Association of depression with socioeconomic status, anticardiolipin antibodies, and organ damage in patients with systemic lupus erythematosus: results from the KORNET registry

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Abstract

Objective

Depression is more common in patients with systemic lupus erythematosus (SLE) compared to the general population. However, few studies have investigated risk factors of depression in SLE patients, and the results are inconsistent. This study evaluated the prevalence of, and risk factors for, depression in ethnically homogeneous Korean SLE patients.

Methods

In this study, 505 consecutive SLE patients were enrolled from the Korean Lupus Network registry. Demographic variables, clinical manifestations, laboratory findings, physician global assessment, and SLEDAI-2000 and SLICC damage index were recorded at enrolment. Patients were identified as having depressive symptoms using the Korean version of the Beck Depression Inventory (BDI) with a cut-off ≥16, and categorised into four groups. Multivariable logistic regression analyses were performed to identify independent risk factors for depression defined as a BDI score ≥16.

Results

Of the 505 patients, 97 (19.2%) were diagnosed with depression. Patients with a higher BDI score were older, more likely to be a current smoker, and had a SLICC score >1. Conversely, they had lower income and educational levels. Regarding the serologic findings, patients with a higher BDI score had lower anti-double-stranded DNA positivity and higher anticardiolipin (aCL) positivity. On multivariate analysis, the following factors were associated with depression: current smoking status (OR 2.533, p=0.049), aCL-positivity (OR 2.009, p=0.035), and a SLICC damage index score >1 (OR 2.781, p=0.039). On the other hand, high-level education (OR 0.253, p=0.024) and a high income (OR 0.228, p=0.008) were negatively associated with depression.

Conclusion

Our results show that depression is prevalent in patients with SLE and multiple factors are associated with depression in SLE. These data could help guide target programmes for those at high risk of depression in SLE.

Key words

systemic lupus erythematosus, depression, damage

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Introduction

Systemic lupus erythematosus (SLE) is a clinically diverse, chronic autoimmune disease that affects patients of all ages, has a greater incidence among women of reproductive age, and is characterised by multisystem involvement (1). The most prevalent SLE manifestations are arthritis, mucocutaneous symptoms, and glomerulonephritis (1). Neuropsychiatric SLE (NPSLE) is also common, and developing in 15–80% of patients with SLE during the course of their disease (2, 3). In 1999, the American College of Rheumatology (ACR) developed a nomenclature system for NPSLE that covers 19 neuropsychiatric syndromes. The classification system includes five types of psychiatric disorder: mood disorder, anxiety disorder, cognitive dysfunction, psychosis, and acute confusional state (4). However, among the NPSLE manifestations, psychiatric symptoms are often underdiagnosed and are not recognised as a symptom of SLE (3).

The psychiatric symptoms of SLE may vary from mild personality disorders to severe psychotic behaviour (4). Studies have shown that depression is the one of the most frequent mental disorders affecting SLE patients. However, because of the variety of diagnostic tools available, the reported prevalence of depression varies widely in SLE patients, ranging from 10% to 60% (2). Depression in SLE has been linked to poor outcomes, such as functional disability (5, 6), impaired quality of life (6), and suicidal ideation (7). However, the exact nature and clinical relevance of the relationship between depression and SLE is not yet fully understood.

A number of studies have been conducted to identify factors predictive of depression in patients with SLE. Suggested risk factors include non-East Asian ethnicity (8), SLE disease activity (5, 9, 10), proinflammatory cytokines (11), and autoantibodies such as anti-ribosomal P (12). Similarly, other SLE or NPSLE symptoms, such as nephritis (9) and longitudinal myelitis (8), a high dose of corticosteroids (8, 13), and the psychological impact of coping with SLE (14) are also reported to be associated with depression. However, these studies show conflicting results. Reports have also suggested that SLE disease activity (8, 15), autoantibodies (15), and corticosteroid dose (5, 16) are not associated with depression. These inconsistencies probably arise from several factors, including study quality, methodological limitations, such as an unclear definition of depression, and diverse screening strategies used to detect depression. In addition to these inconsistencies, some studies included patients of different ethnic backgrounds, lacked clinical data, or involved small numbers of SLE patients. In this study, we estimated the prevalence of depression using a larger, ethnically-homogenous population comprised entirely of Korean SLE patients, and comprehensively evaluated the sociodemographic, clinical, and treatment-related factors associated with depression in patients registered in a nationwide multicentre SLE cohort.

