

ORIGINAL ARTICLE

Impact of chronic urticaria on systemic lupus erythematosus: A nationwide population-based study in Taiwan

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ABSTRACT

Chronic urticaria (CU) may be closely pathogenically related to systemic lupus erythematosus (SLE). This study aims to investigate the association between CU and SLE patients in Taiwan. A nationwide population-based cohort study from 1997 to 2013 was conducted. Investigated subjects were selected from the Taiwan National Health Insurance Research Database using the International Classification of Disease, Ninth Revision code. Participants consisted of 13 845 subjects newly diagnosed with CU from 2003 to 2013. We estimated the incidence risk of SLE among patients with CU by time-to-event analysis. Patients with CU were more likely to be female, and had a significant difference in urbanization and length of hospital stays ($P < 0.0001$). The incidence rates of SLE for the CU and control groups were 3.55 and 1.68, respectively. The crude hazard ratio of SLE among subjects with CU was 2.113 compared with the non-urticarial control group. After adjusting the demographic, length of hospital stay and comorbidity, the adjusted hazard ratio (aHR) of SLE was still significantly higher in the CU group (aHR = 2.113) compared with the control group. The use of non-steroidal anti-inflammatory drugs or corticosteroids may decrease the risk of SLE in patients with CU ($P = 0.0216$ and 0.0120 , respectively). In conclusion, CU is associated with a higher risk of incidental SLE in this population-based, nationwide, cohort study. Inflammation and immune dysregulation are considered two potential mechanisms. Clinically, patients with urticaria should be carefully evaluated for risk of future SLE.

Key words: chronic urticaria, corticosteroids, inflammation, non-steroidal anti-inflammatory drugs, systemic lupus erythematosus.

INTRODUCTION

Urticaria is a common skin manifestation with a lifetime prevalence of 15–25% in the general population.¹ It is characterized by sudden eruption of erythematous and edematous wheals in the superficial layers of skin associated with sting or burning sensation.² Chronic urticaria (CU) is defined as a lesion of urticaria persisting for more than 6 weeks, affecting up to 1% of the population.² The manifestation of CU is diverse with multiple subtypes.³ Several mechanisms have been proposed for the pathogenesis of CU, including autoimmunity.²

Systemic lupus erythematosus (SLE) is a chronic and heterogeneous systemic autoimmune disease characterized by various clinical manifestations involving multiple organ systems, such as

skin, joints, kidneys, central and peripheral nervous system, and cardiovascular system.^{4,5} Early diagnosis and appropriate treatment involving clinicians across many different specialties are crucial for preventing further manifestations and achieving beneficial long-term outcomes for patients.^{6,7} Urticaria may present as the initial symptom in these patients before the more classical form of SLE is confirmed.^{8,9} CU-like lesions may occur in lupus tumidus, urticarial plaque of LE, which is an uncommon LE-specific but distinct subtype of chronic cutaneous LE.¹⁰

Even though CU and SLE have similarities in autoimmune pathogenic mechanism and cutaneous manifestations, large scale epidemiological studies are scarce.⁹ Therefore, we conducted a retrospective nationwide population-based cohort study to evaluate the respective risk estimates of SLE among

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people with CU. We further evaluated the associated confounding factors.

METHODS

Data source

In this study, the nationwide population-based data was retrieved from the National Health Insurance Research Database (NHIRD) in Taiwan. This database was derived from the claims data of the Taiwan National Health Insurance (NHI) Program managed by the National Health Research Institutes. The NHI, a compulsory single-payer health-care system that was established in 1996, covers more than 98% of the Taiwanese population. The NHIRD provides anonymized linked data from NHI for epidemiological research, including patient demographic information, health-care services data, medication dispensation data from hospitals, general practices, community pharmacies, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, and drug codes. The NHIRD has been extensively applied in thousands of published epidemiological research.

