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ORIGINAL ARTICLE

Systemic lupus erythematosus and thyroid disease: A 10-year study

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KEYWORDS
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Background: This large-scale study aims to analyze the association of systemic lupus erythematosus (SLE) with thyroid diseases.
Methods: In this retrospective, nationwide cohort study, 1633 newly diagnosed SLE patients from the National Health Insurance Research Database in 2000 were examined and data on patients with diagnoses of hyperthyroidism, hypothyroidism, and autoimmune thyroiditis were collected from 2000 to 2009. We subdivided these SLE patients by the presence of overlap syndrome. Comparison with 6532 age- and sex-matched controls was performed.
Results: The cumulative incidence of thyroid disease in SLE patients was lower than in controls (8.1% vs. 16.9%, $p < 0.001$). Among SLE patients, 39.7% had overlap syndrome. The overlap syndrome group had a higher cumulative incidence of thyroid diseases (10.96% vs. 4.57%, $p < 0.0001$), hypothyroidism (3.86% vs. 1.93%, $p = 0.017$), and autoimmune thyroiditis (4.63% vs. 0.71%, $p < 0.0001$) than SLE patients without overlap syndrome. Comparing the data with the non-SLE-matched control group by logistic regression model revealed a decreased risk of thyroid diseases with odds ratios (ORs) of 0.25 and 0.62 [95% confidence interval (CI) 0.18–0.33, 0.48–0.80], and hyperthyroidism with ORs of 0.21 and 0.30 (95% CI 0.14–0.31, 0.20–0.45) in SLE patients without and with overlap syndrome. SLE patients without overlap syndrome had a lower risk of hypothyroidism with an OR of 0.53 (95% CI 0.53–0.86) and autoimmune thyroiditis with an OR of 0.26 (95% CI 0.12–0.56). SLE patients with overlap syndrome showed a similar risk of hypothyroidism with an OR of 0.92 (95% CI 0.66–1.53) and a higher risk of autoimmune thyroiditis with OR of 1.69 (95% CI 1.14–2.51).

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Conclusion: SLE patients had a significantly lower rate of thyroid diseases and hyperthyroidism than matched controls. Among SLE patients, risks of hypothyroidism and autoimmune thyroiditis were different in the presence of overlap syndrome. This finding is novel and important for clinical practices.

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease characterized by the production of autoantibodies and chronic inflammation of numerous organs and tissues, including the thyroid gland.[1–6] Prevalence of SLE varies according to age, sex, and geographical differences of the studied population, with reported prevalence rates ranging from 12.5 to 50.8/100,000 persons.[1] One important aspect of SLE morbidity is organ damage and the association of SLE with thyroid disease has been reported by several studies with a wide range of variability.[3–12] Most papers concord that thyroid disease appears to be more frequent in SLE patients than in the general population, but contradictory results exist as to whether hyperthyroidism or hypothyroidism is more commonly associated.[3] Even among studies regarding SLE-associated hypothyroidism, a wide range of variability from 4% to 21% has been documented.[4] One of the reasons for such variability could be due to the smaller sample group studied. Thus, this large-scale study aims to evaluate the prevalence of hyperthyroidism, hypothyroidism, and autoimmune thyroiditis among SLE patients in Taiwan.

Materials and methods

This study was based on data released from the National Health Insurance Research Database (NHIRD) in Taiwan. The National Health Insurance program was started in 1995 with the aim of providing health-care finance for all residents; currently, there are more than 25 million enrollees in the program, representing approximately 99% of Taiwan's entire population. The NHIRD provides a wide range of information, including ambulatory care and inpatient care files, as well as registration records, including the demographic data of the insured. The diagnostic code in the database is based on the system used by the International Classification of Diseases, 9th Revision, Clinical Modifications (ICD-9-CM). For privacy protection, the identities of the patients, physicians, and institutions were scrambled in accordance with the Personal Electronic Data Protection Law.

Data on enrollees with SLE (ICD-9 710.0) were obtained from the Registry of Catastrophic Illness Database, which is a subdivision of the NHIRD. These enrollees have all received a catastrophic illness certificate that grants exemption from co-payment. The certificate is provided only after thorough examination of medical records, laboratory and image studies by at least two specialists and only for those who meet the criteria of these diseases.

