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ORIGINAL RESEARCH

Comprehensive risk assessment for pulmonary manifestations in systemic lupus erythematosus: a large-scale Korean population-based longitudinal study

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To cite: Kim B-G, Kim J, Eun Y, *et al*. Comprehensive risk assessment for pulmonary manifestations in systemic lupus erythematosus: a large-scale Korean population-based longitudinal study. *RMD Open* 2025;**11**:e005267. doi:10.1136/rmdopen-2024-005267

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2024-005267).

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Received 18 November 2024
Accepted 3 February 2025

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ABSTRACT

Objectives Pulmonary involvement is common in systemic lupus erythematosus (SLE), but the relative risk of pulmonary manifestations in SLE versus non-SLE subjects remains unclear. This study aimed to evaluate the risk of pulmonary manifestations in SLE subjects compared with matched controls.

Methods Using data from the Korean National Health Insurance Service (2009–2017), we identified 6074 individuals aged ≥20 years with newly diagnosed SLE and 60 740 matched controls by age and sex (1:10 ratio) who did not have prior pulmonary manifestations.

Results Over a mean follow-up of 9.3±2.7 years, the incidence of pulmonary manifestations was 15.2 per 1000 person-years in the SLE cohort and 4.5 per 1000 person-years in the matched cohort. The SLE cohort had a significantly higher risk of pulmonary manifestations (adjusted HR (aHR) 3.26; 95% CI 2.99 to 3.56). The highest risk was observed for pulmonary hypertension (aHR 14.66; 95% CI 9.43 to 22.80), followed by interstitial lung disease (aHR 9.58; 95% CI 7.99 to 11.49), pleural disorders (aHR 3.29; 95% CI 2.84 to 3.81), pulmonary embolism (aHR 2.66; 95% CI 2.06 to 3.43), tuberculosis (aHR 2.35; 95% CI 1.88 to 2.93), acute respiratory distress syndrome and haemorrhage (aHR 1.85; 95% CI 1.51 to 2.25) and lung cancer (aHR 1.41; 95% CI 1.02 to 1.95).

Conclusions Subjects with SLE have an approximately 3.3-fold higher risk of pulmonary manifestations compared with matched controls. Notably, the risks of pulmonary hypertension and interstitial lung disease are particularly elevated.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies found that subjects with incident systemic lupus erythematosus (SLE) had a higher rate of pulmonary disease compared with the non-SLE population; however; these studies did not consider confounding factors.

WHAT THIS STUDY ADDS

⇒ Subjects with SLE had an approximately 3.3-fold higher risk of pulmonary manifestations, with a particularly elevated risk for pulmonary hypertension and interstitial lung disease compared with those without SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study underscores the need for heightened awareness and proactive management of pulmonary complications in SLE patients, emphasising the importance of routine pulmonary screening in this vulnerable population.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterised by a wide range of clinical manifestations affecting multiple organ systems.[1] Among these, pulmonary involvement is prevalent during the disease course. Pulmonary manifestations in SLE encompass disorders of the pleura, parenchyma and vasculature.[2–4] Additionally, some SLE treatments increase the risk of respiratory infections.[1 5] Much of the knowledge about pulmonary manifestations in SLE comes from small studies conducted in selected clinical cohorts, including the US multiethnic LUpus in MInorities, NAture versus Nurture (LUMINA) cohort, as well as North American and European cohorts.[2 3 6] Thus, the real prevalence or incidence of pulmonary diseases in SLE cannot be fully elucidated, mostly due to small sample sizes and short follow-up periods.

To overcome these limitations, a Swedish study using a population-based dataset examined the incidence of pulmonary diseases (interstitial lung disease (ILD), acute