This database provides a unique and valuable resource with a sufficient sample size suitable for achieving the objectives addressed in this study. The high quality and validity of the diagnostic information from the NHIRD has been previously reported.¹¹ A number of sub-datasets have been created within the NHIRD, including the 2000 Longitudinal Health Insurance Research Dataset (LHIRD) that comprises the complete original medical and pharmaceutical claims data of 1 million randomly sampled beneficiaries enrolled in 2000 of the NHIRD. To validate the representatives of the 2000 LHIRD, there were no significant differences in sex, age or health-care costs between cohorts in the 2000 LHIRD and all insurance enrollees from the NHIRD.¹² We utilized the 2000 LHIRD to analyze the claims data from 1997 to 2013. The 2000 LHIRD provides de-identified secondary data complying with privacy laws for researchers, and thus informed consent was not required in this study. This study was approved by the institutional review board of Chung Shan Medical University Hospital (CS15134).

Exposure to CU

Participants with CU were identified from the NHIRD by using ICD-9-CM code 708.8. These codes have been adopted in previous epidemiological studies that also used the NHIRD. We first selected all patients who had received a first-time diagnosis of CU (ICD-9-CM code 708.8) between 1 January 1997 and 31 December 2013. Because the administrative datasets are always criticized for their poor diagnostic validity, this study only defined the CU patients who had at least two outpatient visits or one admission for CU in their medical claims. We then excluded 5256 patients who were diagnosed with urticaria before 2003; and 87 patients who were diagnosed with SLE before urticaria. Ultimately, 13 845 patients with CU were included as exposed individuals. We assigned the first ambulatory care visit for receiving a diagnosis of urticaria as the index date. The four controls were age and sex, individually matched with one CU patient, and they were still at risk at the index date.

Case definition of SLE

The identification of patients with SLE was based on records ascertained by using ICD-9-CM code 710.0. Patients with SLE needed to have at least one hospital admission and two outpatient department visits to fulfill the case definition and participate in the study. In addition to this, we also found comorbid diseases related to urticaria and SLE, including autoimmune diseases, rheumatoid arthritis (ICD-9-CM code 714.0), ankylosing spondylitis (ICD-9-CM code 720.2), Sjögren's syndrome (ICD-9-CM code 710.2), psoriasis (ICD-9-CM code 696), inflammatory bowel disease (ICD-9-CM code 556), Crohn's disease (ICD-9-CM code 555), obstructive sleep apnea (ICD-9-CM codes 327.23, 780.51, 780.53, 780.57), thyroid disorders (ICD-9-CM codes 240, 241, 242, 244.9, 245.0, 245.1, 245.2), chronic obstructive pulmonary disease (ICD-9-CM codes 490–496), asthma (ICD-9-CM code 493), metabolic syndromes, hypertension (ICD-9-CM codes 401–405), diabetes mellitus (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), major vascular disease including coronary artery disease (ICD-9-CM codes 410–414) and cerebrovascular accident (ICD-9-CM codes 430–438), and upper gastrointestinal diseases including esophageal disease (ICD-9-CM codes 530.0–530.9), peptic ulcer (ICD-9 codes 531.4–531.9, 532.4–532.9, 533.4–533.9, 534.4–534.9), chronic liver disease (ICD-9-CM code 571) and chronic kidney disease (ICD-9-CM code 585). These comorbidities were considered as the covariates in the multivariate analysis.

Statistical analysis

We used the χ^2 -test to analyze the demographic data between the urticarial and non-urticarial groups, and the Cox proportional hazard regression models were used to calculate the hazard ratios (HR). The 95% confidence intervals (CI) of associations between pre-existing urticaria and SLE were obtained after adjusting for age at index date, sex, urbanization, comorbidities or medication usage. The Kaplan–Meier curve was performed for the cumulative probability of SLE for patients with CU. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and $P < 0.05$ was considered to be statistically significant.

RESULTS

Study population

The selection of study participants is shown in Figure 1. After we excluded those cases missing demographic data and who died before 2003, 19 188 CU patients were identified with at least two outpatient visits or one admission for CU. We further excluded those CU cases diagnosed before 2003 and SLE cases diagnosed before the index date. From 2003 to 2013, 13 845 newly diagnosed CU cases were included.

Baseline characteristics of patients with urticaria

Of the sampled urticarial patients, 58.85% were female and 41.15% were male. After matching for sex, age and index date, the data from 13 845 patients with urticaria and relevant demographic information of the study group were obtained (Table 1).

