Systemic lupus erythematosus is a risk factor for atrial fibrillation: a nationwide, population-based study

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Abstract

Objective

Cardiac involvement is present in more than half of the patients with systemic lupus erythematosus (SLE). However, large-scale studies on the prevalence of atrial fibrillation (AF) in this disease do not exist. We aimed to investigate the incidence and clinical significance of AF in SLE.

Methods

Patients with SLE (n=21,143; mean age, 41.8±13.13 years; female, 90.38%) without previous AF were selected from the Korean National Health Insurance Service National Sample Cohort database between 2008 and 2014. Age-and sex-matched controls (n=105,715) were randomly sampled in a 5:1 ratio from the population of individuals without SLE from the same database. Both cohorts were followed-up for incidental AF and death until 2015.

Results

AF was newly detected in 481 (2.27%) patients with SLE and 619 (0.59%) controls (incidence: 3.692 and 0.941 per 1000 person-years, respectively). After multivariate adjustment, SLE was found to be a risk factor for developing AF [hazard ratio (HR), 2.84; 95% confidence interval (CI), 2.50–3.23]. On subgroup analysis, younger (age <40) patients showed a higher incidence of AF. SLE patients with incidental AF had a higher mortality rate compared with patients without SLE with AF (HR, 2.35; 95% CI 1.73–3.20) and those with SLE without AF (HR, 3.53; 95% CI 2.84–4.39) after adjustment.

Conclusion

SLE was an independent risk factor for AF development, especially in younger patients without previous AF, stressing the importance of cardiac assessment in this population. Development of AF in patients with SLE was associated with increased mortality.

Key words

systemic lupus erythematosus, atrial fibrillation, epidemiology, mortality

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Introduction

The cardiac manifestations of systemic lupus erythematosus (SLE) are various, including coronary artery disease, valvular disease, heart failure, conduction system disturbances, and arrhythmias (1, 2). The mechanisms by which these disturbances develop include autoantibody-mediated damage, atherosclerotic complications, or even adverse effects of the treatment, such as chloroquine-induced cardiotoxicity (3-5). Although cardiovascular events are the main cause of death in SLE and the burden of treatable cardiovascular (CV) risk in SLE is elevated, little attention has been given to complications of cardiac arrhythmias (6). Arrhythmias and conduction system disorders can be important causes of death in patients with SLE. The relationship between the presence of arrhythmia or conduction disturbances and mortality in patients with SLE has only been reported in a small number of studies (7). Because of limited information available in the literature, there is no consensus on the prevalence of atrial fibrillation (AF) in patients with SLE. Therefore, we aimed to assess the risk of developing AF in patients with SLE, and its relationship with mortality using a nationwide population-based study with long-term follow-up data.

Materials and methods

Data source and study cohort

The Korean National Health Insurance Service National Sample Cohort (NHIS-NSC), constructed from the NHIS database that includes all citizens in Korea (50 million), includes 105,715 randomly selected individuals enrolled in 2008 with follow-up data for 8 years until December 2015 (Fig. 1). Data regarding patient demographics and medical treatment claims for inpatient and outpatient care, including diagnoses, prescriptions, procedures, and nationwide health examination results, are available. Diagnosis statements were defined by the *International Classification of Diseases*, tenth revision (ICD-10). All patients in whom SLE was diagnosed (ICD-10 code M32) between 2008 and 2014 were extracted from the database. Of these, patients younger than 20 years or those with a history of cancer during a washout period from 2005 to 2007 were excluded. For the non-SLE control cohort, age-and sex-matched controls (n=105,715) were randomly sampled from non-SLE individuals in 2008 at a 5:1 ratio of controls to cases. Randomisation was done using an algorithm within the SAS software. Patients who were diagnosed with mitral stenosis (I050, I052, and I059) or those who had mechanical heart valves (Z952-Z954) from 2005 to 2015 were excluded. The retrospective cohorts included follow-up data for incident AF and death until 2015. The validity of this database and the definitions of covariates and outcomes have been confirmed in previous studies (8, 9). This study adhered to the tenets of the Declaration of Helsinki. As the database used in this study did not include personal identifiers, and this study was of a retrospective observational nature, the need for informed consent was waived and ethical approval was given by the Chonnam National University Hospital Institutional Review Board (CHUN-EXP-2018-026) and the Institutional Review Board of the Republic of the Republic of Korea National Institute for Bioethics Policy (NHIS-2018-1-177).

