

A Retrospective Cohort Study on the Comorbidity in 19,264 Chinese Patients of Different Ages with Urticaria

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To examine the prevalence of comorbidities in Chinese urticaria patients and assess medication use patterns across different ages (6–11 years, 12–17 years, above 18 years), a retrospective cohort study was performed in 192,647 urticaria patients within the Health Database. After 1:1 propensity score matching, 166,921 people were divided into the urticaria group and the control group, and the follow-up data were collected within 2 years. During the 12-month and 24-month follow-up period, significant comorbidities identified included allergic rhinitis and asthma, with distinct patterns observed across age groups. Chronic urticaria patients often have complications, such as allergic rhinitis, upper respiratory infection, oropharyngeal infection, and dental caries. The study underscores the need for age-specific treatment strategies in urticaria management.

Key words: urticaria; comorbidity; chronic urticaria; acute urticaria; medication; Charlson Comorbidity Index.

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Urticaria is a localized oedema reaction in the skin and mucosa (1). It is classified based on its duration, as acute or chronic (2). Acute urticaria (AU) is defined as the occurrence of wheals, angioedema, or both for 6 weeks or less (3). Chronic urticaria (CU) is defined as the occurrence of wheals, angioedema, or both for more than 6 weeks (4–6). With its unknown aetiology and recurrence, urticaria significantly influences the quality of life of patients, especially those with CU, which can be negatively impacted by a wide range of comorbidities (7). According to reports, CU has been related to a specific pattern of comorbidities, such as autoimmune diseases, allergies, asthma, etc (1, 8–14). In terms of medication, a second-generation H1 antihistamine, such as cetirizine, levocetirizine, loratadine, etc., is recommended as first-line treatment for all types of urticaria, which can be increased or combined if necessary for AU while using standard doses for CU (4).

However, there is still a lack of large cohort research on the comorbidities and medication for urticaria in China,

SIGNIFICANCE

During the 12-month and 24-month follow-up period, the common complications of patients with urticaria mainly included allergic rhinitis, allergic asthma, allergic conjunctivitis, atopic dermatitis, *Helicobacter pylori* infection, and parasitic infection. Patients with chronic urticaria are more likely to have complications such as allergic rhinitis, upper respiratory infection, oropharyngeal infection, and dental caries. Between the 12-month and 24-month follow-up periods, there were some slight changes in the spectrum of patients' complications. Loratadine is one of the most used medications for treating acute and chronic urticaria in different ages.

especially relevant reports on children and adolescents. This study investigated the occurrence of comorbidities and medication in urticaria patients of different age groups during the 2-year follow-up period in a huge database and may provide support for the diagnosis and treatment of urticaria in the future.

MATERIALS AND METHODS

Study population

This study was reviewed and approved by the ethical committee of the Tianjin Medical University General Hospital, Tianjin, China (NO: IRB2021-WZ-171). Written informed consent was obtained before study from all patients. The research period was from 1 January 2015 to 31 October 2020, including the identification period from 1 January 2016 to 31 October 2019 (**Fig. 1**). For the urticaria group, the index date was defined as the date when the patient was first diagnosed with urticaria, and the index date needed to be within the identification period. Patients who had ever been diagnosed with keyword "urticaria" previously were included in the urticaria group. The control group consisted of non-urticaria patients who visited the doctor within the same period, and the index date was also defined as the date of first visit within the identification period. The age of all patients was calculated by subtracting the date of birth from the index date and rounded down to an integer. The 3 age groups comprise ages 6–11, 12–17, and >18.

The inclusion and exclusion criteria of the study population:

Inclusion criteria: (i) patients in the Health Database within the above-mentioned periods; (ii) patients aged ≥ 6 years on the index date; (iii) patients having no record of the diagnostic keyword urticaria previously were used as control.

Exclusion criteria: (i) patients of abnormal age; (ii) patients with missing sex; (iii) patients with an abnormal number of visits; (iv) patients whose index date was not in the identification period.

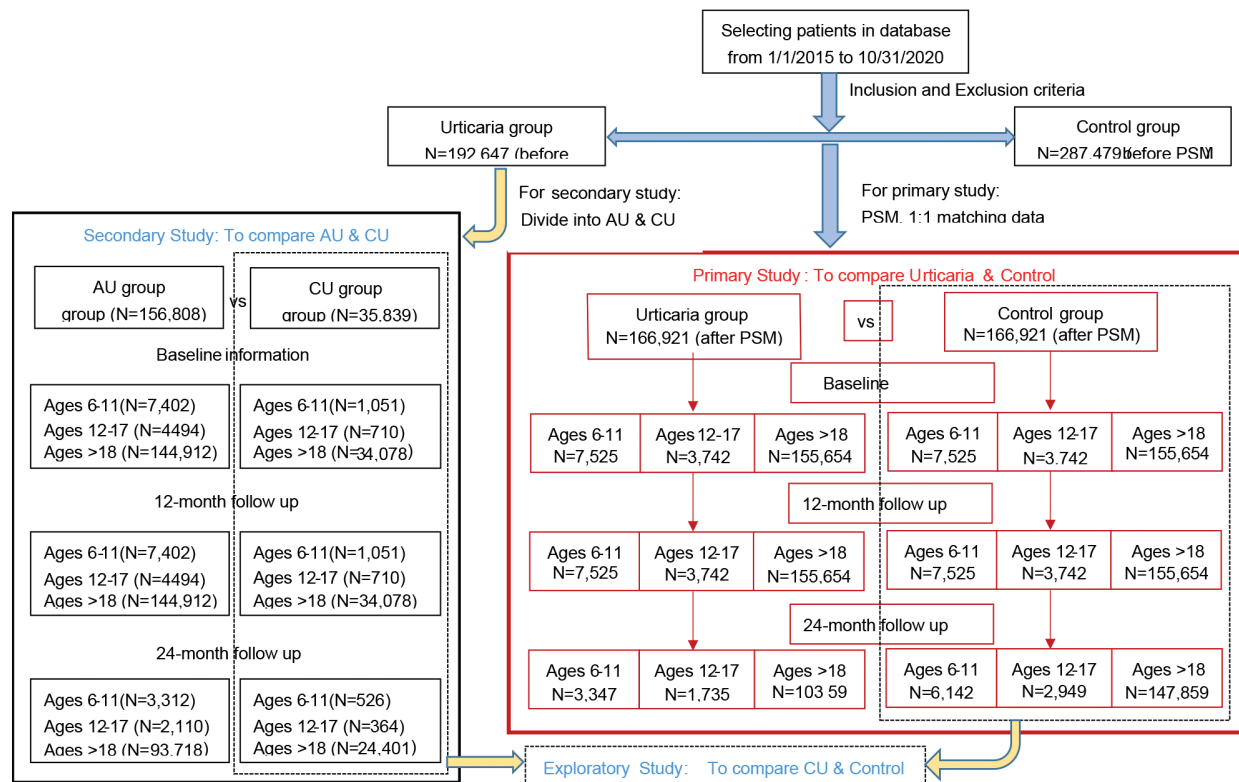


Fig. 1. Flowchart of the retrospective study on comorbidity of urticaria.