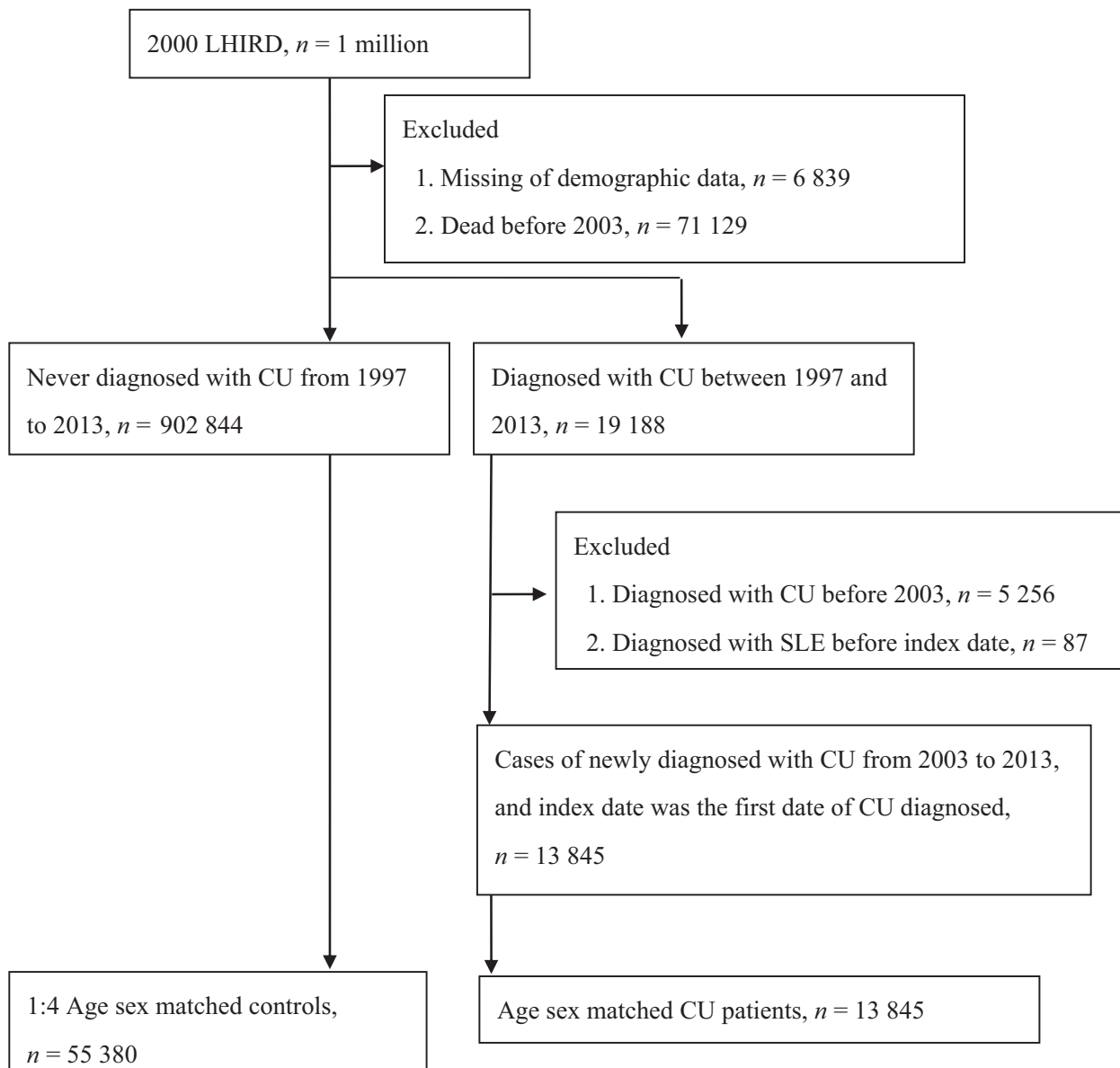


Figure 1. Flowchart of retrospective cohort study. CU, chronic urticaria; LHIRD, Longitudinal Health Insurance Research Dataset; SLE, systemic lupus erythematosus.

