals were weighted by the probability of being SLE, that is, exposure score. Overlap weights were bounded and smoothly reduced the influence of individuals at the tails of the exposure score distribution without making any exclusions.[41 42] We assessed the distribution of the baseline characteristics before and after overlap weights using the standardised mean differences for the comparison groups.[43]

Among the unvaccinated cohort, we calculated the incidence rate of SARS-CoV-2 infection, hospitalisation, death and combined severe outcomes among SLE and the general population, respectively. We performed a Cox proportional hazards model to examine the relation of SLE to the risk of SARS-CoV-2 infection, hospitalisation, death and combined severe outcomes accounting for the competing risk of death[44] using overlap weighting of exposure score. Since >80% unvaccinated subjects received their first dose of vaccine within 3 months after vaccination programme began, we restricted our analyses to 3 months of follow-up time in the unvaccinated cohort to minimise potential selection bias.[44] We tested the proportional hazard assumption by plotting the cumulative incidence curve of each outcome. If the proportional hazard assumption was violated, we conducted a weighted Cox regression to obtain a weighted HR.[45] We took the same approach to compare the risk of COVID-19 breakthrough infection, hospitalisation, death and combined severe outcomes from COVID-19 among the vaccinated cohort. However, the follow-up time was extended to 9 months. Since the main COVID-19 vaccines were demonstrated to be highly efficacious at least 14 days after the first dose,[46–49] we performed a sensitivity analysis beginning on day 14 after the first dose of COVID-19 vaccination.

All p values were two-sided and p<0.05 was considered significant. All statistical analyses were performed with SAS, V.9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The flow chart depicting the selection process of individuals is shown in figure 1. The unvaccinated cohort consisted of 3245 patients with SLE and 1 755 034 individuals from the general population, and the vaccinated cohort comprised 2860 patients with SLE and 1 388 093 individuals from the general population. In general, patients with SLE were older; had a higher percentage of women and were more likely to use the healthcare services, that is, GP visit or hospitalisation, than general population. After overlap exposure score weighting, the characteristics between the two comparison groups were well balanced, with standardised differences <0.001 (table 1).

As shown in table 2, among the unvaccinated cohort the weighted incidences of SARS-CoV-2 infection (10.95 vs 8.50/1000 person-months), COVID-19 hospitalisation (3.21 vs 1.77/1000 person-months), COVID-19 death (1.16 vs 0.53/1000 person-months) and combined severe outcomes (3.86 vs 2.18/1000 person-months) were higher in patients with SLE than in the general population, with the corresponding adjusted HRs being 1.28 (95% CI: 1.03 to 1.59), 1.82 (95% CI: 1.21 to 2.74), 2.16 (95% CI: 1.00 to 4.79) and 1.78 (95%CI: 1.21 to 2.61), respectively (figure 2).

Among the vaccinated cohort, no significant difference was observed in the weighted incidence of SARS-CoV-2 breakthrough infection (4.94 vs 4.92/1000 person-months), COVID-19 hospitalisation (0.45 vs 0.30/1000 person-months), COVID-19 death (0.09 vs 0.07/1000 person-months) or combined severe outcomes (0.49 vs 0.36/1000 person-months) between patients with SLE and the general population over 9 months of follow-up period. The corresponding adjusted HRs were 1.05 (95% CI: 0.87 to 1.26), 1.49 (95% CI: 0.79 to 2.80), 1.46 (95% CI: 0.25 to 8.46) and 1.37 (95% CI: 0.74 to 2.57), respectively (table 2 and figure 3). The results did not change materially when we started the follow-up on day 14 after the COVID-19 vaccination (online supplemental table S2).

DISCUSSION

Using data collected from THIN in the UK, we found that the risks of COVID-19 infection and its severe sequelae (ie, hospitalisation and death from COVID-19 infection) among patients with SLE were significantly higher than those among the general population before receiving COVID-19 vaccine. However, after COVID-19 vaccination, no statistical difference in the risks of COVID-19 breakthrough infection and its related severe sequelae were observed between the two comparison groups. These findings should encourage vaccination among patients with SLE to reduce their risk of SARS-CoV-2 infection and its severe sequelae. However, it is possible that there may be some subgroups of patients with SLE who remain elevated risk for COVID-19 and severe outcomes even after vaccination (eg, those who receive B cell depletion treatment).