Identification of SLE cases

The NHI statisticians compiled data from all patients treated under an ICD-10 code of M32 at each institute nationwide from 2005 to June 2015 (washout period was from 2005 to 2007). The South Korea government provides enhanced coverage for four major conditions: cancer; cardiovascular disease; cerebrovascular disease; and rare diseases, which includes SLE. Within this system, the NHI has established a registration programme for rare intractable diseases (code V136). Due to enforced privacy laws, detailed personal information could not be retrieved; instead, each patient was allocated an identification number.

Baseline comorbidities

Baseline comorbidities were also evaluated during the screening period. Baseline characteristics of the comorbidities were extracted from the medical claims

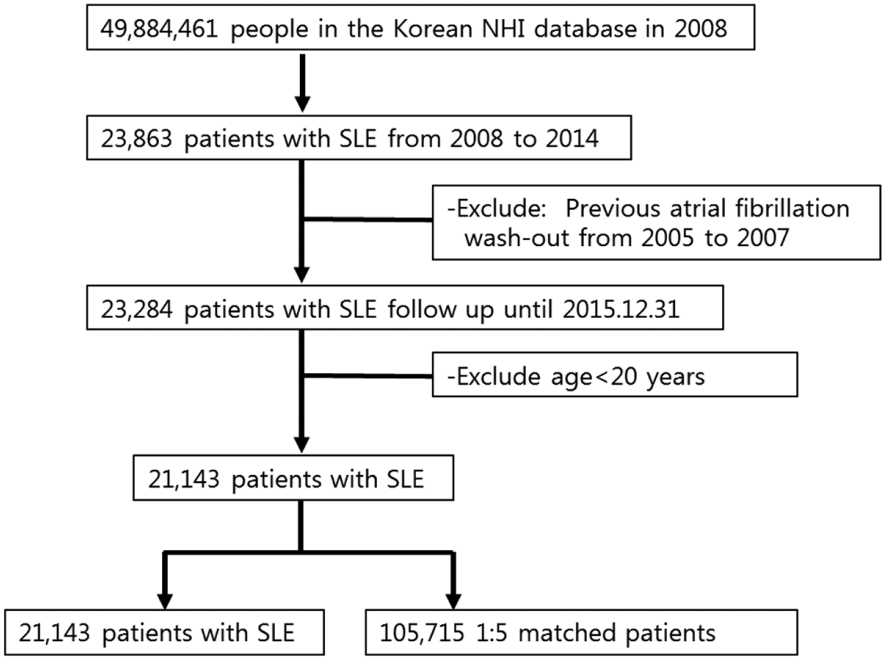


Fig. 1. Study design. NHI: national health insurance; SLE: systemic lupus erythematosus.

Table I. Baseline characteristics of the study population.

	SLE (n=21,143)	Non-SLE (n=105,715)	*p*-value
Sex, female	19109 (90.38%)	95543 (90.38%)	1
Age	41.8 ± 13.13	41.8 ± 13.13	1
20-39	10123 (47.88%)	50615 (47.88%)	
40-64	9690 (45.83%)	48450 (45.83%)	
65-	1330 (6.29%)	6650 (6.29%)	
Diabetes mellitus	907 (4.29%)	3660 (3.46%)	<0.0001
Hypertension	5742 (27.16%)	10432 (9.87%)	<0.0001
Dyslipidaemia	2983 (14.11%)	6100 (5.77%)	<0.0001
Myocardial infarction	566 (2.68%)	540 (0.51%)	<0.0001
Stroke	1008 (4.77%)	1722 (1.63%)	<0.0001
Congestive HF	752 (3.56%)	849 (0.8%)	<0.0001
ESRD	432 (2.04)	107 (0.1)	
COPD	4555 (21.54)	10404 (9.84)	
Income low*	5423 (25.65%)	25579 (24.2%)	<0.0001
CHA_2DS_2-VASc score			
Mean	1.69 ± 1.08	1.2 ± 0.83	<0.0001
0	808 (3.82)	7801 (7.38)	
1	10915 (51.62)	81653 (77.24)	
2	5707 (26.99)	8791 (8.32)	
3	2326 (11)	4253 (4.02)	
4	837 (3.96)	1976 (1.87)	
5	377 (1.78)	819 (0.77)	
≥6	173 (0.8)	422 (0.4)	

