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ORIGINAL ARTICLE

Incidence of cutaneous lupus erythematosus and systemic progression: A Nationwide study in Korea

Seon Young Song[1] | **Jiyeong Kim**[2,3] | **Yu-Mi Kim**[4,5] | **Joo Yeon Ko**[1,6]

[1]Department of Dermatology, Hanyang University Medical Center, Seoul, Republic of Korea

[2]Department of Pre-Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea

[3]Biostatistics Laboratory, Medical Research Collaborating Center, Hanyang University, Seoul, Republic of Korea

[4]Department of Preventive Medicine, College of Medicine, Hanyang University, Seoul, Republic of Korea

[5]Graduate School of Public Health, Hanyang University, Seoul, Republic of Korea

[6]Department of Dermatology, College of Medicine, Hanyang University, Seoul, Republic of Korea

Correspondence
Joo Yeon Ko, Department of Dermatology, College of Medicine, Hanyang University, Wangsimni-ro 222-1, Sungdong-gu, Seoul 04763, Korea.
Email: drko0303@hanyang.ac.kr

Abstract

Background: Cutaneous lupus erythematosus (CLE) is an LE-specific cutaneous manifestation that can occur in isolation or with systemic lupus erythematosus (SLE). Estimates of CLE incidence, skin cancer burden and progression to SLE in Asian populations are limited.

Objectives: To investigate the nationwide incidence of CLE in Korea, its association with premalignant and malignant skin lesions and the risk of progression to SLE.

Methods: This population-based study used the Korean National Health Insurance Service-National Health Information Database (2005–2020). CLE was identified using ICD-10 code L93; cases with SLE were included, whereas cases without SLE required ancillary testing or prescriptions. CLE and SLE diagnoses within 6 months were considered concurrent. Progression to SLE was assessed using time-to-event analyses and cumulative incidence estimates.

Results: Overall, 32,337 patients with CLE were identified [mean (SD) age, 42.9 (17.4) years; 23,436 (72.5%) female], and 5367 (16.6%) had concomitant SLE. Discoid lupus erythematosus (DLE) was the most common subtype (22,463 [69.5%]), followed by other localized LE (8594 [26.6%]) and subacute cutaneous lupus erythematosus (SCLE) (3465 [10.7%]). Mean annual CLE incidence was 3.98 per 100,000 person-years (95% CI, 3.94–4.03), with a modest upward trend (p for trend = 0.014). CLE was associated with higher risks of actinic keratosis and cutaneous malignancies, most pronounced within the first 2 years but remaining significant during follow-up. A total of 563 patients (2.0%) developed SLE after CLE diagnosis, and the mean (SD) time to progression was 3.2 (3.0) years. Overall 5-year cumulative incidence of progression to SLE was 11.4%, higher in SCLE than DLE (20.8% vs. 9.5%).

Conclusions: CLE incidence in Korea was comparable to prior population-based estimates, and CLE was associated with a higher risk of premalignant and malignant skin lesions. Considering progression from CLE to SLE clustered within the first 5 years after CLE diagnosis, risk-stratified evaluation during this period may be warranted.

KEYWORDS
actinic keratosis, cutaneous lupus erythematosus, discoid lupus erythematosus, incidence, melanoma, National Health programs, non-melanoma skin neoplasm, skin neoplasms, systemic lupus erythematosus

S.Y. Song and J.Y Kim are co–first authors and contributed equally to this work.

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INTRODUCTION

Lupus erythematosus (LE) is a chronic autoimmune disease that ranges from cutaneous-limited forms (cutaneous LE [CLE]) to multisystem disease (systemic LE [SLE]). The skin is the second most commonly affected organ in SLE, with cutaneous manifestations occurring in 70%–85% of cases.[1] These manifestations—including photosensitivity, malar rash, erythematous scaly plaques, dyspigmentation, alopecia and scarring—can appear with or without systemic disease and significantly affect patients' quality of life.[2,3] Cutaneous manifestations in SLE are classified as LE-specific or LE-non-specific skin disease. CLE, an LE-specific skin disease, is subdivided into acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE), with discoid LE (DLE) being the most prevalent CCLE subtype.[4]

Global CLE incidence, reported primarily in Western cohorts, ranges from 2.74 to 4.30 per 100,000 person-years, and the female-to-male ratio (2–4:1) is less pronounced than in SLE.[5–8] Population-based studies showed that 5%–18% of CLE cases progress to SLE within 3–5 years.[6,8,9] In Korea, a 2% national sample cohort yielded an incidence of 4.36 per 100,000 person-years and a 4.26% progression rate after a mean follow-up of 1.53 years, comparable to Western data.[10] However, no comprehensive nationwide study has evaluated the entire Korean population.

To address these limitations, we analysed the National Health Insurance Service (NHIS) database of Korea, which covers nearly the entire population, registers SLE as a rare intractable disease (RID), and is approximately 50-fold larger than prior Korean samples.[10,11] This study provides nationwide estimates of CLE incidence and progression to SLE in an Asian population, informing individualized follow-up and clinical management.

Why was the study undertaken?

Data on cutaneous lupus erythematosus (CLE) incidence, risk of premalignant and malignant skin lesions and progression to systemic lupus erythematosus (SLE) in Asian populations is limited. This nationwide, population-based study in Korea provides comprehensive estimates across these clinical domains.