Previous studies have evaluated the risk of SARS-CoV-2 infection and its severe outcomes in unvaccinated people with SLE; however, the results were controversial. While several studies failed to show an increased risk of SARS-CoV-2 infection among patients with SLE, these studies often did not have adequate power because of relatively small sample sizes and did not control adequately

Table 2 Association between SLE and the risk of SARS-CoV-2 infection/breakthrough infection, COVID-19 hospitalisation and death

	Unvaccinated cohort		Vaccinated cohort	
	Three months		Nine months	
	SARS-CoV-2 infection		Breakthrough infection	
	SLE (n=3245)	General population (n=1 755 034)	SLE (n=2860)	General population (n=1 388093)
Event, n	84	37 447	109	54 314
Mean follow-up, months	2.36	2.56	7.71	6.93
Weighted IR*, per 1000 person-months	10.95	8.50	4.94	4.92
HR* (95% CI)	1.28 (1.03 to 1.59)	1.00 (ref)	1.05 (0.87 to 1.26)	1.00 (ref)
	COVID-19 hospitalisation		**COVID-19 hospitalisation**	
	SLE (n=3245)	**General population (n=1 755 034)**	**SLE (n=2860)**	**General population (n=1 388 093)**
Event, n	25	4464	10	2130
Mean follow-up, months	2.39	2.59	7.77	7.02
Weighted IR*, per 1000 person-months	3.21	1.77	0.45	0.30
HR* (95% CI)	1.82 (1.21 to 2.74)	1.00 (ref)	1.49 (0.79 to 2.80)	1.00 (ref)
	COVID-19 death		**COVID-19 death**	
	SLE (n=3245)	**General population (n=1 755 034)**	**SLE (n=2860)**	**General population (n=1 388 093)**
Event, n	9	912	2	167
Mean follow-up, months	2.40	2.60	7.79	7.02
Weighted IR*, per 1000 person-months	1.16	0.53	0.09	0.07
HR* (95% CI)	2.16 (1.00 to 4.79)	1.00 (ref)	1.46 (0.25 to 8.46)	1.00 (ref)
	COVID-19 combined severe outcomes		**COVID-19 combined severe outcomes**	
	SLE (n=3245)	**General population (n=1 755 034)**	**SLE (n=2860)**	**General population (n=1 388 093)**
Event, n	30	5122	11	2243
Mean follow-up, months	2.39	2.59	7.77	7.02
Weighted IR*, per 1000 person-months	3.86	2.18	0.49	0.36
HR* (95% CI)	1.78 (1.21 to 2.61)	1.00 (ref)	1.37 (0.74 to 2.57)	1.00 (ref)

*Estimates were time-stratified overlap weighted of propensity score, weighted Cox regression using coxphw method were applied if proportional hazard assumption was violated.
IR, incidence rate; SLE, systemic lupus erythematosus.

for several important confounders, such as age, socioeconomic factors and swab prescription for COVID-19.[14–16 18] In contrast, three population-based cohort studies reported that risks of COVID-19 hospitalisation and its poor outcomes (eg, intensive care unit admission, mechanical ventilation and death) were higher in patients with SLE than that in the general population.[20–22] However, all these previous studies were conducted during the prevaccination or early vaccination period; thus, they were unable to evaluate whether COVID-19 vaccination could mitigate the risk of breakthrough infection and severe outcomes in patients with SLE when compared with the general population. In the present study, we found that there were no significant differences in the risks of SARS-CoV-2 infection, COVID-19 hospitalisation and death between patients with SLE and the general population after COVID-19 vaccination. Our findings add real-world evidence that COVID-19 vaccination could confer adequate protection to the high-risk patients with SLE from COVID-19 breakthrough infection and severe sequelae.