*Medical aid group: government-aided medical care. HF: heart failure; ESRD: end-stage renal disease; COPD: chronic obstructive lung disease.

according to the ICD-10 codes, and prescription and procedure codes. We included diabetes mellitus (DM), hypertension, dyslipidaemia, congestive heart failure (CHF), end-stage renal disease (ESRD), chronic obstructive pulmonary disease (COPD), and a history of myocardial infarction (MI) and stroke. CHA2DS2-VASc scores were calculated using the aforementioned diagnosis claims. Low income was defined as the lowest 20% of the total population based on the individual's monthly income.

Endpoint

The primary endpoint of this study was newly diagnosed non-valvular AF during the follow-up period. AF was defined using diagnosis codes for paroxysmal, persistent, permanent AF, and atrial flutter (I48.0-I48.4, I48.9). One or more diagnoses during hospitalisation or two or more at outpatient clinics were required for the diagnosis of AF. The secondary endpoint of this study was all-cause mortality. Patients without AF during the follow-up period were censored at the date of dropout (due to death or emigration) or at the end of follow-up, whichever came first.

Statistical analysis

Continuous variables are presented as means ± standard deviation and categorical variables are presented as number and percentage. To compare characteristics between cohorts, Student's *t*-test was used for continuous variables and the chi-square test was used for binary and categorical variables. The incidence rates of AF and mortality rates were calculated per 1000 person-years. The cumulative AF incidence for each group was plotted with Kaplan-Meier curves and compared using the log-rank test. Multivariate Cox regression models were used to assess the risk of new-onset AF and mortality associated with baseline characteristics. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The chi-square test and Fisher's exact test were used to assess the relationship between AF development and mortality. All statistical tests were two-tailed, and the significance level was set at $p<0.05$. Statistical analyses were performed using SPSS Statistics, v. 21.0 (IMB Corp., Armonk, NY, USA) and SAS v. 9.2 (SAS Institute Inc., Cary, NC, USA) for Windows.

Results

Baseline characteristics of this study population

A total of 21,143 patients were included in the SLE cohort: 19,109 (90.38%) were female and the mean age was 41.8±13.13 years; 105,715 individuals without SLE were included in the sex- and age-matched control cohort. The baseline characteristics of both groups

are summarised in Table I. The SLE group had different income distributions and a higher prevalence of comorbidities related to AF, such as DM, hypertension, dyslipidaemia, COPD, ESRD, MI, stroke, and CHF, compared to the non-SLE group, which was adjusted for when estimating AF risk. The SLE group had a mean baseline CHA_2DS_2-VASc score of 1.69±10.8, which was higher than that of the non-SLE group (1.2±0.83, $p<0.0001$).

Incidence and risk of AF in the SLE and control groups

During the mean follow-up of 8 years, 481 (2.27%) individuals in the SLE group and 619 (0.59%) in the non-SLE group were diagnosed with AF. The incidence rates for AF were 3.69 and 0.94 per 1000 person-years in the SLE group and the non-SLE group, respectively. Patients with SLE had an HR of 2.84 (95% CI, 2.50–3.23) for AF development after multivariate adjustment for age, sex, income, and relevant comorbidities such as DM, hypertension, dyslipidaemia, COPD, ESRD, prior MI, prior stroke, and CHF (Table II). Figure 2 demonstrates the higher cumulative incidence of AF in patients with SLE compared to that in patients without SLE (log-rank test $p<0.001$). In all age groups, patients with SLE showed a higher incidence of AF compared to patients without SLE (Table II). During subgroup analysis, SLE increased the risk for AF, especially in younger (age <40 years) patients (Fig. 3). The HR for SLE was >1 for all subgroups, indicating that SLE consistently increased the risk of AF (Fig. 3).

