

Clustering the clinical course of chronic urticaria using a longitudinal database: Effects on chronic urticaria remission

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Abstract

Background: Little is known about the clinical course of chronic urticaria (CU) and predictors of its prognosis. We evaluated CU patient clusters based on medication scores for the initial 3 months of treatment to investigate time to remission and relapse rates and to identify predictors for CU remission. **Methods:** In total, 4552 patients (57.9% female; mean age of 38.6 years) with CU were included in this retrospective cohort study. The K-medoids algorithm was used for clustering CU patients. Kaplan-Meier survival analysis with Cox regression was applied to identify predictors of CU remission. **Results:** Four distinct clusters were identified: patients with consistently low disease activity (cluster 1, n = 1786), with medium-to-low disease activity (cluster 2, n = 1031), with consistently medium disease activity (cluster 3, n = 1332), or with consistently high disease activity (cluster 4, n = 403). Mean age, treatment duration, peripheral neutrophil counts, total IgE, and complements levels were significantly higher for cluster 4 than the other three clusters. Median times to remission were also different among the four clusters (2.1 vs 3.3 vs 6.4 vs 9.4 years, respectively, $P < .001$). Sensitization to house dust mites ([?] class 3) and female sex were identified as significant predictors of CU remission. Around 20% of patients who achieved CU remission experienced relapse. **Conclusion:** In this study, we identified four CU patient clusters by analyzing medication scores during the first 3 months of treatment and found that sensitization to house dust mites and female sex can affect CU prognosis.

KEYWORDS

chronic urticaria, cluster analysis, natural course, relapse, remission

Abbreviations: CI, confidence interval; CU, chronic urticarial; CSU, chronic spontaneous urticarial; HDM, house dust mite; HR, hazard ratio; ICD, international classification of disease; MC_T, tryptase-positive and chymase-negative mast cells; MC_{TC}, tryptase- and chymase-positive mast cells; MRGX2, mas-related gene X2.

1 INTRODUCTION

Chronic urticaria (CU) is defined as transient itchy wheals and/or angioedema present for at least 6 weeks.¹ A common allergic skin disease, CU affects between 0.5% and 5% of the general population,² and its prevalence in adults and children has been increasing worldwide.³ Reportedly, CU poses significant impairments in quality of life, including loss of productivity, psychological distress, and sleep disturbance.^{4,5}

Although higher disease severity and the presence of angioedema are associated with a longer duration of urticaria,⁴ research has yet to propose any significant demographic factors with which to predict the prognosis of CU. In a previous study published in 2004, urticaria was cleared after 1 year in 80% of 5003 Spanish patients with CU, whereas 11% still had CU after 5 years.⁶ For Korea, a 10-year (2004–2013) follow-up, nationwide,

population-based study reported a remission rate for CU at 1 year of 52.6%.⁷ In addition, more than 10% of CU patients were found to be affected for longer than 5 years.⁶⁻⁸

Guidelines for urticaria recommend step-wise treatment.^{1,2,9} In the first step, the use of approved doses of non-sedative antihistamines is recommended. For individuals whose urticaria remains uncontrolled after 2–4 weeks of treatment, increasing doses up to fourfold is considered. For patients with antihistamine-resistant urticaria, the use of omalizumab or cyclosporine is recommended. Based on these stepwise treatment guidelines, a recent study developed medication scores as a means with which to assess treatment intensity or requirements.¹⁰ Although variability in treatment steps over time has been shown to be important for forecasting the clinical prognosis of CU patients, to date, no recommendations have been given on how to incorporate medication scores into characterization of the clinical course of the disease.

Research has shown that stratifying a population into more homogenous sub-groups facilitates better prediction of individualized models.¹¹ Accordingly, by applying medication scores for the initial 3 months of treatment, we attempted to classify CU patients in a longitudinal database into four individual treatment requirement clusters. In doing so, we aimed to estimate remission rates of CU for the identified clusters and to identify prognostic factors of CU remission.

2 METHODS

2.1 Study design

This study was designed as a longitudinal retrospective cohort study of CU patients who had visited a university hospital in Korea from January 1997 to December 2017. We obtained data from electronic medical records of patients who had been diagnosed with CU under the code of L50 in the 10th version of International Classification of Disease (ICD-10). In particular, information on medications prescribed for CU, diagnostic details, laboratory test results, and visit history was extracted and reviewed. Applying unsupervised machine learning techniques, we attempted to identify patterns of the trajectories of the first 3 months of treatment from the index date (i.e., date of starting H1-antihistamines under a L50 diagnosis). Next, we applied this information to evaluate differences in demographics and laboratory test results and to investigate prognostic factors according to the observed clusters. This study was approved by the Ethical Review Board (AJIRB-MED-MDB-18-042).

2.2 Study population

In total, 9256 individuals had code L50 as their primary diagnosis. Next, we applied the following inclusion criteria: (a) H1-antihistamine prescription records within 1 year under a principal diagnosis of L50 (n = 8404); (b) a serial prescription for H1-antihistamines over 6 weeks (n = 4988); and (c) an assessable disease activity over 3 months (n = 4552). Finally, 4552 patients with CU were selected for analysis (see Figure S1 in Supporting Information).