Follow-up

The baseline period was defined as ≥ 12 months before the index date, while the follow-up period was defined as ≥ 12 months after the index date until 31 October 2020. If 1 patient had multiple visits during the 12-month baseline period, all the records were included in the baseline period.

For patients who were followed up for more than 12 months, the comorbidities were presented in the 12-month follow-up period. If the follow-up was longer than 24 months, the comorbidities would be in the 24-month follow-up period.

Statistical methods

General approaches. This study used descriptive statistics. The continuous variables were presented as minimum, maximum, mean, standard deviation (SD), median, and interquartile range (IQR). The categorical variables were expressed as frequencies and percentages. The comparison was based on data distribution. If the continuous variable showed non-normal distribution, the non-parametric test method was used. For all analyses, a p -value of < 0.05 was considered significant.

Statistical analysis to eliminate confounding effects. The baseline characteristics of patients (such as age, sex, healthcare, rank of hospital, and type of medical insurance) were used as matching variables. Propensity score matching (PSM) was used to eliminate the differences between the two groups. The nearest neighbour matching method was used for 1:1 matching, and the caliper value was set to 0.05. The standard mean difference (SMD) was used to evaluate matching results. $SMD < 0.1$ was considered a good matching effect. Age was selected as the exact matching variable among matching factors such as age, gender, healthcare, rank of hospital, and type of medical insurance.

Sensitivity analysis. The primary endpoint of this study was to compare the proportion of patients with comorbidities in the

urticaria group and the control group by χ^2 test of independence or Fisher's exact test.

RESULTS

A total of 192,647 people in the urticaria group met the inclusion and exclusion criteria within the identification period (Fig. 1).

Comparison of the comorbidities in patients with and without urticaria at 3 age levels within the 12-month follow-up period

The primary endpoint of this study focused on the proportion of patients with comorbidities between 2 groups (urticaria vs control). The obtained population after 1:1 matching by PSM was 166,921 in each group, respectively, including 7,525 aged 6–11, 3,742 aged 12–17 and 155,654 patients aged > 18 (Table I). All 25 comorbidities were collected as shown in Table I and Fig. S1.

Within the 12-month follow-up period, the incidences of 6 comorbidities, including allergic rhinitis (AR), allergic asthma (AA), allergic conjunctivitis (AC), atopic dermatitis (AD), *Helicobacter pylori* infection and parasitic infection (PI) with urticaria in those aged > 18 were higher ($p < 0.05$). However, incidences of the other 16 comorbidities were higher in the control group ($p < 0.05$).

Allergic conjunctivitis was significantly more common in urticaria patients aged 6–11 ($p < 0.05$). But the

Table I. Comparison of comorbid characteristics between patients with and without urticaria during the 12-month follow-up period

