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Original Article

Natural course of new-onset urticaria: Results of a 10-year follow-up, nationwide, population-based study

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CSU chronic spontaneous urticaria

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Service–National Sample

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ABSTRACT

Background: Previous epidemiologic studies of the natural course of urticaria mainly focused on chronic spontaneous urticaria and were conducted at hospitals. The natural course of new-onset urticaria in the general population is unknown.

Methods: Patients with new-onset urticaria were identified from the National Health Insurance Service –National Sample Cohort data. Patients who had at least one visit for urticaria in 2002 and 2003 were excluded and the study cohort consisted of 1,027,620 subjects with no history of urticaria. We analyzed cumulative incidences of urticaria, chronic urticaria, and chronic urticaria remission using the life table estimation method from 2004 to 2013. Their association with related factors was analyzed using the Cox proportional hazards analysis.

Results: From 2004 to 2013, a total of 49,129 patients with new-onset urticaria were identified. The 10-year cumulative incidence rate of urticaria for the general population was 4.9% and that of chronic urticaria among patients with new-onset urticaria was 7.8%. Remission rates of chronic urticaria were 52.6% at 1 year and 88.9% at 5 years. Age, sex, residential area, and autoimmune thyroid disease were significantly associated with urticaria or chronic urticaria, but not with chronic urticaria remission, after adjusting for covariates. Female individuals were more likely to have new-onset urticaria but less likely to develop chronic urticaria compared with male individuals.

Conclusions: During the 10-year follow-up period, only a small proportion of patients with new-onset urticaria developed chronic urticaria. Remission was achieved in the majority of patients with chronic urticaria regardless of demographic characteristics or accompanying thyroid disease.

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Introduction

Urticaria is a heterogeneous group of diseases, and the spectrum of clinical manifestations of different urticaria subtypes is extremely wide.¹ Urticaria is classified as either acute or chronic urticaria based on the duration of illness.² Both types of urticaria are fundamentally mast cell-driven diseases.¹ Nevertheless, acute urticaria is self-limited and routine diagnostic measures are not recommended.¹ In contrast, chronic urticaria has an unpredictable

course, treatable causes are rarely identified, and management is based on controlling clinical symptoms until spontaneous remission.³

Chronic urticaria, which includes chronic spontaneous urticaria (CSU) and physical urticaria, has a huge influence on quality of life.^{4,5} Moreover, the duration of chronic urticaria varies depending on the subtype and severity.^{6–8} Understanding the natural course of urticaria is essential for providing accurate information to patients and for preventing unnecessary anxiety for patients and frustration for physicians.⁹

However, published data regarding the natural history of urticaria have some limitations. The majority of previous studies on the natural history of urticaria focused on the duration of CSU.^{10–13} Therefore, only fragmentary results of other aspects of the natural course of urticaria exist, and the frequency of progression from acute urticaria to chronic urticaria has not been established.¹⁴

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Additionally, previous studies were typically performed in a hospital setting¹⁵ and included specific age groups instead of the general population.^{10–12}

The National Health Insurance Service–National Sample Cohort (NHIS-NSC) is a population-based cohort established by the National Health Insurance Service (NHIS) in South Korea. In this study,