2.3 Longitudinal medication score assessment

To quantify the trajectories of disease activity, we employed medication scores for each prescription as described in a previous report.¹⁰ Score assessment was divided into 10 categories depending on drug dosage and substances. Each point reflected guidelines for urticaria treatment steps and a prior report.^{2,9,10} H1-antihistamine doses were described as equivalent doses of loratadine (mg/day): a daily mean dose of H1-antihistamine [?]20 mg/day was scored 2 points and that >20 mg/day was scored 4 points (see Table S1 in Supporting Information). Regarding systemic corticosteroid, 28 days of continuous prescription was calculated. Medication scores for corticosteroids were converted to equivalent doses of prednisolone: <11 mg/day, 5 points; 11-25 mg/day, 10 points; and >25 mg/day, 15 points. Among other alternative medications, cyclosporine use was given a score of 8 points, hydroxychloroquine use 6 points, leukotriene receptor antagonist use 2 points, H2-antihistamine use 2 points, and omalizumab use 12 points. Patients who had no medication records for CU over 1 year despite having visited the hospital for other diseases, were given a medication score of 0 points, and we confirmed CU remission for the patient. The day of CU remission was determined

as the last day when the patient had taken medications. Daily doses of medication were averaged over the first 3 months. Missing values were replaced using linear interpolation methods.

2.4 Cluster generation

We applied K-medoids clustering analysis on trajectory medication scores over the first 3 months using the R package “cluster”.¹² Known as partitioning around medoids, K-medoids is utilized to build a set of partitions in data, and each partition represents a cluster.^{12,13} Monthly medication scores (0 to 70) over the first 3 months for all 4552 patients with CU were the object of clustering. To evaluate inter-and intra-cluster distances, the silhouette method was applied.¹⁴

2.5 CU remission according to clustering and other clinical factors

Survival analysis was conducted to identify differences in CU remission rates among the observed clusters. The treatment duration of CU was defined as the interval from the first date of CU diagnosis to the date of remission. Differences in CU remission rates among clusters were identified using the Kaplan-Meier method. Furthermore, we attempted to discern crucial clinical factors reflective of the noted CU clusters. Demographics, such as age, sex, and treatment duration, as well as laboratory test results, including total IgE and specific IgE to house dust mites (HDM), peripheral blood cell counts, c-reactive protein, erythrocyte sedimentation ratio, and routine chemistry, were compared among the CU clusters.

Relapse of CU was defined as the reappearance of CU documented by the registration of L50 as a principal diagnosis and prescription for urticaria treatment after remission from CU. We also analyzed times to CU relapse and clinical characteristics between patients who experienced relapse and those who did not.

2.6 Statistical analysis

Welch’s ANOVA was used to compare continuous variables among the CU clusters, and the chi-square test was used to compare categorical variables. Multiple comparisons were corrected by Dunnett’s and Bonferroni’s tests for continuous and categorical variables, respectively. Kaplan-Meier survival curves were drawn to compare remission rates among the CU clusters. We used Cox regression analysis to investigate the relationship between clinical and laboratory parameters and CU remission over a 10-year treatment period. All *P*-values under .05 were considered significant. All statistical analyses were conducted with IBM SPSS, version 25 for Windows (IBM SPSS Inc., Chicago, IL, USA) and R 3.5.2 software (R development core team, <http://www.r-project.org>).

3 RESULTS

3.1 Clinical characteristics of the study subjects

Of the 4552 patients included in the present study, 2637 (57.9%) were female. The mean age of the patients was 38.6 ± 14.6 years (Table 1). The mean treatment duration of CU was 31.7 ± 42.6 months. Other than H1-antihistamines, over the first 3 months of treatment, H2-antihistamines were prescribed for 1553 (34.1%), leukotriene receptor antagonist for 1013 (22.3%), hydroxychloroquine for 430 (9.4%), cyclosporine for 205 (4.5%), omalizumab for 203 (4.5%) patients. Systemic corticosteroid treatment for 4 weeks or longer was identified in 311 (6.8%) patients. Gastritis (7.4%) registered as an ICD-10 code of K29 or K21 was the most prevalent comorbidity, followed by allergic rhinitis (6.3%), drug allergy (3.4%), asthma (3.3%), thyroid diseases (3.2%), hypertension (2.4%) and diabetes mellitus (1.7%).

3.2 Cluster profile

Four distinct clusters of medication scores were identified (Figure 1): patients with consistently low disease activity (cluster 1, $n = 1786$), those with medium-to-low disease activity (cluster 2, $n = 1031$), those with consistently medium disease activity (cluster 3, $n = 1332$), and those with consistently high disease activity (cluster 4, $n = 403$). The mean silhouette width of the four clusters was 0.46 and ranged from 0.18 to 0.69, indicating that each object was well matched to its own cluster and poorly matched to adjacent clusters.

3.3 Demographics and laboratory test results stratified by the four CU clusters

Table 1 summarizes the clinical characteristics of study subjects according to the four CU clusters. The mean ages of the clusters ranged from 36.4 ± 14.9 (cluster 1) to 42.8 ± 13.5 (cluster 4) years and were significantly different among the four clusters ($P < .001$). The mean ages of CU patients increased steadily from cluster 1 to 4. Female sex was predominant in all clusters, comprising 54.1% to 61.6% ($P = .03$). There was a higher number of male patients in cluster 4 than in the other clusters. Urticaria treatment duration was longer in cluster 4 (39.3 ± 45.4 months) than the other three clusters (31.2 ± 42.5 , 31.7 ± 43.7 , and 30.3 ± 40.8 months, respectively) ($P = .004$). The proportion of patients aged 60 years or more was also highest in cluster 4. Almost half of the patients in cluster 4 had been prescribed a systemic steroid, while less than 10% of patients in the other three clusters received steroid treatment. The use of cyclosporine was recorded for 38.2% of cluster 4. Less than 5% of patients in clusters 1 and 2 had been treated with cyclosporine. In clusters 3 and 4, respectively, 10.2% and 7.0%, were found to have received omalizumab.

