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Cardiovascular disease risk in Korean patients with systemic lupus erythematosus compared to diabetes mellitus and the general population

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To evaluate the incidence and risk of cardiovascular disease (CVD) among Korean patients with systemic lupus erythematosus (SLE) comparing them to diabetes patients and the general population. This nationwide cohort study focused on incident SLE patients aged over 40 years, matched with diabetes patients and the general population (1:4:4 ratio). CVD was defined as ischaemic heart disease, ischaemic stroke, and cardiac arrest. Incidence rate and incidence rate ratio (IRR) of CVD were calculated using generalised estimating equation models. The Fine-Gray model assessed risk factors for CVD in both SLE and diabetes patients. The study included 4272 incident SLE patients, 17,003 diabetes patients, and 17,088 from the general population. SLE patients had higher CVD risk compared to the general population, with adjusted IRRs of 1.99 for overall CVD. Diabetes patients showed increased CVD risk, but to a lesser extent, with an IRR of 1.39. SLE patients aged 40–59 years displayed a significantly elevated CVD risk. Advanced age, male gender, and current use of glucocorticoids, immunosuppressive, and anti-platelet agents were associated with increased CVD risk in SLE patients. SLE patients have a higher risk of CVD compared to the general population, more so than diabetes patients.

Keywords Systemic lupus erythematosus, Cardiovascular disease, Diabetes mellitus

The mortality rate among patients afflicted with systemic lupus erythematosus (SLE) has shown improvement with advancements in treatment.[1,2] Nevertheless, the quality of life and clinical outcomes for individuals with SLE continue to exhibit disparities that hinge on various factors, including age, comorbidities, and treatment approaches.[3,4] The management of SLE, due to its progressive multi-organ nature, necessitates strategies aimed at averting organ dysfunction and disease relapse.[5] Present therapeutic paradigms for SLE underscore a multidisciplinary approach to disease management, addressing unmet healthcare needs and striving to reduce all-cause mortality.[6]

Cardiovascular disease (CVD) has emerged as a prominent contributor to mortality within the SLE patient.[7] A previous study demonstrated that premature atherosclerosis plays a pivotal role in the long-term mortality experienced by individuals with SLE.[8] The increased risk of CVD in SLE patients extends across age groups, with a notable susceptibility observed among younger individuals, particularly in women of reproductive age.[9,10] Moreover, studies have underscored that SLE patients under the age of 60 face a significantly elevated risk of CVD. The relative risk of CVD in SLE patients is particularly accentuated in younger patients, as evidenced by various cohort studies.[11–13] Notably, the elderly population may exhibit an amplified CVD risk due to additional factors, such as physical activity, obesity, and comorbidities.

In contrast, diabetes mellitus (DM) is another chronic condition associated with a heightened risk of CVD.[13] Extensive research has focused on the role of uncontrolled blood sugar levels and metabolic abnormalities

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in exacerbating CVD complications among diabetes patients.[15,16] Nevertheless, the absence of population-based data quantifying the magnitude of CVD risk in SLE patients compared to that observed in those with more prevalent conditions, such as diabetes, may result in less emphasis on CVD screening and prevention recommendations for SLE patients.[17] Enhancing the understanding of this risk is important to determine optimal strategies for primary cardiovascular prevention.

Given the increased prevalence of DM in individuals aged over 40 years, our study endeavors to assess and compare the relative risk of CVD in Korean patients age over 40 years with newly diagnosed SLE.[18] This assessment was conducted in comparison to age- and gender-matched diabetes patients as well as the general population. We also assessed age and gender-specific incidence rates (IRs) and explored various CVD-related risk factors within each group.

Material and methods

Data source

In this nationwide cohort study, we used the Korean National Health Insurance Service (NHIS) claims database, spanning from 2002 to 2018. The Korean NHIS, established in 1977, operates as a single-payer healthcare system, providing coverage to over 99% of the population.[19] Within the Korean National Health Insurance Database (NHID), a vast repository of health and medical data is available, encompassing demographic details, medical claims, and prescription records.[20] Moreover, we used the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) as an additional data source. The NHIS-HEALS provides comprehensive health information, including lifestyle factors, enabling us to incorporate variables, such as smoking, alcohol consumption, and obesity into our analysis.[21].

Study population

We queried the NHID to identify SLE patients who had been assigned both the international classification of disease 10th code (M32.0) and the rare intractable disease code (V136). SLE patients had to meet the classification criteria for SLE outlined in the 1997 Update of the 1982 American College of Rheumatology Revised Criteria.[22] To ensure the identification of incident SLE cases, individuals with a history of SLE within the preceding 5 years were excluded. Additionally, we focused on incident SLE patients aged over 40 years. As a control group, we recruited age- and gender-matched diabetes patients and the general population with a 1:4 ratio. To ensure the inclusion of only incident CVD cases, individuals with a history of CVD within the 5 years prior to the index date were excluded from both the case and control groups.