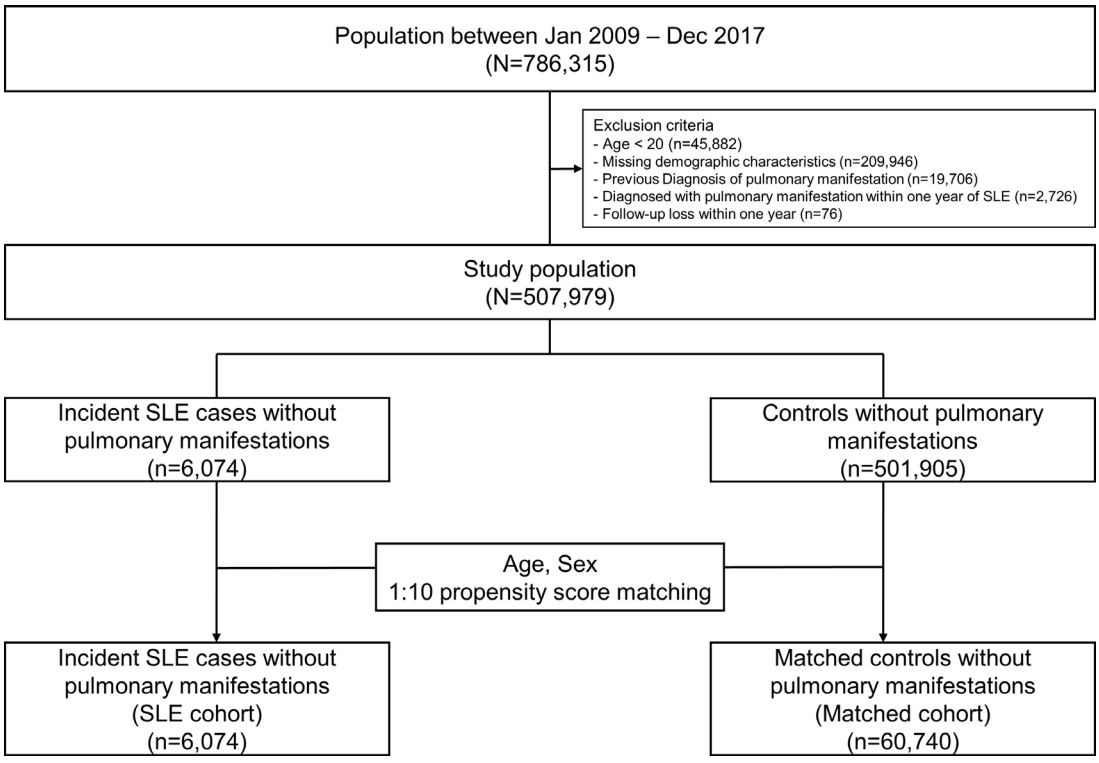

Figure 1 Flow chart of the study population. SLE, systemic lupus erythematosus.

respiratory distress syndrome (ARDS) and haemorrhage, pleural disorders, pulmonary hypertension, pulmonary embolism, diseases of the upper airway and pulmonary oedema) among subjects with SLE compared with the general population.[7] This study provided robust findings that subjects with incident SLE had a nearly 5.8-fold higher rate of pulmonary disease compared with the non-SLE population.[7] However, despite the advantages of a large study population and long follow-up duration, confounding factors such as smoking status, body mass index (BMI) and comorbidities that could affect pulmonary manifestations were not considered.

To provide more detailed information regarding this issue, we performed a population-based longitudinal cohort study involving subjects with SLE and matched controls that comprehensively considered these confounders.

METHODS

Data source

We used a nationwide dataset provided by the Korean National Health Insurance Service (NHIS), a universal insurance provider managed by the South Korean government that covers 97% of the Korean population, a total of approximately 50 million people. The NHIS dataset includes information on socioeconomics, demographic variables, healthcare utilisation, health screening examination findings, disease diagnosis based on the 10th revision of the International Classification of Disease (ICD-10) codes and medical treatment and procedures.[8 9] The NHIS database has been widely used in epidemiological studies to identify risk factors for pulmonary manifestations in subjects with connective tissue diseases.[10–13]

Data from annual or biennial health screening examination programmes for all adults, offered free of charge by the Ministry of Health and Welfare, constitute the health screening database.[8 14 15] Commencing in 2009, the health screening examination encompasses anthropometric measurements such as BMI as well as questionnaires pertaining to smoking and alcohol consumption. With a current participation rate of 70%–80%, the health screening examinations are representative of the Korean population.

Study population

After excluding individuals who had SLE before 1 January 2009, a total of 786 315 individuals were identified between 1 January 2009 and 31 December 2017. We excluded 45 882 subjects who were under 20 years old and 209 946 subjects with missing demographic characteristics. We additionally excluded all subjects diagnosed with pulmonary manifestations between 1 January 2002 and 31 December 2008 (n=19 706). We excluded subjects with pulmonary manifestations diagnosed within 1 year of SLE diagnosis (n=2726) and subjects lost to follow-up within 1 year (n=76). Among the remaining 507 979 patients, 6074 had SLE diagnosis codes and 501 905 did not have SLE diagnosis codes.