Our study has several strengths. First, to our knowledge, this is the first real-world population-based study of evaluating the risk of COVID-19 breakthrough

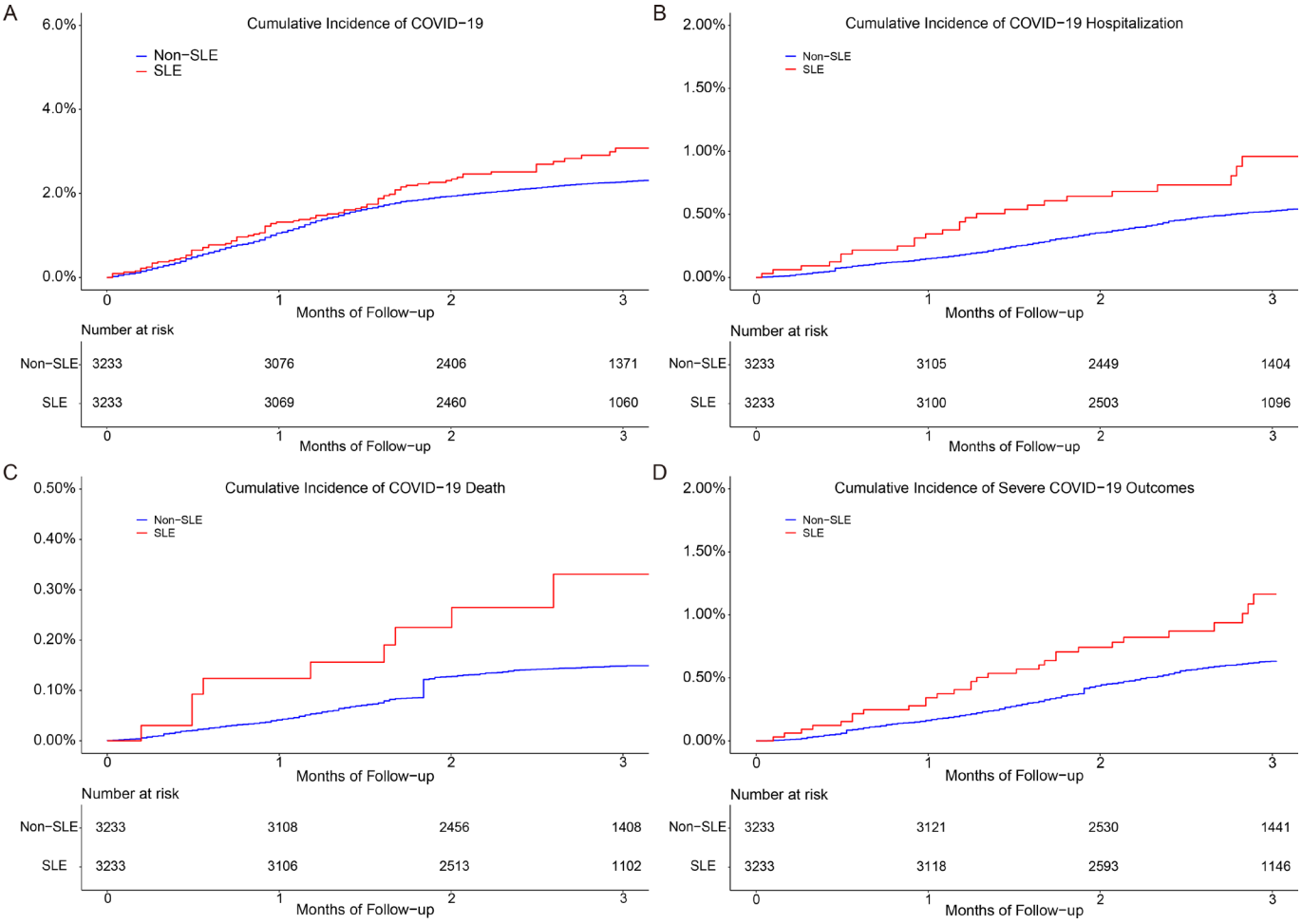

Figure 2 Cumulative incidence of SARS-CoV-2 infection, COVID-19 hospitalisation and death among patients with SLE as compared with the general population in the unvaccinated cohort over 3 months. (A) SARS-CoV-2 infection; (B) COVID-19 hospitalisation; (C) COVID-19 death; (D) COVID-19 combined severe outcomes. SLE, systemic lupus erythematosus.