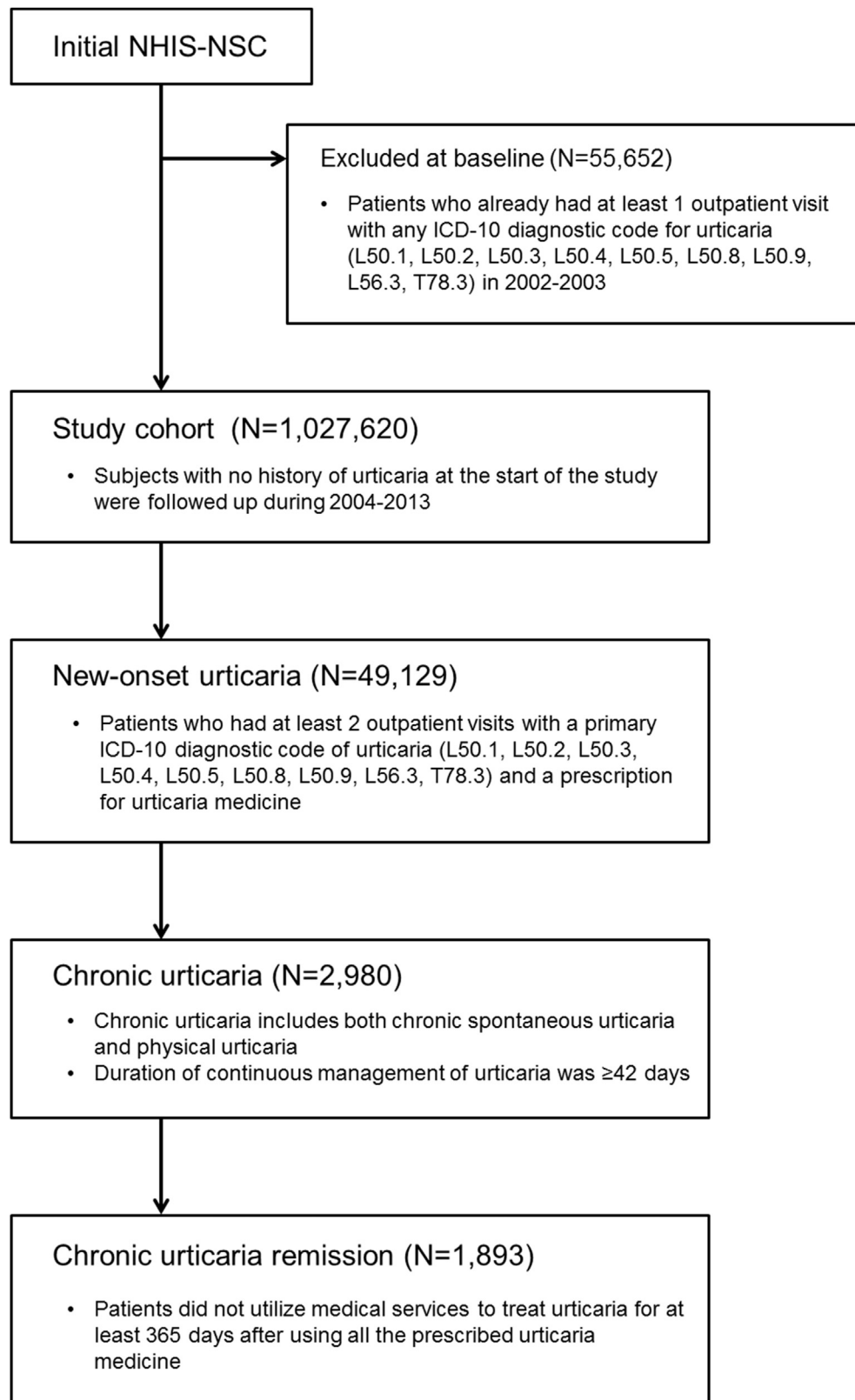


Fig. 1. Selection process of patients with new-onset urticaria, chronic urticaria, and chronic urticaria remission. NHIS-NSC, National Health Insurance Service–National Sample Cohort.

we aimed to investigate the natural course of new-onset urticaria using the NHIS-NSC data.

Methods

Data source

We used the 2002–2013 NHIS-NSC data from the NHIS in South Korea, which is a national representative sample with 1,025,340 individuals in 2002, who were systematically stratified and randomly sampled; the NHIS-NSC represents 2.2% of the Korean population, as an initial cohort, and contains follow-up data until 2013.¹⁶ The initial cohort was restored annually to maintain the representativeness of the data by substituting a representative sample of newborns for follow-up loss due to death or emigration.¹⁶ This study was exempt from the approval of the Institutional Review Board because the data set consisted of deidentified secondary data.

Study population and selection process of patients with urticaria

The selection process for the study is shown in Figure 1. To define new-onset urticaria, a 2-year washout period (2002–2003) was used in this study. Patients who had at least 1 outpatient visit with any diagnostic codes of urticaria (L50.1, L50.2, L50.3, L50.4, L50.5, L50.8, L50.9, L56.3, or T78.3) of the *International Classification of Diseases*, tenth revision (ICD-10) in 2002 and 2003 were excluded ($n = 55,652$). Finally, the study cohort consisted of 1,027,620 subjects with no history of urticaria. They were followed-up during 2004 and 2013. In the study cohort, a patient with urticaria was defined as having at least 2 outpatient visits with a primary diagnostic code of urticaria (L50.1, L50.2, L50.3, L50.4, L50.5, L50.8, L50.9, L56.3, or T78.3) based on the ICD-10 and the prescription of urticaria medicines (H1-antihistamines, systemic steroids, azathioprine, cyclosporine, or methotrexate). We excluded claims without identifiable durations of drug prescriptions that were necessary to define chronic urticaria and chronic urticaria remission.