Patients with urticaria had a significant difference in urbanization and length of hospital stays ($P < 0.0001$). The CU group had a higher proportion of participants who lived in urban areas (62.61%).

Frequency of outpatient visit and medication used in urticarial patients

Table 1 showed that most urticarial patients (84%) were not admitted to hospital. In fact, only 9.73% of urticarial patients were admitted to the hospital for 1–6 days. The three most common comorbidities of urticarial patients included metabolic syndromes (26.35%), upper gastrointestinal diseases (17.79%)

and obstructive airway diseases (14.08%). As shown in Table 2, urticarial patients received medications which included H_1 antihistamines (97.30%), non-steroidal anti-inflammatory drugs (NSAIDs; 62.76%), corticosteroids (50.39%) and H_2 antihistamines (24.70%).

Time-to-event analysis

Table 3 showed incidence rates (per 10 000 persons a month) of SLE of 3.55 (95% CI, 2.45–5.14) and 1.68 (95% CI, 1.28–2.20) in the CU and control groups, respectively, between 2003 and 2013 in Taiwan. The Kaplan–Meier curves of cumulative incidence proportion of SLE are shown in Figure 2; there was

Table 1. Baseline characteristics among groups

	Control <i>n</i> = 55 380	Patients with CU <i>n</i> = 13 845	<i>P</i>
Age at index date, years			1.0000
<20	6348 (11.46%)	1587 (11.46%)	
20–39	20 064 (36.23%)	5016 (36.23%)	
40–59	19 064 (34.42%)	4766 (34.42%)	
≥60	9904 (17.88%)	2476 (17.88%)	
Sex			1.0000
Female	32 592 (58.85%)	8148 (58.85%)	
Male	22 788 (41.15%)	5697 (41.15%)	
Urbanization			<0.0001
Urban	33 627 (60.72%)	8668 (62.61%)	
Suburban	16 458 (29.72%)	4047 (29.23%)	
Rural	5295 (9.56%)	1130 (8.16%)	
Low income	330 (0.60%)	66 (0.48%)	0.0963
Length of hospital stay			<0.0001
0	48 213 (87.06%)	11 630 (84.00%)	
1–6	4229 (7.64%)	1347 (9.73%)	
7–13	1492 (2.69%)	450 (3.25%)	
≥14	1446 (2.61%)	418 (3.02%)	
Comorbidities at baseline			
Other rheumatic diseases	1919 (3.47%)	864 (6.24%)	<0.0001
Obstructive sleep apnea	173 (0.31%)	79 (0.57%)	<0.0001
Thyroid disorders	1476 (2.67%)	532 (3.84%)	<0.0001
Obstructive airway diseases	5415 (9.78%)	1950 (14.08%)	<0.0001
Metabolic syndromes	12 182 (22.00%)	3648 (26.35%)	<0.0001
Major vascular disease	4471 (8.07%)	1350 (9.75%)	<0.0001
Upper gastrointestinal diseases	6748 (12.18%)	2463 (17.79%)	<0.0001
Chronic liver diseases and cirrhosis	3693 (6.67%)	1354 (9.78%)	<0.0001
Chronic kidney disease	1292 (2.33%)	438 (3.16%)	<0.0001

Table 2. Medication among groups within 180 days before or after index date

	Control	Patients with CU	<i>P</i>
NSAIDs	27 416 (49.51%)	8689 (62.76%)	<0.0001
Corticosteroids	7235 (13.06%)	6977 (50.39%)	<0.0001
Antihistamines for systemic use	24 768 (44.72%)	13 471 (97.30%)	<0.0001
PPI	1270 (2.29%)	508 (3.67%)	<0.0001
H ₂ receptor antagonist	7290 (13.16%)	3420 (24.70%)	<0.0001
Aspirin	3462 (6.25%)	1015 (7.33%)	<0.0001
Oral antihypertensive medicine	9112 (16.45%)	2871 (20.74%)	<0.0001
Oral antidiabetic medicine	2748 (4.96%)	802 (5.79%)	<0.0001
Statins	2420 (4.37%)	727 (5.25%)	<0.0001