infection and its sequalae among vaccinated patients with SLE. Second, our findings are likely generalisable to patients with SLE with similar characteristics since the results were derived from the population-based sample in UK. Third, the impact of potential confounding factors, such as social determinants of health (eg, socioeconomic deprivation index score, regions, healthcare utilisation within previous year), sex, age and lifestyle factors, was minimised through exposure score overlap weighting, with baseline characteristics well balanced between patients with SLE and general population. Several limitations of our study are worth commenting. First, we were unable to assess the effect of biological immunoregulatory and immunosuppressant medications on the risk of SARS-CoV-2 infection and its severe sequelae due to the unavailability of information from the THIN. For example, patients with SLE with severe manifestations, such as lupus nephritis, or those requiring potent immunosuppression, particularly high-dose glucocorticoids, mycophenolate and rituximab that blunt vaccine immunogenicity, may still be at elevated risk of poor outcomes even after vaccination. Future studies focusing on patients with SLE who are on immunosuppressive therapies or have severe manifestations are required to assess their risk of COVID-19 infection and its severe sequelae after the COVID-19 vaccination. Second, the number of hospitalisation and death cases were small among vaccinated patients with SLE; thus, in the vaccinated cohort, although incidence rates for hospitalisation and death from COVID-19 were 40% higher among patients with SLE than the general population, the CIs for each point estimate were wide. The availability of a larger cohort with longer follow-up time would be valuable to better understand the impact of COVID-19 and its vaccine on patients with SLE. Third, as in any observational study, we could not rule out the residual confounding effect. Fourth, although the frequency of healthcare utilisation (ie, hospitalisations, general practice visits and specialist referrals) was adjusted in the analyses, other behavioural factors, such as mask-wearing and hand washing, etc, were not assessed and thus cannot be adjusted in the analysis which may potentially bias the effect estimates. Fifth, although the medical information from the hospital specialist is reported back to