Patients and methods

Population and study design

Our analysis was based on data from the KORean lupus NETwork (KORNET) registry, which was initiated in July 2014. The KORNET registry was designed as a nationwide, multicentre, hospital-based registry with the aim of prospectively accessing the clinical manifestations and long-term outcomes of SLE patients. SLE patients were enrolled from 13 tertiary academic rheumatologic centres across Korea and underwent follow-up assessments at 12-month intervals. In total, 571 patients with SLE were enrolled in the KORNET registry from July 2014 to December 2016. In this study, a cross-sectional design was employed to evaluate depression in SLE patients and study subjects were identified from the baseline data of the KORNET registry. At the time of the analysis, 505 consecutive patients were enrolled in the study. All patients fulfilled four or more of the ACR 1997 revised classification criteria for SLE (17).

This research complies with the principles of the Declaration of Helsinki. Identical informed consent forms (ICFs) and study protocols were provided to the independent institutional

review boards/ethics committees (IRB/EC) at each medical centre, and each IRB/EC reviewed the suitability of the protocol and the risks and benefits to the study participants. Ultimately, the IRB/EC at each medical centre independently approved the study without revision of the ICF or study protocol. All participants provided informed consent prior to enrolment. The registration number of the study (KCT0001253) was assigned by the Clinical Research Information Service, which is the primary registry of the World Health Organisation International Clinical Trials Registry Platform.

Patient data collection

All the patient data were transferred into the web server of the internet-based Clinical Research and Trial management (iCReaT) system (http://www.icreat.nih.kr/icreat/webapps/), which was established by the Korean Centers for Disease Control and Prevention. For each SLE patient, medical records were obtained via a patient interview or from patient medical charts at the time of enrolment. At enrolment of the registry, a comprehensive medical history, including demographic data, SLE clinical manifestations, laboratory tests, and treatment history was obtained from the medical records and through a questionnaire. Sociodemographic data, such as age at onset of SLE, gender, disease duration, education and income levels, the presence of hypertension and diabetes mellitus, smoking status, alcohol consumption, blood pressure, body mass index, familial history of autoimmune disease, and concomitant diseases at the time of enrolment were obtained. Clinical manifestations included symptoms listed in the ACR criteria for SLE (malar rash, discoid rash, alopecia, photosensitivity, oral ulcer, arthritis and arthralgia, serositis, renal involvement, central nervous system [CNS] involvement, and haematological disorders) and several lupus-related symptoms such as Raynaud's phenomenon, sicca symptoms (dry eyes and dry mouth), vasculitis, and gastrointestinal and lung involvement. Furthermore, presence of concomitant fibromyalgia was also evaluated in the analyses.

The laboratory tests included a complete blood count, urinalysis, comprehensive metabolic panel, serum creatinine, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level. We also reviewed serologic markers (autoantibodies, complement [C3, C4] levels, anti-phospholipid antibodies [lupus anticoagulant and immunoglobulin G/M-anticardiolipin (aCL)]). Autoantibodies such as antinuclear, anti-double-stranded DNA (anti-dsDNA), anti-ribonucleoprotein (anti-RNP), anti-Sm, anti-Ro, anti-La were also assessed. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)-2000 (18) score was calculated to assess lupus disease activity and flare at the time of enrolment. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (19) was also recorded at enrolment. Furthermore, we investigated the previous and current SLE medication history, including prednisolone (or equivalent), hydroxychloroquine (HCQ), and immunosuppressive agents such as azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, and cyclophosphamide taken for any cause.

Measurement of depressive symptoms

The presence of depressive symptoms was measured by the Beck Depression Inventory (BDI) (20), a self-administered tool for screening and assessing the severity of depression. The BDI consists of 21 questions relating to how the subject has been feeling over the past week. The BDI assesses respondents' mood, pessimism, sense of failure, lack of satisfaction, feelings of guilt, feelings of being punished, self-hate, self-accusation, suicidal ideas, prevalence of crying, irritability, social withdrawal, indecisiveness, body image, work inhibition, sleep disturbances, fatigue, appetite, weight loss, somatic preoccupations, and loss of libido. A value of 0 to 3 is assigned for each response, yielding a total possible score of 63. The standard cut-off scores are as follows: 0–9 (minimal depression), 10–15 (mild depression), 16–23 (moderate depression), and 24–63 (severe depression) (21). The reliability and validity of the BDI have been confirmed in a wide variety of populations, and we applied the Korean version of the BDI in this study. Therefore, in our analysis, a cut-off score of 16 or above was used to define SLE patients with depression, based on a previous study by Lee *et al*. (22) who found that this cut-off score maximised the diagnostic accuracy of the Korean version of the BDI. Furthermore, for a comprehensive analysis, we categorised SLE patients into four groups according to their total BDI score: Group I (BDI 0–9), Group II (BDI 10–15), Group III (BDI 16–23), and Group IV (BDI 24–63). Sociodemographic, clinical, laboratory findings, disease activity, and treatment-related data were then compared between these groups.

