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Epidemiology and comorbidities of patients with chronic urticaria in Taiwan: A nationwide population-based study

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ABSTRACT

Background: Comprehensive data regarding the epidemiology of chronic urticaria (CU) in general populations are scant.

Objectives: To investigate the prevalence, incidence, and comorbidities of CU in general population.

Methods: The data were sourced from the National Health Insurance Research Database (NHIRD) for 2009–2012. Patients who had a primary/secondary ICD-9-CM diagnosis code of 708.1, 708.8, or 708.9 during the year with at least two outpatient visits and an antihistamine prescription, were identified as the cases of CU for each year. The incidence, persistence and comorbidities of CU were examined.

Results: The prevalence of CU ranged from 0.69% to 0.79% for each year from 2009 to 2012, and the incidence was around 0.50% per year from 2010 to 2012. Comparing to the Standard Population, the standardized prevalence ratios (SPRs) for the rheumatic diseases, thyroid disorders, inflammatory diseases, and psychiatric disorders among CU patients were 2.74, 1.81, 1.57 and 1.87, respectively.

Conclusion: The prevalence of CU in Taiwan is about 0.69–0.79%. CU is associated with a significantly increased risk of psychiatric disorders, inflammatory diseases, thyroid disorders, and rheumatic diseases. Except for thyroid disorders, the prevalence of these comorbidities tends to increase the longer CU persists.

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1. Introduction

Chronic urticaria (CU) is defined by the repeated occurrence of itchy hives, angioedema, or both, for 6 weeks or more. It is further classified into chronic inducible urticaria and chronic spontaneous (or idiopathic) urticaria (CSU/CIU), depending on whether a specific trigger can be identified or not [1–3]. Although urticaria is one of the most common skin conditions, only a few studies investigating the prevalence of CU have been published [4]. Most data have involved selected patient populations, usually patients attending special clinics [4,5]. In addition, previous inconsistencies in the classification of CU present further difficulties when

comparing past studies [4]. A 1-year period prevalence for CU of 0.8% was reported in a German study [5], while Gaig et al. reported a point prevalence of 0.6% in the Spanish population [6]. However, the prevalence and incidence of CU in Asian populations are largely unknown.

It has been suggested that CU might be related to other autoimmune processes, rheumatic diseases, or chronic inflammation [7–9]. The association of CU with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), psoriatic arthritis/psoriasis (PsA/PsO), thyroid disorders, inflammatory diseases, and psychiatric disorders has been reported before [7–17]. However, there is limited information on how prevalent they are. In this study, we aimed to investigate the prevalence, incidence, and comorbidities of CU in the general population of Taiwan.

2. Methods

2.1. Setting

The National Health Insurance (NHI) program in Taiwan was put into effect in March of 1995, and is primarily funded by payroll tax

Abbreviations: AS, ankylosing spondylitis; CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria; *H. pylori*, *Helicobacter pylori*; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; PsA/PsO, psoriatic arthritis/psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SPR, standardized prevalence ratio.

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premiums with additional subsidies from the general government revenues. The system covers 99.9% of the total population of Taiwan with a comprehensive benefits package (including preventive medicine, dental care services, outpatient and inpatient services, prescription drugs, and Chinese herbal remedies). Health care providers are reimbursed by the NHI for their services. Patients are free to select the healthcare providers of their choice, although they are required to make co-payments for outpatient/inpatient services and drugs consumed.

2.2. Data sources and study subjects

The National Health Insurance Research Database (NHIRD) was established by the National Health Research Institute, in cooperation with the National Health Insurance Administration, with the

aim of promoting research into current and emerging medical issues in Taiwan. The data for this study were sourced from the NHIRD for 2009–2012.