To establish the matched control cohort, we performed 1:10 matching between the SLE cohort and control cohorts based on age and sex. Finally, we enrolled 6074

Table 1 Baseline characteristics of subjects

	Total (n=66 814)	SLE cohort (n=6074)	Matched control cohort (n=60 740)	P value
Sex, female	59 560 (89.1)	5407 (89.0)	54 153 (89.2)	0.744
Age, years				0.998
20–29	7686 (11.5)	696 (11.5)	6990 (11.5)	
30–39	11 769 (17.6)	1081 (17.8)	10 688 (17.6)	
40–49	19 654 (29.4)	1779 (29.3)	17 875 (29.4)	
50–59	16 197 (24.2)	1478 (24.3)	14 719 (24.2)	
60–69	8627 (12.9)	777 (12.8)	7850 (12.9)	
≥70	2881 (4.3)	263 (4.3)	2618 (4.3)	
Body mass index, kg/m^2				<0.001
<18.5	3796 (5.7)	497 (8.2)	3299 (5.4)	
18.5–22.9	30 942 (46.3)	3098 (51.0)	27 844 (45.8)	
23.0–24.9	13 945 (20.9)	1129 (18.6)	12 816 (21.1)	
≥25.0	18 131 (27.1)	1350 (22.2)	16 781 (27.6)	
Low-income status*	1646 (2.5)	692 (11.4)	954 (1.6)	<0.001
Smoking status				<0.001
Never-smoker	57 650 (86.3)	5151 (84.8)	52 499 (86.4)	
Ex-smoker	3673 (5.5)	404 (6.7)	3269 (5.4)	
Current smoker	5491 (8.2)	519 (8.5)	4972 (8.2)	
Alcohol use	53 998 (80.8)	5188 (85.4)	48 810 (80.4)	<0.001
Comorbidities				
Diabetes mellitus	5961 (8.9)	1019 (16.8)	4942 (8.1)	<0.001
Hypertension	11 448 (17.1)	1606 (26.4)	9842 (16.2)	<0.001
Dyslipidaemia	13 290 (19.9)	2640 (43.5)	10 650 (17.5)	<0.001
Chronic kidney disease	413 (0.6)	217 (3.6)	196 (0.3)	<0.001
Myocardial infarction	122 (0.2)	33 (0.5)	89 (0.2)	<0.001
Airway diseases	7290 (10.9)	1003 (16.5)	6287 (10.4)	<0.001

Data are presented as number (percentage).
*The low-income group was defined as the lowest 30% and individuals supported by the medical aid programme.
SLE, systemic lupus erythematosus.

subjects in the SLE cohort and 60 704 subjects in the matched control cohort (figure 1).

Study exposure

The exposure of our study was newly diagnosed SLE. The NHIS operates the Rare and Intractable Disease (RID) programme for patients with certain diseases, which provides beneficial cost reductions for relevant medical expenses.[16] SLE patients are eligible to be registered in the RID programme if a clinician provides an official document certifying that the patient meets the classification criteria for SLE. SLE was defined when claim records included the ICD-10 diagnostic code M32 and the RID registration code V136.

Study outcome

The outcome of this study was the incidence of pulmonary manifestations. The pulmonary manifestations consisted of the following diseases: ILD (J84, J99),[9 17] ARDS and haemorrhage (J80, R04.2, R04.8, R04.9),[7 18] pleural disorder (J90, J91, J94.8, J94.9, R09.1),[7] pulmonary hypertension (I27.0, I27.2–I27.9),[7 19] pulmonary embolism (I26),[7] lung cancer (C34)[20–22] and tuberculosis (A15, A16).[23–26]

Subjects were followed from 1 year after study enrolment (SLE diagnosis in the SLE cohort or corresponding index date for matched controls) until the date of a pulmonary manifestation diagnosis, the censored date or 31 December 2022. A 1-year lag was implemented to minimise the risk of reverse causal association between SLE and pulmonary manifestations. If there were multiple pulmonary manifestation events during follow-up, the date of the first diagnosis was assigned.

Covariates

Data for basal characteristics of age, sex, BMI, smoking status, alcohol status, physical activity, income status

