Predictors of Incident Depression in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** Findings from previous studies of predictors of depression among patients with systemic lupus erythematosus (SLE) have been inconsistent. The aim of our study was to identify risk factors that preceded incident depression based on a large, closely followed longitudinal cohort.

Methods. Data regarding 1609 patients with SLE in the Hopkins Lupus Cohort who had no history of depression prior to cohort entry were analyzed. Demographic variables, SLE manifestations, laboratory tests, physician's global assessment, Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI), cumulative organ damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index), and onset of depression were recorded at enrollment and each quarterly visit. Rates of incident depression were calculated overall, and in subgroups defined by demographic and clinical variables. Adjusted estimates of association were derived using pooled logistic regression.

Results. The incidence of depression was 29.7 episodes per 1000 person-years. In the multivariable analysis, these variables remained as independent predictors of incident depression: recent SLE diagnosis, non-Asian ethnicity, disability, cutaneous activity, longitudinal myelitis, and current prednisone use of 20 mg/day or higher. Global disease activity (SELENA-SLEDAI) was not a significant predictor after controlling for prednisone use.

Conclusion. Depression in SLE is multifactorial. Higher-dose prednisone (≥ 20 mg daily) is 1 important independent risk factor. Global disease activity is not a risk factor, but cutaneous activity and certain types of neurologic activity (myelitis) are predictive of depression. The independent effect of prednisone provides clinicians with an additional incentive to avoid and reduce high-dose prednisone exposure in SLE. (First Release Aug 15 2014; J Rheumatol 2014;41:1823–33; doi:10.3899/jrheum.140111)

Key Indexing Terms:
DEPRESSION RISK FACTORS SYSTEMIC LUPUS ERYTHEMATOSUS

Neuropsychiatric systemic lupus erythematosus (NPSLE) develops in 17%–75% of patients with SLE during the course of their disease[1]. Although multiple neuropsychiatric manifestations occur in SLE, major depression and cognitive dysfunction are the most common[2]. Depression is frequent in SLE[3,4,5,6,7,8], and is more common than in the general population[9]. A diagnosis of depression ranges from 2% to 60%, whereas a diagnosis of major depression ranges from 20% to 47% in SLE[1]. The variability in reported frequency of depression is predominantly attributed to the variety of assessment methods and length of followup[3]. Depression has been linked to poor clinical outcomes in SLE, including increased work disability[10].

The risk factors for depression in SLE are not adequately understood[4,5,6,7,8,10,11,12,13,14,15,16,17,18,19,20,21,22,23]. SLE activity[7,10,13], other neuropsychiatric manifestations[3,8,15,17], or autoantibodies such as anticardiolipin (aCL) or anti-P lupus antibody[12,16] could directly predispose to depression. Depression could also be a secondary phenomenon caused by other manifestations of the disease (for instance, pain and arthritis[19]), by corticosteroid therapy[24], or as an emotional reaction to the chronicity or social stress caused by having SLE[1]. The results from past studies are inconsistent, with some studies finding no association between depression and disease activity[4,6,11,18,20], other neuropsychiatric manifestations[6], autoantibodies [e.g., anti-P[6,20], antiphospholipid antibodies (aPL)[23]], or corticosteroid usage[10,18]. One previous analysis found that depression was associated with secondary Sjögren syndrome[8].

Besides the inconsistencies in previous studies, most

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prior studies have been cross-sectional, making it difficult to distinguish between the factors that preceded depression versus those that occurred after depression. Here, we report the results of a longitudinal study of incident depression in a large prospective cohort of patients with SLE without prior depression. Using this cohort, we estimated the incidence rate of first depression occurrence, and compared the incidence in subsets of SLE defined by candidate risk factors, including socioeconomic status, SLE disease activity, clinical manifestations, autoantibodies, and medication use.

MATERIALS AND METHODS

Patients and study design. The analysis was based on data from the Hopkins Lupus Cohort, begun in 1987. The study was approved on a yearly basis by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. At cohort entry, a comprehensive medical history, including demographic variables, clinical manifestations, laboratory tests, and treatment was obtained from the medical records and the patient. At each quarterly clinic visit, a battery of laboratory tests were performed, including a complete blood count, urinalysis and urine protein/creatinine ratio, comprehensive metabolic panel, erythrocyte sedimentation rate, serum creatinine, complement factor 3 (C3) and C4 levels, anti-dsDNA, and multiple measures of aPL (lupus anticoagulant by dilute Russell's viper venom time with confirmatory studies, and aCL IgG, IgM, and IgA). In addition, cohort members had 1 or more measurements of other immunologic markers related to SLE, including antinuclear antibody, anti-Sm, anti-RNP, anti-Ro, anti-La, and anti-β2 glycoprotein I. At each visit, clinical assessment of disease activity was done using the physician's global assessment[25] and the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)[26]. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index[27] was also similarly recorded at the first visit and updated at least every 3 months. This analysis is based on the cohort experience through June 2013.