Statistical analysis

Statistical analysis was performed using SPSS software (v. 17.0; SPSS Inc., Chicago, IL, USA). Values are expressed as means ± standard deviation for continuous variables and as percentages for categorical variables. *P*-values <0.05 were considered statistically significant. Data were analysed using the chi-squared test for categorical variables and one-way analysis of variance (ANOVA) with post-hoc test (Tukey's HSD tests) for continuous variables. Multivariate logistic regression analyses were performed to identify independent risk factors for depression in SLE patients. In the multivariate logistic regression analysis, only variables for which $p<0.05$ in the ANOVA test or chi-squared test were included to avoid over-fitting. The area under the receiver operating characteristic (ROC) curve (23) and the Hosmer-Lemeshow goodness-of-fit statistic (24) were calculated to assess model performance and calibration, respectively. There is some missing data on autoantibody profiles at the time of enrolment of KORNET registry. Multiple imputation was performed to impute the antibody status of those patients with missing data.

Results

Comparison of baseline characteristics

The baseline characteristics of the study patients are shown in Table I. At the time of enrolment, the mean age was

Table I. Baseline demographic and clinical features of the SLE patients.

	All patients (n=505)	Group I (n=320)	Group II (n=88)	Group III (n=62)	Group IV (n=35)	*p*-value
Age at enrolment, years	39.7 ± 11.3	38.3 ± 10.8	39.4 ± 11.7	42.6 ± 11.2	47.9 ± 11.6	<0.001
Age at onset of SLE, years	31.4 ± 12.0	29.9 ± 11.2	31.3 ± 12.4	34.5 ± 12.6	40.1 ± 13.2	<0.001
Women (%)	472 (93.5)	298 (93.1)	81 (92.0)	59 (95.2)	34 (97.1)	0.701
Disease duration, months	110.7 ± 79.7	112.3 ± 78.8	110.3 ± 86.3	105.9 ± 82.6	105.6 ± 67.0	0.919
Currents alcohol consumption (%)	143 (28.3)	101 (31.6)	21 (23.9)	13 (21.0)	8 (22.9)	0.916
Current smokers (%)	56 (11.1)	30 (9.4)	7 (8.0)	15 (24.3)	4 (11.4)	0.006
Body mass index (kg/m^2)	21.8 ± 3.43	21.6 ± 3.10	22.0 ± 4.12	22.0 ± 3.80	23.0 ± 3.59	0.092
Monthly income, Korean Won (%)						<0.001
<1,000,000	79 (15.7)	32 (10.0)	12 (13.6)	17 (27.4)	18 (51.4)	
1,000,000–3,000,000	186 (36.9)	114 (35.7)	38 (43.2)	23 (37.1)	11 (31.4)	
3,000,000–5,000,000	146 (29.0)	101 (31.7)	23 (26.1)	17 (27.4)	5 (14.3)	
>5,000,000	93 (18.5)	72 (22.6)	15 (17.0)	5 (8.1)	1 (2.9)	
Insurance (%)						<0.001
Medical aid	44 (8.7)	15 (4.7)	6 (6.8)	12 (19.4)	11 (31.4)	
Health insurance	461 (91.3)	305 (95.3)	82 (93.2)	50 (80.6)	24 (68.6)	
Education level (%)						<0.001
≤6 years	28 (5.5)	7 (2.2)	3 (3.4)	7 (11.3)	11 (31.4)	
6–12 years	202 (40.0)	118 (36.9)	36 (40.9)	29 (46.8)	19 (54.3)	
>12 years	275 (54.5)	195 (60.9)	49 (55.7)	26 (41.9)	5 (14.3)	
PGA (%)	0.85 ± 0.56	0.80 ± 0.50	0.91 ± 0.64	0.90 ± 0.57	1.02 ± 0.72	0.076
SLEDAI-2000 >12 (%)	21 (4.2)	11 (3.4)	5 (5.7)	2 (3.2)	3 (8.6)	0.428
SLICC damage index >1 (%)	30 (6.0)	14 (4.4)	4 (4.5)	6 (9.7)	6 (17.1)	0.011

Values are shown as means ± standard deviation unless otherwise indicated.
SLE: systemic lupus erythematosus; PGA: physician global assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics.