Characteristics	Ages 6–11			Ages 12–17			Ages > 18			Total		
	Control n = 7,525 n (%)	Urticaria n = 7,525 n (%)	p*	Control n = 3,742 n (%)	Urticaria n = 3,742 n (%)	p*	Control n = 155,654 n (%)	Urticaria n = 155,654 n (%)	p*	Control n = 166,921 n (%)	Urticaria n = 166,921 n (%)	p*
Allergic rhinitis	312 (4.1)	316 (4.2)	0.9	124 (3.3)	94 (2.5)	0.039	4,627 (3.0)	6,781 (4.4)	< 0.001	5,063 (3.0)	7,191 (4.3)	< 0.001
Sinusitis	337 (4.5)	167 (2.2)	< 0.001	131 (3.5)	49 (1.3)	< 0.001	3,071 (2.0)	2,590 (1.7)	< 0.001	3,539 (2.1)	2,806 (1.7)	< 0.001
Rhin sinusitis with nasal polyps	3 (< 0.1)	0 (0)	0.2	7 (0.2)	0 (0)	0.016	201 (0.1)	74 (< 0.1)	< 0.001	211 (0.1)	74 (< 0.1)	< 0.001
Asthma	292 (3.9)	142 (1.9)	< 0.001	62 (1.7)	39 (1.0)	0.021	4,250 (2.7)	4,231 (2.7)	0.8	4,604 (2.8)	4,412 (2.6)	0.040
Allergic asthma	9 (0.1)	4 (< 0.1)	0.2	7 (0.2)	3 (< 0.1)	0.2	447 (0.3)	635 (0.4)	< 0.001	463 (0.3)	642 (0.4)	< 0.001
Allergic conjunctivitis	103 (1.4)	141 (1.9)	0.014	17 (0.5)	21 (0.6)	0.5	486 (0.3)	905 (0.6)	< 0.001	606 (0.4)	1,067 (0.6)	< 0.001
Allergic (eosinophilic) gastroenteritis	0 (0)	0 (0)		0 (0)	0 (0)		7 (< 0.1)	8 (< 0.1)	0.8	7 (< 0.1)	8 (< 0.1)	0.8
Atopic dermatitis	8 (0.1)	13 (0.2)	0.3	7 (0.2)	6 (0.2)	0.8	221 (0.1)	536 (0.3)	< 0.001	236 (0.1)	555 (0.3)	< 0.001
Upper respiratory infection	1,899 (25)	1,513 (20)	< 0.001	474 (13)	275 (7.3)	< 0.001	19,969 (13)	17,250 (11)	< 0.001	22,342 (13)	19,038 (11)	< 0.001
Helicobacter pylori infection	53 (0.7)	10 (0.1)	< 0.001	37 (1.0)	10 (0.3)	< 0.001	3,480 (2.2)	3,807 (2.4)	< 0.001	3,570 (2.1)	3,827 (2.3)	0.003
Parasitic infection	1 (< 0.1)	6 (< 0.1)	0.12	8 (0.2)	20 (0.5)	0.023	170 (0.1)	439 (0.3)	< 0.001	179 (0.1)	465 (0.3)	< 0.001
Chronic cholecystitis	0 (0)	0 (0)		4 (0.1)	0 (0)	0.12	569 (0.4)	192 (0.1)	< 0.001	573 (0.3)	192 (0.1)	< 0.001
Oropharyngeal infection and cavity	2,311 (31)	1,874 (25)	< 0.001	594 (16)	355 (9.5)	< 0.001	23,627 (15)	21,448 (14)	< 0.001	26,532 (16)	23,677 (14)	< 0.001
Viral infection	406 (5.4)	359 (4.8)	0.081	213 (5.7)	125 (3.3)	< 0.001	9,944 (6.4)	9,203 (5.9)	< 0.001	10,563 (6.3)	9,687 (5.8)	< 0.001
Vitamin D deficiency	11 (0.1)	9 (0.1)	0.7	6 (0.2)	3 (< 0.1)	0.5	81 (< 0.1)	55 (< 0.1)	0.026	98 (< 0.1)	67 (< 0.1)	0.016
Thyroid disease	83 (1.1)	21 (0.3)	< 0.001	154 (4.1)	30 (0.8)	< 0.001	13,448 (8.6)	9,471 (6.1)	< 0.001	13,685 (8.2)	9,522 (5.7)	< 0.001
Thyroiditis	6 (< 0.1)	0 (0)	0.031	20 (0.5)	2 (< 0.1)	< 0.001	1,773 (1.1)	1,325 (0.9)	< 0.001	1,799 (1.1)	1,327 (0.8)	< 0.001
Autoimmune thyroiditis	5 (< 0.1)	1 (< 0.1)	0.2	10 (0.3)	1 (< 0.1)	0.007	484 (0.3)	438 (0.3)	0.13	499 (0.3)	440 (0.3)	0.054
Hypothyroidism	9 (0.1)	1 (< 0.1)	0.011	36 (1.0)	4 (0.1)	< 0.001	5,239 (3.4)	3,198 (2.1)	< 0.001	5,284 (3.2)	3,203 (1.9)	< 0.001
Hyperthyroidism	25 (0.3)	7 (< 0.1)	0.001	61 (1.6)	12 (0.3)	< 0.001	3,058 (2.0)	1,884 (1.2)	< 0.001	3,144 (1.9)	1,903 (1.1)	< 0.001
Autoimmune hepatitis	0 (0)	0 (0)		1 (< 0.1)	0 (0)	> 0.9	372 (0.2)	188 (0.1)	< 0.001	373 (0.2)	188 (0.1)	< 0.001
Autoinflammatory disease	4 (< 0.1)	1 (< 0.1)	0.4	4 (0.1)	4 (0.1)	> 0.9	72 (< 0.1)	59 (< 0.1)	0.3	80 (< 0.1)	64 (< 0.1)	0.2
Hypocomplementemia	1 (< 0.1)	1 (< 0.1)	> 0.9	0 (0)	0 (0)		2 (< 0.1)	2 (< 0.1)	> 0.9	3 (< 0.1)	3 (< 0.1)	> 0.9
Connective tissue diseases	23 (0.3)	2 (< 0.1)	< 0.001	52 (1.4)	7 (0.2)	< 0.001	2,374 (1.5)	1,418 (0.9)	< 0.001	2,449 (1.5)	1,427 (0.9)	< 0.001
Malignant tumors	102 (1.4)	8 (0.1)	< 0.001	156 (4.2)	4 (0.1)	< 0.001	8,260 (5.3)	2,297 (1.5)	< 0.001	8,518 (5.1)	2,309 (1.4)	< 0.001
Mental disorders	158 (2.1)	30 (0.4)	< 0.001	206 (5.5)	58 (1.5)	< 0.001	17,405 (11)	13,673 (8.8)	< 0.001	17,769 (11)	13,761 (8.2)	< 0.001
Anxiety	5 (< 0.1)	2 (< 0.1)	0.5	62 (1.7)	19 (0.5)	< 0.001	4,853 (3.1)	4,375 (2.8)	< 0.001	4,920 (2.9)	4,396 (2.6)	< 0.001
Depression	7 (< 0.1)	1 (< 0.1)	0.070	98 (2.6)	24 (0.6)	< 0.001	3,393 (2.2)	2,324 (1.5)	< 0.001	3,498 (2.1)	2,349 (1.4)	< 0.001
Sleep disturbance	127 (1.7)	25 (0.3)	< 0.001	41 (1.1)	17 (0.5)	0.002	12,122 (7.8)	10,536 (6.8)	< 0.001	12,290 (7.4)	10,578 (6.3)	< 0.001
Vitiligo	37 (0.5)	13 (0.2)	< 0.001	25 (0.7)	17 (0.5)	0.2	382 (0.2)	374 (0.2)	0.8	444 (0.3)	404 (0.2)	0.2
Diabetes	46 (0.6)	6 (< 0.1)	< 0.001	115 (3.1)	7 (0.2)	< 0.001	25,702 (17)	9,421 (6.1)	< 0.001	25,863 (15)	9,434 (5.7)	< 0.001
Osteoporosis	6 (< 0.1)	0 (0)	0.031	19 (0.5)	5 (0.1)	0.004	5,116 (3.3)	3,659 (2.4)	< 0.001	5,141 (3.1)	3,664 (2.2)	< 0.001

* χ^2 test of independence; Fisher's exact test.

incidences of these 12 comorbidities, such as sinusitis, asthma, upper respiratory infection, etc., were significantly higher in the control group ($p < 0.05$).

At ages 12–17, the incidence of parasitic infection in patients with urticaria was significantly higher ($p < 0.05$). People with these 14 comorbidities, like allergic rhinitis, sinusitis, rhinosinusitis with nasal polyps, etc., were found to be higher in the control group ($p < 0.05$).

The baseline characteristics of the 2 groups were significantly different before PSM. But after PSM, the SMD among covariates were all less than 0.1, and the influence of confounding factors was balanced (Table SI and Table SII).

A logistic regression model was constructed using whether the patient had 25 target comorbidities during the 12-month follow-up as the dependent variable (Fig. 2). The patient group was used as independent variables, while age, gender, healthcare, rank of hospital, type of medical insurance, and whether having comorbidity with urticaria at baseline were used as the covariates. To explore the difference in the probability of the comorbidities listed in the research, the odds ratio (OR) of groups (urticaria vs control) and 95% confidence interval (CI) were calculated by logistic regression.

Within ages 6–11, when controlling for sex, age and baseline diseases, the probability of having 13 comor-

bidities such as sinusitis, asthma, upper respiratory tract infection, etc., in patients with urticaria was significant lower (Fig. 2A).

Regarding ages 12–17, Fig. 2B shows a similar pattern to Fig. 2A. The probability of having most comorbidities in patients with urticaria was significantly lower.

At age > 18, the result also showed a similar pattern to the result at ages 12–17 (Fig. 2C). However, the probability of having allergic asthma, allergic conjunctivitis, atopic dermatitis, and parasitic infection in patients with urticaria was significantly higher. Hypocomplementemia was not included due to the small amount of data.

The Charlson Comorbidity Index (CCI) was used during the 12-month follow-up (Table SIII). The CCI of the control group was significantly higher than that of the urticaria group among the 3 age groups ($p < 0.01$) (Table SIV).