Laboratory test results at initial diagnosis are described in Table 1. Peripheral white blood cell count and neutrophil percentage were significantly different among the four clusters, with patients in cluster 4 showing the highest white blood cell counts and neutrophil ratio. Meanwhile, the proportions of peripheral lymphocytes, eosinophils and basophils were lower in cluster 4 patients than in patients in the other three clusters. Erythrocyte sedimentation ratio was also higher in the patients of cluster 4 than in those of clusters 1, 2, and 3 ($P = .003$).

Serum total IgE levels were significantly higher in cluster 4 patients than in patients in the other three clusters (226.8 ± 361.5 vs 248.1 ± 418.2 vs 249.7 ± 383.0 vs 345.9 ± 603.5 , respectively, $P = .006$). Levels of complement 3 and complement 4 were higher in the sera from cluster 4 patients than in patients in the other three clusters. Rates of HDM sensitization, determined by levels of specific IgEs to D1 (*Dermatophagoides pterygium*) and D2 (*D. farina*), were not different among the four clusters. Other laboratory parameters, such as creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and uric acid, were not different among the four clusters.

The prevalences of hypertension, diabetes mellitus, and thyroid diseases were not different among the four clusters. The rates of CU patients combined with allergic rhinitis and drug allergy were higher in clusters 1 and 2, whereas the prevalence of gastritis was higher in clusters 3 and 4.

3.4 CU remission according to clustering and other clinical factors

Moving from clusters 1 to 4, times to CU remission became longer (Figure 2). As reflected in median years and 95% confidence intervals (CI), times to CU remission were 2.1 (1.8–2.6) for cluster 1, 3.3 (2.9–4.4) for cluster 2, 6.4 (5.6–7.3) for cluster 3, and 9.4 (7.7–10.5) for cluster 4 ($P < .001$). The cumulative incidences of CU remission during the first year of treatment were 37.5% for patients in cluster 1, 32.6% in cluster 2, 11.8% in cluster 3, and 4.2% in cluster 4 (Figure 2). After 5 years of maintenance treatment, the cumulative incidences of CU remission for the four clusters were 63.1%, 56.2%, 41.0%, and 30.1%, respectively. More than 70% of patients in clusters 1 and 2 achieved remission from CU within 10 years of treatment, whereas 66.2% of patients in cluster 3 and 53.1% in cluster 4 were found to have achieved remission over the same period.

To identify predictors for CU remission within a 10-year treatment period, we conducted Cox regression analysis with age, sex, CU clusters, total IgE level, and HDM sensitization as covariates, as shown in Table 2. Cluster 2 showed a longer time to CU remission (hazard ratio [HR] = 0.794 and 95% CI, 0.698 to 0.902, $P < .001$) than cluster 1 as a reference. Compared to cluster 1, clusters 3 (HR = 0.463, 0.401 to 0.534, $P < .001$) and 4 (HR = 0.340, 0.265 to 0.436, $P < .001$) also showed markedly lower probabilities of CU remission. Together with CU clusters, female sex was found to be an independent prognostic factor for remission in CU patients (HR = 0.886, 0.795 to 0.988, $P = .029$). Additionally, sensitization to HDM of at least class 3 (specific IgEs to D1 and/or D2 [?]^{3.5}) was identified as a factor strongly affecting CU remission (HR = 0.731, 0.632 to 0.847, $P < .001$). Serum total IgE levels and age in CU patients showed no influence on CU remission.

3.5 Relapse of CU according to clustering

Among 2385 patients who had ever achieved CU remission at least once, 470 (19.7%) experienced relapse, with a mean time to relapse of 33.0 ± 28.0 months. Of the 470 relapsed patients, 238 (50.6%) finally achieved remission from CU, whereas the other 232 (49.4%) remained in a sustained state of CU. The mean frequency of CU relapse events in patients who experienced remission was 1.19. Relapse rate (18.9% vs 20.4% vs 20.7% vs 20.7%, respectively, $P = .880$) and mean times to CU relapse (33.6 ± 29.1 vs 33.4 ± 29.1 vs 31.3 ± 19.5 vs 35.9 ± 26.6 months, respectively, $P = .600$) were not different among the four clusters (Figure 3). Compared with patients who did not experience relapse, those who did were found to be of younger age at diagnosis and to have frequently used medications other than H1-antihistamines. Sex, presence of allergic diseases, steroid use, total IgE, and HDM sensitization did not differ between these patient groups (Table 3).

4 DISCUSSION

In this retrospective cohort study, we were able to apply medication scores to partition a large number of CU patients treated at a single university hospital over the most recent 20 years. Using K-medoids clustering analysis based on daily medication scores for the initial 3 months of treatment, we noted four distinct clusters of CU patients with discernible differences in disease activity. Moreover, we found that CU clusters were useful in predicting long-term treatment outcomes.