Table II. Comparison of the incidence of cumulative SLE signs and symptoms by SLE patient group.

	All patients (n=505)	Group I (n=320)	Group II (n=88)	Group III (n=62)	Group IV (n=35)	*p*-value
Symptoms listed in the ACR criteria						
Arthritis (%)	263 (52.1)	163 (51.3)	45 (51.1)	35 (56.5)	19 (54.3)	0.882
Malar rash (%)	237 (46.5)	151 (47.2)	41 (46.6)	28 (45.2)	17 (48.6)	0.988
Discoid rash (%)	24 (4.8)	15 (4.7)	4 (4.5)	3 (3.2)	2 (8.6)	0.692
Photosensitivity (%)	148 (29.3)	97 (30.3)	26 (29.5)	12 (19.4)	1 (37.1)	0.245
Oral ulcer (%)	139 (27.5)	82 (25.6)	29 (33.0)	17 (27.4)	11 (31.4)	0.542
Immunologic involvement (%)	427 (84.6)	271 (84.7)	80 (90.9)	49 (79.0)	27 (77.1)	0.130
CNS involvement (%)	23 (4.6)	17 (5.3)	3 (3.4)	3 (3.2)	1 (2.9)	0.760
Seizure	14 (2.8)	9 (2.8)	2 (2.3)	2 (3.2)	1 (2.9)	0.988
Psychosis	9 (1.9)	7 (2.2)	1 (1.1)	1 (1.6)	0 (0.0)	0.764
Renal involvement (%)	170 (33.7)	111 (34.7)	31 (35.2)	19 (30.6)	9 (25.7)	0.685
Haematologic involvement (%)	280 (55.4)	184 (57.5)	50 (56.8)	32 (51.6)	14 (40.0)	0.225
Leukopenia	144 (28.5)	96 (30.0)	25 (28.4)	14 (22.6)	9 (25.7)	0.670
Haemolytic anaemia	44 (8.7)	30 (9.4)	6 (6.8)	7 (11.3)	1 (2.9)	0.451
Thrombocytopenia	94 (18.6)	55 (17.2)	18 (18.0)	14 (22.6)	7 (20.0)	0.726
Other symptoms						
ILD (%)	12 (2.4)	5 (1.6)	4 (4.5)	3 (4.8)	0 (0)	0.160
PAH (%)	15 (3.0)	6 (1.9)	5 (5.7)	2 (3.2)	2 (5.7)	0.212
Serositis (%)	93 (18.4)	59 (18.4)	19 (21.6)	8 (12.9)	7 (20.0)	0.593
Pleuritis	64 (12.7)	37 (11.6)	15 (17.0)	7 (11.3)	5 (14.3)	0.559
Pericarditis	43 (8.5)	28 (8.8)	8 (9.1)	4 (6.5)	3 (8.6)	0.940
Raynaud's phenomenon (%)	144 (28.5)	94 (29.4)	27 (30.7)	12 (19.4)	11 (31.4)	0.389
Vasculitis (%)	36 (7.1)	24 (7.5)	4 (4.5)	5 (8.1)	3 (8.6)	0.766
Lupus enteritis (%)	10 (2.0)	7 (2.2)	0 (0.0)	2 (3.2)	1 (2.9)	0.478
Lupus pancreatitis (%)	7 (1.4)	5 (1.6)	1 (1.1)	0 (0.0)	1 (4.2)	0.673
Myositis (%)	7 (1.4)	7 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.250

ACR: American College of Rheumatology; CNS: central nervous system; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

37.2±11.3 years and most of the patients were female (93.5%; n=472). The mean disease duration since the initial diagnosis of SLE was 110.7±79.7 months. Of the 505 patients, the number of SLE patients in each group was as follows: Group I, n=320; Group II, n=88; Group III, n=65; and Group IV, n=32. There was no significant difference in gender distribution among the groups. Although the disease duration was similar between the groups, patients with a higher BDI score tended to be older than those with a lower score, and patients from Group I through to Group IV had an increasingly older age (38.3±10.8 years *vs*. 39.4±11.7 years *vs*. 42.6±11.2 years *vs*. 47.9±11.6 years, respectively; $p<0.001$). A similar trend was observed in terms of age at the onset of SLE ($p<0.001$).