Antihypertensive medication include alpha-blockers, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. Oral antidiabetic medication include biguanides, sulfonylureas, α -glucosidase inhibitors and thiazolidinediones. The usage of medication among individuals was defined as their prescription at least 30 days within 180 days before or after the index date. PPI, proton pump inhibitors. NSAIDs, non-steroidal anti-inflammatory drugs.

a significantly higher incidence risk in the CU group (log-rank, $P = 0.0010$). The crude hazards ratio for urticaria among subjects with SLE was 2.113 (95% CI, 1.337–3.340; $P = 0.0014$, model 1). The adjusted hazard ratio (aHR) for urticaria among subjects with SLE was 2.140 (95% CI, 1.353–3.383; $P = 0.0011$, model 2) after adjustment of age, sex, and urbanization. Moreover, we added the length of hospital stays and comorbidities into the multivariate analysis, and the aHR was

2.113 (95% CI, 1.331–3.352; $P = 0.0015$, model 3). Despite this, the aHR became non-significant when we put the medication into the model (aHR = 1.388; 95% CI, 0.810–2.378; model 4).

Subgroup analysis

For the sex subgroup, we found there was a higher aHR in females (aHR = 2.164; 95% CI, 1.311–3.570) as compared with

Table 3. Time-to-event analysis of SLE

	Controls	Patients with CU	P
n	55 380	13 845	
Follow up person months	3 153 480	788 370	
Event of SLE	53	28	
Incidence rate (95% CI) [†]	1.68 (1.28–2.20)	3.55 (2.45–5.14)	
Model 1: crude hazard ratio (95% CI)	Reference	2.113 (1.337–3.340)	0.0014
Model 2: aHR (95% CI) [‡]	Reference	2.140 (1.353–3.383)	0.0011
Model 3: aHR (95% CI) [§]	Reference	2.113 (1.331–3.352)	0.0015
Model 4: aHR (95% CI) [¶]	Reference	1.388 (0.810–2.378)	0.2330

[†]Per 100 000 person months. [‡]Model 2: adjusted demographic variables at baseline including age, sex and urbanization. [§]Model 3: adjusted demographics, length of hospital stay and comorbidities at baseline. [¶]Model 4: adjusted demographics, length of hospital stay, comorbidities and medication at baseline. aHR, adjusted hazard ratio; CI, confidence interval; CU, chronic urticaria; SLE, systemic lupus erythematosus.

males (aHR = 1.839; 95% CI, 0.561–6.027), as well as a higher aHR in individuals aged less than 60 years (aHR = 2.482; 95% CI, 1.521–4.049) versus those aged 60 years or more (aHR = 0.632; 95% CI, 0.134–2.981) (Table 4). There was, however, no statistically significant interaction between age or sex with CU exposure.

We found that there was a statistically significant interaction between NSAIDs or corticosteroids with CU exposure on SLE risk. The CU patients that took NSAIDs had a lower incidence rate of SLE than CU patients who did not take NSAIDs, and the aHR of SLE for CU exposure were 4.195 (95% CI, 1.974–8.918) and 1.376 (95% CI, 0.763–2.481) in individuals not taking and taking NSAIDs, respectively. In addition, the aHR of SLE for CU exposure were 2.721 (95% CI, 1.396–5.302) and 1.520 (95% CI, 0.380–6.060) in individuals not taking and taking corticosteroids, respectively (Table 4). However, the incidence rate of SLE was not lower in CU patients taking antihistamines than CU patients not taking antihistamines (Table 4).

DISCUSSION

In this study, CU was proposed as a risk factor for the development of SLE. Furthermore, the use of NSAIDs or corticosteroids may decrease the risk of SLE in patients with CU. To the best of our knowledge, this is the first study to apply a nationwide longitudinal population-based database to estimate the relationship between CU and SLE. The analysis of the NHIRD in Taiwan from 2000 to 2013 suggested that CU is related to SLE.