Study design and outcome

The index date referred to the date of the initial claim for SLE. For the diabetes and general population groups, the index date was assigned to match the corresponding SLE patient's index date to ensure consistency and comparability across groups. The observation period spanned from the index date to the occurrence of each CVD outcome or until the end of the study (December 31, 2018). The primary endpoint was defined as CVD, comprising ischaemic heart disease (IHD) and ischaemic stroke, and cardiac arrest, while the secondary outcomes included each composite for CVD. We assessed the risk of CVD and each composite in SLE and diabetes patients comparing to the general population. Subgroup analyses were conducted by stratifying each cohort into age (40–49, 50–59, and over 60 years) and gender group.

Covariates

Baseline characteristics extracted from the NHID, including age, gender, socioeconomic status, obesity, smoking, alcohol consumption, comorbidities, and medication history, were identified for each group. Age, gender, lifestyle factors, comorbidities, and medication usage were defined based on the index date. Alcohol consumption was defined as drinking at least once per month, while physical activity was defined as engaging in at least 150 min of moderate aerobic activity per week. Cigarette smoking was quantified as more than 5 pack-years and current smoking status. Comorbidities were identified using diagnostic codes and medication prescriptions in medical claims. Medication exposure was defined as use for more than 30 days during the baseline period. We adjusted for variables collected at baseline that were expected to influence CVD prognosis. Income categories, hypertension, hyperlipidaemia, and medication exposure, such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, were included in the adjusted model.

Statistical analysis

Baseline characteristics of patients with SLE, diabetes, and the general population were presented as frequencies (%) or means ± standard deviations. Group comparisons for continuous variables were performed using one-way analysis of variance and categorical variables were compared using the chi-square test. To evaluate CVD risk in age- and gender-matched cohorts, IRs per 1,000 person-years (PYs) were calculated. The IRs were determined by dividing the number of incident cases by the total observational period. The unadjusted IR ratio (IRR) with a 95% confidence interval (CI) was calculated to assess the relative CVD risk in SLE and diabetes patients compared with the general population. Adjusted IRRs were calculated using a generalised estimating equation (GEE) model to compare CVD risk among the SLE group, the diabetes group, and the general population group. The GEE model is an approach for analysing repeated measurement data, and we considered time-varying covariates, such as income, comorbidities (hypertension and hyperlipidaemia), and medication use (NSAIDs and steroids), which were defined annually. Additionally, the Fine-Gray model was applied separately to the SLE group and the diabetes group to identify risk factors for CVD, considering death as a competing risk. The competing risk model is used to analyze multiple potential outcomes where one event can preclude another, ensuring accurate risk estimates and proper evaluation of covariate effects. Hazard ratios (HRs) with 95% CIs

were calculated.[23] Univariate analysis for BMI, smoking, exercise, and alcohol consumption was conducted on a subgroup of patients with available health screening information. Multivariable analysis was conducted on subgroup patients who had information on BMI, smoking, exercise, and alcohol consumption.

Ethics declaration

The databases extracted from NHIS could not be identified directly or through identifiers linked to the subjects; therefore, our study was exempted by the Institutional Review Board (IRB) of Hanyang University Hospital (IRB file No. HYUH 2020–05-041). The requirement for informed consent was also waived by the Hanyang University Hospital IRB due to the use of de-identified data.

Results

Baseline characteristics

In this study, we successfully matched 4,272 SLE patients, 17,003 diabetes patients, and 17,088 individuals from the general population. The baseline characteristics of the study population are summarised in Table 1. The average age across all cohorts was 53.11 ± 9.66 years, with approximately 87% of the participants being female. Notably, chronic kidney disease was more prevalent among SLE patients, and at baseline, 76.64% of SLE patients