Comparison of the comorbidities in patients with and without urticaria at 3 age levels within the 24-month follow-up period

At the 24-month follow-up endpoint, this study also compared the incidences of 25 comorbidities listed above in patients with and without urticaria in 3 different age groups and for the total population. After PSM, there

Table II. Comparison of comorbid characteristics between patients with and without urticaria during the 24-month follow-up

Characteristics	Ages 6–11			Ages 12–17			Ages >18			Total		
	Control	Urticaria	<i>p</i> *	Control	Urticaria	<i>p</i> *	Control	Urticaria	<i>p</i> *	Control	Urticaria	<i>p</i> *
	<i>n</i> = 6,142 <i>n</i> (%)	<i>n</i> = 3,347 <i>n</i> (%)		<i>n</i> = 2,949 <i>n</i> (%)	<i>n</i> = 1,735 <i>n</i> (%)		<i>n</i> = 147,859 <i>n</i> (%)	<i>n</i> = 103,591 <i>n</i> (%)		<i>n</i> = 156,950 <i>n</i> (%)	<i>n</i> = 108,673 <i>n</i> (%)	
Allergic rhinitis	452 (7.4)	206 (6.2)	0.027	172 (5.8)	65 (3.7)	0.002	8,083 (5.5)	7,251 (7.0)	<0.001	8,707 (5.5)	7,522 (6.9)	<0.001
Sinusitis	450 (7.3)	115 (3.4)	<0.001	149 (5.1)	45 (2.6)	<0.001	5,152 (3.5)	3,182 (3.1)	<0.001	5,751 (3.7)	3,342 (3.1)	<0.001
Rhinosinusitis with nasal polyps	5 (<0.1)	0 (0)	0.2	9 (0.3)	0 (0)	0.031	323 (0.2)	96 (<0.1)	<0.001	337 (0.2)	96 (<0.1)	<0.001
Asthma	356 (5.8)	102 (3.0)	<0.001	90 (3.1)	23 (1.3)	<0.001	6,581 (4.5)	4,422 (4.3)	0.028	7,027 (4.5)	4,547 (4.2)	<0.001
Allergic asthma	15 (0.2)	7 (0.2)	0.7	10 (0.3)	4 (0.2)	0.5	830 (0.6)	686 (0.7)	0.001	855 (0.5)	697 (0.6)	0.001
Allergic conjunctivitis	151 (2.5)	91 (2.7)	0.4	27 (0.9)	10 (0.6)	0.2	953 (0.6)	1,027 (1.0)	<0.001	1,131 (0.7)	1,128 (1.0)	<0.001
Allergic (eosinophilic) gastroenteritis	1 (<0.1)	0 (0)	>0.9	0 (0)	0 (0)		9 (<0.1)	7 (<0.1)	0.8	10 (<0.1)	7 (<0.1)	>0.9
Atopic dermatitis	13 (0.2)	10 (0.3)	0.4	10 (0.3)	7 (0.4)	0.7	371 (0.3)	558 (0.5)	<0.001	394 (0.3)	575 (0.5)	<0.001
Upper respiratory infection	2,319 (38)	876 (26)	<0.001	569 (19)	178 (10)	<0.001	31,260 (21)	19,218 (19)	<0.001	34,148 (22)	20,272 (19)	<0.001
<i>Helicobacter pylori</i> infection	64 (1.0)	13 (0.4)	<0.001	56 (19)	12 (0.7)	<0.001	6,242 (4.2)	4,595 (4.4)	0.009	6,362 (4.1)	4,620 (4.3)	0.012
Parasitic infection	1 (<0.1)	3 (<0.1)	0.13	14 (0.5)	8 (0.5)	>0.9	309 (0.2)	363 (0.4)	<0.001	324 (0.2)	374 (0.3)	<0.001
Chronic cholecystitis	0 (0)	0 (0)		5 (0.2)	0 (0)	0.2	883 (0.6)	250 (0.2)	<0.001	888 (0.6)	250 (0.2)	<0.001
Oropharyngeal infection and cavity	2,681 (44)	1,103 (33)	<0.001	713 (24)	251 (14)	<0.001	36,616 (25)	23,843 (23)	<0.001	40,010 (25)	25,197 (23)	<0.001
Viral infection	491 (8.0)	256 (7.6)	0.6	244 (8.3)	85 (4.9)	<0.001	15,385 (10)	9,925 (9.6)	<0.001	16,120 (10)	10,266 (9.4)	<0.001
Vitamin D deficiency	17 (0.3)	4 (0.1)	0.12	6 (0.2)	2 (0.1)	0.7	183 (0.1)	72 (<0.1)	<0.001	206 (0.1)	78 (<0.1)	<0.001
Thyroid disease	103 (1.7)	14 (0.4)	<0.001	178 (6.0)	21 (1.2)	<0.001	20,036 (14)	9,739 (9.4)	<0.001	20,317 (13)	9,774 (9.0)	<0.001
Thyroiditis	7 (0.1)	0 (0)	0.057	30 (1.0)	2 (0.1)	<0.001	3,063 (2.1)	1,498 (1.4)	<0.001	3,100 (2.0)	1,500 (1.4)	<0.001
Autoimmune thyroiditis	5 (<0.1)	1 (<0.1)	0.7	12 (0.4)	1 (<0.1)	0.040	888 (0.6)	497 (0.5)	<0.001	905 (0.6)	499 (0.5)	<0.001
Hypothyroidism	16 (0.3)	2 (<0.1)	0.032	50 (1.7)	5 (0.3)	<0.001	7,779 (5.3)	3,202 (3.1)	<0.001	7,845 (5.0)	3,209 (3.0)	<0.001
Hyperthyroidism	24 (0.4)	3 (<0.1)	0.009	61 (2.1)	8 (0.5)	<0.001	4,204 (2.8)	1,847 (1.8)	<0.001	4,289 (2.7)	1,858 (1.7)	<0.001
Autoimmune hepatitis	0 (0)	0 (0)		1 (<0.1)	0 (0)	>0.9	547 (0.4)	203 (0.2)	<0.001	548 (0.3)	203 (0.2)	<0.001
Autoinflammatory disease	3 (<0.1)	1 (<0.1)	>0.9	4 (0.1)	3 (0.2)	0.7	110 (<0.1)	60 (<0.1)	0.12	117 (<0.1)	64 (<0.1)	0.13
Hypocomplementemia	0 (0)	1 (<0.1)	0.4	0 (0)	0 (0)		3 (<0.1)	3 (<0.1)	0.7	3 (<0.1)	4 (<0.1)	0.5
Connective tissue diseases	31 (0.5)	1 (<0.1)	<0.001	44 (1.5)	4 (0.2)	<0.001	3,315 (2.2)	1,421 (1.4)	<0.001	3,390 (2.2)	1,426 (1.3)	<0.001
Malignant tumours	84 (1.4)	4 (0.1)	<0.001	126 (4.3)	3 (0.2)	<0.001	9,923 (6.7)	2,168 (2.1)	<0.001	10,133 (6.5)	2,175 (2.0)	<0.001
Mental disorders	157 (2.6)	29 (0.9)	<0.001	221 (7.5)	40 (2.3)	<0.001	25,295 (17)	13,812 (13)	<0.001	25,673 (16)	13,881 (13)	<0.001
Anxiety	5 (<0.1)	1 (<0.1)	0.7	68 (2.3)	15 (0.9)	<0.001	7,940 (5.4)	4,665 (4.5)	<0.001	8,013 (5.1)	4,681 (4.3)	<0.001
Depression	13 (0.2)	2 (<0.1)	0.075	101 (3.4)	20 (1.2)	<0.001	5,385 (3.6)	2,458 (2.4)	<0.001	5,499 (3.5)	2,480 (2.3)	<0.001
Sleep disturbance	121 (2.0)	21 (0.6)	<0.001	59 (2.0)	14 (0.8)	0.001	18,818 (13)	11,045 (11)	<0.001	18,998 (12)	11,080 (10)	<0.001
Vitiligo	35 (0.6)	15 (0.4)	0.4	30 (1.0)	12 (0.7)	0.3	622 (0.4)	371 (0.4)	0.014	687 (0.4)	398 (0.4)	0.005
Diabetes	43 (0.7)	6 (0.2)	<0.001	109 (3.7)	8 (0.5)	<0.001	31,246 (21)	9,052 (8.7)	<0.001	31,398 (20)	9,066 (8.3)	<0.001
Osteoporosis	6 (<0.1)	0 (0)	0.10	28 (0.9)	5 (0.3)	0.009	7,988 (5.4)	4,067 (3.9)	<0.001	8,022 (5.1)	4,072 (3.7)	<0.001