Table 2 Risk of pulmonary manifestations according to SLE status

	Number at risk	Incident cases (n)	Incidence per 1000 PY	HR (95% CI)		
				Unadjusted	Model 1	Model 2
Pulmonary manifestation						
Matched controls	60 740	2488	4.46	Reference	Reference	Reference
SLE cohort	6074	775	15.20	3.48 (3.21 to 3.77)	3.48 (3.20 to 3.78)	3.26 (2.99 to 3.56)
Subtype of pulmonary manifestations						
Interstitial lung disease						
Matched controls	60 740	279	0.49	Reference	Reference	Reference
SLE cohort	6074	249	4.70	9.77 (8.23 to 11.59)	10.28 (8.63 to 12.24)	9.58 (7.99 to 11.49)
Acute respiratory distress syndrome and haemorrhage						
Matched controls	60 740	684	1.21	Reference	Reference	Reference
SLE cohort	6074	128	2.40	2.00 (1.66 to 2.42)	1.95 (1.61 to 2.37)	1.85 (1.51 to 2.25)
Pleural disorder						
Matched controls	60 740	829	1.47	Reference	Reference	Reference
SLE cohort	6074	269	5.08	3.53 (3.08 to 4.05)	3.54 (3.07 to 4.08)	3.29 (2.84 to 3.81)
Pulmonary hypertension						
Matched controls	60 740	36	0.06	Reference	Reference	Reference
SLE cohort	6074	59	1.10	17.49 (11.55 to 26.47)	16.46 (10.77 to 25.15)	14.66 (9.43 to 22.80)
Pulmonary embolism						
Matched controls	60 740	322	0.57	Reference	Reference	Reference
SLE cohort	6074	84	1.56	2.87 (2.26 to 3.65)	3.00 (2.34 to 3.84)	2.66 (2.06 to 3.43)
Lung cancer						
Matched controls	60 740	321	0.57	Reference	Reference	Reference
SLE cohort	6074	46	0.86	1.55 (1.14 to 2.11)	1.48 (1.07 to 2.03)	1.41 (1.02 to 1.95)
Tuberculosis						
Matched controls	60 740	445	0.79	Reference	Reference	Reference
SLE cohort	6074	110	2.06	2.62 (2.13 to 3.23)	2.44 (1.96 to 3.03)	2.35 (1.88 to 2.93)

Model 1 was adjusted for sex, age, low-income status, smoking status, alcohol use and body mass index.
Model 2 was adjusted for sex, age, low-income status, smoking status, alcohol use, body mass index, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, myocardial infarction and airway diseases.
PY, person-years; SLE, systemic lupus erythematosus.

and comorbidities were collected from the database. Household income was categorised into quartiles based on insurance premium levels (in Korea, insurance premiums are determined by income level), with those covered by Medical Aid (poorest 3%) being merged into the lowest income quartile. The lowest income quartile group was defined as low income.[27] Personal behaviours, including smoking status and alcohol consumption, were determined based on a self-reported questionnaire. Smoking status was divided into never, ex-smokers and current smokers.[28] Alcohol consumption was divided into non-drinkers and drinkers. According to East Asian criteria, BMI was calculated as body weight divided by the square of height (kg/m^2) and classified into four groups as follows[29–31]: low (<18.5 kg/m^2), normal (18.5–22.9 kg/m^2), overweight (23.0–24.9 kg/m^2) and obese (≥25 mg/k^2). The definitions of comorbidities (diabetes mellitus (DM), hypertension, dyslipidaemia, chronic kidney disease, ischaemic heart disease and airway diseases (asthma or chronic obstructive pulmonary disease)) were based on ICD-10 codes as previously described.[32–42]

Statistical analysis

Descriptive statistics are presented as numbers (percentages) for categorical variables and mean±SD for continuous variables. We compared the two groups using the χ^2 test for categorical variables and t-tests for continuous variables. The incidence rates of pulmonary manifestations were calculated by dividing the number of incident events by the total follow-up period (1000 person-years). A cumulative incidence plot was used to compare the incidence of pulmonary manifestation between the SLE and matched control cohorts, and a log-rank test was used to evaluate significant differences between the groups.

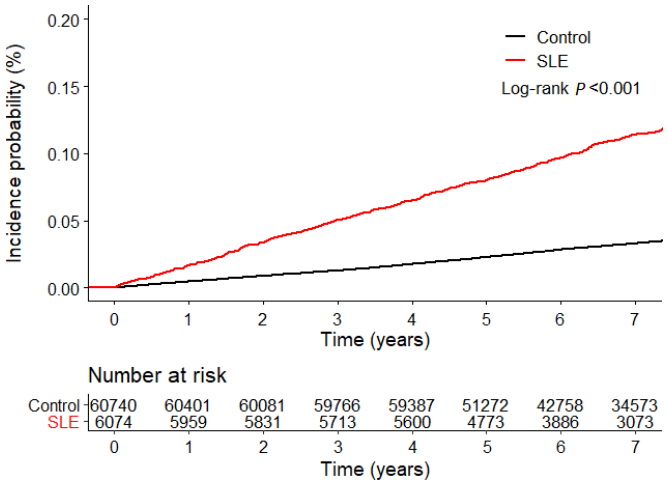

Figure 2 Cumulative incidence of overall pulmonary manifestations in the SLE and matched control cohort. Zero on the x-axis indicates 1 year after index date. SLE, systemic lupus erythematosus.