Data on enrollees with hyperthyroidism (ICD-9 code 242.9), hypothyroidism (ICD-9 code 244.8, 244.9), thyroiditis, subacute and chronic (ICD-9 code 245.1, 245.2, 245.3, 245.8, 245.9), and autoimmune thyroiditis (ICD code 245.2), scleroderma (ICD-9 code 710.1), Sjögren's syndrome (SS; ICD-9 code 710.2), dermatomyositis (ICD-9 code 710.3), polymyositis (ICD-9 code 710.4), and rheumatoid arthritis (RA; ICD-9 code 714) were obtained from the NHIRD. Patients identified were required to have at least one primary or secondary diagnosis of these diseases in at least one hospital admission or three outpatient department visits. Among those identified with thyroid diseases, further subdivisions were classified according to treatments received. Treatment code used were those for thyroidectomy (ICD-9 code 06.3x, 06.4x, 06.5x, 06.6x); I-131 ablation therapy (NHIRD treatment code 26038A, 26038B); antithyroid medication including carbimazole and propylthiouracil (NHIRD drug code A005290100, A017504100, A026328100, A0263281G0, A033933100, B013004100, A043335100, A0433351G0, N007870100); and thyroxin supplements (NHIRD drug code A036236100, AC48191100, AC481911G0, B024708100).

We recruited 1633 patients newly diagnosed as SLE in 2000, and followed their data up to the end of 2009. The 6532 controls who were matched by age and sex were sampled.

The number and percentage of age group and sex were determined for both SLE patients and controls. The prevalence and incidence of hyperthyroidism, hypothyroidism, thyroiditis (subacute and chronic), and chronic lymphocytic thyroiditis were also calculated. In addition, the Chi-square test was used to compare the difference of those diseases between SLE patients and controls. In SLE patients, overlap syndrome was also described by percentage. The odds ratio (OR) and 95% confidence interval (CI) were used to estimate the risk of thyroid diseases in SLE patients with or without overlap syndrome by comparing the data with controls by logistic regression models. Data retrieval and analysis were performed using SAS version 9.3 (SAS Institute Inc., NC, USA) and the significance level was set at 0.05.

Results

The sex and age distribution of the 1633 newly diagnosed SLE patients and 6532 matched control are shown in Table 1. The majority of SLE patients were female (89.7%) and the total female-to-male ratio was 8:1 (Table 1). In addition, more than half of the newly diagnosed SLE patients were between 20 and 39 years of age.

Prevalence and incidence of hyperthyroidism, hypothyroidism, thyroiditis, and autoimmune thyroiditis among the SLE and control groups are also tabulated in Table 1. The prevalence of these thyroid diseases revealed no difference

between the SLE and control groups in 2000. During the 10 years of follow-up, the total case number of hyperthyroidism in the 1633 SLE patients was 52 (3.2%) compared with 10.9% in the control group ($p < 0.0001$); 51.9% of these required treatment such as thyroidectomy, I-131 ablation, and antithyroid medicine ($p < 0.0001$). Hypothyroidism in the SLE patients accounted for 2.7%, and it was 3.5% in the control group ($p = 0.115$). The majority (97.7%) of these patients received thyroxin replacement therapy. The cumulative incidence of thyroiditis (subacute and chronic) was 2.3% and 2.5% in the SLE and control groups, respectively ($p = 0.545$); autoimmune thyroiditis was 2% and 1.5% in these two groups ($p = 0.66$). From Table 1, it can be seen that there are no differences in the prevalence or incidence of hypothyroidism, thyroiditis (subacute and chronic), or autoimmune thyroiditis in 2000 and in the subsequent 9 years between the SLE and control groups. There was also no difference in the prevalence or incidence of hyperthyroidism in 2000. However, the control group had much higher cumulative incidence of hyperthyroidism from 2001 to 2009 than the SLE group ($p < 0.00001$).

In the SLE group, coexistence of these three thyroid diseases was noted, as shown in Fig. 1. Coexisting thyroiditis was found in 15.9% of patients in the SLE group with hypothyroidism; and in 9.6% of patients in the SLE group with hyperthyroidism. Eight patients had both hyperthyroidism and hypothyroidism, which was due to hyperthyroidism therapy.