* χ^2 test of Independence, Fisher's exact test.

were 108,673 people in the urticaria group and 156,950 people in the control group (see **Table II**).

The incidences of 6 comorbidities with urticaria, including allergic rhinitis (AR), allergic asthma (AA), allergic conjunctivitis (AC), atopic dermatitis (AD), *H. pylori* infection and parasitic infection (PI), at age >18, were higher than for the control group ($p < 0.05$). Additionally, the incidences of 14 other comorbidities, such as sinusitis, rhinosinusitis with nasal polyps, asthma, etc., were higher in the control group.

At ages 6–11, the incidences of these 12 comorbidities were significantly higher in the control group than in the urticaria group ($p < 0.05$).

At ages 12–17, the incidences of 14 comorbidities in the control group were significantly higher than that in the urticaria group ($p < 0.05$).

The CCI of patients with and without urticaria in the 3 age groups was studied during the 24-month follow-up (**Table SV**). The CCI of the control group was significantly higher than that of the urticaria group in the 3 age groups ($p < 0.01$).

Comparison of medication usage in urticaria patients at baseline

To investigate the differences in medications among different age groups during the 12-month follow-up, the medicine intake of all urticaria patients was included (**Table SVI**). There was a statistically significant difference in the sex distribution of these groups ($p < 0.01$). The proportion of males in the age group 6–11 was 56% and females was 44%, compared with the 51% male and 49% female in the age group 12–17, and 41% male and 59% female in the age group >18.

The medicines surveyed are as in **Table III**. Avastin, bilastine and mequitazine were not included as there were no data in the database.

For ages 6–11, the top 3 medications used were loratadine (32%), levocetirizine (32%), and dexamethasone (9.4%). For ages 12–17, the top 3 medications used were levocetirizine (30%), ebastine (20%), and loratadine (18%). For age >18, the top 3 medications used were loratadine (14%), dexamethasone (12%), and triamcinolone acetonide (11%).