To date, studies describing the natural course of CU are rare, and those that are available report varying results. Differences in study population, design, and period and in definitions of outcomes may account for the variability in the results. Observational studies have reported 5-year remission rates for CU of 29–86%.^{15,16} Epidemiologic studies have reported remission rates for CU within 3 months ranging from 12.0% to 50%^{6,7,17} and 5-year remission in about 90% of CU patients.^{6,7} In the present study, we found that the proportion of patients who achieved CU remission differed significantly among the four CU clusters. One-year remission rates for clusters 1 and 2, which were reflective of lower disease activity, were similar with those reported in previous epidemiologic studies,^{7,17} while those for clusters 3 and 4 were remarkably less. We believe that because these aforementioned studies were based on data from a health insurance database, in which omalizumab was excluded and some cyclosporine prescriptions were not included, many patients with severe CU may have been lost. This may account for the better CU remission rates in those studies, compared with ours.

A recent review article indicated that female sex, higher age at disease onset, long urticaria duration, and non-steroidal anti-inflammatory drug hypersensitivity may be linked with both severe CU and a longer time to remission.¹⁸ In the current study, female sex was identified as an indicator predictive of difficulty with achieving CU remission. Similar results of a longer time to remission and more heavily impaired CU-specific quality of life have been reported for women with chronic spontaneous urticaria.^{19,20} Considering that estradiol enhances histamine release from mast cell lines,²¹ changes in hormonal milieu in women may be associated with fluctuations in urticaria activity and poor control. Regarding age, we found that mean ages of urticaria onset were higher for clusters 3 and 4 than for clusters 1 and 2. Furthermore, the proportions of patients aged 60 years and older were also higher for clusters 3 and 4. Nevertheless, age, in itself, had no influence on time to CU remission.

Among laboratory markers, increases in total IgE, complement 3 and 4, and peripheral basopenia, lymphocytopenia, and neutrophilia were observed for cluster 4, compared to the other clusters. Kessel et al suggested that elevated total IgE could be a marker for urticaria severity and duration.²² In addition, in a prior study, we found elevated total IgE levels to be significantly correlated with both urticaria activity score and CU-specific quality of life.²³ Highly cytokinergic IgE antibodies against thyroid autoantigens^{24,25} or interleukin 24²⁶ and those against staphylococcal enterotoxins²⁷ have been suggested as potential causes of CSU in a subpopulation of patients. Moreover, previous results have indicated that these IgE antibodies show an association with urticaria activity score and may support our findings of elevated total IgE levels in cluster 4 patients, who showed sustained, high disease activity. However, we found no significant association between serum total IgE levels and CU remission or relapse.

In addition to female sex, a sensitization to HDM was found to be an independent predictor for CU remission, even though proportions thereof did not differ among the four clusters. HDMs are major allergens known to induce allergic rhinitis, asthma, and atopic dermatitis.²⁸ Sensitization to HDM, particularly to *Dermatophagoides*, has increased greatly with rapid industrialization in many countries,²⁹⁻³² as has the prevalence of CU.^{3,17} There are several reports on the relationships between HDMs and CU.³³⁻³⁸ Previous studies have described positive skin reactivity and/or serum specific IgE to HDM in 18% to 63% of patients with CU.^{33-35,37,38} In a Turkish study, only sensitivity to HDM was more common in CU patients without allergic diseases than in healthy controls, whereas rates of skin reactivity to other aeroallergens, such as pollen, mold, and animal dander, were similar.³⁴ Song et al reported significantly higher urticaria activity scores in HDM-sensitive CU patients than in patients with a negative skin test to HDM.³⁵ Furthermore, a clinical benefit for mite immunotherapy in CU patients with mite hypersensitivity has been proven.^{36,39}

The release of histamine and inflammatory mediators from activated mast cells are regarded as the primary mechanism for CU.^{40,41} Currently, primed mast cells ready to release mediators upon exposure to various stimuli are thought to be at play.⁴¹ Sensitization of mast cells with monomeric IgE in the absence of antigen has been found to promote mast cell proliferation, differentiation, survival, and mediator production.^{41,42} As HDMs are considered as key players in the progression of atopic march,⁴³ the presence of specific IgE against HDM may also play a role in priming mast cells in CU patients. However, the clinical relevance of HDM sensitivity to the etiology and management of CU still needs to be established. Although the presence of specific IgE to HDM in CU patients may simply reflect an epiphenomenon of exposure to environmental dust, not a direct cause of the disease, the literature does support a significant association between sensitization to HDM and difficulty with achieving CU remission. Indeed, research has proven that HDMs activate nociceptors to release substance P from sensory neuron,⁴⁴ and there is direct evidence that mast cells are activated by substance P via mas-related gene X2 (MRGX2) signaling, thereby initiating type 2 immune-mediated allergic inflammation in the skin.⁴⁴ Furthermore, MRGX2 has been found to be highly expressed in CSU skin, particularly in severe CSU,⁴⁵ and in CU patients who express MRGX2, exposure to HDM, can induce mast cell degranulation. Since CU has been widely recognized as a chronic allergic skin disease, we now need to investigate further the relationship between HDM sensitization and CU.