Table 1 Comparison of hyperthyroidism, hypothyroidism, thyroiditis (subacute and chronic), and chronic lymphocytic thyroiditis among SLE patients and the general population from 2000 to 2009

Variable	SLE ($n = 1633$)		Non-SLE ($n = 6532$)		p for χ^2 test
	n	(%)	*n*	(%)	
Age at entry, y					
Mean ± SD	34.9 ± 14.8		35.2 ± 15.0		0.493
<10	13	0.8	52	0.8	1.000
10–19	231	14.2	924	14.2	
20–29	454	27.8	1816	27.8	
30–39	407	24.9	1628	24.9	
40–49	276	16.9	1104	16.9	
50–59	127	7.8	508	7.8	
60–69	93	5.7	372	5.7	
≥70	32	2.0	128	2.0	
Sex					
Female	1464	89.7	5856	89.7	1.000
Male	169	10.4	676	10.4	
Hyperthyroidism (242.9)					
Prevalence case (2000)	29	1.8	162	2.5	0.092
Incidence case (2000)	19	1.2	75	1.2	0.959
Incidence case (2000–2009)	52	3.2	710	10.9	<0.0001
Incidence case (2001–2009)	33	2.0	635	9.7	<0.0001
Case number with treatment (2000–2009)	27	1.7	540	8.3	<0.0001
Hypothyroidism (244.8, 244.9)					
Prevalence case (2000)	19	1.2	50	0.8	0.116
Incidence case (2000)	9	0.6	29	0.4	0.569
Incidence case (2000–2009)	44	2.7	227	3.5	0.115
Incidence case (2001–2009)	35	2.1	198	3.0	0.054
Case number with treatment (2000–2009)	43	2.6	197	3.0	0.413
Thyroiditis (subacute and chronic) (245.1, 245.2, 245.3, 245.8, 245.9)					
Prevalence case (2000)	13	0.8	33	0.5	0.160
Incidence case (2000)	8	0.5	17	0.3	0.133
Incidence case (2000–2009)	38	2.3	165	2.5	0.545
Incidence case (2001–2009)	30	1.8	148	2.3	0.224
Case number with treatment (2000–2009)	0	0.0	20	0.3	0.0252
Chronic lymphocytic thyroiditis (245.2)					
Prevalence case (2000)	11	0.7	23	0.4	0.071
Incidence case (2000)	7	0.4	14	0.2	0.126
Incidence case (2000–2009)	32	2.0	140	2.1	0.644
Incidence case (2001–2009)	24	1.5	100	1.5	0.856
Case number with treatment (2000–2009)	0	0.0	4	0.1	0.317

SLE = systemic lupus erythematosus; SD = standard deviation.

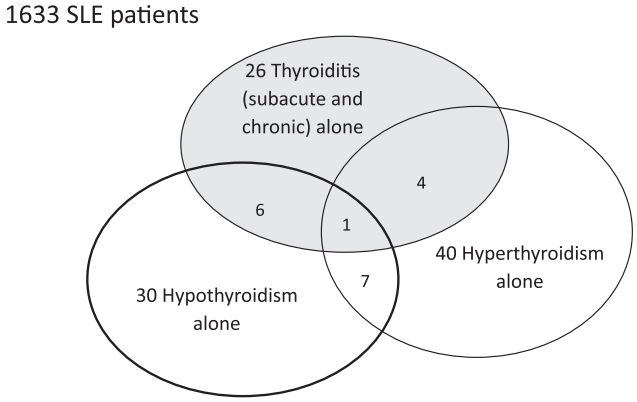

Figure 1. Number of coexistent thyroid diseases among systemic lupus erythematosus (SLE) patients.

A total of 648 (39.7%) SLE patients fulfilled the diagnosis criteria of overlap syndrome in this database. The most commonly associated diagnoses were SS ($n = 449$), followed by RA ($n = 240$), scleroderma ($n = 75$), dermatomyositis ($n = 29$), and polymyositis ($n = 25$). We found that 137 patients had two diagnoses of autoimmune diseases besides SLE; 15 patients had three diagnoses; and one patient had four diagnoses. The cumulative incidence of thyroid diseases in SLE patients with overlap syndrome is shown in Table 2. There were 244 SLE patients younger than the age of 20. Among them, 78 (32%) had overlap syndrome, and SS ($n = 53$) was also the most common association, followed by RA ($n = 27$). These were similar to the SLE adult group. However, the rates of thyroid disease (total), hyperthyroidism, hypothyroidism, thyroiditis (subacute and chronic), and autoimmune thyroiditis were 8.97%, 3.85%, 2.56%, 2.56%, and 1.28% respectively, which were lower than in the SLE adult group.