Variables	SLE (n = 4272)	Diabetes mellitus (n = 17,003)	General population (n = 17,088)	*P*
Age, years	53.11 ± 9.66	53.11 ± 9.66	53.11 ± 9.66	Matched
Sex, female	3724 (87.17)	14,811 (87.11)	14,896 (87.17)	Matched
Payer type				< 0.001
National health insurance	3621 (84.76)	16,174 (95.12)	16,897 (98.88)	
Medical aid	651 (15.24)	829 (4.88)	191 (1.12)	
Income*				< 0.001
Quintile 1	1246 (29.17)	3795 (22.32)	2613 (15.29)	
Quintile 2	518 (12.13)	2877 (16.92)	2160 (12.64)	
Quintile 3	631 (14.77)	3136 (18.44)	2311 (13.52)	
Quintile 4	754 (17.65)	3493 (20.54)	3324 (19.45)	
Quintile 5	1061 (24.84)	3500 (20.58)	6206 (36.32)	
Body mass index, kg/m^2				< 0.001
< 18.5	187 (4.38)	151 (0.89)	418 (2.45)	
18.5–22.9	1617 (37.85)	2996 (17.62)	5981 (35.00)	
23–24.9	695 (16.27)	2909 (17.11)	3273 (19.15)	
≥ 25	746 (17.46)	7139 (41.99)	4078 (23.86)	
Smoking*	241 (5.64)	1333 (7.84)	992 (5.81)	< 0.001
Physical activity*	1819 (42.58)	7379 (43.40)	8568 (50.14)	< 0.001
Alcohol consumption*	519 (12.15)	2697 (15.86)	3372 (19.73)	< 0.001
Comorbidity				
Hypertension	945 (22.12)	7129 (41.93)	2981 (17.44)	< 0.001
Hyperlipidaemia	571 (13.37)	7343 (43.19)	2111 (12.35)	0.0016
Chronic kidney disease	149 (3.49)	199 (1.17)	67 (0.39)	< 0.001
Charlson comorbidity index	2.63 ± 1.57[c]	2.42 ± 1.65[b]	0.89 ± 1.21[a]	< 0.001**
Medication				
NSAIDs	2650 (62.03)	8196 (48.20)	7071 (41.38)	< 0.001
Glucocorticoids	3274 (76.64)	3701 (21.77)	3429 (20.07)	< 0.001
Hydroxychloroquine	2770 (64.84)	28 (0.16)	43 (0.25)	< 0.001
Immunosuppressive agent	1320 (30.90)	160 (0.94)	80 (0.47)	< 0.001
ACE/ARB	789 (18.37)	5397 (31.74)	1878 (10.99)	< 0.001
Anti-platelet agent	472 (11.05)	2818 (16.57)	840 (4.92)	< 0.001
Beta blocker	328 (7.68)	1335 (7.85)	584 (3.42)	< 0.001
Calcium channel blocker	793 (18.56)	3989 (23.46)	1709 (10.00)	< 0.00
Lipid-lowering agent	605 (14.16)	6484 (38.13)	1a710 (10.01)	< 0.001

Table 1. Baseline characteristics of patients with SLE, diabetes and the general population. Numerical quantitative data are presented as means ± standard deviations, while categorical data are presented as frequencies (%). Continuous variables were compared using one-way analysis of variance (ANOVA), and categorical variables were compared using chi-square tests. *Variables with missing values included income, body mass index, smoking, physical activity, and alcohol consumption across the SLE, DM, and general population groups. ACEi/ARB, Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; NSAIDs, Non-steroidal anti-inflammatory drugs; SLE, Systemic lupus erythematosus.

were prescribed glucocorticoids. The use of hydroxychloroquine, NSAIDs, and immunosuppressive agents was observed in 64.84%, 62.03%, and 30.90% of SLE patients, respectively. Conversely, the use of other medications, including antihypertensive drugs, anti-platelet agents, and cholesterol-lowering agents, was significantly higher in diabetes patients (Table 1).

The IR and relative risk of CVD in SLE patients

Table 2 presents the IRs and IRRs for CVD among SLE patients, diabetes patients, and the general population. In SLE patients, a total of 322 CVD cases occurred during a follow-up period spanning 19,137 PYs, resulting in an IR of 16.83 per 1,000 PYs. Comparing to the general population, both unadjusted and adjusted IRRs in SLE patients were significantly elevated, with values of 3.27 (95% CI, 2.78–3.85) and 1.99 (95% CI, 1.66–2.38), respectively. Similarly, diabetes patients exhibited an IR of 11.66 per 1,000 PYs, with 934 CVD cases identified during a follow-up period of 80,131 PYs. In comparison to the general population, unadjusted and adjusted IRRs for diabetes patients were 2.27 (95% CI, 2.02–2.56) and 1.39 (95% CI, 1.22–1.58), respectively.

Our analysis also revealed adjusted IRRs for specific CVD components in SLE patients, including IHD, ischaemic stroke, and cardiac arrest. The adjusted IRRs for these components were 1.84 (95% CI, 1.47–2.30), 1.67 (95% CI, 1.24–2.26), and 12.48 (95% CI, 4.27–32.99), respectively. In contrast, the adjusted IRRs for the same CVD components in diabetes patients were 1.35 (95% CI, 1.16–1.58), 1.29 (95% CI, 1.04–1.60), and 2.33 (95% CI, 0.86–6.34), respectively. These findings collectively suggest that while the risk of CVD is higher in SLE patients compared to the general population, it has the potential to exceed that of diabetes patients.