Chronic urticaria is caused by degranulation of skin mast cells and a perivascular leukocyte infiltrate composed of lymphocytes, eosinophils, neutrophils and basophils, characterized by the recurrence of wheals, angioedema or both for more than 6 weeks.² Patients with CU having a high degree of comorbidity for autoimmune diseases respond to immunosuppression, such as antihistamines, cyclosporin and corticosteroids.^{5,7,8}

Systemic lupus erythematosus is an autoimmune multisystemic disease with a highly variable course, affecting the skin and mucosal membrane.^{5,7,8} SLE is characterized by the loss

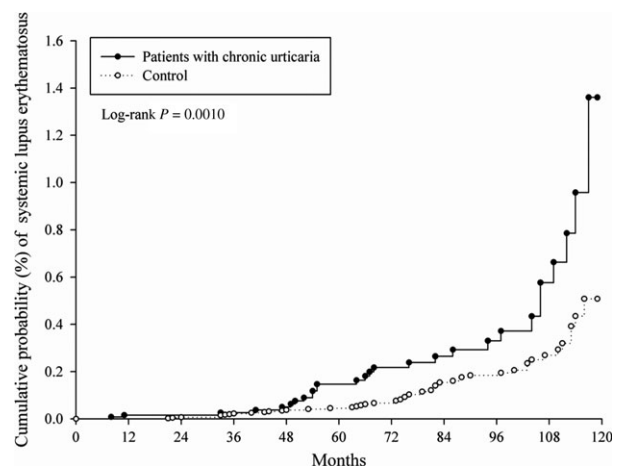


Figure 2. Kaplan-Meier curve of cumulative incidence proportion of systemic lupus erythematosus in the chronic urticarial patients and the control population.

of immune tolerance to self-antigens and immune system aberrations that involve B cells, T cells and cells of the monocytic lineage, resulting in deregulated production of a variety of autoantibodies, mainly against nuclear antigens, complement fragments and DNA followed by immune complex formation, deposited in different organs. Most of these autoantibodies are dsDNA-specific immunoglobulin (Ig)G.^{5,8,13,14} In clinical observation, many patients with SLE have clinical manifestations following the appearance of antibodies for many years, even more than 10 years.⁷

Approximately 40% of cases of CU are characterized by production of IgG autoantibodies.^{7,9,14,15} Chronic spontaneous urticaria and urticarial vasculitis are the two most common underlying causes of CU rash in SLE. Urticaria and urticarial vasculitis are present as histologically non-specific lesions of SLE.^{7,8}

Most epidemiological data has revealed that the prevalence of urticaria among SLE patients is significant. The appearance of urticaria in active SLE patients is due to the deposition of

Table 4. Subgroup analysis of SLE

	Controls			CU patients			aHR (95% CI) [‡]
	Person months	Event of SLE	Incidence (95% CI) [†]	Person months	Event of SLE	Incidence (95% CI) [†]	
Sex subgroups							
Female	1 861 876	44	2.36 (1.76–3.18)	465 469	24	5.16 (3.46–7.69)	2.164 (1.311–3.570)
Male	1 291 604	9	0.70 (0.36–1.34)	322 901	4	1.24 (0.46–3.30)	1.839 (0.561–6.027)
<i>P</i> for interaction							0.7814
Age subgroups, years							
<60	2 625 852	43	1.64 (1.21–2.21)	656 463	26	3.96 (2.70–5.82)	2.482 (1.521–4.049)
≥60	527 628	10	1.90 (1.02–3.52)	131 907	2	1.52 (0.38–6.06)	0.632 (0.134–2.981)
<i>P</i> for interaction							0.0847
NSAIDs							
No	1 588 267	16	1.01 (0.62–1.64)	288 531	12	4.16 (2.36–7.32)	4.195 (1.974–8.918)
Yes	1 565 213	37	2.36 (1.71–3.26)	499 839	16	3.20 (1.96–5.22)	1.376 (0.763–2.481)
<i>P</i> for interaction							0.0216
Corticosteroids							
No	2 738 006	33	1.21 (0.86–1.70)	381 579	12	3.14 (1.79–5.54)	2.721 (1.396–5.302)
Yes	415 474	20	4.81 (3.11–7.46)	406 791	16	3.93 (2.41–6.42)	1.520 (0.380–6.060)
<i>P</i> for interaction							0.0120
Antihistamines							
No	1 750 032	24	1.37 (0.92–2.05)	20 766	–	–	–
Yes	1 403 448	29	2.07 (1.44–2.97)	767 604	28	3.65 (2.52–5.28)	1.874 (1.113–3.156)
<i>P</i> for interaction							0.9783