A patient was considered to have depression if (1) there was a record of persistent depression (2 or more mentions of depression separated by several weeks in rheumatology clinic notes) and/or a diagnosis of affective disorder was made by a psychiatric professional; and (2) treatment for those symptoms with psychotherapy or antidepressant medications was documented. Antidepressant use for reasons other than depression was not counted. All Johns Hopkins Hospital records, outpatient rheumatology records, and psychiatric records were reviewed by 1 rheumatologist. All patients met the ACR neuropsychiatric case definition of major depressive-like episode or mood disorder with depressive features[28]. Other neuropsychiatric manifestations of SLE were defined by the ACR neuropsychiatric case definitions[28] and included seizures, stroke or transient ischemic attack, aseptic meningitis, organic brain syndrome, psychosis, and longitudinal myelitis.

From 1987 to 2013, 2104 patients were in the cohort. Patients who had an episode of depression prior to cohort entry were excluded. Those who had a history of depression, but for whom the onset year was uncertain, were also excluded. For those included, the study was based on the experience of each patient from cohort entry until the patient's last cohort visit, or at the time of the first episode of depression (whichever came first).

Statistical analysis. To facilitate the analysis, the dataset was formatted to consist of 1 record for every month of followup for each patient. Each record contained the clinical and medication history of the patient up until that time based on information from the most recent quarterly visit. Each person-month record also contained a variable indicating whether new depression had occurred during that month. For some variables (such as anti-Sm, anti-Ro, and anti-La), which were not part of the quarterly battery of tests and were measured only once, we assigned the value of the measurement at that time to all of a patient's person-months.

To estimate the association between a predictor (e.g., age) and incidence rates of depression, each month was classified into a subgroup based on that predictor (e.g., age 18–39 yrs). Then we estimated the rate of depression per month in each subgroup by calculating the number of incident events of depression divided by the number of person-months observed in that subgroup. Results were converted to rates per person-year. To assess whether associations between risk factors and rates of depression persisted after controlling for potential confounding variables (e.g., age), we applied pooled logistic regression to the monthly data. Pooled logistic regression is a form of discrete survival analysis that is about equivalent to a Cox model. An advantage of this approach is that it facilitates data exploration and incorporation of time-varying predictors[29]. Using this approach, we fit multiple regression models for specific variables, controlling for additional confounders relevant to those specific variables. Finally, we fit a final multivariable model including the variables that were most important in the univariate and multivariate models.

RESULTS

Characteristics of the patients with SLE. The analysis was based on 1609 patients with SLE recruited between 1987 and June 2013. The majority (92%) of this cohort were women, and most were either white (51%) or African American (41%). About 76% of the patients were less than 40 years of age at cohort entry. Over the study, 46% of patients in the cohort were followed up for more than 5 years. The SLICC/ACR Damage Index indicated minimal cumulative organ damage with a score of 0 in 940 patients (58%), 1 in 357 patients (22%), 2–3 in 250 patients (15%), and more than 4 in 62 patients (5%) at cohort entry (Table 1).

Rate of incident depression. In our study, 282 (17%) of 1609 patients had a first depression occurrence during the followup. The 1609 patients were observed for a total of 9487 person-years. This equates to an incidence rate of 29.7 episodes per 1000 person-years (95% CI, 26.4 to 33.4; Table 2).

Association between demographic factors and depression in the univariate analysis. Rates of incident depression declined consistently with age (Table 2). The rates of depression were found to be 1.4 times higher in patients with disability than in those without ($p = 0.0084$), and 1.5 times higher in those separated or divorced compared to married individuals ($p = 0.021$). The rate of depression was significantly lower in patients with college education [rate ratio (RR) = 0.6, $p = 0.031$], or family income more than $100,000 US (RR = 0.6, $p = 0.014$). Importantly, depression was substantially (90%) less frequent in those of Asian ethnicity than in others (RR = 0.1, $p = 0.018$; Table 2).

Association between SLE disease duration, activity, non-neuropsychiatric symptoms, and depression in the univariate analysis. The association of SLE disease-related variables and depression is summarized in Table 3. The rate of incident depression in patients with SLE disease duration more than 3 years was 40% to 60% lower than in those with disease duration less than 3 years ($p < 0.0001$). The rate of

Table 1. Characteristics of patients in the Hopkins Lupus Cohort who did not have precohort history of depression.