Subgroup analysis for CVD risk in age and gender stratified group

We conducted a comprehensive analysis of CVD risk according to age and gender (Table 3). In comparison to the general population, both SLE and diabetes patients exhibited an increased risk of CVD across all age groups and genders. When we categorised the age groups as 40–49, 50–59, and over 60 years, we observed a significant difference in CVD risk between SLE and diabetes patients specifically in the 50–59 years group. In this group, SLE patients had a notably higher CVD risk with an adjusted IRR of 2.83 (95% CI, 2.11–3.79), whereas diabetes patients exhibited an adjusted IRR of 1.52 (95% CI, 1.21–1.91). In contrast, for other age groups, the CVD risk was comparable between SLE and diabetes patients (Table 3). Moreover, both SLE and diabetes patients aged over 60 years showed a reduction in adjusted IRR to 1.52 (95% CI, 1.15–2.02) and 1.21 (95% CI, 1.01–1.45), respectively.

Risk factors for CVD in SLE patients

Table 4 presents the results of univariate and multivariable hazard ratios for risk factors associated with CVD in both SLE and diabetes patients. In the univariate analysis, several conventional risk factors, such as age and hypertension, were significantly associated with CVD in both groups. However, body mass index, smoking, and alcohol consumption did not demonstrate significant associations. Most medications, including glucocorticoids, immunosuppressive agents, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, anti-platelet agents, beta blockers, and calcium channel blockers (CCBs), were associated with a higher risk of CVD.

	Observational period (PYs)	No. of cases	IR (n/1,000 PYs)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI) *
Cardiovascular disease					
SLE patients	19,137	322	16.83	3.27 (2.78–3.85)	1.99 (1.66–2.38)
Diabetes patients	80,131	934	11.66	2.27 (2.02–2.56)	1.39 (1.22–1.58)
General population	82,557	468	5.67	Ref	Ref
Ischaemic heart disease					
SLE patients	19,350	207	10.70	3.45 (2.79–4.26)	1.84 (1.47–2.30)
Diabetes patients	81,178	650	8.01	2.36 (2.05–2.72)	1.35 (1.16–1.58)
General population	82,917	320	3.86	Ref	Ref
Ischaemic stroke					
SLE patients	19,715	93	4.72	3.07 (1.31–2.71)	1.67 (1.24–2.26)
Diabetes patients	82,300	321	3.90	2.25 (1.85–2.73)	1.29 (1.04–1.60)
General population	83,462	179	2.14	Ref	Ref
Cardiac arrest					
SLE patients	19,973	46	2.30	17.17 (8.62–34.19)	12.48 (4.27–32.99)
Diabetes patients	83,490	28	0.34	3.27 (1.47–7.26)	2.33 (0.86–6.34)
General population	83,997	11	0.13	Ref	Ref

Table 2. The incidence rate and relative risk of CVD risk and each composite in SLE patients, diabetes patients, and the general population. * Adjusted for income categories, comorbidities (hypertension and hyperlipidaemia), and medication (NSAIDs and glucocorticoids). The general population served as the reference group (denoted as "Ref" in the tables). ACEi/ARB, Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CI, Confidence interval; IR, Incidence rate; IRR, Incidence rate ratio; NSAIDs, Non-steroidal anti-inflammatory drugs; PY, Person-year; SLE, Systemic lupus erythematosus.

	Observational period (PYs)	No. of cases	IR (n/1000 PYs)	Unadjusted IRR (95% CI)	Adjusted IRR (95% CI) *
Age 40–49 years					
SLE patients	9,258	84	9.07	4.13 (3.06–5.59)	2.56 (1.73–3.78)
Diabetes patients	37,272	306	8.21	3.74 (2.94–4.76)	2.38 (1.78–3.18)
General population	38,724	85	2.20	Ref	Ref
Age 50–59 years					
SLE patients	6,303	129	20.47	4.03 (3.17–5.11)	2.83 (2.11–3.79)
Diabetes patients	26,980	293	10.86	2.14 (1.75–2.61)	1.52 (1.21–1.91)
General population	27,539	140	5.08	Ref	Ref
Age over 60 years					
SLE patients	3,575	109	30.49	2.04 (1.63–2.56)	1.52 (1.15–2.02)
Diabetes patients	15,879	335	21.10	1.41 (1.20–1.67)	1.21 (1.01–1.45)
General population	16,924	243	14.91	Ref	Ref
Female					
SLE patients	17,156	249	14.51	2.84 (2.42–3.33)	1.88 (1.53–2.31)
Diabetes patients	70,871	766	10.81	2.11 (1.87–2.39)	1.39 (1.20–1.61)
General population	72,973	373	5.11	Ref	Ref
Male					
SLE patients	1,981	73	36.85	3.72 (2.74, 5.04)	2.57 (1.75, 3.76)
Diabetes patients	9,260	168	18.14	1.83 (1.42–2.35)	1.44 (1.08–1.92)
General population	9,584	95	9.91	Ref	Ref