Regarding the socioeconomic variables, patients with a higher BDI score were more likely to be current smokers (Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 9.4% *vs*. 8.0% *vs*. 24.3% *vs*. 11.4%; $p<0.006$). In addition, the incidence of a monthly income of <1 × 10^6 Korean Won (0.9 × 10^3 US dollars)/month was also higher among patients with a higher BDI score (Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 10.0% *vs*. 13.6% *vs*. 27.4% *vs*. 51.4%), whereas patients with a lower BDI score were more likely to have an annual income of >5 × 10^6 Korean Won (4.5 × 10^3 US dollars)/month (Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 22.6% *vs*. 17.0% *vs*. 8.1% *vs*. 2.9%); these differences were statistically significant ($p<0.006$). Furthermore, it is noteworthy that the patients with a higher BDI score had a lower level of education ($p<0.001$).

In terms of clinical features, patients with a higher BDI score were also more likely to have an SLICC damage index score >1 (Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 4.4% *vs*. 4.5% *vs*. 9.7% *vs*. 17.1%; $p=0.011$). However, the physician global assessment and SLEDAI scores did not differ among the four groups.

SLE signs and symptoms

Table II shows the incidence of cumulative SLE signs and symptoms. However, among the four groups, there were no significant differences in terms of clinical manifestations, including the symptoms listed in the ACR criteria for SLE and several lupus-related symptoms such as Raynaud's phenomenon, sicca symptoms (dry eyes and dry mouth), vasculitis, and gastrointestinal and lung involvement. In particular, NPSLE was not associated with the severity of depression in SLE patients. Furthermore, we found no difference in the cumulative number of ACR criteria fulfilled by the various Groups. Although the data are not shown, we found no association between fibromyalgia and depression ($p=0.345$).

Comparison of laboratory findings

A comparison of the laboratory findings among the groups is presented in Table III. Anti-dsDNA and aCL antibodies showed a significantly different distribution among the groups. Patients with a higher BDI score were more likely to have a lower anti-dsDNA positivity (Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 57.0% *vs*. 58.0% *vs*. 40.3% *vs*. 40.0%; $p=0.042$) and a higher aCL positivity (Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 14.7% *vs*. 21.7% *vs*. 33.3% *vs*. 15.6%; $p=0.012$). Although not shown in the table, laboratory findings, such as the complete blood count, serum creatinine, ESR, CRP, and complement levels, including C3 and C4, were not significantly different among the groups.

Comparison of past and current treatments

The medication histories of the SLE patients at enrolment are shown in Table IV. Overall, the medication histories were not significantly different among the groups. In particular, the proportion of patients taking >5 mg/day of mean cumulative prednisolone (or equivalent) did not differ among the groups. In terms of prior medication, HCQ or any immunosuppressive drug use was not associated with, and was not protective against, depression. Likewise, although not shown in the table, there were no significant differences in the current medications, including HCQ and immunosuppressive drugs.

Risk factors of depression in SLE patients

Multivariate logistic regression analyses were performed to identify independent risk factors for depression in SLE patients (Table V). Various factors were associated with depression in SLE patients. Being a current smoker was an independent risk factor of depression (odds ratio (OR), 2.533; 95% confidence interval (CI), 1.006–6.378; $p=0.049$), and education and income levels were also strongly associated with depression. In particular, a higher level of education, such as an educa-

Table III. Comparison of SLE autoantibodies by SLE patient group.

	All patients (n=505)	Group I (n=320)	Group II (n=88)	Group III (n=62)	Group IV (n=35)	*p*-value
Autoantibodies (%)						
Anti-dsDNA	269/504 (53.4)	179/319 (57.0)	51/88 (58.0)	25/62 (40.3)	14/35 (40.0)	0.037
Anti-Sm	107/472 (22.7)	65/299 (21.7)	21/80 (26.3)	13/59 (22.0)	8/34 (23.5)	0.859
Anti-RNP	186/461 (40.3)	119/292 (40.8)	36/77 (46.8)	16/58 (27.6)	15/34 (44.1)	0.141
Anti-SS-A/Ro	280/469 (59.7)	182/299 (60.9)	44/8 (55.0)	36/57 (63.2)	18/3 (54.5)	0.670
Anti-SS-B/La	106/476 (22.3)	66/303 (21.8)	18/81 (22.2)	16/58 (27.6)	6/34 (17.6)	0.704
LAC	55/448 (12.3)	36/283 (12.7)	7/77 (9.1)	7/55 (12.7)	5/33 (15.2)	0.794
IgG/M aCL	74/407 (18.2)	38/258 (14.7)	15/69 (21.7)	16/48 (33.3)	5/32 (15.6)	0.017

Anti-dsDNA: anti–double-stranded DNA; RNP: ribonucleoprotein; LAC: lupus anticoagulant; IgG/M: immunoglobulin G/M; aCL: anticardiolipin.