To date, only a few studies have investigated CU relapse, and how CU relapse ought to be defined is still unclear. Kim et al⁴⁶ has defined recurrent CU as urticaria recurring at least 6 months after stopping controller medications and resolution of prior urticarial symptoms. They reported that 13% of 341 patients had recurrent CU under this definition. In our study, relapse of CU was defined as the reappearance of H1-antihistamine and/or immunomodulators prescriptions for urticaria under the primary diagnosis of L50 after previously achieving CU remission (no medication for more than a year). Similar with Kim et al's report, we found the relapse rate of CU patients overall to be 19.7%.⁴⁶ Furthermore, we also found the use of immunomodulators to pose a higher risk of CU relapse, similar to a previous study.⁴⁶ Considering that relapse rates and mean times to relapse of CU did not differ among the four clusters, we believe that maintaining proper treatment steps for controlling urticarial symptoms is important and that patients who need immunomodulators, such as omalizumab and cyclosporin, should be more cautious about stopping medications.

There are potential limitations in the present study. First, the operational definitions of CU, remission, and relapse from a retrospective investigation were incontrovertibly different from the actual epidemiology of the disease. Thus, we used strict definitions to minimize misclassification of CU and to avoid overestimation of CU remission. As a result, about half of all cases with L50 as a principal diagnosis were excluded. Since this study institution was a tertiary referral center for CU, some patients with mild CU and some referred patients who had already maintained H1-antihistamines at the initial visit, but had not stayed for more than 3 months, might have been excluded. Due to a nature of retrospective study, differences in compliance with treatment among patients could not be considered. Nonetheless, we were able to identify four distinct clusters of CU based on medication scores during the first 3 months, and then, a longitudinal cohort covering up to 21 years was established. Second, this study did not include information specific to CU, such as urticaria activity score, the presence of autoantibodies, and urticaria subtypes. Third, the subjects of the present

study were from a single ethnicity. In the future, expanding this study to include multiple clinical sites from various regions would be helpful to improving the generalizability of the CU clusters.

In conclusion, we established four CU clusters using the medication scores for the first 3 months of treatment as a reliable surrogate marker for CU progress. These four clusters were able to depict differences in clinical features of CU, including demographics, laboratory results, and the remission rate of CU. A strong sensitization against HDM and female sex were also found to affect the prognosis of CU. The use of immunomodulators was implicated in the risk for CU relapse.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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TABLE 1 Clinical characteristics of the study subjects according to the four clusters

Characteristic	Overall population (n = 1786)	Cluster 1 (n = 1031)	Cluster 2 (n = 1031)	Cluster 3 (n = 1332)	Cluster 4 (n = 403)	*P-value	+P values for Cluster 4 vs	+P values for Cluster 4 vs	+P values for Cluster 4 vs
							1	2	3
Female (%)	2637 (57.9)	1026 (57.4)	635 (61.6)	758 (56.9)	218 (54.1)	.030	1.000	.067	1.000
Age, mean ± SD	38.6 ± 14.6	36.4 ± 14.9	38.4 ± 14.6	40.3 ± 14.1	42.8 ± 13.5	<.001	<.001	<.001	.001

Characteristic	Overall population (n = 1786)	Cluster 1 (n = 1031)	Cluster 2 (n = 1031)	Cluster 3 (n = 1332)	Cluster 4 (n = 403)	*P-value	+P values for Cluster 4 vs	+P values for Cluster 4 vs	+P values for Cluster 4 vs
<20 years (%)	510 (11.2)	293 (16.4)	114 (11.1)	91 (6.8)	12 (3.0)	<.001	<.001	<.001	.03
20–39 (%)	1907 (41.9)	754 (42.2)	431 (41.8)	556 (41.7)	166 (41.2)	.982	1.000	1.000	1.0
40–59 (%)	1763 (38.7)	620 (34.7)	407 (39.5)	563 (42.3)	173 (42.9)	<.001	.014	1.000	1.0
[?]60 (%)	372 (8.2)	119 (6.7)	79 (7.7)	122 (9.2)	52 (12.9)	<.001	<.001	.016	.21
CU duration (month)	31.7 ± 42.6	31.2 ± 42.5	31.7 ± 43.7	30.3 ± 40.8	39.3 ± 45.4	.004	.006	.023	.00
Medication use (%)									
H1AH	4552 (100)	1786 (100)	1031 (100)	1332 (100)	403 (100)	NA	NA	NA	NA
H2AH	1553 (34.1)	313 (17.5)	371 (36.0)	604 (45.3)	265 (65.8)	<.001	<.001	<.001	<.001
LTRA	1013 (22.3)	182 (10.2)	322 (31.2)	347 (26.1)	162 (40.2)	<.001	<.001	.009	<.001
Hydroxychloroquine	400 (9.4)	13 (0.7)	40 (3.9)	196 (14.7)	181 (44.9)	<.001	<.001	<.001	<.001
Cyclosporine	205 (4.5)	0 (0.0)	4 (0.4)	47 (3.5)	154 (38.2)	<.001	<.001	<.001	<.001
Omalizumab	203 (4.5)	20 (1.1)	49 (4.7)	93 (7.0)	41 (10.2)	<.001	<.001	.001	.27
Corticosteroid	111 (6.8)	10 (5.6)	18 (1.7)	90 (6.8)	193 (47.9)	<.001	<.001	<.001	<.001
Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD	Laboratory test, mean ± SD
WBC (10 ³ /μL)	7.6 ± 3.4	7.0 ± 2.7	7.9 ± 3.8	7.8 ± 3.4	8.9 ± 4.1	<.001	<.001	<.001	<.001
Neutrophil (%)	59.3 ± 11.5	57.4 ± 10.5	60.2 ± 12.0	60.0 ± 11.5	63.1 ± 12.2	<.001	<.001	<.001	<.001
Lymphocyte (%)	31.0 ± 9.8	32.6 ± 9.2	30.2 ± 10.1	30.4 ± 9.8	28.0 ± 10.4	<.001	<.001	.002	<.001
Eosinophil (%)	2.3 ± 2.3	2.5 ± 2.4	2.4 ± 2.5	2.2 ± 2.1	2.0 ± 2.4	.001	.002	.056	.32
Basophil (%)	0.5 ± 0.3	0.6 ± 0.4	0.51 ± 0.3	0.5 ± 0.3	0.4 ± 0.2	<.001	<.001	<.001	<.001
Platelet (10 ³ /μL)	256.6 ± 62.0	253.9 ± 61.6	260.9 ± 61.1	254.9 ± 61.2	263.0 ± 67.5	.007	.091	.995	.20