Table 3. Incidence rate ratio of CVD risk stratified by age and sex for SLE patients, diabetes patients and general population. * Adjusted for income categories, comorbidities (hypertension and hyperlipidaemia), and medication (NSAIDs and glucocorticoids). The general population served as the reference group (denoted as "Ref" in the tables). CI, Confidence interval; CVD, Cardiovascular disease; IR, Incidence rate; IRR, Incidence rate ratio; NSAIDs, Non-steroidal anti-inflammatory drugs; PY, Person-year; SLE, Systemic lupus erythematosus.

In the multivariable analysis, age remained significantly associated with CVD risk in both SLE and diabetes patients. Female gender and physical activity also retained significance, indicating a lower risk of CVD in both groups. Among SLE patients, factors, such as glucocorticoid and immunosuppressive agent use, as well as anti-platelet agent use, were associated with an increased risk of CVD. Conversely, in diabetes patients, NSAID and CCB use, in addition to glucocorticoid and anti-platelet agent use, were associated with an increased risk of CVD. Notably, alcohol consumption was found to be protective in diabetes patients, contrasting with its lack of significant association in SLE patients.

Discussion

In this population-based cohort study, we investigated the heightened risk of CVD among Korean patients with SLE aged over 40 years with SLE in comparison to the general population. Our findings indicated an increased risk of CVD in both SLE and diabetes patients, with SLE patients demonstrating a higher CVD risk than those with diabetes, particularly in 50–59 years. Furthermore, our study identified distinct risk factors associated with CVD in SLE and diabetes patients. Age consistently emerged as a significant factor associated with elevated CVD risk in both groups. Notably, specific medication users, including glucocorticoids, immunosuppressive agents, and anti-platelet agents, were associated with CVD risk in SLE patients. These findings underscore the importance of personalized strategies for CVD prevention and management in SLE patients.

Numerous studies have consistently highlighted the association between SLE and CVD, revealing a multifaceted relationship that extends beyond traditional risk factors alone.[24] The elevated CVD risk in SLE patients, compared to diabetes patients, may be explained by the distinct pathophysiological mechanisms driving cardiovascular complications in these two diseases. In patients with diabetes, cardiovascular risk is largely driven by metabolic factors, such as hyperglycaemia, insulin resistance, and dyslipidaemia.[25] These factors contribute to a well-established pathophysiological process leading to atherosclerosis. SLE is characterized by systemic inflammation, immune dysregulation, and endothelial damage, which drive more aggressive forms of atherosclerosis.[26] Systemic inflammation in SLE plays a central role in accelerating atherosclerosis, leading to premature adverse cardiovascular events. Inflammatory mediators, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-alpha (IFN-α) not only perpetuate immune dysregulation but also promote endothelial damage and plaque formation, contributing to a more aggressive form of atherosclerosis compared to that in diabetes.[27,28] Furthermore, modifiable risk factors affect CVD risk differently depending on the underlying disease. For example, smoking is a significant risk factor for diabetes but not for SLE, and alcohol consumption appears to have a protective effect in diabetes, whereas its role in SLE is unclear. In addition, the use of anti-inflammatory medications and steroids introduces varying levels of CVD risk in these populations. Consequently, while the diabetes-related CVD risk tends to accumulate gradually over time through sustained