What does this study add?

This study shows that CLE incidence in Korea is comparable to prior population-based estimates. CLE was associated with a higher risk of premalignant and malignant skin lesions. Compared with prior studies, fewer patients with CLE progressed to SLE (2.0%), and the mean time to progression was relatively longer (3.2 years). The 5-year cumulative incidence was 11.4%, with subacute cutaneous lupus erythematosus showing the highest and earliest risk.

What are the implications of this study for disease understanding and/or clinical care?

These findings inform population-level CLE incidence and subtype-specific risk of progression to SLE. They may support risk-stratified evaluation and counselling, particularly during the first 5 years after CLE diagnosis.

METHODS

Study design and database

We conducted a nationwide retrospective cohort study using health-insurance claims data from the Korean National Health Insurance Service-National Health Information Database (NHIS-NHID). The NHIS is a compulsory single-payer social health insurance system that covers 97.2% of the Korean population, and the NHID contains comprehensive medical information, including demographics, diagnoses and prescriptions.[11]

We used an NHIS-Customized Database that covers claims for nearly the entire Korean population, more than 50 million individuals.[12] The NHIS database uses International Classification of Diseases, Tenth Revision (ICD-10) codes for diagnoses. Within the NHIS, SLE has a designated RID (code V136), a status introduced in 2005 that lowers out-of-pocket expenses for registered patients.[13] RID registration for SLE requires physician confirmation that the patient fulfills either the 1997 revised American College of Rheumatology (ACR) classification criteria or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria.

Study population

SLE cases were identified from 2002 to 2022 using ICD-10 code M32 in conjunction with RID code V136. However, analyses were restricted to 2005–2020 to ensure accurate identification of incident cases after implementation of the RID program in 2005 and to allow at least 2 years of follow-up for outcome ascertainment. Age at SLE diagnosis was assigned from the first M32 claim, regardless of the presence of code V136.

CLE was operationally defined using ICD-10 code L93 with the following criteria during the same period (Figure 1). All patients with an additional diagnosis of SLE (M32) were included. For patients without SLE, CLE required at least one of the following: (i) blood antinuclear antibody (ANA) test or skin biopsy performed within 6 months prior to CLE

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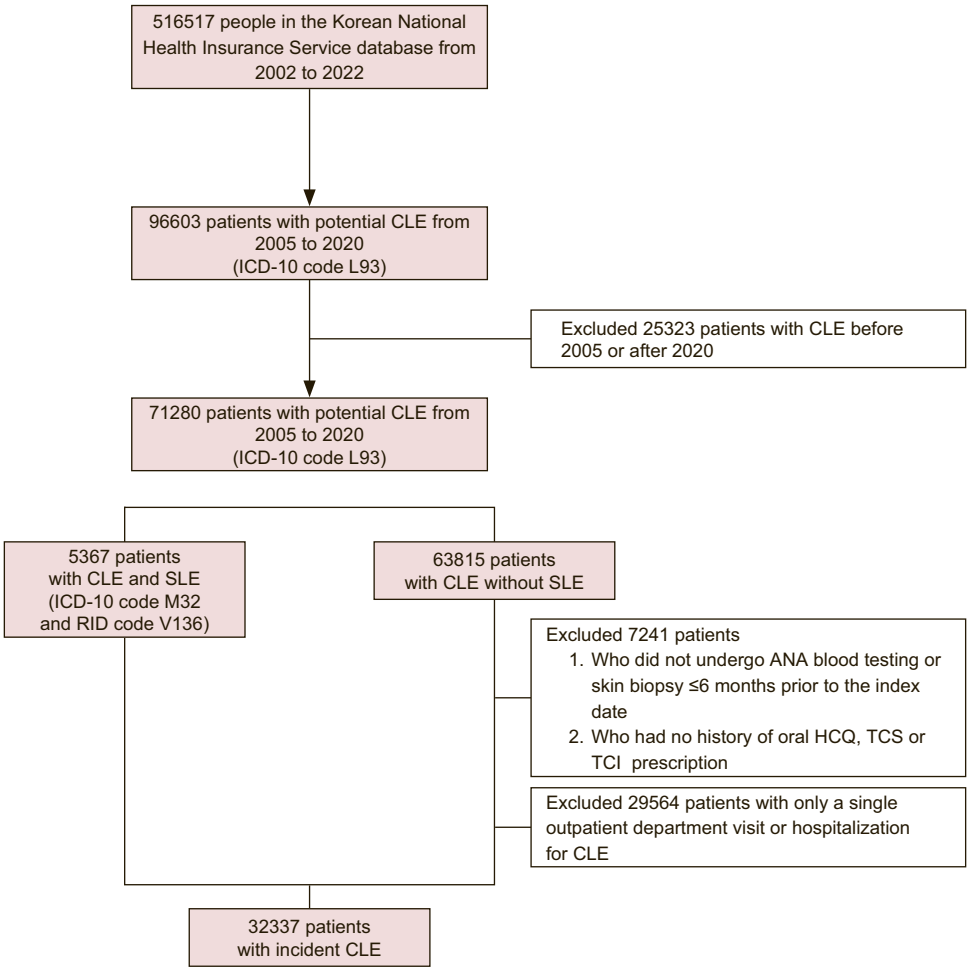