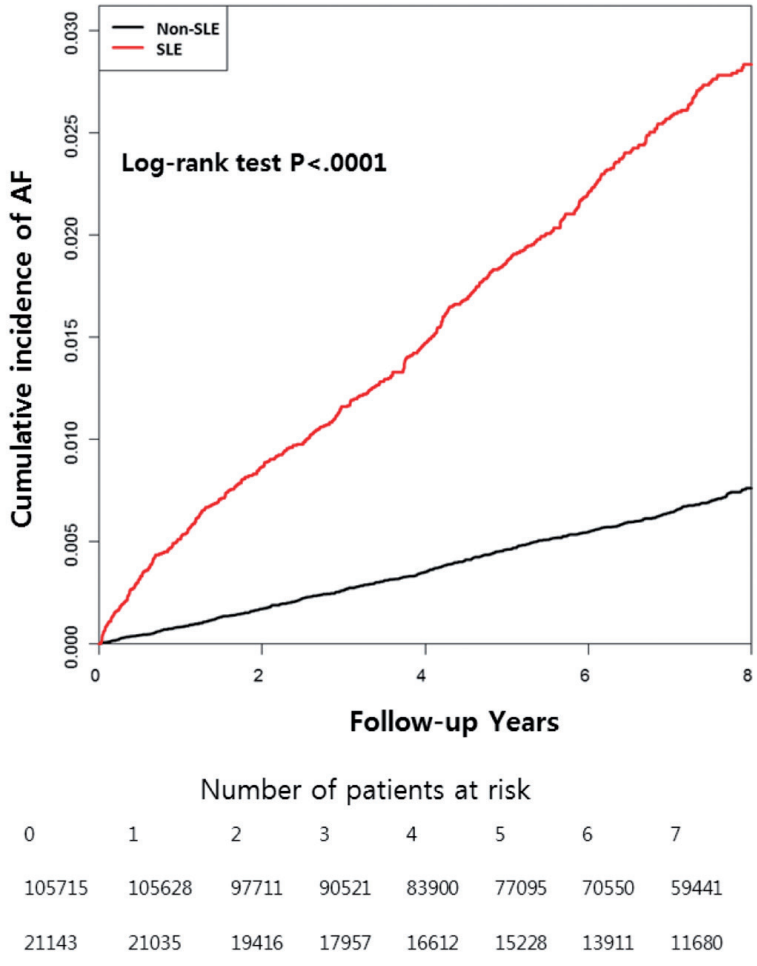
Mortality in SLE and AF

The overall mortality rate was greater in the SLE group with incidental AF compared to that in the non-SLE group with incidental AF (57.21 *vs*. 38.15 per 1000 person-years) (Table III). In the SLE group, patients who developed AF were associated with an increased risk for mortality after adjustment for age, sex, DM, hypertension, dyslipidaemia, MH, CHF, stroke, ESRD, COPD, and low income (Table III). During the follow-up period, a significantly higher proportion of the SLE group (25.8%) compared to the non-SLE group (16.5%) died of any cause (Table IV). Cox regression analysis with multivariate adjustment showed that patients with SLE with AF had an increased risk of all-cause death (HR, 3.53; 95% CI, 2.84–4.39) compared to those with SLE without AF (Table IV, Fig. 4A). In non-SLE controls, patients who developed AF also showed significantly higher mortality rates (HR, 5.65; 95% CI, 3.74–5.78) than those who remained AF-free (Ta-

Table II. Incidence and risk of atrial fibrillation (AF) in SLE and non-SLE patients.

	SLE (n=21,143)	Non-SLE (n=105,715)	*p*-value
AF cases, n (%)	481 (2.27)	619 (0.59)	<0.0001
Follow up duration, years	6.16±2.24	6.22±2.2	0.0005
AF incidence (per 1000 person-years)	3.69	0.94	
By sex			<0.0001
Male	6.00	1.73	
Female	3.46	0.86	
By age group			<0.0001
20-39	2.83	0.28	
40-64	3.79	1.07	
65-	10.79	5.89	
Hazard ratio (HR)			
Crude H .^$95% CI)	3.92 (3.48-4.41)	1 (ref.)	<0.0001
*Adjusted HR(95% CI)	3.84 (2.50-3.23)	1 (ref.)	<0.0001

*Age, sex, diabetes mellitus, hypertension, dyslipidaemia, MI, stroke, CHF, ESRD, COPD and low income matched.



Number of patients at risk

Year	0	1	2	3	4	5	6	7	8
Non-SLE	105715	105628	97711	90521	83900	77095	70550	59441	1915
SLE	21143	21035	19416	17957	16612	15228	13911	11680	369

Fig. 2. Kaplan-Meier curves showing incidence of atrial fibrillation in SLE and non-SLE patients.