	SLE patients				Diabetes patients			
	Univariate analysis		Multivariable analysis**		Univariate analysis		Multivariable analysis**	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years)	1.04 (1.03–1.05)	< 0.001	1.04 (1.02–1.06)	< 0.001	1.04 (1.03–1.05)	< 0.001	1.03 (1.02–1.04)	< 0.001
Gender (female)	0.44 (0.34–0.57)	< 0.001	0.49 (0.32–0.76)	0.001	0.61 (0.52–0.72)	< 0.001	0.59 (0.46–0.75)	< 0.001
Income								
Quintile 1	Ref		Ref		Ref		Ref	
Quintile 2	1.19 (0.83–1.71)	0.342	1.08 (0.64–1.82)	0.766	0.95 (0.78–1.16)	0.595	0.96 (0.73–1.24)	0.733
Quintile 3	1.21 (0.86–1.70)	0.270	1.27 (0.79–2.02)	0.324	0.88 (0.72–1.07)	0.190	1.02 (0.80–1.31)	0.856
Quintile 4	1.12 (0.80–1.55)	0.514	1.08 (0.68–1.72)	0.759	0.81 (0.67–0.99)	0.038	0.82 (0.64–1.06)	0.131
Quintile 5	0.76 (0.55–1.06)	0.101	0.66 (0.41–1.06)	0.086	0.76 (0.62–0.92)	0.006	0.96 (0.75–1.22)	0.727
Body mass index (kg/m^2) *								
< 18.5	Ref		Ref		Ref		Ref	
18.5–22.9	0.85 (0.44–1.62)	0.614	1.04 (0.56–1.93)	0.898	0.90 (0.42–1.91)	0.774	0.85 (0.40–1.84)	0.683
23–24.9	0.98 (0.50–1.96)	0.964	1.02 (0.53–1.98)	0.954	1.01 (0.47–2.15)	0.980	0.96 (0.44–2.06)	0.907
≥ 25	1.20 (0.61–2.37)	0.590	1.14 (0.59–2.18)	0.702	0.98 (0.46–2.07)	0.956	0.95 (0.45–2.03)	0.897
Smoking*	1.48 (0.86–2.54)	0.156	1.22 (0.68–2.17)	0.511	1.36 (1.04–1.77)	0.025	1.29 (0.96–1.75)	0.094
Physical activity*	0.49 (0.36–0.66)	< 0.001	0.54 (0.39–0.73)	< 0.001	0.72 (0.61–0.84)	< 0.001	0.78 (0.66–0.93)	0.004
Alcohol consumption*	0.63 (0.38–1.03)	0.067	0.71 (0.42–1.19)	0.193	0.40 (0.55–0.89)	0.004	0.69 (0.53–0.90)	0.007
Comorbidity								
Hypertension	1.71 (1.35–2.17)	< 0.001	0.89 (0.52–1.51)	0.653	1.45 (1.28–1.65)	< 0.001	0.80 (0.58–1.11)	0.176
Diabetes mellitus	1.45 (0.96–2.21)	0.080	1.00 (0.55–1.82)	0.989			-	-
Hyperlipidaemia	1.09 (0.78–1.51)	0.624	0.60 (0.32–1.12)	0.108	0.87 (0.76–0.99)	0.040	0.79 (0.56–1.12)	0.180
Chronic kidney disease	1.62 (0.99–2.66)	0.056	1.01 (0.46–2.22)	0.990	1.81 (1.11–2.93)	0.017	1.64 (0.88–3.06)	0.117
Medication								
NSAIDs	1.03 (0.82–1.29)	0.786	1.19 (0.85–1.65)	0.309	1.36 (1.20–1.55)	< 0.001	1.36 (1.14–1.61)	< 0.001
Glucocorticoids	2.15 (1.55–2.98)	< 0.001	2.03 (1.25–3.31)	0.004	1.37 (1.18–1.59)	< 0.001	1.24 (1.02–1.49)	0.029
Hydroxychloroquine	0.96 (0.76–1.20)	0.705	1.05 (0.75–1.48)	0.775	0.67 (0.09–4.88)	0.694	0.61 (0.08–4.89)	0.638
Immunosuppressive agents	1.54 (1.23–1.92)	< 0.001	1.41 (1.03–1.94)	0.033	1.55 (0.89–2.70)	0.119	1.68 (0.77–3.68)	0.196
ACEi/ARB	1.69 (1.31–2.17)	< 0.001	0.91 (0.57–1.46)	0.704	1.32 (1.15–1.51)	< 0.001	1.14 (0.88–1.49)	0.322
Anti-platelet agent	2.88 (2.24–3.71)	< 0.001	2.39 (1.60–3.59)	< 0.001	1.53 (1.32–1.77)	< 0.001	1.32 (1.09–1.60)	0.005
Beta blocker	1.72 (1.23–2.40)	0.002	1.20 (0.70–2.04)	0.510	1.69 (1.40–2.05)	< 0.001	1.30 (0.99–1.72)	0.062
Calcium channel blocker	1.95 (1.54–2.48)	< 0.001	1.30 (0.81–2.08)	0.272	1.57 (1.37–1.81)	< 0.001	1.35 (1.05–1.72)	0.018
Cholesterol-lowering agent	1.34 (1.00–1.81)	0.049	1.16 (0.69–1.94)	0.576	0.90 (0.78–1.03)	0.121	1.04 (0.73–1.48)	0.840