The risk of incident pulmonary manifestation in the SLE cohort compared with the matched control cohort was estimated using univariable and multivariable Cox proportional hazards regression analyses. In multivariable models, potential variables that may affect the development of SLE as well as pulmonary manifestations were adjusted. Model 1 was adjusted for sex, age, BMI, low-income status, smoking status and alcohol use. Model 2 was adjusted for variables in model 1 and DM, hypertension, dyslipidaemia, chronic kidney disease, myocardial infarction and airway diseases. Stratified analyses were performed according to baseline demographics (sex, age and BMI), personal habits (smoking and alcohol drinking) and comorbidities, and results were visualised using forest plots. The same analysis was repeated for each subtype of pulmonary manifestations. Two-sided p values <0.05 were considered statistically significant. All statistical analyses were performed using SAS Enterprise Guide Software V.7.1 (SAS Institute) and R V.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

The baseline characteristics of the study population are summarised in table 1. The most common age group was 40–49 years, and 89.1% of the subjects were female. Both groups were well balanced in terms of age (p=0.998) and sex (p=0.744). The proportions of low-income status, ever smokers, alcohol consumption, low BMI and comorbidities were significantly higher in the SLE cohort than in the matched control cohort (p<0.001 for all).

Incidence and risk of pulmonary manifestations

During the mean follow-up period of 9.3±2.7 years, 12.8% (n=775/6,074) of the SLE cohort and 4.1% (n=2488/60 740) of the matched control cohort developed pulmonary manifestations, with incidence rates of 15.2 and 4.5 per 1000 person-years, respectively (p<0.001 for both). Even after adjusting for potential confounders, the risk of incident pulmonary manifestation was also significantly higher in the SLE cohort than in the matched control cohort: unadjusted HR 3.48, 95% CI 3.21 to 3.77; adjusted HR (aHR) in model 1=3.48, 95% CI 3.20 to 3.78; aHR in model 2=3.26, 95% CI 2.99 to 3.56) (table 2). Similarly, the cumulative incidence plot depicts a significantly higher incidence of pulmonary manifestation in the SLE cohort than in the matched control cohort (log-rank p<0.001; figure 2).

The proportions of subjects who developed each subtype of pulmonary manifestations were significantly higher in the SLE cohort compared with the matched control cohort (p<0.05 for all; online supplemental table 1). For each subtype of pulmonary manifestation, the relative risk in the SLE cohort compared with the matched control cohort was highest for pulmonary hypertension (aHR (95% CI) 14.66 (9.43 to 22.80)), followed by ILD (9.58 (95% CI 7.99 to 11.49)), pleural disorder (3.29 (95% CI 2.84 to 3.81)), pulmonary embolism (2.66 (95% CI 2.06 to 3.43)), tuberculosis (2.35 (95% CI 1.88 to 2.93)), ARDS and haemorrhage (1.85 (95% CI 1.51 to 2.25)) and lung cancer (1.41 (95% CI 1.02 to 1.95)) (table 2). The cumulative incidence plot depicts a significantly higher incidence of each pulmonary manifestation in the SLE cohort than in the matched control cohort (log-rank p<0.001 for all; online supplemental figure 1).

Subgroup analysis

Sex, age, DM and airway disease had significant interactions on the association of SLE with pulmonary manifestation development (p for interaction <0.05 for all). The associations between SLE and pulmonary manifestations were more prominent in females compared with males and in younger subjects compared with older subjects. Regarding the association of the risk of pulmonary manifestations with DM and airway diseases, subjects without DM and subjects without airway disease had higher risks of pulmonary manifestations compared with their counterparts (table 3). Other variables did not have significant effect modifications on the association between SLE and pulmonary manifestation development (table 3). The interactions between each subtype of pulmonary manifestation and baseline covariates are summarised in online supplemental figure 2.

DISCUSSION

This study provides longitudinal evidence from a large population using a nationwide dataset with a mean follow-up of 9 years, exploring the association between SLE and the risk of pulmonary manifestations. We investigated whether SLE is a predisposing factor for the development of various pulmonary manifestations. The results showed that the SLE cohort had an overall pulmonary manifestation incidence rate of 15.2 per 1000 person-years, which was approximately 3.3-fold higher than that

Table 3 Subgroup analysis of pulmonary manifestation incidence in the SLE and matched control cohort