FIGURE 1 Flow diagram showing the selection of patients with cutaneous lupus erythematosus from the National Health Insurance Service database. ANA, antinuclear antibody; CLE, cutaneous lupus erythematosus; HCQ, hydroxychloroquine; ICD-10, International Classification of Diseases, 10th Revision; RID, Rare and Intractable Diseases (registration program in South Korea); SLE, systemic lupus erythematosus; TCI, topical calcineurin inhibitors; TCS, topical corticosteroids.

diagnosis or (ii) a prescription history of oral hydroxychloroquine, topical corticosteroid or topical calcineurin inhibitor for CLE.[6,14,15] Patients with only a single outpatient visit or hospitalization for CLE and those with missing age or sex data were excluded. The CLE subtypes were classified as DLE (L93.0), SCLE (L93.1) and other localized CLE (L93.2, including lupus erythematosus profundus and lupus panniculitis). For temporal classification, CLE and SLE claims occurring within 6 months of each other were considered concurrent. For each cohort, follow-up began on the index date (first qualifying claim for the condition of interest) and continued until death or 31 December 2022. Precancerous and malignant skin lesions were ascertained using ICD-10 codes (Table 1). For each patient with SLE or CLE, two age- and sex-matched controls without either condition were randomly selected from the same database and assigned the same index date. Skin lesions were tracked from 1 year before the index date through the end of follow-up.

Statistical analysis

The incidence of CLE was calculated per 100,000 person-years and stratified by calendar year, sex and CLE subtype. Progression to SLE was assessed by identifying incident SLE among patients with CLE and calculating time to event in years. Descriptive statistics were used to summarize baseline characteristics. Group comparisons, including the occurrence of premalignant lesions and skin cancers in patients with CLE and matched controls, were performed using chi-squared tests for categorical variables and *t*-tests for continuous variables, as appropriate. Sex-specific differences in the distribution of SLE-associated CLE subtypes and in time to SLE progression were also analysed. Kaplan–Meier methods were used to estimate cumulative incidence according to CLE subtype and sex, and differences between groups were compared using the log-rank test. Multivariable Cox proportional hazards models were used to estimate adjusted hazard

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TABLE 1 Baseline characteristics and healthcare utilization among patients with CLE and matched controls.

	No.							
	CLE, total (Group 1) (*n* = 32,337, 100.0)	**CLE without SLE (Group 2) (*n* = 26,970, 83.4)**	**SLE-associated CLE (Group 3) (*n* = 5367, 16.6)**	**Control (*n* = 111,652)**	***p*-Value 1**	***p*-Value 2**	***p*-Value 3**	***p*-Value 4**
Age, mean (SD), years	42.9 (17.4)	44.0 (17.6)	37.4 (15.1)	42.8 (17.2)	0.326	<0.001	<0.001	<0.001
Sex					<0.001	<0.001	<0.001	<0.001
Male	8901 (27.5)	8254 (30.6)	647 (12.1)	24,314 (21.8)				
Female	23,436 (72.5)	18,716 (69.4)	4720 (87.9)	87,338 (78.2)				
Comorbidity								
Diabetes mellitus	13,137 (40.6)	10,992 (40.8)	2145 (40.0)	36,950 (33.1)	<0.001	<0.001	<0.001	0.282
Hypertension	14,582 (45.1)	11,385 (42.2)	3197 (59.6)	38,712 (34.7)	<0.001	<0.001	<0.001	<0.001
Dyslipidemia	14,752 (45.6)	12,236 (45.4)	2516 (46.9)	42,534 (38.1)	<0.001	<0.001	<0.001	0.043
Chronic kidney disease	1963 (6.1)	1360 (5.0)	603 (11.2)	2782 (2.5)	<0.001	<0.001	<0.001	<0.001
Precancerous lesion and skin malignancy comorbidity								
AK	863 (2.7)	805 (3.0)	58 (1.1)	597 (0.5)	<0.001	<0.001	<0.001	<0.001
NMSC	169 (0.5)	140 (0.5)	29 (0.5)	174 (0.2)	<0.001	<0.001	0.844	0.844
Melanoma	18 (0.1)	15 (0.1)	3 (0.1)	27 (0.0)	0.005	0.008	0.994	1.000F
Death	2137 (6.6)	1618 (6.0)	519 (9.7)	5108 (4.6)				
Follow-up time, median (IQR), years	8.5 (4.4–13.3)	8.4 (4.4–13.3)	8.7 (4.8–13.1)					0.489
Health care visits, median (IQR), *N*	4.0 (2.0–16.0)	3.0 (2.0–8.0)	48.0 (22.0–89.0)					<0.001
Specialty								<0.001
Dermatology	23,814 (73.6)	20,602 (76.4)	3212 (59.9)					
Internal medicine	7041 (21.8)	4936 (18.3)	2105 (39.2)					
Other physicians	1482 (4.6)	1432 (5.3)	50 (0.9)					
Healthcare provider								<0.001
Tertiary hospital	19,679 (60.9)	15,019 (55.7)	4660 (86.8)					
General hospital	5787 (17.9)	5181 (19.2)	606 (11.3)					
Hospital	475 (1.5)	452 (1.7)	23 (0.4)					
Clinic	6396 (19.8)	6318 (23.4)	78 (1.5)					