Patients who had at least two outpatient visits and a primary or secondary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis code of 708.1 (idiopathic urticaria), 708.8 (other specified urticaria), or 708.9 (urticaria unspecified) and an H1 anti-histamine prescription were identified as the cases of CU for each year from 2009 to 2012. The first outpatient visit in the year was defined as the index date of the given case in that year. Patients who met either of the following two criteria were excluded. First, if the interval between the index date and the date of the last CU outpatient visit in the same year was less than 6 weeks. Second, any patient who had at least two outpatient visits with a primary or secondary ICD-9-CM

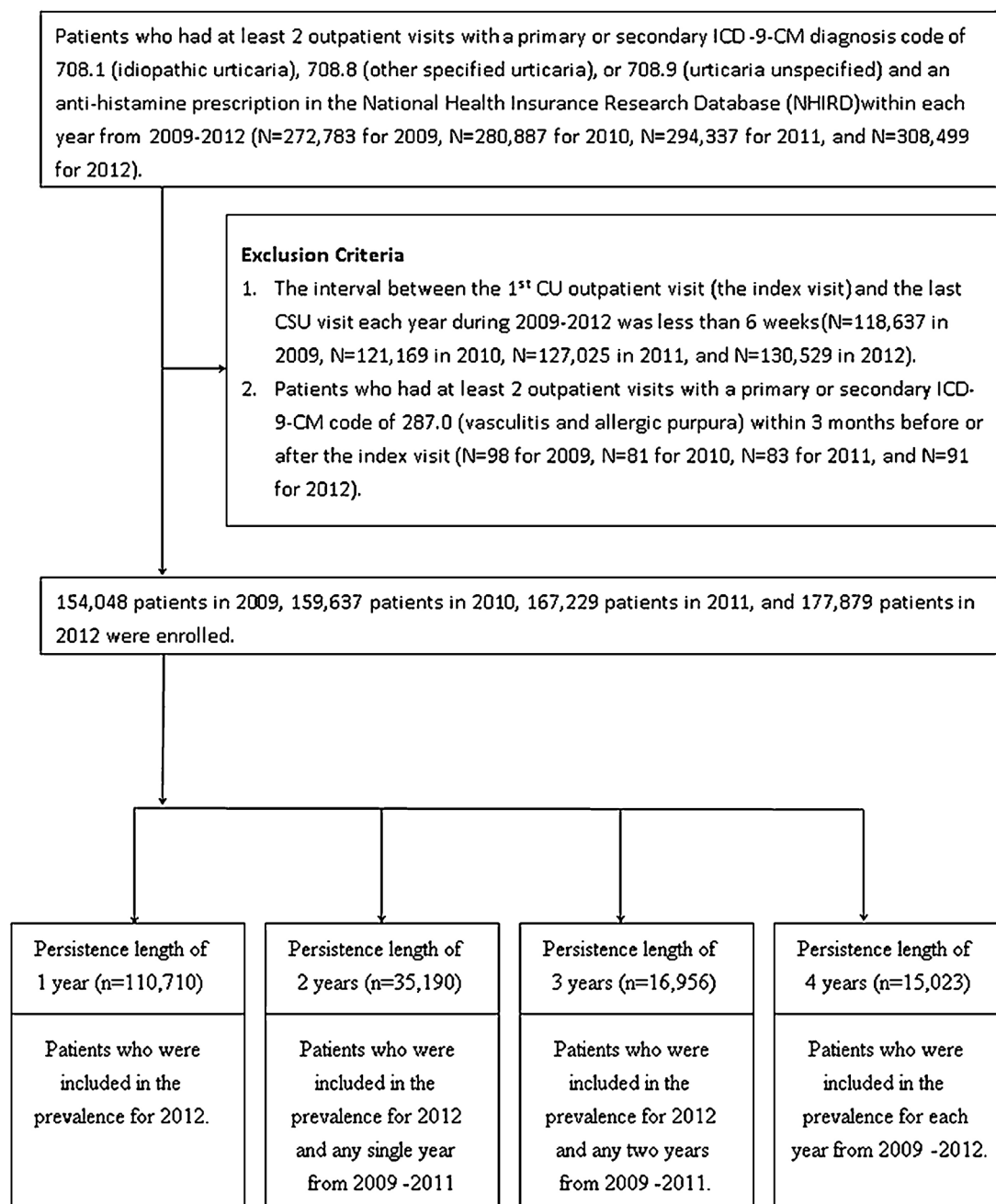


Fig. 1. Selection process for cases of CU from 2009 to 2012.

code of 287.0 (vasculitis and allergic purpura) within 3 months before or after the index date.