Characteristic	Overall population (n = 1786)	Cluster 1 (n = 1031)	Cluster 2 (n = 1031)	Cluster 3 (n = 1332)	Cluster 4 (n = 403)	*P-value	+P values for Cluster 4 vs	+P values for Cluster 4 vs	+P values for Cluster 4 vs
ESR (mm/hr)	11.2 ± 10.5	10.6 ± 10.0	11.6 ± 11.1	11.2 ± 10.4	12.8 ± 10.9	.003	.004	.427	.11
BUN (mg/dL)	12.6 ± 3.9	12.3 ± 3.4	12.7 ± 4.2	12.6 ± 4.1	13.0 ± 4.4	.012	.027	.699	.34
Creatinine (mg/dL)	2.1 ± 13.6	2.3 ± 16.0	2.3 ± 13.8	1.6 ± 9.5	1.8 ± 12.9	.415	.982	.993	1.0
Uric acid (mg/dL)	4.8 ± 1.4	4.8 ± 1.4	4.7 ± 1.4	4.75 ± 1.42	4.8 ± 1.4	.222	.909	1.000	1.0
Total Protein (g/dL)	7.3 ± 0.4	7.3 ± 0.4	7.3 ± 0.5	7.26 ± 0.43	7.2 ± 0.5	<.001	<.001	.207	.57
Total Bilirubin (mg/dL)	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.3	0.79 ± 0.3	0.7 ± 0.4	.152	.978	.997	.99
Total IgE (kU/L)	249.6 ± 410.3	226.8 ± 361.5	248.1 ± 418.2	249.7 ± 383.0	345.9 ± 603.5	.006	.005	.049	.04
IgE to HDM <3.5 kU/L	2496 (77.3%)	967 (78.1)	570 (76.6)	728 (76.6)	231 (78.3)	.768	1.000	1.000	1.0
IgE to HDM [?]3.5 kU/L	732 (22.7%)	271 (21.9)	174 (23.4)	223 (23.4)	64 (21.7)	.768	1.000	1.000	1.0
ALT (U/L)	26.0 ± 38.4	26.7 ± 53.5	24.8 ± 25.6	25.4 ± 23.5	27.6 ± 24.1	.238	.996	.319	.50
AST (U/L)	24.2 ± 29.0	25.4 ± 40.1	23.7 ± 26.0	23.2 ± 11.5	23.6 ± 16.4	.224	.658	1.000	.99
Complement 3 (mg/dL)	115.0 ± 25.0	113.4 ± 23.8	114.0 ± 23.8	115.2 ± 25.0	123.05 ± 30.2	<.001	<.001	<.001	<.001
Complement 4 (mg/dL)	26.86 ± 8.9	26.0 ± 8.3	26.4 ± 8.7	27.3 ± 9.1	29.1 ± 9.9	<.001	<.001	<.001	.02
ANA positivity (%)	459/2348 (19.5)	154/897 (17.2)	104/510 (20.4)	143/701 (20.4)	58/240 (24.2)	.071	0.104	1.000	1.0
Comorbidities (%)									
Gastritis	339 (7.4)	111 (6.2)	79 (7.7)	108 (8.1)	41 (10.2)	.027	.040	.906	1.0

Characteristic	Overall population (n = 1786)	Cluster 1 (n = 1031)	Cluster 2 (n = 1031)	Cluster 3 (n = 1332)	Cluster 4 (n = 403)	*P-value	+P	+P	+P
							values for Cluster 4 vs	values for Cluster 4 vs	values for Cluster 4 vs
Allergic rhinitis	289 (6.3)	133 (7.4)	86 (8.3)	53 (4.0)	17 (4.2)	<.001	.163	.055	1.0
Drug allergy	154 (3.4)	70 (3.9)	43 (4.2)	28 (2.1)	13 (3.2)	.017	1.000	1.000	1.0
Asthma	149 (3.3)	59 (3.3)	45 (4.4)	29 (2.2)	16 (4.0)	.023	1.000	1.000	.42
Thyroid diseases	146 (3.2)	59 (3.3)	27 (2.6)	45 (3.4)	15 (3.7)	.643	1.000	1.000	1.0
Hypertension	109 (2.4)	41 (2.3)	28 (2.7)	27 (2.0)	13 (3.2)	.477	1.000	1.000	1.0
Diabetes mellitus	77 (1.7)	26 (1.5)	18 (1.7)	25 (1.9)	8 (2.0)	.777	1.000	1.000	1.0

Abbreviations: CU, chronic urticaria; H1AH, H1-antihistamine; H2AH, H2-antihistamine; LTRA, leukotriene receptor antagonist; WBC, white blood cell; ESR, erythrocyte sedimentation ratio; BUN, blood urea nitrogen; HDM, house dust mites; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANA, antinuclear antibody.