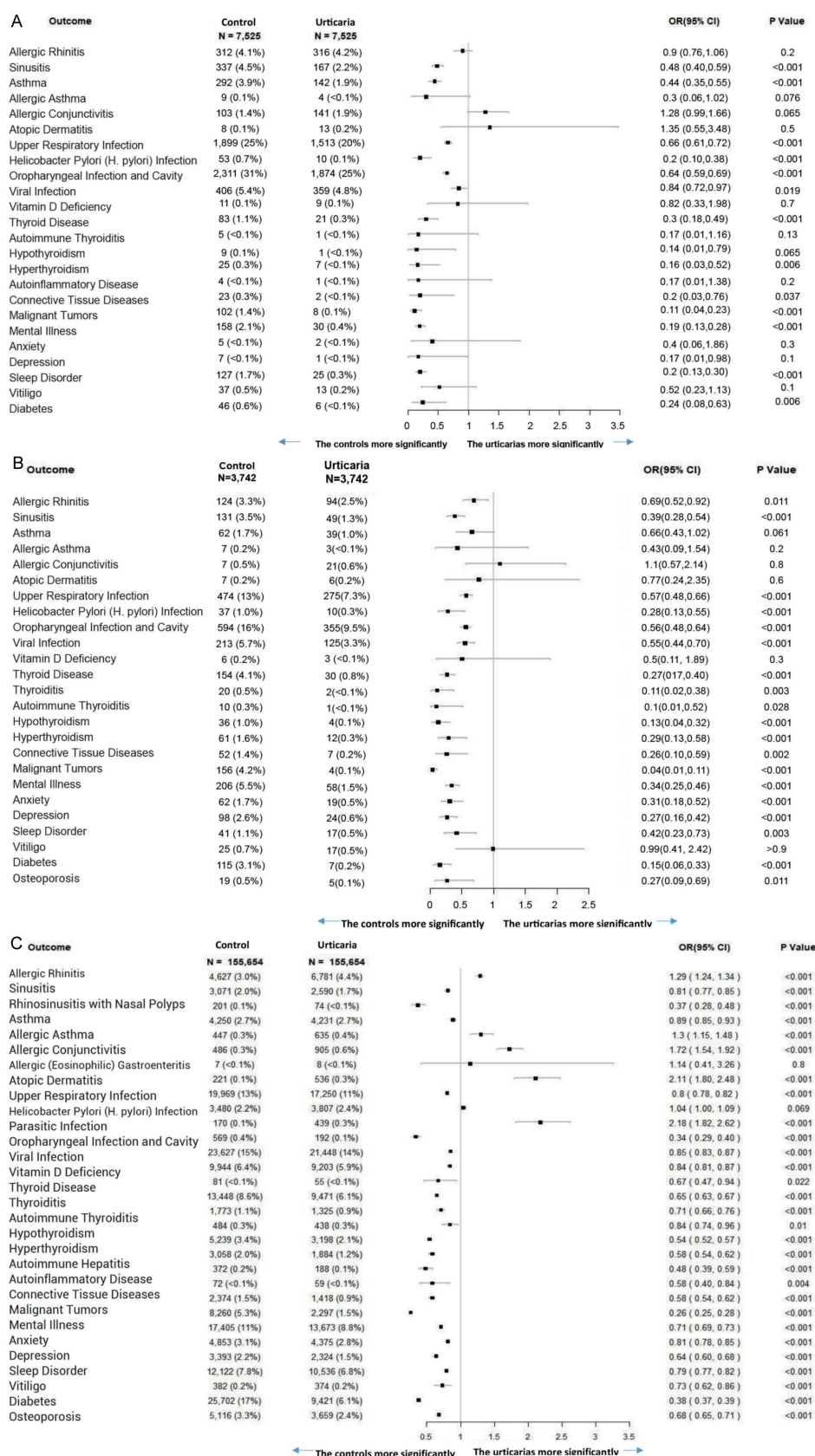


Fig. 2. Differences in comorbidities of patients with and without urticaria at different ages using a logistic regression model. (A) Differences in comorbidities of patients with and without urticaria at ages 6–11 using a logistic regression model. (B) Differences in comorbidities of patients with and without urticaria at ages 12–17 using a logistic regression model. (C) Differences in comorbidities of patients with and without urticaria at age >18 using a logistic regression model.

Table III. Ration of medical usage in patients with urticaria during the 12-month follow-up period

Characteristics	Ages 6–11 n=8,453 n (%)	Ages 12–17 n=5,204 n (%)	Ages >18 n=178,990 n (%)	p*
Hormones	1,261 (15)	1,052 (20)	42,937 (24)	<0.001
Prednisone	390 (4.6)	253 (4.9)	4,983 (2.8)	<0.001
Methylprednisolone	0 (0)	0 (0)	4 (<0.1)	
Dexamethasone	791 (9.4)	579 (11)	21,408 (12)	<0.001
Triamcinolone	22 (0.3)	41 (0.8)	1,845 (1.0)	<0.001
Triamcinolone acetonide	167 (2.0)	278 (5.3)	19,023 (11)	<0.001
Second generation of H1 antihistamines	5,841 (69)	3,507 (67)	130,756 (73)	<0.001
Loratadine	2,740 (32)	946 (18)	25,810 (14)	<0.001
Cetirizine	550 (6.5)	161 (3.1)	2,665 (1.5)	<0.001
Levocetirizine	2,736 (32)	1,563 (30)	61,769 (35)	<0.001
Desloratadine	252 (3.0)	231 (4.4)	8,725 (4.9)	<0.001
Desloratadine citrate	85 (1.0)	96 (1.8)	1,007 (0.6)	<0.001
Fexofenadine	51 (0.6)	444 (8.5)	17,862 (10.0)	<0.001
Mizolastine	0 (0)	21 (0.4)	1,673 (0.9)	<0.001
Ebastine	609 (7.2)	1,038 (20)	56,176 (31)	<0.001
Olopatadine	27 (0.3)	153 (2.9)	6,354 (3.5)	<0.001
Rupatadine	5 (<0.1)	115 (2.2)	2,398 (1.3)	<0.001
Bepotastine besilate	20 (0.2)	80 (1.5)	985 (0.6)	<0.001
H1 antihistamines	803 (9.5)	504 (9.7)	23,899 (13)	<0.001
Ketotifen	396 (4.7)	86 (1.7)	2,000 (1.1)	<0.001
Chlorpheniramine	316 (3.7)	42 (0.8)	2,165 (1.2)	<0.001
Cyproheptadine	1 (<0.1)	8 (0.2)	307 (0.2)	0.002
Diphenhydramine	115 (1.4)	340 (6.5)	16,999 (9.5)	<0.001
Doxepin	2 (<0.1)	10 (0.2)	755 (0.4)	<0.001
Tripolidine	0 (0)	40 (0.8)	3,317 (1.9)	<0.001
Tripterygium wilfordii	3 (<0.1)	5 (<0.1)	1,296 (0.7)	<0.001
Cyclosporine	1 (<0.1)	1 (<0.1)	131 (<0.1)	
Omalizumab	0 (0)	0 (0)	1 (<0.1)	
Hydroxychloroquine	0 (0)	1 (<0.1)	50 (<0.1)	
Thalidomide	0 (0)	0 (0)	217 (0.1)	<0.001

* χ^2 test of independence.

Comparison of comorbidities in acute urticaria and chronic urticaria patients

This was a subgroup analysis that focused on exploring the incidence of comorbidities in patients grouped by acute and chronic urticaria at different ages. All urticaria patients were included. There were 156,808 patients in the acute group, including 7,402 aged 6–11, 4,494 aged 12–17 and 144,912 aged >18. There were 35,839 patients in the chronic group, including 1,051 aged 6–11, 710 aged 12–17 and 34,078 ages >18 (Table IV).

Demographic characteristics of the AU and CU groups are listed in Table SVII. Within ages 12–17, there is no difference in the average age between patients in the acute and chronic groups ($p > 0.05$). For age >18 and the total population, the average age of chronic patients was older than that of the acute group ($p < 0.01$).

Comparison of the comorbidities occurring in AU and CU patients in the 3 age groups and the total population at baseline are detailed in Table IV. The incidences of 14 comorbidities, in the age group >18 were higher in the CU than that in the AU group ($p < 0.05$) at baseline.

At ages 6–11, the incidence of viral infection in AU patients was higher than among CU patients ($p < 0.05$). The number of CU patients with allergic rhinitis, asthma, allergic conjunctivitis, etc. was higher than that of AU patients ($p < 0.05$).

In the age group 12–17, the proportion of CU patients suffering from mental disorders (anxiety, depression,

sleep disturbance) was significantly higher than that of AU patients ($p < 0.01$).

During the 12-month follow-up, the proportions of comorbidities concerned were detailed in Table SVIII. The incidences of these 19 comorbidities in the age group >18 were higher in the chronic group than in the acute group ($p < 0.05$). The number of CU patients suffering from allergic rhinitis, asthma, allergic asthma, allergic conjunctivitis, upper respiratory infection, oropharyngeal infection/cavity and viral infection was higher than that of AU patients ($p < 0.05$).

During the 24-month follow-up, the incidences of 20 comorbidities, at age >18 were higher in CU than that in AU patients ($p < 0.05$) (Table SIX).

At ages 6–11, the number of CU patients with allergic rhinitis, asthma, upper respiratory infection, oropharyngeal infection and cavity, viral infection, and sleep disturbance was higher than among AU patients ($p < 0.05$).

At ages 12–17, the number of CU patients suffering from allergic rhinitis, allergic asthma, atopic dermatitis, etc. was higher than that of AU patients ($p < 0.05$).

The CCI of patients with AU and CU are given in Tables SX–SXI, respectively. Within 12-month follow-up, the CCI of CU at ages 12–17 and age >18 was significantly higher than that of acute patients ($p < 0.001$). Within 24-month follow-up, the CCI of CU at age >18 and the total population was significantly higher than that of acute patients ($p < 0.001$).