A patient with chronic urticaria was defined as having continuous management of ≥ 42 days. The period from the start date of the urticaria episode to the date when all prescribed urticaria drugs had been used was considered the duration of continuous management. If the patient returned within 7 days from the time when all the prescribed urticaria drugs had been used, this was also considered a visit for continuous management of the same urticaria episode. Chronic urticaria in this study includes both CSU and physical urticaria because a specific ICD-10 code for CSU is lacking. Remission of chronic urticaria was defined if a patient with chronic urticaria never utilized medical services to treat urticaria for ≥ 365 days, even after using all the prescribed urticaria medicines.

Statistical analysis

To describe the general characteristics of the study population, the χ^2 test was performed using dependent variables, including urticaria, chronic urticaria, and chronic urticaria remission, and independent variables, including sex, age group (0–9, 10–19, 20–44, 45–64, ≥ 65 years), residential area, income level, and level of medical institution during the first visit. For urticaria patients, the values of the covariates were those recorded at the first visit for urticaria during the follow-up period. The presence of autoimmune thyroid disease during 2002–2013 was also entered as an independent variable. A patient with autoimmune thyroid disease was defined as a patient with diagnostic codes for Grave's disease

(E05.0) and Hashimoto's thyroiditis (E06.3). Annual incidence rates of urticaria per 100,000 person-years were calculated.

Cumulative incidences of urticaria, chronic urticaria, and chronic urticaria remission were calculated using the life table estimation method.¹⁷ Cox proportional hazards analysis was performed to evaluate the association between the dependent and independent variables at baseline. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 24 (IBM, Armonk, NY, USA). All statistical tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

General characteristics of the study population and incidence of new-onset urticaria

In 2004 and 2013, the NHIS-NSC contained data for 1,027,620 individuals with no history of urticaria (518,757 males and 508,863 females). A total of 49,129 patients were identified as having new-onset urticaria (Table 1). The annual incidence rates of urticaria ranged from 45.7 to 82.5 per 100,000 person-years (Fig. 2). The 5-year and 10-year cumulative incidence rates of urticaria were 2.1% and 4.9%, respectively (Fig. 3a). A significantly greater proportion of women developed new-onset urticaria (5.4% women vs. 4.2% men) (Table 1). However, the female predominance was clearly found only for patients aged 20–44 and 45–64 years (Table 2). Moreover, patients aged 10–19 and 20–44 years were less likely to develop urticaria compared with those in other age groups (Table 1).

The multivariable Cox regression analysis showed that these variables were significantly associated with urticaria (Table 3). After adjusting for covariates, the risk of urticaria was significantly higher for females (hazard ratio [HR], 1.25; 95% confidence interval [CI], 1.23–1.28) than for males. Patients aged 10–19, 20–44, and 45–64 years had a lower risk of urticaria than those aged 0–9 years. Rural residence was significantly associated with a higher risk of urticaria than urban residence, even after adjusting for income levels and level of medical institutions. Both autoimmune thyroid diseases (Grave's disease and Hashimoto's thyroiditis) were associated with a higher risk of the development of urticaria (Table 3).