Variable	N (%)
Patients	1609 (100)
Sex	
Female	1486 (92)
Male	123 (8)
Ethnicity	
White	823 (51)
African-American	663 (41)
East Asian	63 (4)
Other	60 (4)
Age at cohort entry, yrs	
< 30	585 (36)
30–44	642 (40)
45–59	305 (19)
60+	77 (5)
Education	
< High school	150 (10)
High school	404 (26)
Some college	437 (28)
College graduate+	563 (36)
Income ($ US)	
< 25,000	418 (29)
25,000–60,000	464 (32)
60,000–100,000	314 (22)
100,000	264 (18)
Year of cohort entry	
1987–1995	425 (26)
1996–2004	692 (43)
2005–2013	492 (31)
Followup duration, yrs	
< 2	515 (32)
2–5	377 (23)
5–10	374 (23)
10+	343 (21)
SLICC Damage Score at cohort entry	
0	940 (58)
1	357 (22)
2–3	250 (15)
4+	62 (5)

SLICC: Systemic Lupus International Collaborating Clinics.

incident depression was 1.6 times higher in patients with SLE with higher current SLE disease activity as measured by a SELENA-SLEDAI score of 5 or more versus 0 ($p = 0.0077$). The rate of incident depression in patients with SLE with current cutaneous SLE activity was 1.5 times higher than in those without ($p = 0.0031$). Moreover, the rate of incident depression in patients with SLE with cutaneous SLE activity over the last 12 months was also 1.5 times higher than in those without ($p = 0.027$). In contrast, there was no significant association between depression and either musculoskeletal activity or renal SLE ($p > 0.05$).

Association between NPSLE symptoms and depression in the univariate analysis. Of the 282 incident depressions, 183 (65%) occurred in the absence of other neuropsychiatric conditions within the same period of observation. As noted in Table 4, the rate of incident depression in the months after onset of longitudinal myelitis was 4 times higher than in the other months without a history of myelitis ($p = 0.0064$). This finding is based on 8 patients with longitudinal myelitis in our cohort, of whom 4 developed depression. We found no association between depression and prior history of any other neuropsychiatric disorders, including seizure, psychosis, organic brain syndrome (encephalopathy), aseptic meningitis, stroke, SLE headache, mononeuritis multiplex, cognitive impairment, cranial or peripheral neuropathy ($p > 0.05$). Abnormal brain computed tomography (CT) and magnetic resonance imaging (MRI) scans were also not associated with depression ($p > 0.05$; Table 4).

Association of SLE immunological markers and SLE medication use with depression in the univariate analysis. As noted in Table 5, we found no significant association between depression and lower C3/C4, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, aCL, or lupus anticoagulant. The rate of incident depression during months with low C3 was 1.3 times higher than during those without low C3, but it did not quite reach statistical significance ($p = 0.066$). Notably, the rate of incident depression increased significantly as the dose of current prednisone increased. Among those taking 20–39 mg/day, the rate of incident depression was 2.3 times higher than the rate among those not taking prednisone ($p = 0.0002$). Among those taking 40 or more mg/day, the rate was increased by a factor of 3.1 ($RR = 3.1$, $p = 0.0001$). Hydroxychloroquine or immunosuppressive drug use was not associated with and was not protective against depression (Table 5).

Multivariable analyses of independent predictors of incident depression in the Hopkins Lupus Cohort. To tease out the relative importance of correlated risk factors, we fit multivariable models that estimated the association between risk factors and depression, controlling for other variables. In separate multivariate analyses, we found the following results: (1) age was not a significant predictor of depression after controlling for SLE duration; (2) global disease activity (SELENA-SLEDAI) was not a significant predictor after controlling for prednisone use; (3) education and income were strongly related to each other, and neither was a significant predictor after adjusting for the other; and (4) smoking was not a significant predictor after controlling for education and/or income. Thus, in a single full multivariable model, we did not include age, SELENA-SLEDAI, education, and smoking. Estimates from the final multivariate model are shown in Table 6. We found that the rate of incident depression appeared to decline as the time since SLE diagnosis increased ($RR = 0.7$, $p = 0.0006$). East Asians had a significantly lower rate of depression ($RR = 0.1$, $p = 0.031$). The incidence of depression declined within recent cohort years ($RR = 0.6$, $p = 0.0008$). Notably, disability ($RR = 1.4$, $p = 0.034$), cutaneous activity ($RR = 1.7$, $p = 0.0008$), history of myelitis ($RR = 4.5$, $p = 0.0033$), and prednisone

Table 2. Relationship between demographic factors and incident episodes of depression in the Hopkins Lupus Cohort.