Subgroup		SLE	Number at risk	Pulmonary manifestations	Incidence per 1000 PY	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Sex	Male	No	6587	375	6.50	Reference	Reference	Reference
		Yes	667	92	17.36	2.73 (2.17 to 3.43)	2.77 (2.20 to 3.49)	2.52 (2.00 to 3.18)
	Female	No	54153	2113	4.22	Reference	Reference	Reference
		Yes	5407	683	14.94	3.62 (3.32 to 3.94)	3.60 (3.29 to 3.93)	3.39 (3.10 to 3.71)
	P for interaction					0.021	0.033	0.015
Age	20–29	No	6990	136	1.99	Reference	Reference	Reference
		Yes	696	62	9.84	5.04 (3.73 to 6.80)	4.97 (3.68 to 6.72)	4.79 (3.54 to 6.47)
	30–39	No	10688	213	2.06	Reference	Reference	Reference
		Yes	1081	100	10.29	5.10 (4.02 to 6.47)	4.98 (3.92 to 6.31)	4.72 (3.72 to 5.99)
	40–49	No	17875	499	2.99	Reference	Reference	Reference
		Yes	1779	209	13.62	4.66 (3.97 to 5.48)	4.51 (3.84 to 5.31)	4.25 (3.60 to 5.00)
	50–59	No	14719	702	5.29	Reference	Reference	Reference
		Yes	1478	191	15.75	3.06 (2.61 to 3.59)	2.96 (2.51 to 3.48)	2.76 (2.35 to 3.26)
	60–69	No	7850	587	8.89	Reference	Reference	Reference
		Yes	777	147	25.55	2.97 (2.48 to 3.56)	2.85 (2.37 to 3.42)	2.64 (2.20 to 3.18)
	≥70	No	2618	351	16.82	Reference	Reference	Reference
		Yes	263	66	37.46	2.36 (1.81 to 3.07)	2.31 (1.78 to 3.01)	2.16 (1.66 to 2.82)
	P for interaction					<0.001	<0.001	< 0.001
Smoking status	Never smokers	No	52499	2090	4.31	Reference	Reference	Reference
		Yes	5151	651	14.96	3.54 (3.24 to 3.87)	3.57 (3.27 to 3.91)	3.37 (3.07 to 3.69)
	Ex-smoker	No	3269	174	6.06	Reference	Reference	Reference
		Yes	404	60	18.59	3.13 (2.34 to 4.20)	3.05 (2.27 to 4.09)	2.75 (2.05 to 3.70)
	Current smoker	No	4972	224	4.97	Reference	Reference	Reference
		Yes	519	64	15.00	3.09 (2.34 to 4.08)	2.98 (2.25 to 3.94)	2.77 (2.09 to 3.68)
	P for interaction					0.508	0.307	0.207
Alcohol use	No	No	11930	321	2.90	Reference	Reference	Reference
		Yes	886	81	10.43	3.64 (2.85 to 4.65)	3.60 (2.82 to 4.60)	3.39 (2.65 to 4.33)
	Yes	No	48810	2167	4.84	Reference	Reference	Reference
		Yes	5188	694	16.05	3.39 (3.11 to 3.69)	3.46 (3.17 to 3.78)	3.25 (2.97 to 3.56)
	P for interaction					0.589	0.769	0.744

Continued

Table 3 Continued

Subgroup		SLE	Number at risk	Pulmonary manifestations	Incidence per 1000 PY	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Body mass index, kg/m^2	<18.5	No	3299	113	3.62	Reference	Reference	Reference
		Yes	497	67	15.85	4.48 (3.32 to 6.07)	3.91 (2.89 to 5.29)	3.65 (2.70 to 4.95)
	18.5–23	No	27844	994	3.85	Reference	Reference	Reference
		Yes	3098	375	14.19	3.76 (3.34 to 4.23)	3.65 (3.24 to 4.12)	3.43 (3.03 to 3.87)
	23–25	No	12816	552	4.70	Reference	Reference	Reference
		Yes	1129	146	15.41	3.34 (2.79 to 4.01)	3.33 (2.77 to 4.00)	3.14 (2.61 to 3.77)
	≥25	No	16781	829	5.48	Reference	Reference	Reference
		Yes	1350	187	17.19	3.23 (2.76 to 3.78)	3.19 (2.71 to 3.74)	2.99 (2.54 to 3.52)
	P for interaction					0.176	0.459	0.472
Diabetes mellitus	No	No	55798	2090	4.05	Reference	Reference	Reference
		Yes	5055	610	14.13	3.56 (3.25 to 3.89)	3.64 (3.32 to 4.00)	3.49 (3.18 to 3.84)
	Yes	No	4942	398	9.49	Reference	Reference	Reference
		Yes	1019	165	21.07	2.27 (1.90 to 2.73)	2.58 (2.15 to 3.11)	2.51 (2.09 to 3.02)
	P for interaction					<0.001	<0.001	0.001
Hypertension	No	No	50898	1741	3.69	Reference	Reference	Reference
		Yes	4468	490	12.84	3.55 (3.22 to 3.93)	3.53 (3.19 to 3.91)	3.40 (3.06 to 3.77)
	Yes	No	9842	747	8.69	Reference	Reference	Reference
		Yes	1606	285	22.17	2.61 (2.27 to 2.99)	3.17 (2.76 to 3.65)	3.02 (2.62 to 3.48)
	P for interaction					<0.001	0.212	0.176
Dyslipidaemia	No	No	50090	1816	3.88	Reference	Reference	Reference
		Yes	3434	412	13.66	3.57 (3.21 to 3.98)	3.64 (3.27 to 4.06)	3.49 (3.13 to 3.89)
	Yes	No	10650	672	7.48	Reference	Reference	Reference
		Yes	2640	363	17.41	2.37 (2.08 to 2.69)	3.00 (2.63 to 3.42)	2.96 (2.59 to 3.38)
	P for interaction					<0.001	0.024	0.056
Chronic kidney disease	No	No	60544	2471	4.44	Reference	Reference	Reference
		Yes	5857	740	14.98	3.44 (3.17 to 3.74)	3.47 (3.19 to 3.77)	3.27 (3.00 to 3.57)
	Yes	No	196	17	10.61	Reference	Reference	Reference
		Yes	217	35	21.64	2.08 (1.16 to 3.71)	2.76 (1.55 to 4.94)	2.77 (1.55 to 4.94)
	P for interaction					0.101	0.455	0.578