Development of chronic urticaria among patients with new-onset urticaria

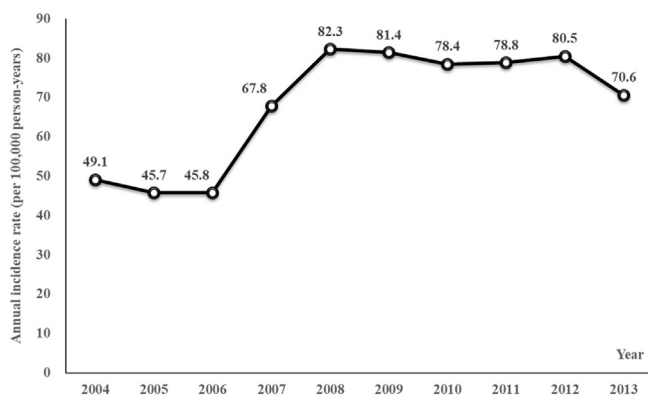
In this study population, among all patients with new-onset urticaria, 2980 patients (6.1%) were finally identified as having chronic urticaria (Table 1). Therefore, most patients (93.9%) with new-onset urticaria were classified as having acute urticaria (non-chronic urticaria). Of the 2980 patients with chronic urticaria, 1389 patients (46.6%) already had chronic urticaria when they were first diagnosed with urticaria. The remaining 1591 (53.4%) had acute urticaria at their first diagnosis of urticaria, but they subsequently developed chronic urticaria when the disease recurred after an average of 613.6 days (standard deviation, 760.6 days). The 5-year and 10-year cumulative incidence rates of chronic urticaria among all patients with new-onset urticaria were 6.3% and 7.8%, respectively (Fig. 3b).

The proportion of those who developed chronic urticaria among patients with new-onset urticaria was significantly lower for women than for men (5.6% vs. 6.6%). However, the number of chronic urticaria cases was higher for women than for men (1548 vs. 1432), which could be attributed to the higher number of women with new-onset urticaria (27,510 vs. 21,619). Regarding age groups, patients aged 0–9 years had the lowest proportion of chronic urticaria among those with urticaria (Table 1).

Table 1
General characteristics of patients with new-onset urticaria, chronic urticaria, and chronic urticaria remission (2004–2013).

	Total	New-onset urticaria			Chronic urticaria from new-onset urticaria			Chronic urticaria remission		
	N (a)	N (b)	% (b/a)	P	N (c)	% (c/b)	P	N (d)	% (d/c)	P
Overall	1,027,620	49,129	4.8		2980	6.1		1893	63.5	
Sex										
Male	518,757	21,619	4.2	<0.001	1432	6.6	<0.001	910	63.5	0.979
Female	508,863	27,510	5.4		1548	5.6		983	63.5	
Age group (years)										
0–9	175,806	11,440	6.5	<0.001	132	1.2	<0.001	73	55.3	0.257
10–19	128,759	4116	3.2		289	7.0		179	61.9	
20–44	410,908	14,890	3.6		1209	8.1		766	63.4	
45–64	223,757	12,820	5.7		903	7.0		582	64.5	
65 and older	88,390	5863	6.6		447	7.6		293	65.5	
Residential area at onset										
Urban	708,081	33,495	4.7	<0.001	2192	6.5	<0.001	1378	62.9	0.213
Rural	319,539	15,634	4.9		788	5.0		515	65.4	
Income level at onset (quintile)										
0 (lowest)	25,162	962	3.8	<0.001	62	6.4	0.003	28	45.2	0.045
1st	126,936	6226	4.9		402	6.5		260	64.7	
2nd	157,297	6927	4.4		423	6.1		262	61.9	
3rd	201,686	9100	4.5		502	5.5		325	64.7	
4th	245,803	11,957	4.9		670	5.6		439	65.5	
5th (highest)	270,736	13,957	5.2		921	6.6		579	62.9	
Level of medical institution visited at onset										
Clinic	854,071	41,723	4.9	<0.001	2439	5.8	<0.001	1572	64.5	0.025
Hospital	70,203	2799	4.0		74	2.6		38	51.4	
Referral hospital	103,346	4607	4.5		467	10.1		283	60.6	
Autoimmune thyroid disease (present vs. absent)										
Grave's disease	10,295	669	6.5	<0.001	70	10.5	<0.001	45	64.3	0.893
Hashimoto's thyroiditis	9080	671	7.4	<0.001	74	11.0	<0.001	49	66.2	0.626

P value was calculated using the Pearson chi-square test.