Subgroup	Incident Episodes of Depression	Person-yrs of Followup	Rate of Depression Events Per 1000 Person-yrs	RR [1], 95% CI	p
All	282	9487	29.7		
Age, yrs					
18–39	152	4694	32.4	1.0 (Ref. Group)	
40–49	72	2416	29.8	0.9 (0.7, 1.2)	0.56
50–59	40	1513	26.4	0.8 (0.6, 1.2)	0.25
60–69	15	678	23.2	0.7 (0.4, 1.2)	0.22
70+	3	216	13.9	0.4 (0.1, 1.3)	0.15
Sex					
Female	262	8780	29.8	1.0 (Ref. Group)	
Male	20	707	28.3	0.9 (0.6, 1.5)	0.82
Ethnicity					
White	152	4760	31.9	1.0 (Ref. group)	
African American	121	4147	29.2	0.9 (0.7, 1.2)	0.45
East Asian	1	335	3.0	0.1 (0.01, 0.7)	0.018
Other	8	245	32.7	1.0 (0.5, 2.1)	0.95
Education					
< High school	37	1044	35.5	1 0 (Ref. Group)	
High school	86	2919	29.5	0.8 (0.6, 1.2)	0.35
Some college	80	2210	36.2	1.0 (0.7, 1.5)	0.92
College graduate	74	3218	23.0	0.6 (0.4, 1.0)	0.031
Combined family income, mean					
< $25,000 US	98	2992	39.9	1.0 (Ref. group)	
$25,000–$60,000	92	2916	38.7	1.0 (0.7, 1.3)	0.80
$60,000–$100,000	47	1774	35.3	0.8 (0.6, 1.1)	0.23
$100,000+	28	1447	28.0	0.6 (0.4, 0.9)	0.014
Disability pension					
No	208	7535	27.6	1.0 (Ref. group)	
Yes	74	1877	39.4	1.4 (1.1, 1.9)	0.0084
Marital status					
Married	136	5109	26.6	1.0 (Ref. group)	
Single	96	3062	31.4	1.2 (0.9, 1.5)	0.22
Separated/divorced	42	1049	40.0	1.5 (1.1, 2.1)	0.021
Widowed	7	240	29.2	1.1 (0.5, 2.4)	0.81
Smoker					
No	155	5783	26.8	1.0 (Ref. group)	
Yes	127	3697	34.4	1.3 (1.0, 1.6)	0.038
Alcohol abuse					
No	255	8808	29.0	1.0 (Ref. group)	
Yes	27	668	40.4	1.4 (0.9, 2.1)	0.099
Insurance type					
Private	211	7193	29.3	1.0 (Ref. group)	
Medical assistance	54	1872	28.9	1.0 (0.7, 1.3)	0.91
None	13	350	37.1	1.3 (0.7, 2.2)	0.41
Calendar year					
1987–1995	48	1513	31.7	1.0 (Ref. group)	
1996–2004	140	3539	39.6	1.2 (0.9, 1.7)	0.19
2005–2013	94	4435	21.2	0.7 (0.5, 0.9)	0.023

[1] The rate ratio (RR) stands for the ratio of rates in one group relative to another group.

(RR = 2.0, p = 0.0006) were independently associated with a higher risk of incident depression (Table 6).

DISCUSSION

Depression is frequent in SLE. We observed an incidence rate of 29.7 episodes of depression per 1000 person-years. This rate is substantially higher than the rate reported of 15.9 cases per 1000 person-years based on a study by Eaton, *et al*[30] of 4 urban sites in the United States (1 of which was Baltimore).

In multivariable analyses, we found that the rate of incident depression was higher within the first 3 years of diagnosis of SLE, after periods of cutaneous disease activity, with current prednisone use, and among those with

Table 3. Relationship between SLE–related disease activities or symptoms and incident episodes of depression in the Hopkins Lupus Cohort.