The comparison of cumulative incidence of thyroid disease, hyperthyroidism, hypothyroidism, and autoimmune thyroiditis from 2000 to 2009 in the control group, SLE group with and without overlap syndrome is summarized in Fig. 2. Both subgroups of SLE had lower rates of thyroid diseases than the control group; the SLE without overlap syndrome subgroup showed an even lower rate of thyroid diseases than the SLE with overlap syndrome subgroup. Both subgroups had lower rate of hyperthyroidism and there was no difference of cumulative incidence between these two subgroups. The subgroup of SLE without overlap syndrome had a lower rate of hypothyroidism than the subgroup of SLE with overlap syndrome and the control group. In terms of thyroiditis (subacute and chronic) and autoimmune thyroiditis, the subgroup of SLE with overlap syndrome showed significantly higher rate than the control group; by contrast, the subgroup of SLE without overlap syndrome had a lower rate than the control group. Table 3 further calculated the OR for thyroid diseases in these three groups.

Discussion

Historically, higher rates of thyroid dysfunction and autoantibodies have been described in patients with autoimmune diseases, including SLE, RA, and SS.[13,14] In this

Table 2 Analysis of patients with SLE overlap syndrome and total thyroid diseases from 2000 to 2009 ($n = 648$)

Condition	SLE ($n = 1633$)	SLE + total thyroid disease ($n = 116$)	SLE + hyperthyroidism ($n = 52$)	SLE + hypothyroidism ($n = 44$)	SLE + thyroiditis (subacute and chronic) ($n = 37$)	SLE + chronic lymphocytic thyroiditis ($n = 32$)
	Case number (%)	Case number (%)	Case number (%)	Case number (%)	Case number (%)	Case number (%)
SLE + scleroderma	75 (100%)	8 (10.33%)	5 (6.67%)	1 (1.33%)	2 (2.67%)	2 (2.67%)
SLE + SS	449 (100%)	56 (12.46%)	16 (3.56%)	21 (4.68%)	27 (6.01%)	21 (4.68%)
SLE + dermatomyositis	29 (100%)	2 (6.90%)	1 (3.45%)	0 (0.00%)	1 (3.45%)	1 (3.45%)
SLE + polymyositis	25 (100%)	3 (12.00%)	1 (4.00%)	2 (8.00%)	0 (0.00%)	0 (0.00%)
SLE + RA	240 (100%)	26 (10.83%)	13 (5.42%)	9 (3.75%)	8 (3.33%)	7 (2.92%)
Total (SLE overlap syndrome)	648 (100%)	71 (10.96%)	25 (3.86%)	25 (3.86%)	30 (4.63%)	24 (3.70%)

RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; SS = Sjögren syndrome.

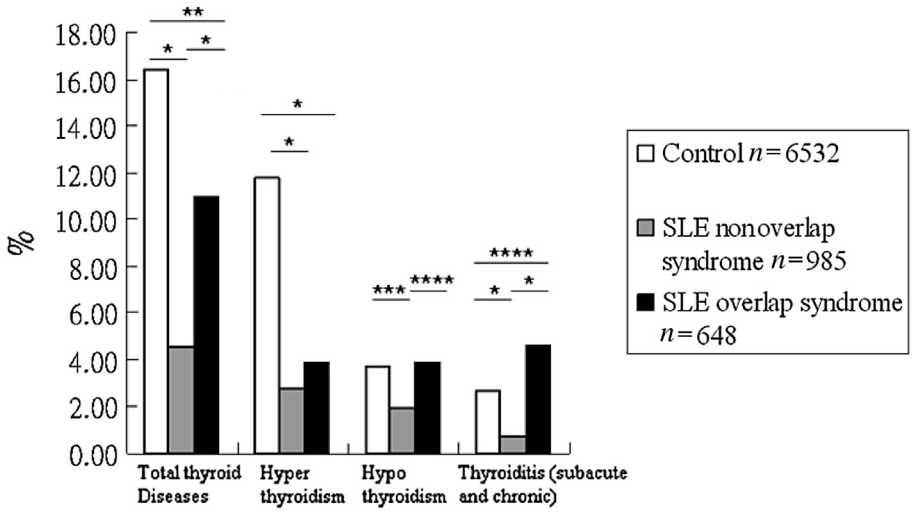

Figure 2. Comparison of total thyroid diseases, hyperthyroidism, hypothyroidism, thyroiditis (subacute and chronic), and chronic lymphocytic thyroiditis in the control, systemic lupus erythematosus (SLE) nonoverlap syndrome, and SLE overlap syndrome groups.