Table IV. Comparison of comorbidities in acute urticaria (AU) and chronic urticaria (CU) patients at baseline

Characteristics	Ages 6–11			Ages 12–17			Ages > 18			Total		
	Acute urticaria n = 7,402 n (%)	Chronic urticaria n = 1,051 n (%)	p*	Acute urticaria n = 4,494 n (%)	Chronic urticaria n = 710 n (%)	p*	Acute urticaria n = 144,912 n (%)	Chronic urticaria n = 34,078 n (%)	p*	Acute urticaria n = 156,808 n (%)	chronic urticaria n = 35,839 n (%)	p*
Allergic rhinitis	240 (3.2)	46 (4.4)	0.057	100 (2.2)	25 (3.5)	0.036	4,709 (3.2)	1,682 (4.9)	<0.001	5,049 (3.2)	1,753 (4.9)	<0.001
Sinusitis	171 (2.3)	26 (2.5)	0.7	56 (1.2)	12 (1.7)	0.3	2,035 (1.4)	615 (1.8)	<0.001	2,262 (1.4)	653 (1.8)	<0.001
Rhinosinusitis with nasal polyps	0 (0)	0 (0)		1 (<0.1)	0 (0)	>0.9	85 (<0.1)	22 (<0.1)	0.7	86 (<0.1)	22 (<0.1)	0.6
Asthma	127 (1.7)	22 (2.1)	0.4	28 (0.6)	14 (2.0)	<0.001	3,070 (2.1)	996 (2.9)	<0.001	3,225 (2.1)	1,032 (2.9)	<0.001
Allergic asthma	4 (<0.1)	2 (0.2)	0.2	3 (<0.1)	3 (0.4)	0.037	455 (0.3)	170 (0.5)	<0.001	462 (0.3)	175 (0.5)	<0.001
Allergic conjunctivitis	97 (1.3)	18 (1.7)	0.3	13 (0.3)	7 (1.0)	0.013	571 (0.4)	186 (0.5)	<0.001	681 (0.4)	211 (0.6)	<0.001
Allergic (eosinophilic) gastroenteritis	0 (0)	0 (0)		0 (0)	0 (0)		5 (<0.1)	2 (<0.1)	0.6	5 (<0.1)	2 (<0.1)	0.6
Atopic dermatitis	12 (0.2)	2 (0.2)	0.7	7 (0.2)	2 (0.3)	0.4	278 (0.2)	150 (0.4)	<0.001	297 (0.2)	154 (0.4)	<0.001
Upper respiratory infection	1,521 (21)	239 (23)	0.1	237 (5.3)	45 (6.3)	0.2	14,003 (9.7)	4,172 (12)	<0.001	15,761 (10)	4,456 (12)	<0.001
<i>Helicobacter pylori</i> infection	12 (0.2)	1 (0.1)	>0.9	14 (0.3)	3 (0.4)	0.7	2,762 (1.9)	733 (2.2)	0.003	2,788 (1.8)	737 (2.1)	<0.001
Parasitic infection	9 (0.1)	0 (0)	0.6	15 (0.3)	1 (0.1)	0.7	417 (0.3)	83 (0.2)	0.2	441 (0.3)	84 (0.2)	0.12
Chronic cholecystitis	0 (0)	0 (0)		0 (0)	1 (0.1)	0.14	217 (0.1)	59 (0.2)	0.3	217 (0.1)	60 (0.2)	0.2
Oropharyngeal infection and cavity	1,819 (25)	283 (27)	0.10	304 (6.8)	59 (8.9)	0.13	17,184 (12)	4,969 (15)	<0.001	19,307 (12)	5,311 (15)	<0.001
Viral infection	385 (5.2)	36 (3.4)	0.013	132 (2.9)	15 (2.1)	0.2	7,979 (5.5)	1,936 (5.7)	0.2	8,496 (5.4)	1,987 (5.5)	0.3
Vitamin D deficiency	3 (<0.1)	0 (0)	>0.9	2 (<0.1)	0 (0)	>0.9	33 (<0.1)	8 (<0.1)	>0.9	38 (<0.1)	8 (<0.1)	0.8
Thyroid disease	11 (0.1)	4 (0.4)	0.11	28 (0.6)	5 (0.7)	0.8	6,919 (4.8)	1,888 (5.5)	<0.001	6,958 (4.4)	1,897 (5.3)	<0.001
Thyroiditis	1 (<0.1)	0 (0)	>0.9	0 (0)	0 (0)		972 (0.7)	253 (0.7)	0.15	973 (0.6)	253 (0.7)	0.067
Autoimmune thyroiditis	1 (<0.1)	0 (0)	>0.9	0 (0)	0 (0)		259 (0.2)	83 (0.2)	0.014	260 (0.2)	83 (0.2)	0.008
Hypothyroidism	1 (<0.1)	0 (0)	>0.9	5 (0.1)	0 (0)	>0.9	2,345 (1.6)	666 (2.0)	<0.001	2,351 (5.0)	666 (1.9)	<0.001
Hyperthyroidism	5 (<0.1)	3 (0.3)	0.066	10 (0.2)	2 (0.3)	0.7	1,472 (1.0)	360 (1.1)	0.5	1,487 (0.9)	365 (1.0)	0.2
Autoimmune hepatitis	0 (0)	0 (0)		0 (0)	0 (0)		126 (<0.1)	37 (0.1)	0.2	126 (<0.1)	37 (0.1)	0.2
Autoinflammatory disease	2 (<0.1)	0 (0)	>0.9	4 (<0.1)	0 (0)	>0.9	80 (<0.1)	16 (<0.1)	0.6	86 (<0.1)	16 (<0.1)	0.4
Hypocomplementemia	0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)		0 (0)	0 (0)	
Connective tissue diseases	0 (0)	0 (0)		1 (<0.1)	1 (0.1)	0.3	1,057 (0.7)	358 (1.1)	<0.001	1,058 (0.7)	359 (1.0)	<0.001
Malignant tumours	6 (<0.1)	0 (0)	>0.9	3 (<0.1)	0 (0)	>0.9	1,617 (1.1)	353 (1.0)	0.2	1,626 (1.0)	353 (1.0)	0.4
Mental disorders	24 (0.3)	3 (0.3)	>0.9	28 (0.6)	11 (1.5)	0.008	9,848 (6.8)	2,877 (8.4)	<0.001	9,900 (6.3)	2,891 (8.1)	<0.001
Anxiety	1 (<0.1)	0 (0)	>0.9	12 (0.3)	5 (0.7)	0.071	2,763 (1.9)	725 (2.1)	0.008	2,776 (1.8)	730 (2.0)	<0.001
Depression	1 (<0.1)	0 (0)	>0.9	8 (0.2)	3 (0.4)	0.2	1,527 (1.1)	414 (1.2)	0.010	1,536 (1.0)	417 (1.2)	0.002
Sleep disturbance	20 (0.3)	3 (0.3)	0.8	7 (0.2)	1 (0.1)	>0.9	7,428 (5.1)	22,33 (6.6)	<0.001	7,455 (4.8)	2,237 (6.2)	<0.001
Vitiligo	9 (0.1)	3 (0.3)	0.2	13 (0.3)	2 (0.3)	>0.9	308 (0.2)	86 (0.3)	0.2	330 (0.2)	91 (0.3)	0.11
Diabetes	6 (<0.1)	0 (0)	>0.9	6 (0.1)	2 (0.3)	0.3	7,311 (5.0)	1,895 (5.6)	<0.001	7,323 (4.7)	1,897 (5.3)	<0.001
Osteoporosis	0 (0)	0 (0)		1 (<0.1)	0 (0)	>0.9	2,783 (1.9)	844 (2.5)	<0.001	2,784 (1.8)	844 (2.4)	<0.001