Table 4. Risk factors for CVD risk in SLE and diabetes patients. *Univariate analysis for BMI, smoking, exercise, and alcohol consumption was conducted on a subgroup of patients with available health screening information. ** Multivariable analysis was conducted on subgroup patients who had information on BMI, smoking, exercise, and alcohol consumption. The number of subgroups was 3,023 in SLE patients and 12,591 in DM patients. ACEi/ARB, Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CI, Confidence interval; CVD, Cardiovascular disease; HR, Hazard ratio; NSAIDs, Non-steroidal anti-inflammatory drugs; SLE, Systemic lupus erythematosus.

metabolic disturbances, SLE patients may experience sudden and severe CVD-associated events due to inflammation-driven vascular damage.

A previous study reported that SLE patients had a two- to three-fold higher risk of developing CVD.[29] In our study, the IRRs for CVD in SLE patients and diabetes patients compared to the general population were 1.99 (95% CI, 1.66–2.38) and 1.39 (95% CI, 1.22–1.58), respectively. Notably, the CVD risk in SLE patients aged in their fifties was 2.83 (95% CI, 2.11–3.79) compared to 1.52 (95% CI, 1.21–1.91) in diabetes patients. Several factors may contribute to the differences between studies, including racial disparities, age group, and confounding factors. However, our study reveals a significant increase in IRRs in SLE patients over 40 years compared to those of diabetes patients.[30].

To ensure a meaningful comparison of CVD risk between SLE and diabetes patients, we specifically focused on individuals aged over 40 years. This decision was driven by the relatively low prevalence of DM among individuals under 40 years of age in Korea, which could lead to an under-representation of diabetes cases in younger people.[31,32] By using this age criterion, we aimed to differentiate our study from previous studies. Our previous study highlighted that younger SLE patients (< 40 years) exhibit a significantly higher risk of adverse cardiovascular events, such as cardiac death, than the general population. Including younger patients in this study would likely to have amplified the observed CVD risk.[33,34] However, to improve the comparability of our findings and better align with the demographic patterns documented in existing literature, we opted to focus on

the > 40 years age group.[35] For instance, a United States-based study conducted between 2007 and 2010 assessed the CVD risk among SLE patients, diabetes patients, and the general population, revealing a particularly high CVD risk in SLE patients aged 18–39 years.[36] We excluded this younger age group from our analysis to account for the significantly lower prevalence of diabetes in the Korean population aged < 40 years, thus ensuring a balanced and relevant comparison.

Our study harnessed a comprehensive 10-year nationwide claims database encompassing all patients with SLE in Korea, offering valuable insights into the long-term outcomes of newly diagnosed patients with SLE. We conducted a comparative analysis of overall CVD risk, including angina, myocardial infarction, stroke, and cardiac arrest. In contrast to prior studies that employed various adjustment models with multiple covariates, our research integrated these adjustments and identified specific CVD risk factors within each cohort.

We explored the relationship between SLE and CVD risk, considering a spectrum of factors, including age, gender, and medication usage. Although glucocorticoids and immunosuppressive agents are critical for managing SLE, their apparent protective effects against CVD must be interpreted with caution. Patients receiving these medications may have more severe disease, which itself increases CVD risk, leading to confounding by indication.[37] As such, the elevated CVD risk observed in these patients may reflect the severity of SLE rather than the direct effects of the medications, highlighting the need for further investigation. Nevertheless, consistent with prior studies, our analysis revealed a higher prevalence of the use of glucocorticoids and immunosuppressive agents among patients with SLE with heightened CVD risk, suggesting a nuanced interplay between medication effects and disease activity.[38,39] Moreover, the use antiplatelet agents resulted in a reduction in CVD risk, although conflicting evidence makes their association with cardiovascular outcomes unclear. The apparent link between the use of antiplatelet agents and increased CVD risk may be attributed to underlying confounding factors influencing medication use in high-risk patients. Similarly, the high prevalence of NSAID and steroid use among diabetic patients with elevated CVD risk underscores the intricate relationship between medication use and disease profile. This underscores the need for approaches that assess the cardiovascular risk profile of SLE patients, taking into account the multifaceted impact of medications on disease progression and cardiovascular outcomes.