nationwide, cohort study, the overall rate of hyperthyroidism in the SLE group was 3.2%, which is comparable with those found in previous studies,[4,7–9] and the rates of hypothyroidism and autoimmune thyroiditis were lower than previously reported.[3–10] Nevertheless, if we subdivide SLE patients based on the presence or absence of overlap syndrome, we can find significantly higher cumulative incidence of hypothyroidism and autoimmune thyroiditis in those SLE patients with overlap syndrome. In comparison with the control group, SLE patients had a lower cumulative incidence and risk of thyroid diseases and hyperthyroidism, which is different from previous studies summarized in Table 4.[3–5,7–10] One possible explanation is the much higher rate of hyperthyroidism in the control group[15] (64.4% of patients with thyroid disease in the control group had hyperthyroidism). To ascertain the accuracy of these data, we performed an analysis on thyroid diseases among the Taiwanese general population and found the data to be comparable with our control group. Besides, we checked the treatment of thyroid diseases for additional confirmation. Among the 52 patients with both SLE and hyperthyroidism, 51.9% received treatment and 76% of the hyperthyroidism cases in the control group received treatment. In terms of hypothyroidism, 97.7% of SLE patients and 87% of the control group received thyroxin supplements.

A brief review of previous studies revealed high variability with prevalence of hyperthyroidism ranging from 0% to 5.8%, hypothyroidism from 3.9% to 17.4%, and autoimmune thyroiditis from 14% to 46.7%.[3–10] This might be due to the limited case numbers (45—300 patients), differences in statistical analysis, and study designs. Most of these were observational studies performed at various medical centers, and some had control groups for comparison. Diagnoses of thyroid disease were derived mainly from thyroid serology tests. In the 22-year retrospective study performed by Pyne and Isenberg, a larger sample group (n = 300 patients) was recruited and clinical records and laboratory data including thyroid serology results were analyzed. The prevalence of hypothyroidism (5.7%) was reported to be higher than the general population (1%), whereas that of hyperthyroidism (1.7%) was not significantly different.[8] In the Italian study of 213 SLE patients (with 426 sex- and age-matched control groups), it was found that 5.9% of studied female SLE patients had clinical hypothyroidism; OR for subclinical hypothyroidism in female patients with SLE with respect to controls was 4.5 (95% CI, 2.0—4.4) and as high as 34.7% of patients had antithyroid antibodies.[4] In addition, Mader et al attempted to correlate thyroid dysfunction (measured by antithyroid antibodies level) in SLE patients with SLE disease severity as measured by the SLE disease activity index score. However, no association was found. In fact, among the different variables tested in this study, hypothyroidism was the only significant abnormal finding with increased prevalence (11.6%) found in SLE patients as compared with 1.9% of the control group.[5] Our study differs by including a much larger sample size of 1633 SLE patients with 6532 control, and then we longitudinally checked the cumulative incidence up to 10 years, demonstrating a lower incidence of thyroid diseases and hyperthyroidism among SLE patients.

Coexistent thyroid diseases can also occur. It was interesting to note that among the SLE patients with hypothyroidism, 15.9% had coexisting autoimmune thyroiditis, and only 9.6% of SLE patients with hyperthyroidism had coexisting autoimmune thyroiditis. This suggests that in the course of autoimmune thyroiditis, decreased thyroid function is more commonly found.

Clustering of multiple autoimmune diseases has been described.[16–18] At one end are organ-specific diseases such as autoimmune thyroiditis, whereas at the other end are diseases with systemic involvement such as SLE. Specifically related to SLE, previous study results have emphasized that a higher prevalence of polyautoimmunity was found in SLE patients (41%).[16] Our study also revealed a similar trend with 39.7% of SLE patients having polyautoimmunity. Higher association between SLE, SS, and autoimmune thyroiditis was noted in previous studies.[16,18,19] Some authors even considered these three conditions as "chaperones".[19] Previous studies have shown that SLE patients who develop SS

Table 3 Logistic regression analysis of SLE predicting total thyroid disease adjusted for age and sex

Variable	*N*	Total thyroid disease ($n = 1190$)				Hyperthyroidism ($n = 820$)				Hypothyroidism ($n = 285$)				Thyroiditis (subacute and chronic) ($n = 215$)				Chronic lymphocytic thyroiditis ($n = 172$)			
		OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper	
Non-SLE	6532	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—	—	1	—	—	—
SLE nonoverlap syndrome	985	0.245	0.181	0.333	<0.0001	0.211	0.143	0.311	<0.0001	0.533	0.332	0.855	0.0091	0.26	0.122	0.556	0.0005	0.38	0.18	0.77	0.007
SLE overlap syndrome	648	0.617	0.478	0.796	0.0002	0.301	0.2	0.452	<0.0001	1.008	0.662	1.535	0.9708	1.69	1.137	2.511	0.0095	1.74	1.12	2.71	0.014

CI = confidence interval; OR = odds ratio; SLE = systemic lupus erythematosus.