Table IV. Comparison of prior treatments at the time of enrolment by SLE patient group.

	All patients (n=505)	Group I (n=320)	Group II (n=88)	Group III (n=62)	Group IV (n=35)	*p*-value
Hydroxychloroquine, ever (%)	493 (97.6)	311 (97.2)	85 (96.6)	62 (100.0)	35 (100.0)	0.387
Mean cumulative prednisolone >5 mg/day (%)	280 (55.4)	184 (57.5)	51 (58.0)	28 (45.2)	17 (48.6)	0.251
Immunosuppressive agents (%)						
Methotrexate	58 (11.5)	36 (11.3)	10 (11.4)	9 (14.5)	3 (8.6)	0.832
Azathioprine	154 (30.5)	101 (31.6)	30 (34.1)	11 (17.7)	12 (34.3)	0.127
Tacrolimus	50 (9.9)	32 (10.0)	10 (11.4)	3 (4.8)	5 (14.3)	0.314
Cyclosporine	50 (9.9)	3 (9.4)	9 (12)	9 (14.5)	2 (5.7)	0.571
Mycophenolate mofetil	111 (22.0)	75 (23.4)	20 (22.7)	10 (16.1)	6 (17.1)	0.544
Cyclophosphamide (oral or intravenous)	85 (16.8)	51 (15.9)	15 (17.0)	10 (16.1)	9 (25.7)	0.536
Biologic agents (%)						
Rituximab	4 (0.8)	3 (0.9)	1 (1.1)	0 (0.0)	0 (0.0)	0.803
Belimumab	16 (3.2)	11 (3.4)	2 (2.3)	1 (1.6)	2 (5.7)	0.674

Table V. Multivariate logistic regression analyses of the risk factor of depression in patients with systemic lupus erythematosus.

Variables	Multivariate analysis OR	*p*-value
Age, years	1.020 (0.990–1.051)	0.188
Male	0.312 (0.079–1.001)	0.098
Disease duration, years	0.997 (0.994–1.001)	0.123
Current smoker	2.533 (1.006–6.378)	0.049
Education level		
≤6 years	Reference	-
6–12 years	0.346 (0.123–0.969)	0.043
>12 years	0.253 (0.064–0.835)	0.024
Monthly income, Korean Won		
<1,000,000	Reference	-
1,000,000–3,000,000	0.462 (0.219–0.973)	0.042
3,000,000–5,000,000	0.423 (0.180–0.993)	0.048
>5,000,000	0.228 (0.076–0.681)	0.008
Anti-dsDNA positivity	0.745 (0.418–1.326)	0.317
aCL positivity	2.009 (1.052–3.837)	0.035
SLEDAI-2000 > 12	1.520 (0.486–4.755)	0.471
SLICC damage index > 1	2.781 (1.011–7.650)	0.039

OR: odds ratio; Anti-dsDNA: anti–double-stranded DNA; aCL: anticardiolipin; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics.

tional period of >12 years (OR, 0.253; 95% CI, 0.064–0.835; p=0.024) and an annual income of >5 × 10^6 Korean Won/year (OR, 0.228; 95% CI, 0.076–0.681; p=0.008), were protective against depression. Furthermore, aCL positivity (OR, 2.009; 95% CI, 1.052–3.837; p=0.035) and an SLICC damage index score >1 (OR, 2.781; 95% CI, 1.011–7.650; p=0.039) were associated with depression in SLE patients. Turning to individual SLICC damage index items, although SLE patients with the highest BDI scores (Group IV) were more likely to score higher on neuropsychiatric items than the other groups [Group I *vs*. Group II *vs*. Group III *vs*. Group IV = 11 (3.4%) *vs*. 5 (5.7%) *vs*. 2 (3.2%) *vs*. 5 (14.3%); p=0.029], this was not associated with depression on multivariable logistic regression analyses (OR 1.036, 95% CI: 0.318–3.382, p=0.953).