To further investigate the persistence of CU, the CU patients for 2012 were tracked back in terms of their prior disease history of CU and were further classified into four groups according to the overall duration of CU (Fig. 1).

A sample cohort of 1 million enrollees representative of the Taiwanese population in 2005, in addition to all the claims records for those 1 million enrollees up to the end of 2012 compiled and published by the NHRI, was used to construct the Standard Population. The final sample size of the Standard Population decreased to 996,356 by 2012 due to death or loss of enrolment status.

Confidentiality assurances were addressed by abiding by the data regulations of the NHI Administration and the study was approved by the National Taiwan University Hospital Research Ethics Committee (201402045RINB).

2.3. Definition of measurements

The incidence rate of CU was defined as the number of incident cases of CU divided by the number of the population at risk in 2010, 2011, and 2012, respectively. Incident cases of CU were defined as the number of CU patients in the given year minus the number of CU patients in the previous years. The population at risk for CU was defined as all the beneficiaries from the NHIRD registry file for the given years, which were 22,282,479 in 2009, 22,336,029 in 2010, 22,537,021 in 2011 and 22,532,255 in 2012, minus the CU cases in the previous year.

Four types of comorbidities were considered to be associated with CU, which was defined according to whether the study cases had at least three outpatient visit claims with principal/secondary diagnoses of the following diseases (ICD-9-CM code) in 2012: (1) rheumatic diseases, including RA (714), SLE (710), AS (720), PsA/PsO (696.0, 696.1); (2) thyroid disorders, including simple and unspecified goitre (240), nontoxic nodular goitre (241), thyrotoxicosis with or without goitre (242), unspecified acquired hypothyroidism (244.9), acute thyroiditis, sub-acute thyroiditis, and

chronic lymphocytic thyroiditis (245.0, 245.1, 245.2); (3) inflammatory diseases, including chronic sinusitis (473), otitis media (381.1–381.4, 382.1–382.9), periodontitis (523.1, 523.4, 523.5, 523.8, 523.9), diverticulitis (562.0, 562.1), *Helicobacter (H.) pylori* infection (041.86), peptic ulcer (531.4–531.9, 532.4–532.9, 533.4–533.9, 534.4–534.9), hepatitis B/hepatitis C (070.3, 070.5–070.9); and (4) psychiatric disorders, including episodic mood disorders (296), anxiety, dissociative and somatoform disorders (300), obsessive-compulsive personality disorder (301.4), drug dependence (304), nondependent abuse of drugs (307.4), specific disorders of sleep of nonorganic origin (531.4, 531.5, 531.6), adjustment reaction (309), depressive disorder, not elsewhere classified (311).

2.4. Statistical analyses

Pearson chi-square tests were performed to examine differences in age and sex distribution among the four persistence length groups. The observed prevalence of CU-related comorbidities among the four persistence length groups was calculated. The standardized prevalence ratios (SPRs; the ratio of observed to expected CU-related comorbidities) was used to estimate the relative risk. The expected number of comorbid cases in patients with CU was calculated by multiplying the number of persons accumulated in each stratum of age and sex by the corresponding specific rate of the Taiwanese Standard Population. 95% CI for these ratios were calculated with the assumption that the observed number of comorbidities cases followed a Poisson distribution. All analyses were performed using the SAS/Stat system for Windows, version 9.3 (SAS Institute, Cary, NC).

3. Results

There were 154,048, 159,637, 167,229, and 177,879 cases of CU identified in the NHIRD for the respective years from 2009 to 2012. The prevalence varied from 0.69% to 0.79% from 2009 to 2012, and the average incidence rate was about 0.50% from 2010 to 2012 (Fig. 2). Regarding to the patient profile of the 2012 CU cases, 56% of