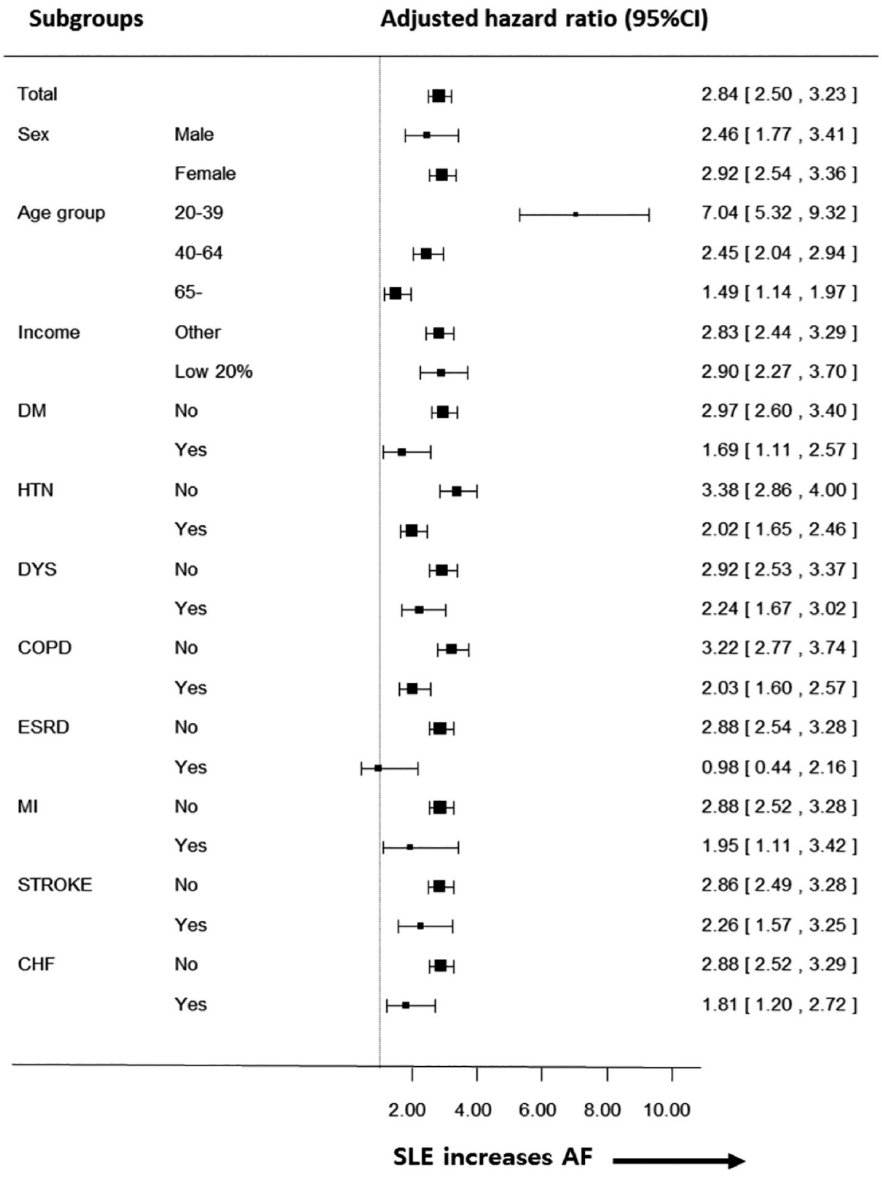


Fig. 3. Kaplan-Meier curves showing cumulative overall death in (**A**) SLE patients with and without atrial fibrillation development, (**B**) non-SLE controls with and without atrial fibrillation development.

Table III. Death rate in SLE and non-SLE patients with incidental AF.

Group	n	Death	Rate	M1	M2	M3
Non SLE with incidental AF	619	92	38.15	1(Ref.)	1(Ref.)	1(Ref.)
SLE with incidental AF	481	103	57.21	1.48 (1.12-1.96)	2.40 (1.78-3.22)	2.35 (1.73-3.20)

Model 1, non-adjusted.
Model 2, age, sex, DM, Hypertension, dysplididaemia and income low adjusted.
Model 3, age, sex, diabetes mellitus, hypertension, dyslipidaemia, MI, stroke, CHF, ESRD, COPD and low income matched.

ble IV, Fig. 4B). There was a significant association between development of AF and increased overall death.