Discussion

In our study, depression was observed in a significant proportion (19.2%) of a large SLE patient cohort. The most significant finding was that a variety of factors were associated with depression in SLE patients. Socioeconomic factors, such as smoking status, and education and income levels were related to depression in SLE patients. Furthermore, we showed that aCL positivity and the SLICC damage index score were significantly associated with depression in this population.

We found that depression was present in 19.2% of our patients when a BDI cut-off score of 16 or above was used to define depression. The prevalence of depression shows considerable variability among distinct study populations. Zakeri *et al*. (25) reported a rate of 60% among Iranian SLE patients. Bachen *et al*. (11) showed a 47% frequency in Caucasian women with SLE. In addition, Liang *et al*. (26), in Canadian SLE patients, Magner *et al*. (27), in African SLE patients, and Migquel *et al*. (28), in Brazilian SLE patients reported a rate of depression of about 40% in their SLE cohorts. Of course, there are also studies that have reported lower prevalence rates than ours, such as 12.7% in a multiethnic SLE cohort by Hanly *et al*. (29), 13% in a study of Korean SLE patients by Jung *et al*. (10), and 16.1% in a US study by Harrison et al. (30). Such a wide range of findings may reflect differences in patient populations and sample sizes, as well as cultural and social backgrounds. Furthermore, methodological variation in the screening tools used to detect depression in SLE patients exists among these studies. In fact, a recent meta-analysis found that the prevalence of depression depends on the diagnostic tool used. In that study, Zhang *et al*. (31) revealed the prevalence of depression to be 24% according to the Diagnostic and Statistical Manual of Mental Disorders and/or International Classification of Diseases criteria, 30% for the Hospital Anxiety and Depression Scale

criteria (with a threshold of 8), 38% for the Center for Epidemiologic Studies – Depression criteria (with a threshold of 16), and 39% with a BDI cut-off of 14 or more. Therefore, although it may be somewhat lower than that described by other studies, the prevalence of depression in our cohort was still significantly higher than that of the general population, which was reported to be 5–10% (32). Because depression can negatively impact on clinical outcomes, including functional abilities (5, 6) and quality of life (6), clinicians should screen for depression in SLE patients and provide appropriate strategies for preventing and treating depression in cooperation with mental health providers.

We found that smoking was significantly related to depression in SLE patients. Previous studies have shown that smoking may not only be associated with the development of SLE (33), but also has a serious impact on the disease activity of SLE (34). In addition, smoking has a serious impact on cumulative chronic organ damage in SLE patients, and may have a deleterious impact on lupus morbidity. Montes *et al*. (35) showed that SLE patients who were never exposed to smoking had a 0.78-fold risk of progressing towards a cumulative damage status. In terms of depression, the risk of development of depression is ~2.0 times higher among smokers than non-smokers (36). Moreover, individuals with depression find it more difficult to quit smoking than those who are not depressed (36). Although the relationship between smoking and depression is still unclear, they may actually perpetuate each other in SLE patients. Additionally, considering that it has a wide range of adverse effects on patients with SLE (34), smoking may have some additive interactions with depression in SLE. Therefore, the link between depression and smoking status in SLE may need to be considered, and more effective tobacco control programmes developed in SLE patients.

Various sociodemographic factors, including age, gender, marital status, education, immigrant status, and income have been identified as important factors associated with depression (37, 38). Among these, socioeconomic factors such as education and income were significantly associated with depression in our patients with SLE. In a multivariate logistic regression analysis, these variables showed strong relationships with depression, and SLE patients with the highest educational and income levels had a lower risk of depression. Although a causal link has yet be clearly identified, social causation (adversity and stress) and social selection (downward mobility of those genetically predisposed) were suggested as possible mechanisms that may underlie the relationship between socioeconomic status and depression (39). The social causation model posits that increased adversity and stress, and a reduced capacity to cope related to a low socioeconomic position, increase the risk of the developing mental disorders (39). On the other hand, the social selection hypothesis suggests that mental illness can inhibit socioeconomic attainment and lead people to drift into a lower social class due to genetic factors, hospitalisations related to mental illness, and/or loss of work (39). Collectively, although a causal relation between a low socioeconomic status and depression could not be shown because of our case-control study design, there is a need for targeted interventions to treat and prevent depression in this low-income, low-educated group of SLE patients.