Continued

Table 3 Continued

Subgroup		SLE	Number at risk	Pulmonary manifestations	Incidence per 1000 PY	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Myocardial infarction	No	No	60651	2478	4.45	Reference	Reference	Reference
		Yes	6041	771	15.21	3.49 (3.22 to 3.79)	3.49 (3.21 to 3.79)	3.28 (3.01 to 3.57)
	Yes	No	89	10	12.48	Reference	Reference	Reference
		Yes	33	4	13.33	1.07 (0.34 to 3.41)	1.65 (0.52 to 5.28)	1.57 (0.49 to 5.00)
	P for interaction					0.034	0.189	0.194
Airway disease	No	No	54453	2088	4.16	Reference	Reference	Reference
		Yes	5071	617	14.33	3.51 (3.21 to 3.84)	3.57 (3.26 to 3.92)	3.42 (3.11 to 3.75)
	Yes	No	6287	400	7.15	Reference	Reference	Reference
		Yes	1003	158	19.89	2.86 (2.38 to 3.44)	2.81 (2.33 to 3.39)	2.69 (2.23 to 3.25)
	P for interaction					0.048	0.022	0.022

Model 1 was adjusted for sex, age, low-income status, smoking status, alcohol use and body mass index.
Model 2 was adjusted for sex, age, low-income status, smoking status, alcohol use, body mass index, diabetes mellitus, hypertension, dyslipidaemia, chronic kidney disease, myocardial infarction and airway diseases.
PY, person-years; SLE, systemic lupus erythematosus.

in the matched control cohort. The SLE cohort had a higher risk for a variety of pulmonary manifestations compared with the matched control cohort: pulmonary hypertension about 14.7-fold, ILD about 9.6-fold, pleural disorders about 3.3-fold, pulmonary embolism about 2.7-fold, tuberculosis about 2.4-fold, ARDS and haemorrhage about 1.9-fold and lung cancer about 1.4-fold higher. Notably, certain groups, including females, younger individuals, subjects without DM and subjects without airway disease, exhibited higher susceptibility to pulmonary manifestation development than their counterparts.

Several previous studies reported relationships between SLE and pulmonary manifestations. Most studies of pulmonary manifestations of SLE have come from relatively small studies in select clinical cohorts, or have looked at prevalence only, or have analysed the occurrence of pulmonary manifestations within the SLE cohort without comparison to the general population.[2–4 6] Overcoming these limitations, a recent Swedish population-based study evaluated a total of 3209 incident and 6908 prevalent cases of SLE and found that subjects with SLE had a nearly 5.8-fold higher rate of pulmonary manifestations compared with the non-SLE population.[7] When considering each pulmonary manifestation group separately, the highest relative risk was found for ILD (aHR 14.3 (95% CI 10.8 to 18.8)) and the lowest for pulmonary embolism (aHR 3.8 (95% CI 3.1 to 4.6)). However, this study could not consider confounding variables such as smoking status, BMI and comorbidities. Additionally, subjects were followed only until 2013. Considering the confounding effects of these variables and recent advances in SLE treatment, updated data would be more informative.