* χ^2 test of independence, Fisher's exact test.

In terms of medication differences between AU and CU patients during the 12-month follow-up (Table SXII), the study showed that the rates of 4 types of medications, including triamcinolone acetonide, second-generation H1 antihistamines, H1 antihistamines (ketotifen), and Tripterygium wilfordii, were higher in patients with CU than those in the AU group at ages 6–11 ($p < 0.05$), while there was no significant difference in other medications between the acute and the chronic groups ($p > 0.05$). At ages 6–11, the top 3 medications used in chronic patients were levocetirizine (50%), loratadine (44%) and ketotifen (12%), while the top 3 for the acute group were loratadine (31%), levocetirizine (30%), and dexamethasone (9.3%).

At ages 12–17, the rates of 3 types of medications, including triamcinolone acetonide, second-generation H1 antihistamines, and H1 antihistamines, were higher in patients with CU than for those in the acute group ($p < 0.05$). The top 3 medications used for CU patients were levocetirizine (45%), ebastine (28%), and loratadine (20%), and the top 3 for AU patients were levocetirizine (28%), ebastine (19%), and loratadine (18%).

At age >18, only prednisone and desloratadine citrate used in acute patients in a higher proportion than

for chronic patients ($p < 0.05$). The rates of using these 6 types of medications, including hormones, second-generation H1 antihistamines, H1 antihistamines, *Tripterygium wilfordii*, cyclosporine and thalidomide, were higher in patients with chronic urticaria than in acute patients ($p < 0.05$). The top 3 medications used by chronic patients were levocetirizine (46%), ebastine (43%), and loratadine (19%), while the top 3 in the acute group were levocetirizine (32%), ebastine (29%), and loratadine (13%).

DISCUSSION

Primary study on comorbidities among patients with and without urticaria in children, adolescents, and adults

In this study, the average age of children and adolescents with urticaria was 8 and 15, respectively. Mazur et al. (15) reported that the prevalence of urticaria in Polish children aged 7–8 and adolescents aged 16–17 was 3.6% and 2.8%, which was comparable to our study.

The children with urticaria were more likely to suffer from AC (1.9% vs 1.4%), and adolescents were more likely to suffer from PI (0.5% vs 0.2%) during 12-month

follow-up, which is in line with previous reports (28, 29). Parasites have also been proposed to be an underlying factor in CSU, but a causal relationship between them has not been described (16). However, there are few reports on CU concomitant with PI in adolescents, rather than in children. The prevalence of PI in children with CSU was found to have a wide range of 0–37.8%. The prevalence of 5 comorbidities in adult urticaria was higher, with PI 2.19 times, AD 2.04 times, AC 1.62 times, AA 1.27 times, and AR 1.25 times that of the control group. The high prevalence of these comorbidities was maintained during the 2-year follow-up.

We found that the prevalence of PI and AC in adult patients with urticaria was also higher. The incidence of PI was about 0.3% in adults with urticaria. AC and AR are common allergic diseases in China (18). Research based on a large adult population in north China showed that the prevalence rates of AR, asthma, and AR combined with asthma were 13.9%, 9.8%, and 2.9%, respectively (19). At present, there are few epidemiological investigations on adult patients with urticaria suffering from AR, AC, and AA. We found the incidences of AR, AC, and AA were 4.4%, 0.6%, and 0.4%, respectively, in urticaria adults and 3.0%, 0.3%, and 0.3% in non-urticaria adults sequentially.

AD is a common chronic inflammatory skin disorder affecting one-fifth of the population in developed countries (20). The prevalence of AD has been reported to have increased from 3.1% in 2002 to 12.9% in 2014 among children in China (21, 22) but population-based epidemiological data on CU and AD in adults is lacking. We found that the prevalence of AD in Chinese adults with or without urticaria was 0.3% and 0.1%, respectively.

Secondary study on acute urticaria vs chronic urticaria

Comorbidities between AU and CU in children, adolescents, and adults. In this research, the CCI of CU (1.34%) was significantly higher than that of AU (1.12%). AR, upper respiratory tract infection, and oropharyngeal infection/ cavity are common comorbidities in AU/CU.

At baseline, the proportion of children with viral infection (VI) in AU was significantly higher than that in CU. Meanwhile, the proportions of adolescent with mental illness, AR, asthma, AA, and AC were significantly higher than that in AU. Regarding the comorbidities of AU and CU in children and adolescents, the prevalence of AR, asthma, upper respiratory tract infection, oropharyngeal infection/dental caries, and virus infection were higher than that in AU patients.

For adult patients, the incidences of AR, sinusitis, asthma, AA, AC, AD, etc. were higher in CU than in AU at baseline. We also found higher rates of *H. pylori* infection in patients with CU, like previous studies (23, 24).

The incidence of rhinosinusitis with nasal polyps, viral infection, thyroiditis, etc. were all higher in CU than in AU. Kolkhir et al. (10) reported that the thyroid dysfunction

rate was increased in patients with CSU, especially in adult patients with CSU rather than in children. The results of this study further confirmed this conclusion.

Usage of medications in different groups. The results of the study show that the top 3 commonly used medications in each group are as follows: loratadine, levocetirizine, and dexamethasone in children; levocetirizine, ebastine, and loratadine in adolescents; loratadine, dexamethasone, and triamcinolone acetonide in adults. Desloratadine citrate used in adult AU was higher than for CU. Levocetirizine, ebastine, and loratadine in CU, and levocetirizine, ebastine, and loratadine in AU are often used.

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The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval was given by the Tianjin Medical University General Hospital, Tianjin, China (NO: IRB2021-WZ-171). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from individual participants.

The authors have no conflict of interest to declare.

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