*Welch’s ANOVA for continuous variables, Pearson’s Chi-squared test for categorical variables.

+Multiple comparisons were corrected by Dunnett’s test and Bonferroni correction for categorical and continuous variables, respectively.

TABLE 2 Predictors of remission over 10 years of treatment in patients with chronic urticaria

Variables	HR (95% CI)	P-value
Age (years)	0.998 (0.995 to 1.002)	.371
Female	0.886 (0.795 to 0.988)	.029
Cluster		
Cluster 1	Reference	Reference
Cluster 2	0.794 (0.698 to 0.902)	<.001
Cluster 3	0.463 (0.401 to 0.534)	<.001
Cluster 4	0.340 (0.265 to 0.436)	<.001
Total IgE (kU/L)	1 (1.000 to 1.000)	.542
Specific IgE to house dust mites (kU/L)		
<3.5	Reference	Reference?;?
3.5	0.731 (0.632 to 0.847)	<.001

Abbreviations: HR, hazard ratio; CI, confidence interval.

TABLE 3 Clinical characteristics and medication use according to chronic urticaria relapse

Variables	Subjects achieving CU remission once	Subjects achieving CU remission twice
	Relapsed (n = 470)	Not relapsed (n = 1915)
Age	36.9 ± 13.4	38.7 ± 14.8
Female (%)	281 (59.8)	1104 (57.7)

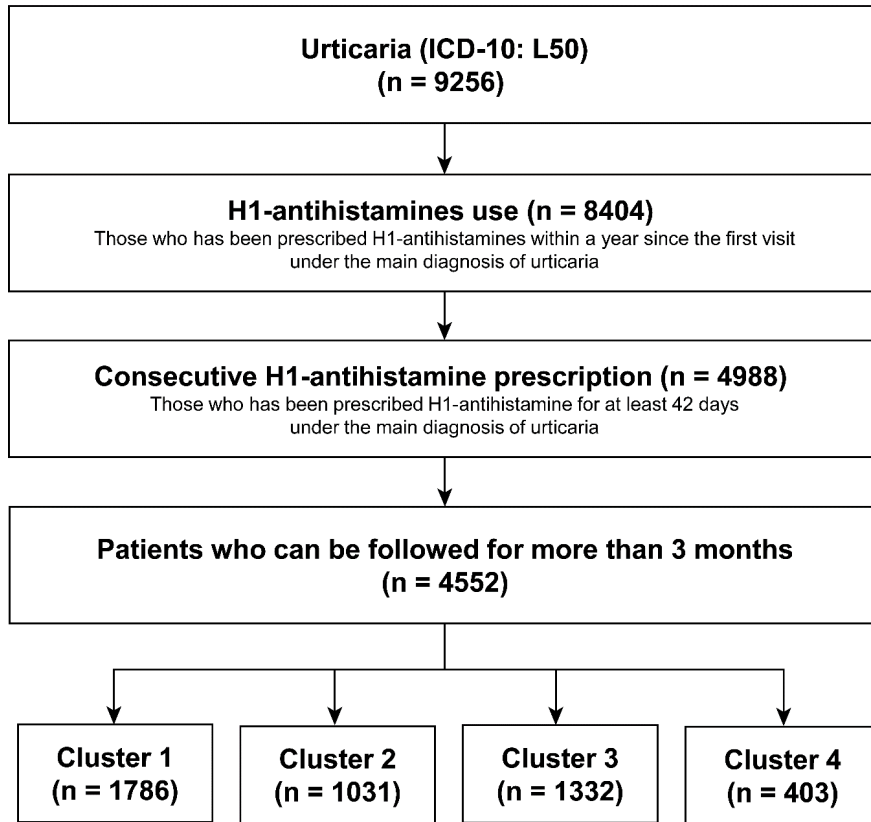
Variables	Subjects achieving CU remission once	Subjects achieving CU remi
Combined allergic diseases (%)	50 (10.6)	183 (9.6)
Use of medications other than H1AH (%)*	264 (56.2)	955 (49.9)
Systemic steroid use (%)	34 (7.2)	125 (6.5)
Serum total IgE (kU/L)	217.3 ± 318.8	230.3 ± 386.4
HDM sensitization [?] class 3	74 (20.8)	283 (18.2)

Abbreviations: CU, chronic urticaria; H1AH, H1-antihistamines; HDM, house dust mites.

*Medications including omalizumab, cyclosporine, montelukast, H2-antihistamines, and hydroxychloroquine.