Note: Actinic keratosis (L57.X), non-melanoma skin cancer (C44.X, C46.0, D04.X, D07.1, D07.4), melanoma (C43.X, D03.X). For NMSC and melanoma, case ascertainment required both the relevant ICD-10 code and RID code V193 (registration in the Korean Rare and Intractable Disease program for cancer). Comorbidities were defined using ICD-10 diagnosis codes: diabetes mellitus (E10–E13), hypertension (I10–I13, I15), dyslipidaemia (E780–E784) and chronic kidney disease (N18). *p*-Value 1, Group 1 vs. Control; *p*-value 2, Group 2 vs. Control; *p*-value 3, Group 3 vs. Control; *p*-value 4, Group 2 vs. 3.

Abbreviations: AK, actinic keratosis; CLE, cutaneous lupus erythematosus; NMSC, non-melanoma skin cancer; SLE, systemic lupus erythematosus.

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ratios (aHRs) for skin cancer outcomes and progression to SLE, adjusting for age, sex, comorbidities (diabetes mellitus, hypertension, dyslipidaemia and chronic kidney disease) and immunosuppressant use. A two-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SAS Enterprise Guide, version 7.1 (SAS Institute, Cary, NC, USA) or R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From 2002 to 2022, 516,517 individuals with at least one claim for SLE (ICD-10M32) or CLE (ICD-10L93) were identified in the NHIS customized database. Among the 96,603 potential CLE patients identified between 2002 and 2020, 25,323 were excluded due to CLE-related visits before 2005 or after 2020, leaving 71,280 eligible patients. All 5367 patients with an additional diagnosis of SLE (defined as M32 with V136) were enrolled. Among patients without SLE, 7241 were excluded if they had neither an ANA test nor a skin biopsy within 6 months prior to the index date and had no prescription for oral HCQ, topical corticosteroids or topical calcineurin inhibitors. An additional 29,564 were excluded for insufficient follow-up, defined as only a single outpatient visit or hospitalization. The final incident CLE cohort comprised 32,337 patients—8901 males (27.5%) and 23,436 females (72.5%) (Figure 1).

Among the 43,977 individuals who met the validated definition for SLE (M32 with V136) in the same database, 28,901 incident SLE patients—3940 males (13.6%) and 24,961 females (86.4%)—were identified.

DLE accounted for the largest proportion of CLE, with 22,463 patients (69.5%), followed by other localized LE with 8594 patients (26.6%) and SCLE with 3465 patients (10.7%), with patients allowed to be counted in more than one category.

Baseline characteristics and healthcare utilization

Among the 32,337 patients with CLE, 5367 (16.6%) also carried an SLE diagnosis (i.e., SLE-associated CLE). The mean (SD) age at CLE diagnosis was 42.9 (17.4) years in the overall cohort. Patients with SLE-associated CLE were diagnosed significantly younger than those with CLE without SLE (37.4 vs. 44.0 years, $p < 0.001$). Female predominance was observed across all groups and was greatest in SLE-associated CLE (female-to-male ratio, 7.26) (Table 1). Figure S1 presents the age- and sex-specific distribution of incident CLE cases and population-adjusted incidence rates. CLE predominantly affected females aged 21–60 years and males aged 21–70 years.

Premalignant lesions (actinic keratosis, AK) and two skin cancers—non-melanoma skin cancer (NMSC) and melanoma—were more common in patients with CLE than in matched controls. AK was more prevalent in CLE without SLE than in SLE-associated CLE (3.0% vs. 1.1%, $p < 0.001$), whereas excess NMSC and melanoma were observed only in CLE without SLE (Table 1). A considerable proportion of AK (52.6%) and NMSC (40.2%) diagnoses in CLE occurred within 2 years after the index date (Table S1). In multivariable Cox models adjusted for age, sex, comorbidities and immunosuppressant use, CLE was associated with higher adjusted hazard ratios (aHRs) for actinic keratosis (5.00; 95% CI, 4.45–5.62), non-melanoma skin cancer (3.54; 2.80–4.47) and melanoma (2.32; 1.19–4.53) compared with controls. Time-stratified analyses showed that aHRs within the first 2 years were 13.48 (10.63–17.09) for actinic keratosis, 8.68 (4.78–15.76) for non-melanoma skin cancer, and 2.94 (0.49–17.77) for melanoma. After 2 years, these values were 3.29 (2.85–3.80), 2.90 (2.29–3.85) and 2.23 (1.08–4.59), respectively.

The median follow-up time was similar between groups, but SLE-associated CLE required substantially more healthcare visits than CLE without SLE ($p < 0.001$). Although dermatology remained the most common specialty for all groups, the proportion of internal medicine visits was higher in SLE-associated CLE than in CLE without SLE (39.2% vs. 18.3%, $p = 0.01$) (Table 1). The rates of diagnostic evaluations and oral medication prescriptions are detailed in Table S2.