**Fig. 2.** Annual incidence rates of urticaria per 1000 person-years (2004–2013).

The multivariable Cox regression analysis showed that some risk factors for the development of chronic urticaria were almost the opposite of those for new-onset urticaria. Women were at significantly lower risk for the development of chronic urticaria after adjusting for other demographic differences (HR, 0.75; 95% CI, 0.70–0.81) compared with men. Patients aged 0–9 years had a lower risk of chronic urticaria than patients in other age groups. Rural residence was associated with a lower risk of chronic urticaria compared with urban residence after adjusting for covariates. In contrast, both autoimmune thyroid diseases showed similar associations with new-onset urticaria (Table 3).

Chronic urticaria remission

Of 2980 patients with chronic urticaria in the study population, 1893 patients experienced remission (63.5%) (Table 1).

Approximately 50% of patients with chronic urticaria experienced remission after 11 months. After 3 months, 25.2% of patients with chronic urticaria experienced remission. The remission rates of chronic urticaria were 52.6% at 1 year, 77.7% at 3 years, and 88.9% at 5 years (Fig. 3c). The multivariable Cox regression analysis found that income level was the only variable that was significantly associated with chronic urticaria remission. The middle to highest income level was significantly associated with higher rates of chronic urticaria remission compared with the lowest income level (Table 3).

Discussion

This study investigated the long-term natural course of new-onset urticaria using a nationally representative cohort. We showed that the 10-year cumulative incidence rate of urticaria for the general population was 4.9%, whereas that of chronic urticaria among patients with new-onset urticaria was 7.8%. Half of the patients with chronic urticaria achieved remission after 11 months, and approximately 90% achieved remission within 5 years. Age, sex, residential area, and autoimmune thyroid disease were significantly associated with urticaria or chronic urticaria, but not with chronic urticaria remission.

The main advantage of this study was that it was possible to follow the same individuals for up to 10 years. We used a single data source including all age groups to investigate the whole natural course of urticaria (e.g., onset of urticaria, chronic urticaria development, and chronic urticaria remission). Additionally, we used a nationally representative sample, which enabled the analysis of the natural course of urticaria in the unselected general population.

Little is known about the frequency and risk factors of new-onset urticaria for progression to chronic urticaria. We estimated that the cumulative incidence of chronic urticaria was 7.8% among patients with new-onset urticaria during the 10-year follow-up.