[†]Per 100 000 person months. [‡]Adjustment for age, sex, urbanization, length of hospital stay and comorbidities at baseline. aHR, adjusted hazard ratio; CI, confidence interval; CU, chronic urticaria; NSAIDs, non-steroidal anti-inflammatory drugs; SLE, systemic lupus erythematosus.

immune complex and activation of complement.⁹ In clinical practise, low levels of complement and anti-C1-q antibodies are features often observed, but the information about the prevalence of SLE and urticaria in patients is lacking. An unidentified subpopulation of urticarial patients can progress to SLE through autoimmune immunopathogenesis.⁹ It is difficult to predict the mechanisms of urticaria leading to SLE. IgG- and IgE-mediated chronic inflammatory autoimmune pathogenesis are suggested to play a role linking both entities.^{9,16} Chronic stimulation of immune response in urticarial patients can result in increased levels of inflammatory cytokines which initiate local inflammation and consistently progress to adaptive immune disorders that can damage organs with lymphatic infiltration. Although the identified causes of urticaria are diverse, studies show anti-inflammatory medications are effective for the remission of symptoms of urticaria.¹⁷ However, which inflammatory pathway dominantly mediates the inflammation process of urticaria needs to be analyzed.¹⁸ In SLE patients, type 1 interferon is considered as a risk factor of SLE.¹⁹ Serum and tissue profiles of inflammation cytokines, such as interleukin (IL)-6, IL-12 and IL-23, are reported to be associated with SLE.^{20–24} Except for belimumab targeting B cells, ustekinumab aimed at IL-23 cytokine pathways are being studied on SLE patients currently.

The association between urticaria and autoimmune diseases has long been discussed. Urticaria causing either systemic or organ-specific inflammation may lead to SLE.^{19–24} Other studies have also been established to investigate the linkage

between urticaria and SLE, but there is still no specific evidence for the relevant mechanism of CU and SLE. However, the mechanism by which patients with urticaria are susceptible to SLE still remains obscure. Likewise, our previous study demonstrated that the incidence rate of anaphylaxis is significantly high in patients with urticaria in Taiwan; both share common causal immune-mediated pathways.²⁵

Additionally, urticaria must be differentiated from hypocomplementemic urticarial vasculitis in SLE patients. This manifestation generally has a fixed location and may be associated with pain or with a burning sensation that may result in hyperpigmentation, but has been rarely reported in children.⁹

The treatment of chronic autoimmune urticaria includes antihistaminic drugs, corticosteroids and antimalarials. The use of sunscreen protection is required, particularly in photosensitive patients. In patients who do not respond to conventional therapies, immunosuppressive drugs, such as cyclosporin, are effective 1–4 weeks after administration.^{5,7,20–24,26} Not surprisingly, baseline medication usage would affect the results of multivariate and subgroup analysis.

A particular strength of this study is the use of a nationwide population-based dataset. Therefore, resulting from the use of the dataset, this study should be free from the effects of selection bias.

There are some potential limitations in our study. First, with the great variation in clinical manifestations and diagnostic definition, the diagnosis of SLE may possibly be disregarded by clinicians. SLE patients treated without hospitalization were

thus not included in our study. Second, the NHIRD does not include data on covariates, such as family history, personal lifestyle, social adversity, laboratory data and environmental factors. We found significant associations between CU and SLE, indicating the key role of SLE in CU etiopathogenesis. Based on our data, we highlight the importance of patients with CU being carefully evaluated for risk of future SLE. Prospective studies should investigate the cost-effectiveness of screening for SLE in patients with CU.

In conclusion, CU is associated with a higher risk of incidental SLE in this population-based, nationwide, cohort study. Inflammation and immune dysregulation are considered two potential mechanisms. Clinically, patients with CU should be carefully evaluated for risk of future SLE.

CONFLICT OF INTEREST: None declared.

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