Discussion

There are two main findings in our study. First, SLE was found to be an independent risk factor for development of AF after adjusting for other covariates. Second, AF development was significantly associated with increased mortality in patients with SLE.

The mechanism of arrhythmias in SLE has not been completely elucidated, and they may be related to the inflammatory processes of pericarditis and myocarditis and the myocardial ischaemia caused by atherosclerotic changes, or they may develop as a consequence of vasculitis of small vessels with collagen and fibrotic deposits that affect the conduction system (3, 4, 10). In fact, clinical myocarditis is identified in 3% to 15% of patients with SLE (11), and it can be associated with the presence of anti-Ro/SSA antibodies (12). On the other hand, myocardial involvement could be present even in asymptomatic patients. Myocardial perfusion studies with technetium-^{99m}sestamibi scintigraphy have documented abnormal perfusion in patients with SLE, even in the absence of coronary artery obstruction (13). In addition to the previously described associations between anti-Ro/SSA and myocarditis, Logar *et al*. also observed a relationship with conduction disturbances in 67 patients with SLE (12). The direct participation of specific antibodies, such as anti-Ro/SSA and anti-RNP, is controversial. Conduction disruption is commonly permanent in neonatal lupus and it can be associated with structural cardiac disorders (14). Sinus bradycardia and prolonged QTc have also been reported in those patients (15). However, there is no evidence that the development of arrhythmias in adult patients with SLE is similar to the changes observed in neonatal lupus.

The increased incidence of AF in patients with SLE may be associated with the medication used in the treatment of lupus. High-dose steroids can induce AF in patients with SLE. A few reports have stated that intravenous methylprednisolone can induce AF in patients with SLE (16). Furthermore, AF following methylprednisolone therapy has also been reported in the treatment of different diseases, such as membranoproliferative glomerulonephritis and multiple sclerosis, suggesting a drug-related effect rather than a disease-specific predisposition (17, 18). Nonetheless, the hypothetical arrhythmogenicity of high-dose methylprednisolone has yet to be substantiated, presumably because of the small number of

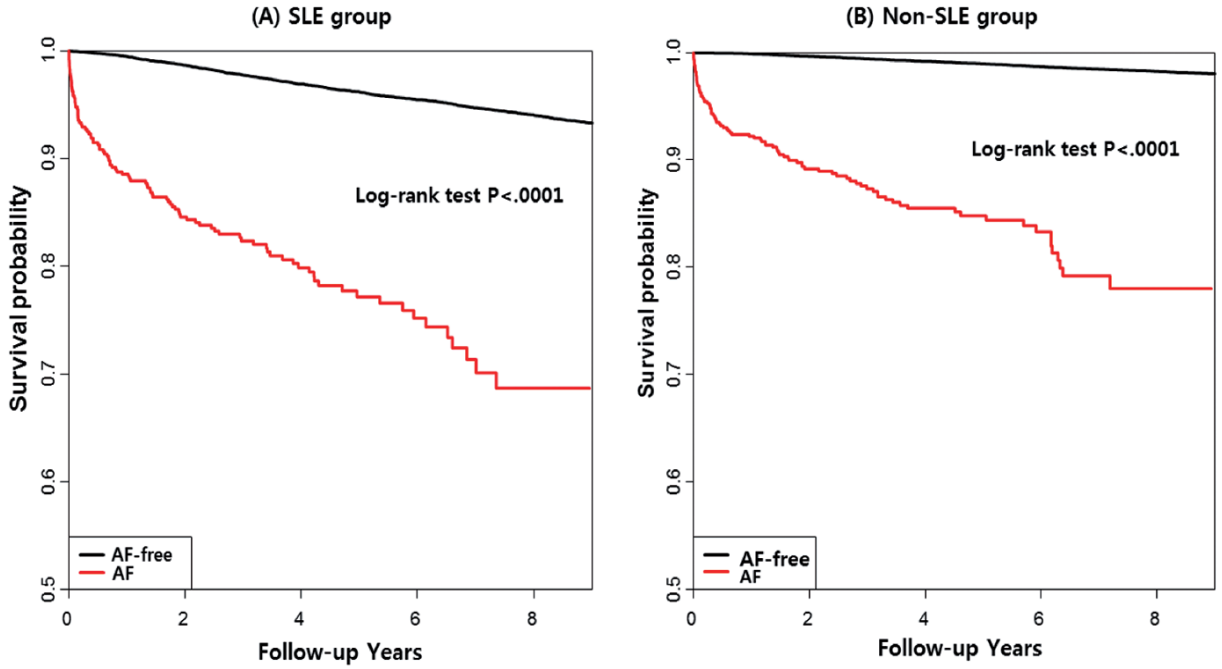


Fig. 4. Kaplan-Meier curves showing cumulative overall death in (**A**) SLE patients with and without atrial fibrillation development, (**B**) non-SLE controls with and without atrial fibrillation development.