Subgroup	Incident Episodes of Depression	Person-yrs of Followup	Rate of Events Per 1000 Person-yrs	RR, 95% CI	p
Duration of SLE, yrs					
0–3	84	1715	49.0	1.0 (Ref. group)	
3–6	55	1810	30.4	0.6 (0.4,0.9)	0.0058
6–10	61	2054	29.7	0.6 (0.4,0.8)	0.0029
10–15	36	1743	20.7	0.4 (0.3,0.6)	< 0.0001
15+	46	2164	21.3	0.4 (0.3,0.6)	< 0.0001
Age of diagnosis					
< 40	212	2736	29.3	1.0 (Ref. group)	
40–49	43	1454	29.6	1.0 (0.7,1.4)	0.96
50–59	19	562	33.8	1.2 (0.7,1.8)	0.55
60+	7	212	33.1	1.1 (0.5,2.4)	0.75
Current SLEDAI					
0	87	3364	25.9	1.0 (Ref. group)	
1–2	77	2202	35.0	1.4 (1.0, 1.8)	0.053
3–4	54	1564	34.5	1.3 (1.0, 1.9)	0.095
5+	53	1289	41.1	1.6 (1.1, 2.2)	0.0077
Average SLEDAI last 12 mos[1]					
0	28	1273	22.0	1.0 (Ref. group)	
0–2	39	2042	19.1	0.9 (0.5, 1.4)	0.57
2–5	84	2490	33.7	1.5 (1.0, 2.4)	0.050
5+	23	875	26.3	1.2 (0.7, 2.1)	0.053
Current physical global assessment					
0	83	2950	28.1	1.0 (Ref. group)	
0–1	78	2563	30.4	1.1 (0.8, 1.5)	0.62
1–1.5	62	1609	38.5	1.4 (1.0, 1.9)	0.061
1.5+	48	1302	36.9	1.3 (0.9, 1.9)	0.14
Average physical global assessment last 12 mos[1]					
0	17	786	21.6	1.0 (Ref. group)	
0–1	122	4495	27.1	1.3 (0.8, 2.1)	0.38
1–1. 5	26	895	29.1	1.3 (0.7, 2.5)	0.34
1.5+	9	514	17.5	0.8 (0.4, 1.8)	0.61
SLICC damage score					
0	112	3979	28.1	1.0 (Ref. group)	
1–2	121	3729	32.4	1.2 (0.9, 1.5)	0.28
3–5	46	1463	32.5	1.1 (0.8, 1.6)	0.53
6+	3	316	9.5	0.3 (0.1, 1.1)	0.063
Musculoskeletal activity[2]					
None	249	7841	31.8	1.0 (Ref. group)	
Some	22	583	37.8	1.2 (0.8, 1.8)	0.44
Musculoskeletal activity[2] in last 12 mos[1]					
None	138	5582	24.7	1.0 (Ref. group)	
Some	36	1006	32.5	1.3 (0.9, 1.9)	0.14
Cutaneous SLE activity[3]					
None	205	6952	29.6	1.0 (Ref. group)	
Some	66	1473	44.8	1.5 (1.2, 2.0)	0.0031
Cutaneous SLE activity[3] in last 12 mos[1]					
None	97	4267	22.7	1.0 (Ref. group)	
Some	77	2420	31.8	1.5 (1.0, 1.9)	0.027
Renal involvement					
None	157	4934	31.8	1.0 (Ref. group)	
Proteinuria[4]	56	2044	27.4	0.9 (0.6, 1.2)	0.34
Nephrotic syndrome	29	896	32.4	1.0 (0.7, 1.5)	0.93
Renal insufficiency	28	1085	25.8	0.8 (0.5, 1.2)	0.31
ESRD	12	527	22.8	0.7 (0.4, 1.3)	0.26
Sjögren syndrome					
No	225	7644	29.4	1.0 (Ref. group)	
Yes	40	1364	29.3	1.0 (0.7, 1.4)	0.98

[1] Unknown and not included in the analysis for followup that occurred within the first year of cohort participation. [2] Based on SLEDAI items (arthritis, myositis). [3] Based on SLEDAI items (new rash, alopecia, mucosal ulcers). [4] Proteinuria, urine dipstick protein (3+). SLE: systemic lupus erythematosus; RR: rate ratio; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics; ESRD: endstage renal disease.

Table 4. Relationship between neurologic manifestation of SLE and incident episodes of depression in the Hopkins Lupus Cohort.

Subgroup	Incident Episodes of Depression	Person-yrs of Followup	Rate of Events Per 1000 Person-yrs	RR[1], 95% CI	p
Any neuropsychiatric disorder (other than depression)					
No	183	6162	29.7	1.0 (Ref. group)	
Yes	99	3324	29.8	1.0 (0.7, 1.3)	0.98
Seizure					
No	259	8831	29.3	1.0 (Ref. group)	
Yes	23	652	35.3	1.2 (0.8, 1.8)	0.39
Psychosis					
No	277	9225	30.0	1.0 (Ref. group)	
Yes	5	261	19.1	0.6 (0.3, 1.5)	0.32
Organic brain syndrome (encephalopathy)					
No	269	9142	29.4	1.0 (Ref group)	
Yes	13	345	37.7	1.3 (0.7, 2.2)	0.38
Aseptic meningitis					
No	275	9324	29.5	1.0 (Ref. group)	
Yes	7	162	43.1	1.5 (0.7, 3.1)	0.32
Stroke					
No	260	8943	29.1	1.0 (Ref. group)	
Yes	21	528	39.8	1.4 (0.9, 2.1)	0.17
SLE headache					
No	254	8617	29.5	1.0 (Ref. group	
Yes	27	869	31.1	1.1 (0.7, 1.6)	0.79
Mononeuritis multiplex					
No	279	9414	29.6	1.0 (Ref. group)	
Yes	3	73	41.1	1.4 (0.4, 4.3)	0.57
Cognitive impairment					
No	272	9112	29.9	1.0 (Ref. group)	
Yes	10	366	27.4	0.9 (0.5, 1.7)	0.79
Cranial or peripheral neuropathy					
No	256	8896	28.8	1.0 (Ref. group)	
Yes	24	570	42.1	1.5 (1.0, 2.2)	0.074
Longitudinal myelitis					
No	278	9452	29.4	1.0 (Ref. group)	
Yes	4	34. 5	115.9	4.0 (1.5, 10.7)	0.0064
Abnormal CT of the brain					
No	262	8983	29.2	1.0 (Ref. group)	
Yes	20	503	39.8	1.4 (0.9, 2.2)	0.18
Abnormal MRI of the brain					
No	245	8096	30.3	1.0 (Ref. group)	
Yes	37	1391	26.6	0.9 (0.6, 1.2)	0.46

[1] The rate ratio (RR) stands for the ratio of rates in one group relative to another group. SLE: systemic lupus erythematosus; MRI: magnetic resonance imaging; CT: computed tomography.

a history of longitudinal myelitis. It was lower among those who were East Asian or had high socioeconomic status.