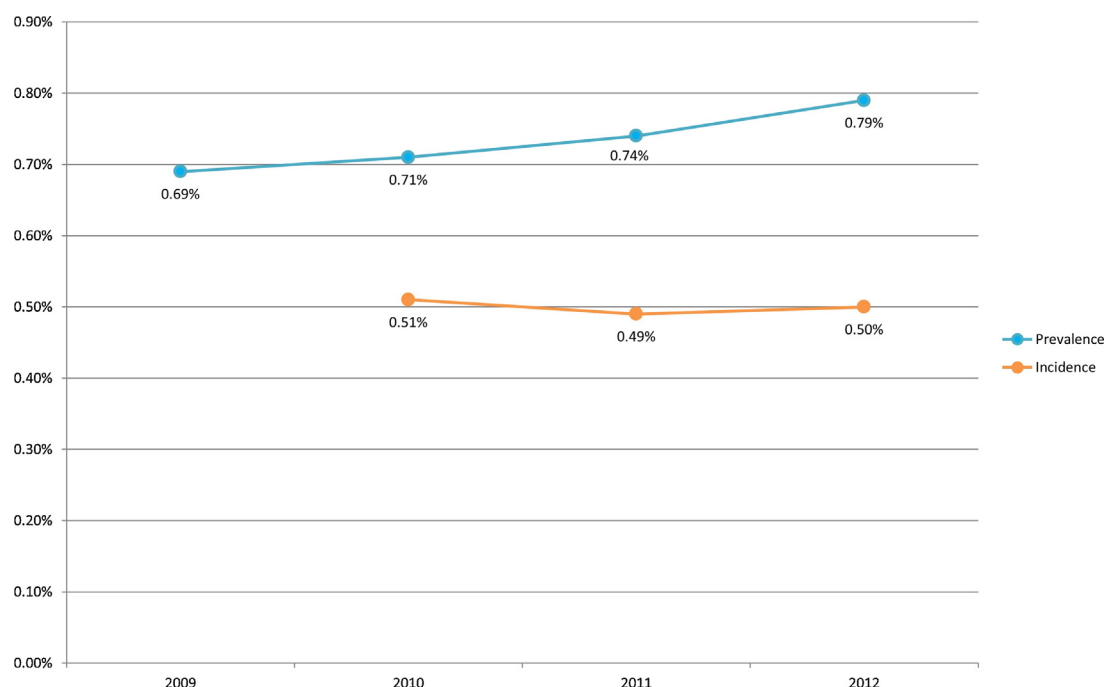


Fig. 2. Prevalence and incidence rates of CU from 2009 to 2012 in Taiwan.

Table 1
Patient profiles in terms of disease persistence for CU cases in 2012.

Persistence of CU												χ ²	p
All			1 year		2 years		3 years		4 years				
N	%	n	%	n	%	n	%	n	%				
Total	177,879	100	110,710	100	35,190	100	16,956	100	15,023	100			
Age group in years	Gender											7326.562	<0.0001
<20	Male	13,212	7.43	10,500	9.48	1860	5.29	556	3.28	296	1.97		
	Female	13,146	7.39	10,251	9.26	2045	5.81	563	3.32	287	1.91		
20–29	Male	7132	4.01	4990	4.51	1298	3.69	485	2.86	359	2.39		
	Female	12,082	6.79	8893	8.03	2047	5.82	717	4.23	425	2.83		
30–39	Male	10,268	5.77	6282	5.67	2120	6.02	955	5.63	911	6.06		
	Female	18,240	10.25	11,905	10.75	3648	10.37	1596	9.41	1091	7.26		
40–49	Male	12,566	7.06	7066	6.38	2521	7.16	1449	8.55	1530	10.18		
	Female	19,592	11.01	11,424	10.32	4154	11.80	2092	12.34	1922	12.79		
50–59	Male	13,861	7.79	7445	6.72	2952	8.39	1640	9.67	1824	12.14		
	Female	16,964	9.54	9580	8.65	3580	10.17	1943	11.46	1861	12.39		
60–69	Male	9582	5.39	5088	4.60	2101	5.97	1214	7.16	1179	7.85		
	Female	9961	5.60	5759	5.20	2100	5.97	1111	6.55	991	6.60		
≥70	Male	11,048	6.21	5677	5.13	2597	7.38	1455	8.58	1319	8.78		
	Female	10,225	5.75	5850	5.28	2167	6.16	1180	6.96	1028	6.84		