Incidence of CLE by year and subtype, 2005–2020

In the total Korean population, the mean annual incidence of CLE between 2005 and 2020 was 3.98 per 100,000 person-years (95% CI, 3.94–4.03) and, despite a slight decline in 2020, showed a modest overall increase across the period (p for trend = 0.014) (Figure 2). Incidence was higher in females than in males (5.78 vs. 2.19 per 100,000 person-years; female-to-male ratio, 2.63). Incidence differed by SLE status: CLE without SLE accounted for the majority of cases, whereas SLE-associated CLE was rarer, with a relatively stable incidence and marked female predominance (Table S3). DLE was the most common subtype (2.77 cases per 100,000 person-years; female-to-male ratio, 2.48), followed by other localized LE and SCLE.

Characteristics of SLE-associated CLE

Among the 32,337 patients with CLE, 5367 (16.6%) had a concomitant SLE diagnosis (Table 2a). DLE predominated across timing categories, and female predominance was pronounced in patients with CLE diagnosed after SLE. The progression rate to SLE was 2.0% (563/27,533) following the exclusion of patients with pre-existing ($n = 2527$) or concurrent ($n = 2277$) SLE at the index date. By subtype, SCLE

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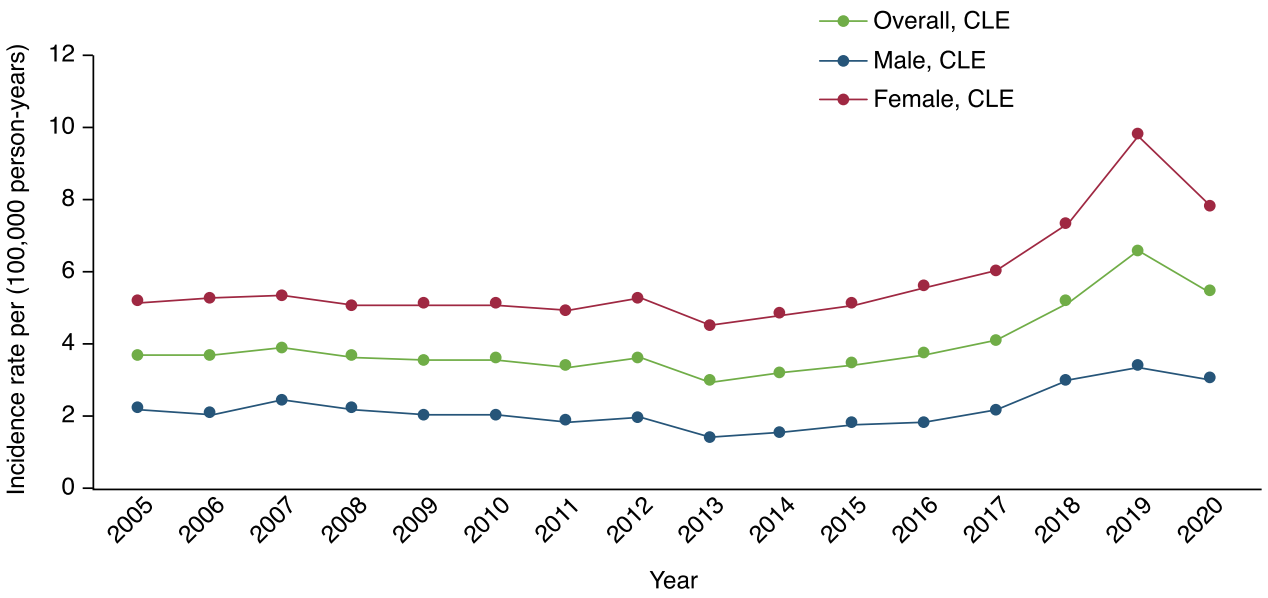

FIGURE 2 Annual incidence of cutaneous lupus erythematosus in the Korean populations, 2005–2020.

showed the highest proportion of progression to SLE (3.3%; 115/3465), compared with DLE (2.0%; 440/22,463) and other localized LE (2.3%; 199/8594).

The mean (SD) progression time from an initial CLE diagnosis to SLE was 3.2 (3.0) years. Females had a longer progression time than males (3.2 vs. 2.9 years), with a significant difference only in SCLE ($p = 0.02$). By subtype, DLE showed the longest time to progression from CLE to SLE, followed by other localized CLE and SCLE. When CLE was diagnosed after SLE, the mean interval lengthened to 4.7 (3.5) years (Table 2b).

The cumulative incidence of SLE after CLE diagnosis was 8.4%, 11.4% and 13.0% at 1, 5 and 10 years of follow-up, respectively (Figure 3a). Cumulative incidence differed by CLE subtype, with the highest risk in SCLE, followed by other localized LE and DLE (log-rank test, $p < 0.001$). SCLE was associated with an approximately twofold risk of progression compared to DLE, with 5-year cumulative incidences of 20.8% versus 9.5% (Figure 3b). In multivariable Cox models adjusted for age, sex, comorbidities and immunosuppressant use, the hazard of progression to SLE was higher for SCLE (aHR, 1.95; 95% CI, 1.79–2.11) and other localized LE (aHR, 1.36; 95% CI, 1.26–1.46) compared with DLE. Sex-specific curves demonstrated a consistently greater risk in females, with an approximately 1.6-fold higher risk compared with males ($p < 0.001$; Figure 3c).