Interestingly, anti-platelet agents, typically prescribed for secondary prevention of cardiovascular events, showcased an association with CVD risk in our study. While these agents demonstrated a protective effect in some contexts,[40] our findings revealed an unexpected association with increased CVD risk in both SLE and diabetes patients. This apparent discrepancy warrants careful consideration, as conflicting evidence exists regarding the cardiovascular effects of anti-platelet agents in different patient populations. It is plausible that the observed association stems from the underlying confounding effect of factors driving medication usage in high-risk patients, highlighting the intricacies of interpreting medication-related outcomes in real-world clinical settings. Similarly, the higher prevalence of NSAIDs and glucocorticoids among diabetic patients with elevated CVD risk underscores the intricate relationship between medication usage and disease profile. This finding accentuates the importance of comprehensive risk assessment in patients with comorbid conditions, such as diabetes and SLE, where overlapping risk factors and medication regimens may significantly influence cardiovascular outcomes.

One of strength in our study was to investigate the overall CVD risk, specifically focusing on the composite of IHD, ischaemic stroke, and cardiac arrest, among patients with SLE and patients with diabetes compared to the general population. Leveraging data from the NHIS and NHIS-HEALS in Korea enabled us to conduct a large-scale analysis with robust statistical power over a relatively long period. Additionally, the utilisation of strict classification criteria for identifying incident SLE cases ensured the inclusion of individuals with a confirmed diagnosis, while the exclusion of those with a history of CVD prior to the study period and matching of comparison groups based on age and gender enhanced cohort comparability. Adjustment for covariates to account for factors influencing CVD outcomes increased statistical power and precision in estimating the effect of SLE. Moreover, the identification of several risk factors associated with CVD and the composite assessment in SLE accounted for cardiovascular events and offered a comprehensive evaluation of disease burden. These factors shed light on the unique risks faced by patients with SLE and may contribute to the development of preventive strategies.

However, our study has several limitations. The claims database used in this study may lead to a lack of comprehensive clinical details regarding SLE, such as laboratory findings and disease activities. Although the use of glucocorticoids and immunosuppressive agents can serve as surrogate markers of disease activity, they do not provide direct adjustment. It may be difficult to assess how variations in disease progression influence outcomes and lead to residual confounding or misclassification, particularly in terms of disease severity. Therefore, the lack of specific variables or insufficient data may limit the analysis and interpretation of the results. Additionally, some risk factors, such as diet, exercise, and family history were not fully accounted for in this study. These factors can vary significantly based on underlying conditions, such as SLE and diabetes, potentially influencing CVD risk. Furthermore, the lack of comprehensive data on these variables resulted in a reduced sample size. Nonetheless, we attempted to mitigate this limitation by incorporating lifestyle factors using NHID-HEALS data. Second, this study may lack representativeness as it focuses on incident patients with SLE aged over 40, rather than including the entire population of patients with SLE. This approach was chosen to facilitate a more focused comparative analysis between SLE and diabetes patients, given the prevalence of diabetes typically emerging after the age of 40 years. Finally, the reduced sample size resulting from the incident patients with SLE and CVD outcomes may constrain statistical power and precision in estimate calculations. Concurrently, the complexity introduced by disease heterogeneity, characterised by diverse manifestations and courses, poses challenges in capturing all relevant subgroups and adequately adjusting for covariates. Despite these limitations, narrowing the study population aimed to enhance exposure assessment and discern risk factors within this cohort.

Conclusions

Our study highlights a significantly increased risk of CVD among newly diagnosed SLE patients in Korea, exceeding the risk typically observed in diabetes patients. Particularly noteworthy is the elevated CVD risk observed in SLE patients aged 40–59, a demographic displaying significantly higher risk than both older SLE patients and diabetes patients of the same age range. Additionally, treatment with glucocorticoids or immunosuppressant agents appears to exacerbate this risk, in contrast to the protective effects of physical activity. This highlights midlife as a critical period where targeted interventions and tailored management strategies could mitigate long-term cardiovascular outcomes in SLE patients. Interestingly, certain factors associated with CVD risk in diabetes patients, such as alcohol consumption and NSAID usage, did not demonstrate significant implications in SLE patients. Given these findings, further research is imperative to elucidate the underlying mechanisms driving these disparities and to optimise cardiovascular outcomes in SLE patients.

Data availability

The National Health Service System in Korea, the data provider, requires all involved researchers to pledge not to share, release, or review the data with other entities. Any request regarding data and the study itself should be directed to the corresponding authors, who have signed the data release agreement form of the National Health Service System in Korea.

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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval and Consent to Participate
The data used in this study were obtained from the National Health Insurance Service (NHIS) database, which does not contain information that can directly identify individuals or link subjects through identifiers. Consequently, the Institutional Review Board (IRB) of Hanyang University Hospital (IRB file No. HYUH 2020–05-041) granted an exemption from review. The requirement for informed consent was also waived by the Hanyang University Hospital IRB due to the use of de-identified data. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Additional information
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