Table IV. Death rate of atrial fibrillation (AF) in SLE and non-SLE patients.

	SLE (n=21,143)		Non-SLE (n=105,715)		*p*-value for interation
	AF (n=481)	Non-AF (n=20,662)	AF (n=619)	Non-AF (n=105,096)	
Death case, n (%)	103 (21.4%)	1122 (5.4%)	92 (14.9%)	1661 (1.6%)	
Death rate (per 1000 person-years)	57.21	7.72	38.15	2.20	
Model 1	7.40 (6.04-9.08)	1 (ref.)	18.39 (14.89-22.71)	1 (ref.)	<.0001
Model 2	4.85 (3.95-5.97)	1 (ref.)	5.65 (4.56-6.70)	1 (ref.)	0.0598
Model 3	3.53 (2.84-4.39)	1 (ref.)	5.65 (3.74-5.78)	1 (ref.)	<.0001

Model 1, non-adjusted.
Model 2, age, sex, DM, Hypertension, dysplididaemia and income low adjusted.
Model 3, age, sex, diabetes mellitus, hypertension, dyslipidaemia, MI, stroke, CHF, ESRD, COPD and low income matched.

reported cases. Another lupus-related drug, chloroquine, may also be a candidate for inducing AF. Similar to other drugs, such as amiodarone and chlorpromazine, chloroquine accumulates in lysosomes, causing direct inhibition of its enzymes and increasing lysosomal pH, resulting in the formation of cytoplasmic inclusion bodies (5). Thus, it can promote a significant reduction in the velocity of the action potential, prolonging its duration and increasing the refractory period of the cells of the cardiac conduction system. For this reason, chloroquine could have antiarrhythmic properties as well as cause the development of severe arrhythmias (19). The contribution of dose, duration of exposure, and individual or genetic predisposition to the development of chloroquine toxicity is unknown. However, the diagnosis of chloroquine toxicity can be confirmed by drug history and endomyocardial biopsy with ultra-structural study by transmission electron microscopy. Recently, magnetic resonance imaging has proved to be extremely useful in the detection of chloroquine-induced cardiomyopathy, representing an excellent non-invasive option for the diagnosis of this complication (20). Improvement of cardiac dysfunction after withdrawal of the drug in patients who developed cardiomyopathy has also been reported (21). However, it has recently been reported that anti-malarial drugs decrease the odds of cardiac conduction abnormality (22). Therefore, further elucidation of the mechanism of the development of AF in SLE and identifying the parameters related to the development of these electrical disruptions is necessary. There are several limitations to this study. First, there was no way to clarify the dose and duration of steroids as well as chloroquine or other arrhythmogenic drugs. Consequently, we were not able to examine whether lupus-treatment medications increased AF risk. Second, SLE, AF, and other comorbidities were identified from claims data using diagnostic codes; therefore, misdiagnosis or omission is possible. Therefore, we could not estimate the accuracy of the definition of SLE (sensitivity, specificity, positive predictive value, and negative predictive value). Nevertheless, efforts were made to minimise errors by

refining the definition of diseases, as in previous studies (8, 9). Furthermore, this study could not determine the exact method used by each physician to diagnose AF due to the limitations inherent to claims data. Although claims data included billing codes for Holter monitoring and 12-lead electrocardiography, the methods used by each physician to detect AF were not included when the diagnosis was entered. Finally, although this study found a statistically significant association between SLE and AF development, the pathologic mechanisms underlying this relationship require further research.

In conclusion, our data indicate that SLE is a predisposing factor for AF development, stressing the importance of cardiac assessment in patients with SLE. Moreover, patients with SLE and AF had an increased risk of all-cause death compared to patients without SLE.

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