Supporting Information TABLE S1 Medication score applied for clustering analysis

Medication	Dose	Score
H1-antihistamine (equivalent dose of loratadine)	[?]20mg/day	2
	>20mg/day	8
Steroid (equivalent dose of prednisolone)	<11mg/day	5
	11–25mg/day	10
	>25mg/day	15
Cyclosporine	Any dose	8
Hydroxychloroquine		6
Montelukast		2
H2-antihistamine		2
Omalizumab		12



Supporting Information Figure S1

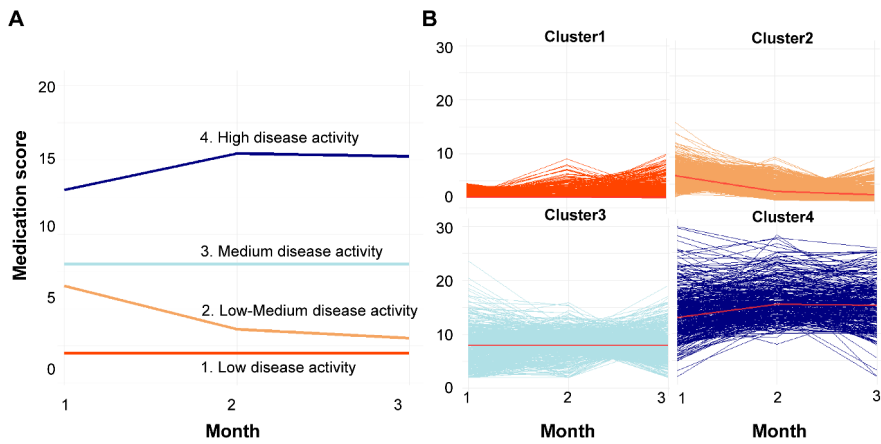


Figure 1

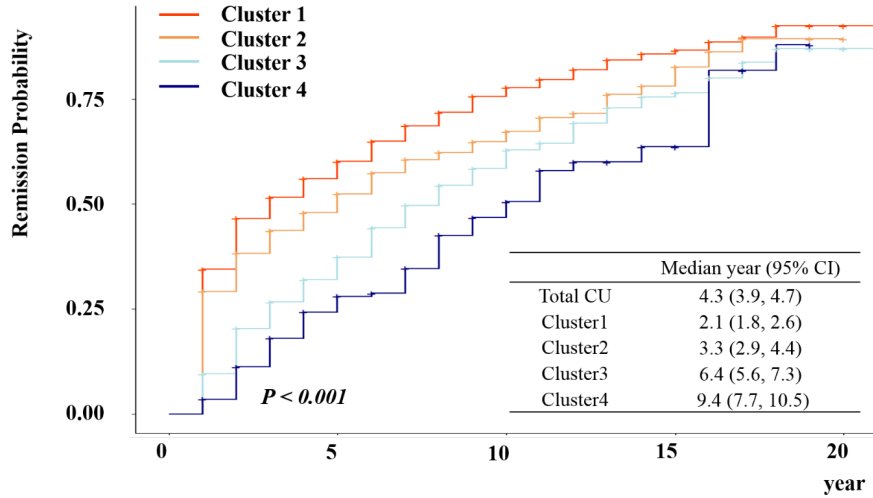


Figure 2

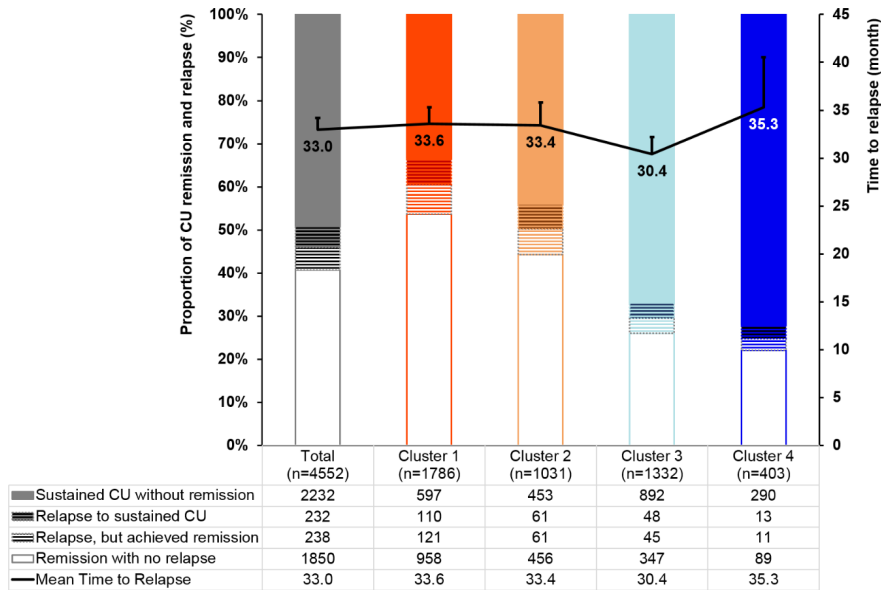


Figure 3

FIGURE LEGENDS

FIGURE 1 Chronic urticaria clustering with the K-medoids algorithm. Centroids (A) and line plot (B) of clustered groups

FIGURE 2 Kaplan-Meier survival curves for remission from chronic urticaria (CU) among the four CU clusters

FIGURE 3 Proportions of relapsed patients with chronic urticaria (CU) and times to the relapse (mean \pm standard error) among the four CU clusters. sustained CU, CU remission CU relapse

FIGURE S1 Scheme of study subject selection