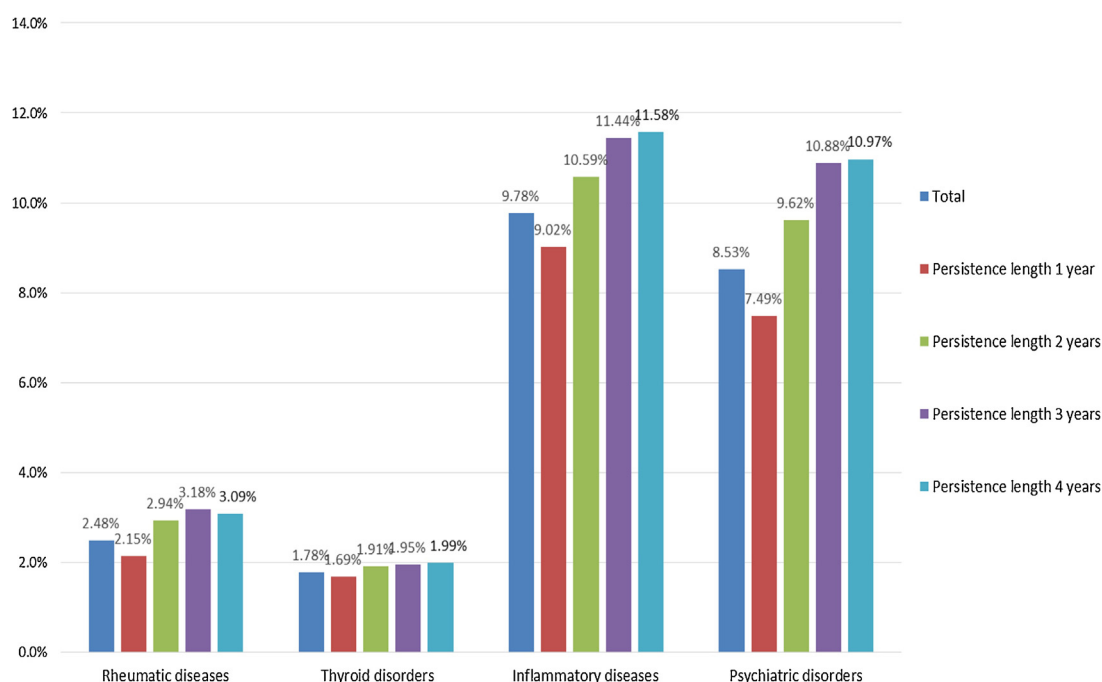
them were females and about 62% were 30–69 years old. The majority of CU patients was in the age of 40–59 years old (35.4%), followed by patients aged 20–39 years old (26.8%). Of the CU cases in 2012, 62.2%, 20.0%, 9.5%, and 8.5% respectively, had CU which had persisted for 1, 2, 3, or at least 4 years. There were significant differences in the age and sex distributions among the four persistence length groups (Table 1).

The observed prevalence of rheumatic diseases, thyroid disorders, inflammatory diseases, and psychiatric disorders among CU patients was 2.48%, 1.78%, 9.78%, and 8.53%, respectively (Fig. 3). Their prevalences increased when CU persisted into the second year, but the prevalence of thyroid disorders did not increase steadily as CU persisted longer. In contrast, the prevalence of rheumatic diseases, inflammatory diseases and psychiatric disorders increased steadily as the persistence duration of CU increased, but till reached plateau when CU persisted for 3 years.

Comparing to the Standard Population, the risk of rheumatic diseases (SPR: 2.74, 95% CI: 2.70–2.77), thyroid disorders (SPR: 1.81, 95% CI: 1.78–1.83), inflammatory diseases (SPR: 1.57, 95% CI: 1.56–1.58) and psychiatric disorders (SPR: 1.87, 95% CI: 1.85–1.88) among CU patients was significantly higher (Fig. 4). The risk for rheumatic diseases, inflammatory diseases, and psychiatric disorders increased steadily as CU patients persisted longer until the fourth year. However, there was no significant difference in the risk of thyroid disorders between CU patients persisted for more than 1 year. Detailed information regarding the four types of CU-related comorbidities is provided in Supplementary Tables S1–4.