Our results showed that depression tended to occur early in the course of SLE. A similar finding was observed with seizure in SLE[31]. The incidence of depression might decline later in the course of SLE as a result of better control of disease activity, less prednisone use, and increased ability to cope over time.

We observed a decline in the incidence of first depression occurrence with older age. Our findings suggest that older patients with SLE who have not had a prior episode of depression are at relatively low risk of developing a first occurrence of depression. Because we were describing incidence of a first episode of depression, it should be noted that this does not imply that depression was less frequent or less prevalent among older patients in our cohort. Also, in this cohort, the association between incidence of depression and younger age appears to be explained by the fact that the rates of depression are highest in the years close to the diagnosis of SLE.

Consistent with a prior study[32], we found that depression was independently associated with disability in patients with SLE. A previous study showed that patients with SLE and work disability were more likely to have depression, fibromyalgia, and arthralgia[32]. Our multivariate analysis confirmed that disability was associated with depression[10].

Table 5. Relationship between immunologic variables, medication use, and incident episodes of depression in the Hopkins Lupus Cohort.

Subgroup	Incident Episodes of Depression	Person-yrs of Followup	Rate of Events Per 1000 Person-yrs	RR, 95% CI	p
Current low C3					
No	196	6471	30.3	1.0 (Ref. group)	
Yes	74	1902	38.9	1.3 (1.0, 1.7)	0.066
Ever low C3					
No	103	3425	30.1	1.0 (Ref. group)	
Yes	179	6062	29.5	1.0 (0.8, 1.3)	0.88
Current low C4					
No	221	6896	32.0	1.0 (Ref. group)	
Yes	49	1475	33.2	1.0 (0.8, 1.4)	0.82
Ever low C4					
No	124	4374	27.4	1.0 (Ref group)	
Yes	158	5112	30.9	1.1 (0.9, 1.4)	0.47
Current anti-dsDNA					
No	191	6089	31.4	1.0 (Ref. group)	
Yes	80	2261	35.4	1.1 (0.9, 1.5)	0.36
Ever anti-dsDNA					
No	93	2669	34.8	1.0 (Ref. group)	
Yes	189	2261	27.7	0.8 (0.6, 1.0)	0.071
Anti-Sm					
No	221	7704	28.7	1.0 (Ref. group)	
Yes	57	1699	33.6	1.2 (0.9, 1.6)	0.29
Anti-RNP					
No	201	7017	28.6	1.0 (Ref. group)	
Yes	77	2387	32.3	1.1 (0.9, 1.5)	0.38
Anti-Ro					
No	196	6594	29.7	1 0 (Ref. group)	
Yes	81	2800	28.9	1.0 (0.8, 1.3)	0.84
Anti-La					
No	240	8227	29.2	1.0 (Ref. group)	
Yes	37	1164	31.8	1.1 (0.8, 1.5)	0.63
Anticardiolipin					
No	118	3751	31.5	1.0 (Ref. group)	
Yes	157	5566	28.2	0.9 (0.7, 1.1)	0.37
Lupus anticoagulant					
No	183	6330	28.9	1.0 (Ref. group)	
Yes	92	3063	30.0	1.0 (0.8, 1.3)	0.76
Current prednisone dose					
None	124	4373	28.4	1.0 (Ref. group)	
1–9	66	2282	28.9	1.0 (0.8, 1.4)	0.90
10–19	45	1218	36.9	1.3 (0.9, 1.8)	0.13
20–39	24	374	64.3	2.3 (1.5, 3.5)	0.0002
40+	13	150	86.5	3.1 (1.7, 5.4)	0.0001
Mean prednisone dose last 12 mos[1]					
None	74	3062	24.2	1.0 (Ref group)	
1–9	65	2399	27.1	1. 1 (0. 8, 1.6)	0.50
10–19	37	904	40.9	1.7 (1.1, 2. 5)	0.0089
20+	12	220	54.6	2.5 (1.3, 4.5)	0.0038
Current hydroxychloroquine					
No	102	3001	31.4	1.0 (Ref. group)	
Yes	170	5415	30.2	0.9 (0.7, 1.2)	0.53
Hydroxychloroquine over last 12 mos[1]					
None	56	1857	30.2	1.0 (Ref. group)	
Some	29	917	31.6	1.0 (0.7, 1.6)	0.84
Always	103	3826	26.9	0.9 (0.6, 1.2)	0.49
Current immunosuppressant use					
No	195	5980	32.6	1.0 (Ref. group)	
Yes	77	2435	31.6	1.0 (0.7, 1.3)	0.82
Mean immunosuppressant use last 12 mos[1]					
None	116	4281	27.1	1.0 (Ref. group)	
Some	25	732	34.2	1.3 (0.8, 1.9)	0.29

[1] Unknown and not included in the analysis for followup that occurred within the first year of cohort participation. C3: complement factor 3; C4: complement factor 4; RR: rate ratio.