DISCUSSION

In this nationwide study, we analysed the epidemiologic profile of CLE in the Korean population. The overall incidence of CLE (3.98 per 100,000 person-years) was comparable to that in Western cohorts (4.0–4.3)[7–9] and a previous Korean sample-cohort study (4.36).[10] The Danish registry reported a lower incidence (2.74),[6] likely reflecting the predominantly White Danish population, in which LE is generally less common.[16,17] Our female-to-male ratio was lower than that in Western studies (3–4:1) but higher than in the previous Korean study (2.14).[6,9,10] The mean age at CLE diagnosis was 42.9 years, which was 5–10 years younger than in Western cohorts (47.6–54 years).[6–9] In Korean studies, including ours, DLE was the most common subtype, followed by other localized LE and SCLE,[10] whereas SCLE has been reported more frequently than other localized LE in Western cohorts.[6,8,9]

Although frequent systemic corticosteroid exposure was observed—likely reflecting management of disease flares—hydroxychloroquine remained the most commonly used guideline-recommended first-line systemic agent.[18–20] Only 20%–40% of patients underwent serologic testing or skin biopsy within 6 months before diagnosis, and DLE/SCLE were more often evaluated in tertiary centres and by dermatologists than other localized LE. Given the diagnostic challenges of LE in primary care and non-specialist settings, diagnostic misclassification in claims data may occur, particularly within the heterogeneous ICD-10L93.2 category (other localized LE). A more fundamental issue is that the current ICD-10 system does not sufficiently reflect the clinical subtypes of CLE. Most notably, ACLE—the most prevalent subtype that affects approximately 50% of patients with SLE—lacks a distinct diagnostic code.[2,21,22] Furthermore, even for subtypes with existing codes, such as SCLE and DLE—which have estimated clinical frequencies of 8%–15%[1,2,22] and 11%–20% in SLE,[21–23] respectively—cutaneous involvement is often under-recorded when clinical priority is placed on systemic management. While a direct comparison with these clinical reports is limited given our study design using CLE as the index event, our findings reflect a combination of structural coding limitations and the methodological constraints of claims-based research. These results underscore the need for a more granular coding system

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TABLE 2 SLE-associated CLE and time to progression from CLE to SLE, 2005–2020. (a) Number of patients with SLE-associated CLE. (b) Time to progression from CLE to SLE.

(a)

	Total, *N* (%)	Male, *N* (%)	Female, *N* (%)	Female-to-male ratio	*p*-Value[a]
SLE-associated CLE	5367	647	4720		
CLE before SLE	563 (10.5)	99 (15.3)	464 (9.8)	4.7	<0.001
DLE before SLE	440 (8.2)	75 (11.6)	365 (7.7)	4.9	<0.001
SCLE before SLE	115 (2.1)	24 (3.7)	91 (1.9)	3.8	<0.001
Other localized LE before SLE	199 (3.7)	39 (6.0)	160 (3.4)	4.1	<0.001
CLE and SLE (±6 months)	2277 (42.4)	317 (49.0)	1960 (41.5)	6.2	<0.001
DLE and SLE	1611 (30.0)	241 (37.2)	1370 (29.0)	5.7	<0.001
SCLE and SLE	381 (7.1)	61 (9.4)	320 (6.8)	5.3	<0.001
Other localized LE and SLE	673 (12.5)	83 (12.8)	590 (12.5)	7.1	<0.001
CLE after SLE	2527 (47.1)	231 (35.7)	2296 (48.6)	9.9	<0.001
DLE after SLE	1782 (33.2)	160 (24.7)	1622 (34.4)	10.1	<0.001
SCLE after SLE	282 (5.3)	24 (3.7)	258 (5.5)	10.8	<0.001
Other localized LE after SLE	750 (14.0)	80 (12.4)	670 (14.2)	8.4	<0.001

(b)

	Overall (years)	Male, years	Female, years	
	Mean (SD)	Mean (SD)	Mean (SD)	*p*-Value[b]
CLE before SLE	3.2 (3.0)	2.9 (2.7)	3.2 (3.1)	0.413
DLE before SLE	3.3 (3.1)	2.9 (2.7)	3.4 (3.2)	0.207
SCLE before SLE	2.8 (2.6)	2.0 (1.6)	3.1 (2.8)	0.022
Other localized LE before SLE	3.2 (2.8)	2.7 (2.2)	3.3 (3.0)	0.216
CLE after SLE	4.7 (3.5)	4.1 (3.2)	4.7 (3.5)	0.007
DLE after SLE	4.7 (3.5)	4.2 (3.2)	4.8 (3.5)	0.045
SCLE after SLE	4.2 (3.1)	4.1 (3.0)	4.2 (3.1)	0.867
Other localized LE after SLE	4.5 (3.4)	3.8 (2.9)	4.6 (3.4)	0.070

Abbreviations: CLE, cutaneous lupus erythematosus; DLE, discoid lupus erythematosus; LE, lupus erythematosus; SLE, systemic lupus erythematosus.

[a]*p*-Value for the comparison between males and females.