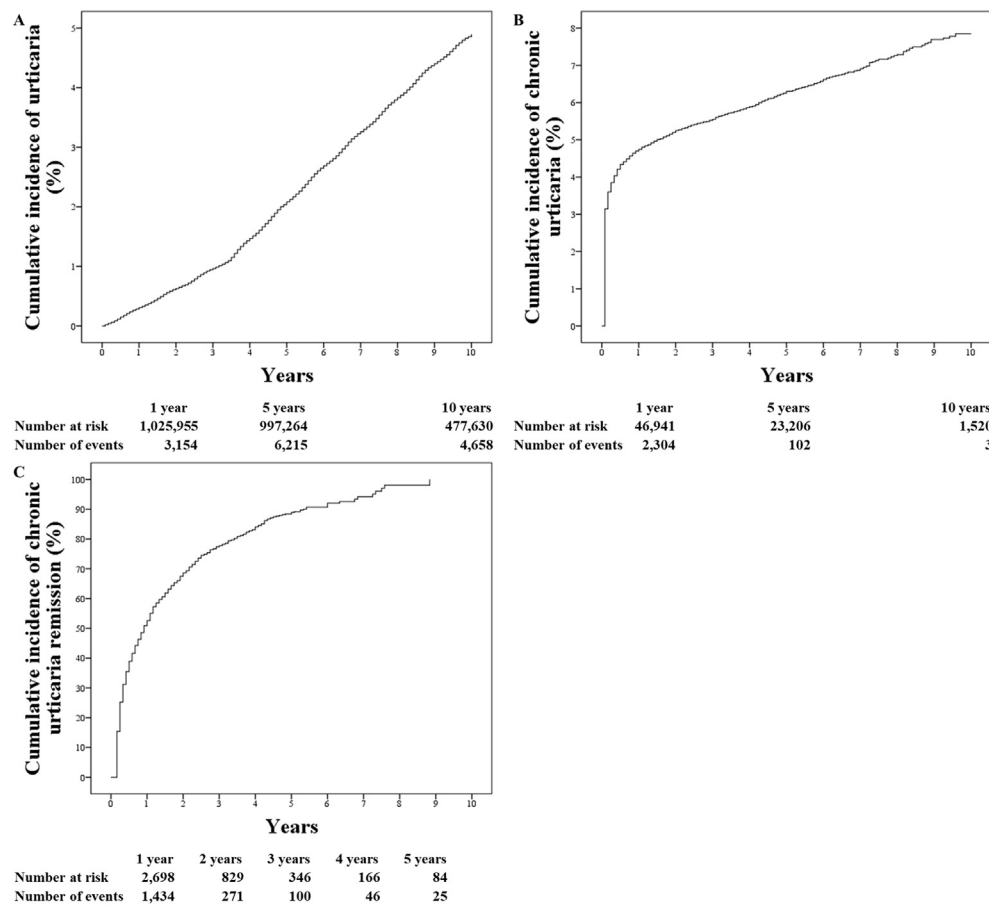


Fig. 3. Cumulative incidence curves for 10-year incidence of urticaria among the general population (a), chronic urticaria among patients with new-onset urticaria (b), and chronic urticaria remission (c).

Table 2

Sex ratios of the study population according to age groups.

	Control (Non-urticaria)				New-onset urticaria					Chronic urticaria				
	Male		Female		Male		Female		P	Male		Female		P
	N	%	N	%	N	%	N	%	(vs. control)	N	%	N	%	(vs. control)
Overall	497,138	50.8	481,353	49.2	21,619	44.0	27,510	56.0	<0.001	1432	48.1	1548	51.9	0.003
Age group (years)														
0-9	84,896	51.7	79,470	48.3	6156	53.8	5284	46.2	<0.001	78	59.1	54	40.9	0.087
10-19	66,191	53.1	58,452	46.9	2098	51.0	2018	49.0	0.007	171	59.2	118	40.8	0.039
20-44	204,750	51.7	191,268	48.3	5675	38.1	9215	61.9	<0.001	538	44.5	671	55.5	<0.001
45-64	108,082	51.2	102,855	48.8	5372	41.9	7448	58.1	<0.001	418	46.3	485	53.7	0.003
65 and older	33,219	40.3	49,308	59.7	2318	39.5	3545	60.5	0.281	227	50.8	220	49.2	<0.001

P value was calculated by the Pearson chi-square test.

period. This finding means that most patients with new-onset urticaria maintain acute urticaria. A retrospective study conducted at a primary dermatology clinic in Japan reported that approximately 85% of patients with acute spontaneous urticaria experienced remission within 1 month and only 7% still had symptoms for 1 year.¹⁸ Our results indicated several clinical factors affecting progression to chronic urticaria: patients aged 10 years or older, male sex, urban residence and autoimmune thyroid disease were associated with a higher risk of progression to chronic urticaria.

It has been believed that women are more likely to have urticaria than men.⁹ However, recent studies revealed that a female predominance of urticaria is observed only in specific age groups.^{10,19–21} Our study also showed a clear female predominance

for new-onset urticaria only for those aged 20–44 and 45–64 years. A female predominance of urticaria in specific age groups could be due to estrogen. Estrogen is believed to enhance humoral immunity and antibody synthesis.¹ Experimental data have shown that estradiol could enhance mast cell activation and allergic sensitization in rodent models.²²

Autoimmunity is thought to be a frequent underlying cause of CSU,²³ and chronic urticaria could be related to other autoimmune processes.²⁴ Thyroid disease is the most frequently investigated disease that is associated with CSU.^{24,25} Similar to previous studies, we also found that autoimmune thyroid disease was associated with a higher risk of urticaria and progression to chronic urticaria.

Table 3
Relative risks of factors affecting the occurrence of urticaria, chronic urticaria, and chronic urticaria remission.