Table 4 Summary of hyperthyroidism, hypothyroidism, and autoimmune thyroiditis diseases in SLE patients from previous studies

Reference (year of publication)	Number of SLE patients	Control group	Study method	Study period	% of hyperthyroidism	% of hypothyroidism	% of patients with antithyroid antibody
Kumar et al (2010)[3]	100	100	Observational	2 y	0	14	30
Antonelli et al (2010)[4]	213	426	Observational cross sectional	—	1.5 (female: $p = 0.01$)	5.9 (female: $p < 0.001$)	34.7 ($p < 0.001$)
Mader et al (2007)[5]	77	52	Observational cross sectional	—	0	11.6% ($p = 0.048$)	23.4
Pyne and Isenberg (2002)[8]	300	—	Retrospective	22 y	1.7	5.7	14
Chan et al (2001)[7]	69	—	Observational cross sectional	—	5.8	17.4	23.2
Tsai et al (1993)[9]	45	—	Observational	1 y	2.2	4.4	46.7
Boey et al (1993)[10]	129	—	Observational cross sectional	—	0.8	3.9	32.2

SLE = systemic lupus erythematosus.

had significantly frequent anti-Ro antibodies[20] and that patients with SLE and anti-Ro antibodies can also develop autoimmune thyroiditis.[20,21] In our study, SS was the most commonly coexisting autoimmune disease in SLE. Nevertheless, other autoimmune diseases, including RA, showed comparable cumulative incidence of thyroid diseases The SLE overlapping with dermatomyositis, polymyositis, or scleroderma had lower rates than other overlapping syndromes in this aspect; however, the rates were much higher than in those SLE patients without overlap syndrome.

In the 1st year of SLE diagnoses the following cases were diagnosed: 36.5% hyperthyroidism, 20.5% hypothyroidism, and 21.6% autoimmune thyroiditis. The incidence of thyroid diseases dropped significantly from the 2nd year of SLE diagnosis, with the average annual incidence rate decreasing to approximately 3% for all thyroid diseases. Systemic conditions, whether acute or chronic, were associated with a significant decrease in serum concentration of total triiodothyronine and free triiodothyronine[22] and could result in disturbed thyroid function. This euthyroid sick syndrome has been described as a functional thyroid disorder in nonthyroidal illness[23] and has been found in patients with various medical and surgical conditions including SLE. This could provide one explanation for increased thyroid diseases found within the initial period of SLE diagnoses. Incidence of thyroid diseases might decrease with SLE treatment; at least, we did not find an increase in the rate of thyroid disease following SLE treatment.

The strengths of our study are its use of population-based data that are highly representative of the general population. However, certain limitations to our findings should be considered. First, this study was based on diagnostic codes released from the NHIRD, and thus, details on thyroid serological tests, presence of thyroid autoantibodies, or SLE autoantibodies were not available. Second, the evidence derived from a retrospective cohort study is generally inferior in statistical quality to that originating from randomized trials because of the potential biases related to adjustments for confounding variables. Despite our meticulous study design and control measures for confounding factors, bias resulting from unknown confounders might have affected our results. However, the data regarding the diagnoses of SLE, thyroid diseases, and autoimmune diseases were nonetheless reliable.

In conclusion, this nationwide, cohort study in SLE patients demonstrated several unique data not published previously. We found that the hyperthyroidism in SLE patients was lower than the matched control group (8.1% vs. 16.9%). SLE patients with overlap syndrome carried a higher risk of hypothyroidism and autoimmune thyroiditis than those SLE patients without overlap syndrome. We suggest that the presence of overlap syndrome should be considered in clinical practice and future studies involving thyroid disease(s) in SLE patients.

Conflicts of interest

All authors have no conflicts of interest to declare. The interpretation and conclusions contained herein do not represent those of the Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

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