[b]*p*-Value for comparison of progression time between males and females.

and closer dermatologic–rheumatologic collaboration to accurately characterize the full spectrum of LE.

Precancerous and malignant skin lesions in CLE

AK was more frequent in CLE without SLE than in SLE-associated CLE, which may reflect clinical overlap between AK and CLE lesions with potential diagnostic misclassification as well as differences in photoprotection counselling and adherence in patients with SLE-associated CLE. Importantly, skin cancer outcomes in patients with CLE may be influenced by detection bias due to more frequent dermatologic follow-up compared with matched controls. In line with this, AK and NMSC diagnoses in our cohort were predominantly observed early after the CLE index date, with aHRs being most pronounced within the first 2 years of follow-up. This clustering may reflect increased dermatologic surveillance rather than a true short-term carcinogenic effect; melanoma was rare, limiting temporal inference. Nevertheless, the persistence of a significantly increased risk beyond this initial period suggests that detection bias alone may not fully account for the increased skin cancer risk in patients with CLE. Therefore, maintaining clinical awareness of skin malignancy may be warranted as part of comprehensive care for patients with CLE.

Prior studies are conflicting: a US claims-based analysis found no increased skin cancer risk in CLE,[24] whereas a Swedish registry reported nearly a two-fold overall cancer risk and an NMSC aHR of 5.2 within the first year after CLE diagnosis.[25] Laboratory data further suggest that chronic inflammation in DLE could promote carcinogenesis.[26] Given that about 65% of LE patients are photosensitive,[27] and most mild-to-moderate CLE is managed with topical rather than systemic agents, the early clustering of AK and NMSC diagnoses after the CLE index date may reflect cumulative pre-diagnostic UV exposure or heightened dermatologic evaluation rather than immunosuppressive treatment. These findings should be

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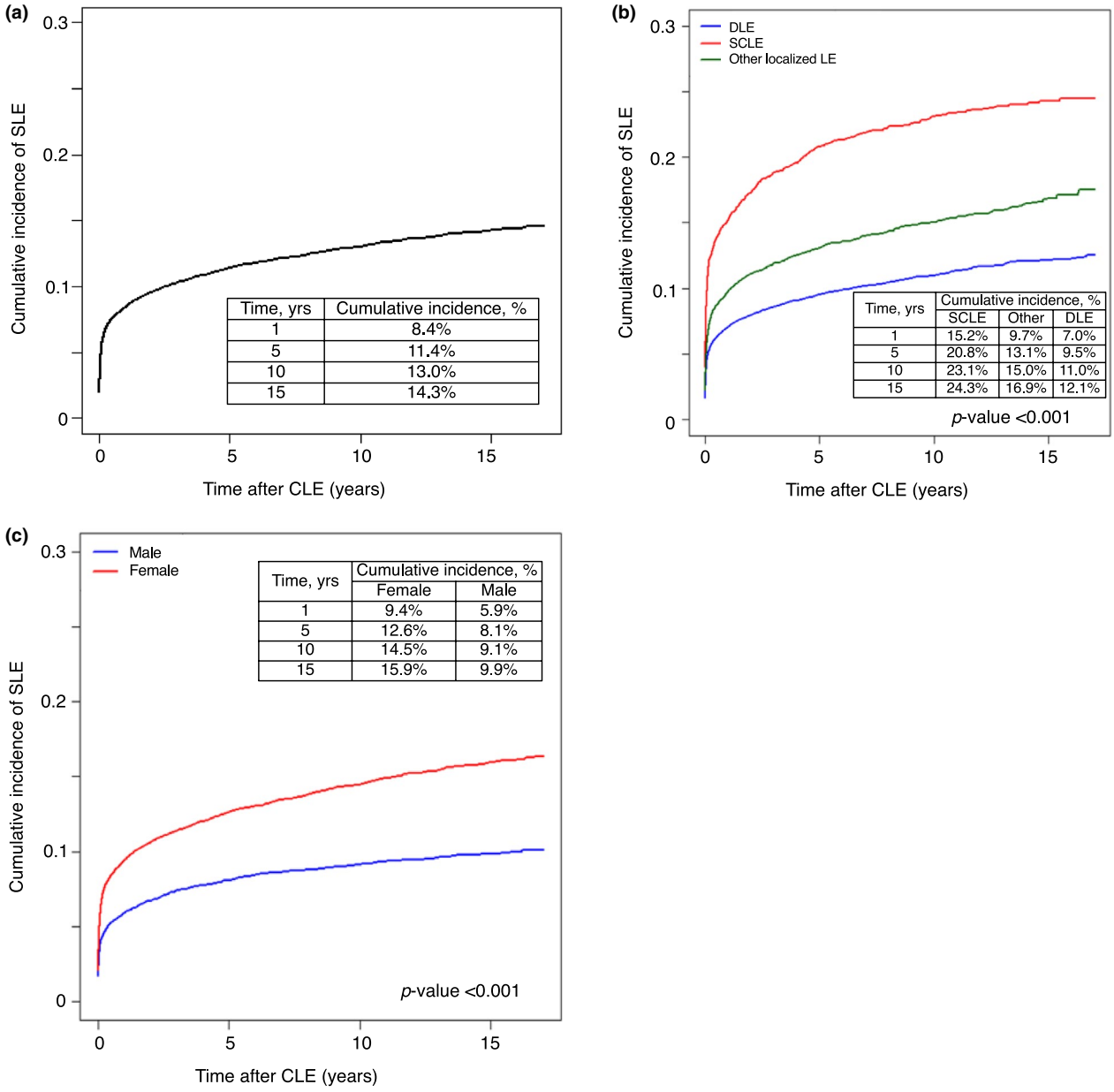

FIGURE 3 Cumulative incidence of progression to systemic lupus erythematosus among patients with cutaneous lupus erythematosus (CLE). (a) Overall, (b) by CLE subtype, (c) by sex.

interpreted cautiously in light of potential detection bias and support consideration of photoprotection in routine care.