The present study has advantages due to analysing large number of subjects (about 6000 subjects with incident SLE) and considering confounding factors such as age, sex, BMI, smoking and comorbidities up to 2021. We found a 3.3-fold increased risk of pulmonary manifestations in the SLE cohort, which is about half that reported in the Swedish study. The highest risk was observed for ILD, followed by pulmonary hypertension, with the lowest risk for lung cancer. The differences between the studies might have been caused by several factors. First, while the Swedish study included upper airway diseases, ours did not. Second, our study implemented a 1-year lag period to ascertain the causal association between SLE and pulmonary manifestations. However, excluding patients diagnosed with pulmonary manifestations within 1 year of their SLE diagnosis might also explain the lower incidence of pulmonary manifestations in our study compared with the Swedish study.

Despite these differences, both studies highlighted the high risk of ILD. A previous study examining the relationship between SLE and lung cancer using meta-analysis and Mendelian randomisation analysis found a less than two-fold increased risk of lung cancer, which aligns with our findings.[43] This suggests that while the risk of lung cancer in subjects with SLE is significantly higher than in

the general population, it is lower compared with other pulmonary manifestations.

In our subgroup analysis, we found that the risk of pulmonary manifestations was higher in certain subgroups, including those without DM and those without airway disease, compared with their counterparts. The reasons for this phenomenon are not fully explainable, as our study is observational in nature. However, there might be some explanations. While systemic corticosteroid use in SLE could lead to the development of DM,[44] the anti-inflammatory effects of systemic corticosteroids may reduce the development of pulmonary manifestations. This hypothesis can also be extended to airway diseases (such as asthma or chronic obstructive pulmonary disease) where inhaled corticosteroid use is prevalent. Further studies are needed to confirm our hypothesis.

The findings of our study have significant clinical and research implications. Clinically, the identification of a higher risk of pulmonary manifestations in SLE patients underscores the need for vigilant monitoring and early intervention strategies to manage and mitigate these risks. The particularly high risks of ILD and pulmonary hypertension suggest that these conditions should be prioritised in routine screenings and follow-up care for SLE patients. From a research perspective, our study highlights the importance of considering confounding factors such as smoking status, BMI and comorbidities in future investigations. Notably, our study is the first to involve a non-white population,[2–4 6 7 45] providing valuable insights into the risk of pulmonary manifestations in a different cohort. The use of a large, population-based dataset with comprehensive adjustments for these variables provides a more accurate assessment of the true burden of pulmonary manifestations in SLE. Additionally, our findings call for further research into the mechanisms underlying the increased susceptibility to pulmonary manifestations in SLE patients and the development of targeted therapies to address these specific risks. Overall, our study contributes valuable insights that can inform both clinical practice and future research endeavours in the field of SLE and pulmonary health.

Our study has several limitations. First, the diagnoses of SLE, pulmonary manifestations and other comorbidities were based on ICD-10 codes, which may lead to overestimation or underestimation. To mitigate this issue, we adopted a conservative approach by using both ICD-10 codes and the RID programme registration code for SLE. Second, the absence of serological and radiologic data prevented us from including these factors in our analyses, highlighting the need for future studies to incorporate such data. Thus, we could not incorporate some important factors into our analyses. For example, we did not have information on the presence of autoantibodies, and thus, the impact of disease overlap (eg, coexisting Sjögren's disease) and antiphospholipid syndrome. In particular, antiphospholipid syndrome has been suggested to be important in the development of severe pulmonary manifestations such as ARDS, intra-alveolar haemorrhage, pulmonary embolism and pulmonary hypertension.[46] Third, this study was conducted using a Korean dataset, and therefore, additional studies in other countries or among different ethnicities are necessary to generalise our findings.

In conclusion, the risk of pulmonary manifestation was approximately 3.3-fold higher in subjects with SLE compared with matched control cohort. In particular, the risks of ILD and pulmonary hypertension were relatively high compared with other pulmonary manifestations.

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Contributors HL is the guarantor of the manuscript and takes responsibility for the content of the manuscript, including the data and analysis. All authors contributed to the conception and design of the study. B-GK, JK and HL were involved in the collection and interpretation of the data. B-GK and JK were involved in the statistical analyses. B-GK and HL were major contributors to writing the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by Hanyang University (HY-202400000002955).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Institutional Review Board of Hanyang University Hospital (No. 2024-08-017). The requirement for informed consent was waived because all patient records were anonymised before use.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data that support the findings of this study are available from the Korean National Health Insurance Service. Restrictions apply to the availability of these raw data, which were used under licence for the current study, and so are not publicly available. Data are however available from the corresponding authors on reasonable request and with permission of the Korean National Health Insurance Service.

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