Interestingly, we observed that aCL positivity was among the risk factors for depression. Researchers have found that several autoantibody specificities may play a role in the pathogenesis of NPSLE. However, to date, the pathogenic role of autoantibodies in depression in SLE patients is not well understood. Although controversial, anti-ribosomal P antibody has received great attention (40, 41) and has been reported to be positive in 45% to 90% of SLE patients with psychosis including depression (40); the anti-P level appeared to decrease as the symptoms of psychosis or depression improved after immunosuppressive treatment (41). However, although these data are not shown in our table, anti-ribosomal P antibody was not associated with depression in our cohort. Regarding antiphospholipid antibodies, many studies have reported that increased aCL titres were associated with thrombosis or pregnancy morbidity, and that the most prevalent neurologic manifestations are cerebrovascular ischemic events (42). Furthermore, antiphospholipid antibodies can also cause neuropsychological impairments unrelated to thrombosis. Since Schmidt *et al*. raised the possibility that increased aCL titres may be associated with other neuropsychological dysfunctions (43), researchers have found that the aCL antibody is also elevated in the serum of patients with psychoses such as schizophrenia or bipolar disorder, and who had no history of SLE or vascular events (44, 45). In addition, depression associated with the aCL antibody has also been mentioned in the literature. Maes *et al*. (46) found that aCL antibody titres were significantly increased in depressed patients. In another study, Maes *et al*. showed a trend towards higher aCL antibodies in the same patients, although the result was not statistically significant (47). Similarly, the presence of aCL antibodies was associated with depression in our SLE patients. Although these results suggest that aCL may play a role in the pathogenesis of neuropsychiatric manifestations, including depression, studies of the exact roles of aCL antibody-induced CNS pathology in SLE are needed.

Finally, we showed that a higher SLICC damage index score was significantly associated with depression, and that patients with more severe depressive symptoms were more likely to have an SLICC damage index score >1. Considering that we were unable to find any association between the SLEDAI-2000 score and depression, depression in our SLE cohort may be mainly affected by organ damage related to the overall disease control status, rather than by disease activity at a single time point. In fact, organ damage was associated with decreased health-related quality of life (HRQoL), and especially with impacted physical function, in SLE patients (48). Indeed, Doria *et al*. (49) suggested that physical damage could mainly influence HRQoL through depression. Importantly, organ damage in SLE was

associated with suicidal ideation, which is the most devastating consequence of depression. In a recent study, Mok *et al*. (50) found that suicidal ideation was common in their SLE patients and more intense in those with a higher cardiovascular SLICC damage index score. In conclusion, our study highlighted the importance of recognising depression in SLE patients with cumulative organ damage. At the same time, clinicians should focus specifically on suicidal thoughts and behaviours, and their prevention, in these patients.

Our study had several strengths. First, we conducted a large-scale investigation of the association between SLE and depression using a nationwide, multicentre SLE cohort. Indeed, many previous studies regarding depression in SLE were performed using a sample size of less than 100 patients (2, 31). Furthermore, we attempted to collect comprehensively patient data to reduce the likelihood of excluding potential risk factors for depression in patients with SLE. However, several limitations need to be considered when interpreting our results. First, as mentioned previously, this study was conducted using a case-control study design, and thus we are unable to clearly establish a causal relationship between depression and any of the independent variables. Further prospective studies are required to determine causality definitively. Second, in our analysis, a BDI cut-off score of 16 or above was used to define SLE patients with depression. However, although a cut-off score of 16 or above was shown to maximise the diagnostic accuracy of the Korean version of the BDI in a previous study (22), no widely accepted consensus regarding such a cut-off score for depression in chronic conditions, including SLE, is yet available. Third, we did not fully investigate other psychological stresses, such as academic and job-related stress, as well as interpersonal relationships, which may act as environmental triggers for depression; also, data regarding the treatment of depression were not collected. Fourth, we performed (subgroup) multivariable analyses seeking risk factors for severe depression (in Group IV). Only educational level was so associated. Further prospective studies are needed to confirm our findings. However, despite these limitations, we believe that our results are useful in highlighting underdiagnosis of depression in SLE patients. Lastly, we unfortunately did not evaluate APS-related symptoms in patients with SLE. Further research is needed because such symptoms may affect the relationship between aCL-positivity and depression. In summary, we conducted a large-scale investigation on the prevalence and risk factors of depression in Korean patients with SLE. Our results showed that depression was prevalent in patients with SLE, and that multiple factors were associated with depression in such patients. In this study, smoking, education and income levels, aCL positivity, and cumulative organ damage were independently associated with depression in patients with SLE. Our study provides information important for the recognition and prevention of depression in SLE patients, and could also help to guide target programmes for those at high risk of depression in SLE.

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