Progression from CLE to SLE

A prior systematic review showed highly variable progression rates from CLE to SLE (0%–42%) and times to progression (5.6 months to 8.2 years), underscoring methodological heterogeneity.[28] Using the 2019 European League Against Rheumatism (EULAR)/ACR criteria, the progression rate was 2.8% over a median follow-up of 3.5 years—substantially lower than with earlier criteria (ACR, 13.1%; SLICC criteria, 8.4%).[29] Population-based studies have yielded more consistent rates (4.3–12.9%) and times to progression (mean 1.53 years; median 2.05 years).[6,9,10] Danish data showed a longer time to progression in DLE than in SCLE (3.04 vs. 1.65 years) and a 10-year cumulative incidence of 12.9%, with higher risk in females than males (14.5% vs. 6.9%).[6] A Swedish study reported a higher 3-year probability of SLE diagnosis (18.1%), with the highest risk in SCLE (24.7%) compared with DLE (16.7%), and a notable sex disparity.[9] Notably, US cohorts including a prospective study reported comparable progression proportions (12.2–17%) but a substantially longer mean time to progression (8.0–8.2 years), potentially due to differences in cohort design and case ascertainment.[8,30] A prior Korean claims-based study reported a 4.26% SLE progression rate with a mean time to

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progression of 1.53 years and no significant sex difference.[10] In comparison, our study found a lower progression rate (2.0%) and a substantially longer mean time to progression (3.2 years). Our stricter 6-month diagnostic window to exclude concomitant SLE may partly account for this pattern. Cumulative incidence curves suggested that most progression occurred within the initial 5 years after CLE diagnosis. Consistent with prior studies, SCLE showed the highest risk and the earliest progression to SLE compared with DLE. These findings support a subtype- and sex-specific follow-up strategy, with closer attention to systemic features during the first 5 years following a CLE diagnosis.

Prior studies suggest that clinically meaningful systemic manifestations are infrequent (5.6%–7% overall) among patients with CLE fulfilling SLE classification criteria[20,30,31] and that the risk of progression to severe SLE is higher in CLE with laboratory SLE than in isolated CLE.[20,32] Several factors, including younger age at CLE onset, darker skin phototype, arthralgia/arthritis, cytopenia and higher ANA titers, have been proposed as predictors of progression to SLE.[20,28,30,33,34] The evaluation of these predictors was beyond the scope of this study but warrants further investigation in future clinically detailed cohorts to clarify their prognostic value.

LIMITATIONS

ICD-10-based case identification may lead to miscoding and misclassification, particularly because acute CLE—the most common LE-specific skin manifestation—lacks a dedicated code. In addition, claims data lack clinical granularity, including laboratory results, disease severity, and coded information on individual SLE classification criteria. Detection bias for skin cancer is possible because patients with CLE may undergo more intensive dermatologic surveillance. Finally, because SLE has been registered as a RID only since 2005, analyses before that year were not feasible.

CONCLUSIONS

This nationwide study, leveraging operational case definitions and a stringent 6-month diagnostic window, provides a comprehensive longitudinal assessment of CLE in an Asian setting. In this large Korean cohort, CLE incidence was comparable to that reported in Western populations. Patients with CLE showed an increased risk of precancerous and malignant skin lesions, although detection bias from increased dermatologic surveillance may have contributed. While the overall progression from CLE to SLE was relatively low, most progression occurred within the first 5 years after CLE diagnosis, with SCLE showing the highest and earliest risk. These real-world estimates support a risk-stratified, individualized follow-up strategy, prioritizing assessment for systemic features, particularly during the critical initial 5-year period following CLE diagnosis, to inform clinical counselling and routine practice.

AUTHOR CONTRIBUTIONS

S.Y. Song: Data collection and curation, Drafting of manuscript. **J.Y. Kim:** Methodology, Statistical analysis, Revisions of the manuscript. **Y.M. Kim:** Study design, Data collection, Data curation, Revisions of the manuscript. **J.Y. Ko:** Study design, Supervised the overall project, Final approval of manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Korean National Health Insurance Service (NHIS), but restrictions apply to the availability. These data were used under license for the current study and are not publicly available. However, they are available from the authors upon reasonable request and with permission of the NHIS.

ETHICAL APPROVAL

This study was approved by the Hanyang University Institutional Review Board (No. 2022-11-045).

ETHICS STATEMENT

The requirement for informed consent was waived because only anonymized data were used.

ORCID

Joo Yeon Ko https://orcid.org/0000-0003-4240-9675

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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