Table 6. Independent predictors of incident depression in the Hopkins Lupus Cohort based on a multivariate model.

Variables	Comparison	Adjusted RR, 95% CI	p
Time since SLE diagnosis	Per 10-yr difference	0.7 (0.5, 0.9)	0.0006
Ethnicity	East Asian vs others	0.1 (0.01, 0.8)	0.031
Disability	Yes vs no	1.4 (1.0, 1.8)	0.034
Income	Combined Income > 100,000	0.7 (0.5, 1.1)	0.15
Year of enrollment	Year after 2005	0.6 (0.5, 0.8)	0.0008
Cutaneous activity	Some vs none	1.7 (1.2, 2.2)	0.0008
History of longitudinal myelitis	Yes vs no	4.5 (1.6, 12.2)	0.0033
High dose of prednisone	20 mg/day+ vs less	2.0 (1.3, 2.9)	0.0006

RR: rate ratio; SLE: systemic lupus erythematosus.

Depression was also associated with disability in systemic sclerosis[33] and multiple sclerosis[34].

We found that East Asians had a significantly lower rate of depression compared with other ethnicities. To our knowledge, this is the first study to find this protective effect of East Asian ethnicity in SLE. The findings of a protective effect of East Asian ethnicity will require independent confirmation, because the East Asian ethnic subgroup in our cohort was small (< 8%) compared to the white and African American groups, and there was only 1 incident depression event in the East Asian group. However, our finding is supported by other studies that found a lower level of depression in East Asians with rheumatoid arthritis (RA)[35] and in the general population[36,37,38,39]. Cross-national comparative community studies found that the prevalence of lifetime depression in Taiwan and Korea was 1.5% and 2.9%, respectively, as opposed to 5.2% in the United States[36]. One study examined data from 10 countries and found that East Asian countries reported the lowest rates (3.0% in Japan), while Western countries reported the highest prevalence of depression (16.9% in the United States)[37]. Pacific Islanders were 3 times more likely to have severe or moderately severe depression compared to East Asians (4.8% vs 1.5%)[38]. The reduced incidence of depression in East Asian patients with SLE, both in our study and in other non-SLE studies cited, might be related to cultural factors affecting the likelihood of acknowledging depression. East Asians who have depression could be less likely to have the disorder detected and treated, which may result in a lower prevalence of depression. However, genetic, biologic, social, and other causative factors require further study[40].

Prior research[19] showed an association of depression with other symptoms and signs in patients with SLE. The most significant variables associated with depression were pain and arthritis[19]. In our cohort, cutaneous SLE activity was an independent predictor of incident depression in SLE, but we did not observe a strong association between depression and musculoskeletal activity, renal SLE, or global disease activity, after adjustment for corticosteroid exposure in multivariate analysis. The reasons that cutaneous manifestations are most strongly related to depression are unclear. It is possible that cutaneous SLE activity (or sequelae thereof) could lead to psychosocial stress as a precipitant of depression.

We found that longitudinal myelitis was independently associated with a higher risk of incident depression. The independent effect of longitudinal myelitis on depression was based on 4 cases of depression in 8 patients with myelitis. Because myelitis is so rare in SLE, it will be difficult to independently confirm our finding. This statistically significant finding is the first documentation of the association of longitudinal myelitis and depression, although an association of depression with other neuropsychiatric SLE manifestations was found in several studies[3,8,15,17]. Hanly, *et al*[15] found that patients with SLE with neuropsychiatric syndromes reported more symptoms of depression compared to patients with RA with neuropsychiatric syndromes[15]. Patients with SLE with clinical evidence of recent or previous central nervous system disorder scored significantly higher (more pathology) than did other patients with SLE on the subscales that measure psychotic depression[41]. Utset, *et al* found that some types of neuropsychiatric SLE (such as seizures, psychosis, aseptic meningitis, poorer cognitive function, and encephalopathy) were independently associated with depression[8]. Lim, *et al*[4] failed to find a significant association between current and previous neurological disease and psychiatric symptoms.