Covariates	New-onset urticaria		Chronic urticaria from new-onset urticaria		Chronic urticaria remission	
	HR	95% CI	HR	95% CI	HR	95% CI
Sex						
Male	1.00		1.00		1.00	
Female	1.25	1.23–1.28	0.74	0.69–0.79	1.05	0.96–1.15
Age group (years)						
0–9	1.00		1.00		1.00	
10–19	0.47	0.46–0.49	6.19	5.03–7.61	0.84	0.64–1.11
20–44	0.54	0.53–0.56	7.48	6.25–8.96	0.87	0.68–1.11
45–64	0.88	0.86–0.90	6.74	5.61–8.10	0.85	0.66–1.08
65 and older	1.16	1.13–1.20	7.80	6.41–9.50	0.91	0.70–1.17
Residential area at onset						
Urban	1.00		1.00		1.00	
Rural	1.02	1.00–1.04	0.75	0.69–0.81	1.03	0.93–1.14
Income level at onset (quintile)						
0 (lowest)	1.00		1.00		1.00	
1st	1.51	1.41–1.62	0.90	0.68–1.17	1.47	0.99–2.18
2nd	1.39	1.30–1.49	0.84	0.64–1.10	1.42	0.96–2.10
3rd	1.41	1.31–1.50	0.81	0.62–1.06	1.51	1.02–2.23
4th	1.48	1.38–1.58	0.88	0.67–1.14	1.60	1.09–2.35
5th (highest)	1.57	1.47–1.68	0.93	0.72–1.20	1.50	1.02–2.20
Level of medical institution visited at onset						
Clinic	1.00		1.00		1.00	
Hospital	0.80	0.77–0.83	0.49	0.39–0.62	0.73	0.53–1.02
Referral hospital	0.89	0.87–0.92	1.89	1.71–2.09	0.98	0.86–1.11
Autoimmune thyroid disease (present vs. absent)						
Grave's disease	1.26	1.16–1.36	1.36	1.06–1.73	1.10	0.81–1.51
Hashimoto's thyroiditis	1.43	1.32–1.54	1.50	1.19–1.90	1.06	0.79–1.43

CI, confidence interval; HR, hazard ratio.

Approximately 90% of patients with chronic urticaria had remission within 5 years, and more than half of the patients with chronic urticaria achieved remission after 1 year. Our study cohort showed a higher remission rate for chronic urticaria compared with previous reports.^{6–8,15} One possible explanation for the higher remission rate of chronic urticaria is that our study included more mild cases that were frequently excluded from the studies conducted at referral hospitals. Disease severity is associated with the duration of chronic urticaria.^{6–8} A study conducted at referral outpatient allergy clinics in Israel reported that all patients with mild chronic urticaria had remission within 2 years, whereas moderate to severe chronic urticaria persisted in 59% of patients for up to 2 years.⁶ Additionally, patients who controlled their symptoms with OTC antihistamines might have been classified as experiencing remission during this study; therefore, the remission rate of chronic urticaria may have been overestimated in this study. However, the ability to control symptoms with OTC antihistamines indicates that the severity of urticaria had become milder.

Similar to other studies using claims data, this study had some limitations. First, the operational definitions of diseases from claims data were inevitably different from the actual diagnoses of diseases. For example, a physician could claim different diagnostic codes to get a reimbursement for off-label use of medications. Therefore, we used a strict case definition to minimize misclassification of urticaria. We used only the primary diagnostic codes for urticaria and considered prescription data combined with diagnostic codes to define urticaria cases. Some researchers used only diagnostic codes to define urticaria, and some also used secondary diagnostic codes; however, these approaches have a higher risk of misclassification. Second, this study did not distinguish CSU from physical urticaria. It is difficult to define CSU using our data because a specific ICD-10 code for CSU is lacking. Furthermore, two or more different subtypes of urticaria can coexist.^{8,14,15} Even with physical urticaria, the

avoidance of triggers is often not feasible and patients need to continue using medication. Therefore, the natural history of chronic urticaria (including CSU and physical urticaria), not just CSU alone, is also important. Finally, the data used in this study did not include information about disease severity or specific subtypes of urticaria. A few studies have reported the association between disease severity and the natural course of CSU.^{6,8}

Despite these limitations, our study showed the long-term natural course of urticaria using a large, nationally representative sample. During the 10-year follow-up period, less than 10% of patients with new-onset urticaria progressed to chronic urticaria, and most patients with chronic urticaria experienced remission within 5 years regardless of age, sex, residential area, or associated thyroid disease. The results of this study could enable physicians to not only provide more accurate information to their patients but also achieve a better understanding of the nature of the disease.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

HSJ contributed to the conception and design of study and drafted the article. SJE and JYL performed the statistical analyses and interpretation of the results. DYK substantially critically revised the article for important intellectual content. All authors have read and approved the final form of the manuscript.

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