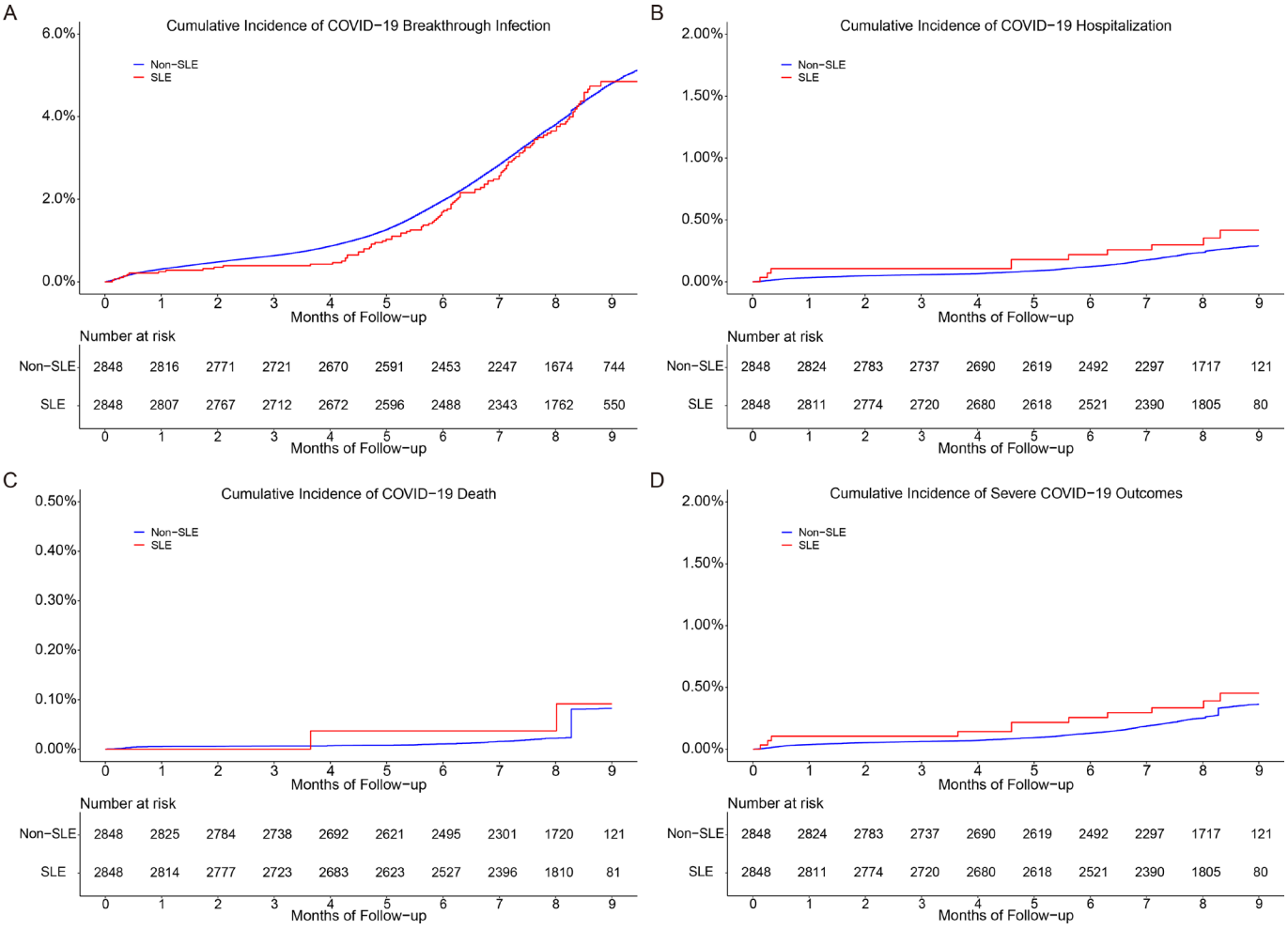

Figure 3 Cumulative incidence of SARS-CoV-2 infection, COVID-19 hospitalisation and death among patients with SLE as compared with the general population in the vaccinated cohort during the 9 months follow-up. (A) SARS-CoV-2 infection; (B) COVID-19 hospitalisation; (C) COVID-19 death; (D) COVID-19 combined severe outcomes. SLE, systemic lupus erythematosus.

the GP in general, and GPs hold information on significant health-related events (including the diagnosis of COVID-19), we cannot access the data that were held in the hospital and were not reported back to GPs (eg, tests were performed at the hospital and were not reported back to GPs). As a result, misclassification of the COVID-19 diagnosis could occur and bias the study findings. Nevertheless, such bias, if it occurred, is likely to be small and non-differential between the two comparison groups. Sixth, since the present study was conducted in the pre-Omicron era, we did not examine the effectiveness of current COVID-19 vaccines as well as the booster doses against the Omicron variant. Although previous studies reported that an additional dose of the COVID-19 vaccine could protect patients with SLE from the COVID-19 infection during the Omicron BA.1 wave,[23] future studies are needed to evaluate the COVID-19 vaccines against new variant of COVID-19 among patients with SLE.

In conclusion, while unvaccinated patients with SLE were at higher risk of SARS-CoV-2 infection, hospitalisation and death than the general population, no statistically significant difference was observed between two comparison groups after receiving COVID-19 vaccine. These findings offer more evidence that COVID-19 vaccination should be recommended to patients with SLE since this could provide an adequate protection to patients with SLE from COVID-19 breakthrough infection and its severe sequelae.

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