4. Discussion

In this study, we found the prevalence of CU in Taiwan to be about 0.69–0.79%, which is compatible with the previous reports

**Fig. 3.** Observed prevalence of comorbid diseases among patients with CU.

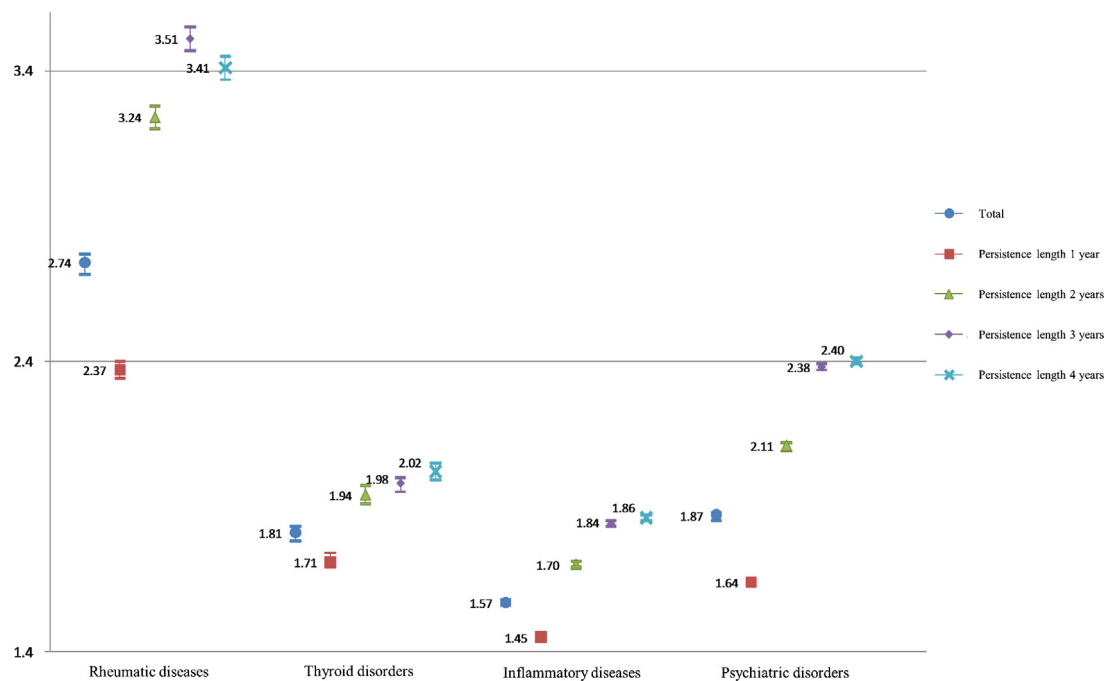


Fig. 4. The standardized prevalence ratios of comorbid diseases among patients with CU.

[4–6]. An earlier study from Sweden found a point prevalence of CU of around 0.1% in the total population [18], but their definition of CU and study methods were different [4]. We used the NHIRD combined with consultation and prescription patterns to estimate the annual prevalence, which would be more accurate than questionnaire-based patient surveys. To our knowledge, this is the largest set of population-based data to demonstrate the prevalence and incidence of CU [1–4].

Most previous studies have clearly demonstrated that women suffer from urticaria about twice as often as men do [4–6,19–24]. Almost all of those results were obtained from highly selected patients attending specialized urticaria treatment centres. In contrast, we found a female-to-male ratio of around 56:44 for CU patients in this large population study. In addition, the female-to-male ratio of CU patients with symptoms lasting for at least four years was almost the same as in the Standard Population (51:49). The prevalence of CU in males might have been underestimated previously as some adult males may not be able to visit special clinics or participate in active studies in medical centers during regular working hours, thus leading to higher female-to-male ratios in previous studies including those published by researchers in Taiwan [8,23,24]. The primary advantage of the current study was its use of a national insurance database, such that every patient who used medical resources would be included, even if he or she only visited local clinics or primary care physicians. In Taiwan, most primary care physicians have night-time or weekend outpatient consultation services, which would potentially encourage male patients to access medical resources at times that would not interfere with their daytime work.