Depression in the general population (in particular, major depression) has been shown to be accompanied by signs of an immune response and cell-mediated immune activation[42], which include increased serum levels of soluble CD8 molecule, interleukin 1 (IL-1)-β, the soluble IL-2 receptor, tumor necrosis factor-α, increased numbers of T cell activation markers such as CD3+CD25+, and higher neopterin[42]. In our study, depression was associated only with myelitis and cutaneous activity, and not global activity, serologic activity, or aPL. We found that abnormalities in MRI or CT scans were not associated with depression, confirming a previous study[4].

The association of disease activity with depression had been previously investigated with conflicting results. Although some prior studies found an association between depression and SLE disease activity[7,10,13], other studies found no relation between disease activity and depression[4,6,11,18,20]. In our univariate analysis, we found an association of disease activity with depression. However, our multivariable analysis concluded that SLE disease activity was not a significant independent predictor after

controlling for prednisone use, which was consistent with the majority of the prior studies[4,6,11,18,20].

The most striking finding in our study was the association of incident depression in SLE with prednisone, in a dose-dependent manner. The effect of corticosteroids on mood (including depression) has been well recognized and suggested to be dose-dependent to some extent in non-SLE disease[43,44,45,46]. The Boston Collaborative Drug Surveillance Program examined psychiatric symptoms in 676 patients free of psychiatric disease prior to steroid treatment and found that severe psychiatric symptoms (psychosis, profound depression, mania) were less frequent (1.3%) at doses of < 40 mg of prednisone daily, but increased to 18.4% at doses > 80 mg of prednisone daily[44], strongly suggesting that these psychiatric symptoms are dose-dependent. Naber, *et al* found that 10% of 50 ophthalmologic patients developed depression after receiving high doses of corticosteroids (methylprednisolone and fluocortolone at doses of 119 ± 41 mg/day at baseline and 75 ± 22 mg after 8 days of treatment)[45]. Compared with short-term higher prednisone therapy, longterm therapy might be more associated with depressive than with manic symptoms[47,48].

However, previous studies have been inconsistent with respect to the association of corticosteroids and depression in SLE. In a study of 70 patients, Nery, *et al* found that patients with SLE with major depression did not differ significantly from patients without major depression based on the mean dose of prednisone[10]. In fact, Denburg, *et al* found actual improvement in mood following exposure to corticosteroid use (a dose of 0.5 mg/kg of prednisone daily for at least 6 months), but that small study included only 10 women with SLE[49]. In contrast, Shah, *et al* found an association of depression with corticosteroid use in a retrospective study of claims data in 2717 patients with SLE ($p = 0.0443$)[24]. Karol, *et al* found that a current prednisone dose higher than 7.5 mg per day was perhaps associated with depression in patients with SLE, although the association did not reach statistical significance ($p = 0.07$)[19]. Our findings showed that current prednisone therapy was associated with incident depression in a dose-dependent manner, with the statistical effect of current prednisone dose seen at or above 20 mg/day. Because these higher doses of prednisone are generally used in patients with SLE with higher disease activity, especially renal, central nervous system, and hematologic involvement, our results reinforce the need for noncorticosteroid approaches to control SLE activity, to avoid inducing depression.

The mechanism of the association of depression and corticosteroid use is not well understood. Compared with controls of similar age, sex, ethnicity, education, height, and medical history, the patients treated with corticosteroid may have lower N-acetyl aspartate ratios (a putative marker of neuronal viability) and smaller hippocampal volumes, and greater depressive symptom severity[48]. Increased levels of glucocorticoid hormones — the main product of the hypothalamic pituitary adrenal (HPA) axis — have been considered "depressogenic". Abnormalities of the HPA axis with hypercortisolemia and elevated plasma cortisol concentrations are found in patients with major depressive disorder, and the effect of corticosteroids on the HPA axis might be a mechanism that induces depression[50].

We did not find any association of SLE autoantibodies or of low complement with depression. In previous studies, depression has been linked to anti-P[16]. We could not address anti-P, as it was not part of our cohort protocol. In spite of an association of aPL with seizures and headache, Sanna, *et al* similarly found no association between aPL and depression[23], which was consistent with our results.

A limitation of our study was that some of the major findings were based on very small numbers of actual events (such as East Asian ethnicity and longitudinal myelitis). In addition, our case finding was based on the ACR neuropsychiatric case definition and not on a prospective DSM-IV interview at every visit. The strengths of our study, including large size, the standardized approach to data collection, and the prospective multiethnic cohort analyses, enabled us to estimate the incidence rate of first occurrence of depression, to assess risk factors before the onset of depression, and to detect the important association with prednisone.

Our results showed that depression in SLE was multifactorial. Depression usually occurred early in the course of SLE, in patients with non-East Asian ethnicity, and was independently associated with prior cutaneous lupus and myelitis activity. Current prednisone therapy was associated with incident depression in a dose-dependent manner. Our findings may help to guide prevention of and management of depression in SLE.

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