The peak age of CU patients was between 20 and 40 years in most of the previous studies [4,20–24], while we found the peak age for CU to be 40–49 (18.1%). When we stratified the age distribution by every 2 decades, we still found the peak age of CU patients to be 40–59 years (35.4%), followed by 20–39 years (26.8%), which is in agreement with the results of a German study [5]. Interestingly, the peak age of CU among females being 40–49 years, while that among males was 50–59 years. The females predominate in the age groups of 20–49, but among CU patients

older than 50, the female-to-male ratio was reversed. The age difference between female and male CU patients might reflect different underlying causes or different treatment patterns among women and men.

Little is known about the proportion of CU patients for whom the disease will persist for more than one year. One previous study demonstrated that 80% of patients with CU were symptom-free after 1 year, but 11% of the patients still suffered after 5 years [4]. Various studies have clearly demonstrated that a certain ratio of CSU patients does suffer for more than 1 year [4,6,19,22]. In this study, we found that at least 18% of CU patients suffer from the disease for more than 2 years. In addition, we also found that a difference of age-related disease duration of CU. Patients younger than 40 had a highest percentage in the 1-year duration group and the percentage decreased as the disease duration getting longer, while those older than 40 had the lowest percentage in the 1-year duration group, and reversely, an increasing trend was found with longer disease duration (Table 1). This may reflect different etiologies among different age groups of CU, some age-related aggravating factors associated with persistence of CU, and time-dependent factors related to the study design as patients older than the peak age group would have longer disease duration.

Among the four categories of comorbidities we examined in this study, inflammatory diseases were the most prevalent, followed by psychiatric disorders, rheumatic diseases, and thyroid disorders. There was a trend of increasing prevalence of the comorbidities as CU persisted into the second year, but the prevalence of thyroid disorders did not increase steadily as CU persisted longer. In contrast, the prevalences of rheumatic diseases, inflammatory diseases and psychiatric disorders were higher as CU persisted into the third year. The increased prevalence of these comorbidities in CU patients might reflect a common association of autoimmune-based pathogenesis among CU and rheumatic/thyroid diseases [7,8]. Genetic factors might explain these common origins. In addition, a common pathogenic mechanism might be implied by the high prevalence of chronic inflammatory processes expressed by the high mean platelet volume in one study [7]. Others have suggested that anti-thyroid antibodies cause inflammation in the

thyroid, leading to a release of cytokines, which in turn decrease the threshold for mast cell degranulation [8]. Several reports suggest that CU may emerge through interactions between the nervous and immune systems [17]. Symptoms might result from mast cell activation, elicited through channels such as the hypothalamic–pituitary–adrenocortical axis, the sympathetic and adreno-medullary system and local skin nerve fibers [17]. Other studies propose that stress-related mechanisms provide links to CU. Acute psychological stress results in cutaneous mast cell activation [17]. On the other hand, there are several physical symptoms of CU that can be inducers of stress, or enhance anxiety symptoms, including: itching, the occurrence of wheals, fatigue, pain, and insomnia, which may further increase psychiatric symptoms such as depression and anxiety [14].

CU has been reported to be associated with autoimmune thyroiditis and several rheumatic diseases in the literature [7–13]. Except for one population study from Israel [7], most of the other studies collected data from selected patients [8–13]. Interestingly, we found the SPR of PsO/PsA was the highest among the rheumatic diseases in CU patients. An Israeli study using a healthcare database showed that CU had significant association with type 1 diabetes, Sjögren's syndrome, RA, celiac disease, and SLE. However, they did not describe the prevalence of rheumatic diseases in their study.

Thyroid disorders have been the diseases most commonly found among CU patients, with the reported prevalence ranging from 12.1% to 57.4% based on different criteria [7–13]. Association studies using the presence of anti-thyroid antibodies as the criteria usually obtained higher frequencies. In this study, we defined the presence of thyroid disorders based on the classification of ICD-9-CM codes and with the criterion that the study cases must have at least three outpatient visit claims with principal/secondary diagnoses of the diseases. We found that 1.78% of the CU patients had thyroid disorders with a SPR of 1.81. Compared to a previous large population study showing that 9.8% and 2.6% of CU patients had hypothyroidism and hyperthyroidism respectively, the lower prevalence presented in the current study might be due to the strict inclusion criteria or different population/ethnic background. Our data demonstrated that the persistence length of CU did not have a significant correlation with the prevalence of thyroid disorder, indicating that thyroid disorders are associated with the development, rather than the persistence, of CU.

We found the prevalence of inflammatory diseases among CU patients was about 9.78%, which has a SPR of 1.57 than that of the Standard Population. Peptic ulcer was the most prevalent inflammatory disease (4.83%), followed by hepatitis B/hepatitis C (1.64%) and periodontitis (2.82%). In addition, the prevalence of inflammatory diseases increased steadily as patients persisted into longer periods, indicating chronic inflammation might play some roles in persistence of CU. However, these patients may also take medications including non-steroidal anti-inflammatory drugs and antibiotics, which could also induce CU in some patients.

The presence of *H. pylori* infection based on clinical diagnosis was found in 0.18% of CU patients, which was only 1.76-fold higher than the rate of the Standard Population. The association of *H. Pylori* infection and CU is less likely to be related to the prescription of corticosteroids for CU, because previous studies have shown that corticosteroid alone is not a risk factor for either peptic ulcer or *H. Pylori* infection [25,26]. In the study population, *H. pylori* infection was diagnosed on the basis of rapid urease test and histological examination according to the NHI regulations.

Previous studies have shown high prevalence of psychiatric comorbidities in CU patients, with the rates ranging from 35 to 60% [15,16,27–29]. Anxiety, depression, and somatoform disorders have been reported to be the most prevalent mental disorders in CU patients [15,16,30–32], although depression was

most prevalent in a few studies [15,29]. We found that anxiety, dissociative, and somatoform disorders were the most prevalent psychiatric disorders, especially when CU persisted longer. Anxiety/dissociative/somatoform disorders, peptic ulcer, and sleep disorders of nonorganic origin are associated with stress. Increased prevalence of these comorbidities as CU persisted longer indicates that stress may not only contribute to the development but also the severity/duration of CU [15–17,23]. On the other hand, persistent symptoms of CU may also become a source of stress to the patients.

Comparing to former studies conducted mainly in Europe-Israel and USA [5–7,9–12,14–20,22–24,27–33], the current study revealed several unique features of CU in Taiwan: patients were relatively older with the peak age at 40–49, male predominance in older age group, lower prevalence of thyroid disorders, and higher prevalence of peptic ulcer. These discrepancies might be related to the difference in study cohort (large population database vs. database from tertiary referral centers), patterns of healthcare service utilization (national health insurance vs. private practice), genetic background (Asian vs. Caucasian), certain environmental factors (prevalence of chronic infection), and potential inclusion of allergic urticaria or chronic inducible urticaria in the studied population.

This study may have several limitations. First, bias due to miscoding and misclassification can still happen even we use strict inclusion/exclusion criteria combined with prescription patterns to define CU. Furthermore, even though all the general physicians in Taiwan have received dermatological trainings for at least 4 weeks per year during the 5th to 7th year of medical school, the diagnosis of CU might not be accurate. Some cases of drug-induced urticaria/angioedema might be misdiagnosed as CU. Second, the prevalence of comorbidities might be underestimated as we only use ICD-9-CM diagnosis code to determine the diseases. Third, the estimation of CU persistence may not be accurate in patients with earlier disease onset.

5. Conclusion

We found the prevalence and annual incidence of CU in Taiwan to be about 0.69–0.79% and 0.50% respectively from 2010 to 2012. The female-to-male ratio among the CU patients was around 56:44. CU patients had higher prevalence of psychiatric disorders, inflammatory diseases, thyroid disorders, and rheumatic diseases.

Declaration of interests

Chia-Yu Chu is a clinical trial investigator of Novartis and has received travel support, consulting fees and payment for lectures from Novartis. Yung-Tsu Cho, Jhih-Hua Jiang, and Chao-Hsiun Tang declare no competing interest. Eve I-Chun Lin is an employee of Novartis (Taiwan) Co., Ltd., Taipei, Taiwan.

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Ethical approval

The study was approved by the National Taiwan University Hospital Research Ethics Committee (201402045RINB).

Prior presentation

Global Urticaria Forum (GUF 2016), Berlin, November 29–30, 2016.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jdermsci.2017.07.006>.

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