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Original Article

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Clustering the Clinical Course of Chronic Urticaria Using a Longitudinal Database: Effects on Urticaria Remission

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ABSTRACT

Purpose: 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 during the initial 3 months of treatment in an attempt to investigate time to remission and relapse rates for CU and to identify predictors for CU remission.
Methods: In total, 4,552 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 = 1,786), with medium-to-low disease activity (cluster 2, n = 1,031), with consistently medium disease activity (cluster 3, n = 1,332), or with consistently high disease activity (cluster 4, n = 403). Mean age, treatment duration, peripheral neutrophil counts, total immunoglobulin E, and complements levels were significantly higher for cluster 4 than the other 3 clusters. Median times to remission were also different among the 4 clusters (2.1 vs. 3.3 vs. 6.4 vs. 9.4 years, respectively, $P < 0.001$). Sensitization to house dust mites (HDMs; at least class 3) and female sex were identified as significant predictors of CU remission. Around 20% of patients who achieved CU remission experienced relapse.
Conclusions: In this study, we identified 4 CU patient clusters by analyzing medication scores during the first 3 months of treatment and found that sensitization to HDMs and female sex can affect CU prognosis. The use of immunomodulators was implicated in the risk for CU relapse.

Keywords: Chronic urticaria; cluster analysis; recurrence; database; cohort studies; survival analysis; prognosis; house dust mites

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]

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There are no financial or other issues that might lead to conflict of interest.

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 predicting the prognosis of CU. In a previous study published in 2004, urticaria was cleared after 1 year in 80% of 5,003 Spanish patients with CU, whereas 11% still had CU after 5 years.[5] 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%.[6] Another study using the Korean Health Insurance Database (2010-2014) noted that 38.2% of CU patients achieved remission within 1 year.[7] In addition, more than 10% of CU patients were found to be affected for longer than 5 years.[5,6,8]

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 4-fold 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 subgroups facilitates better prediction of individualized models. Therefore, by applying medication scores during the initial 3 months of treatment, we attempted to classify CU patients in a longitudinal database into 4 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.

MATERIALS AND METHODS

Study design

We designed this longitudinal retrospective cohort study of CU patients who 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 clusters observed. This study was approved by the Ethical Review Board (AJIRB-MED-MDB-18-042).

Study population

The study scheme is depicted in **Fig. 1**. In total, 9,256 individuals had code L50 as their primary diagnosis. We applied the following inclusion criteria: (a) H_1-antihistamine prescription records within 1 year under a principal diagnosis of L50 (n = 8,404); (b) a serial prescription for H_1-antihistamines over 6 weeks (n = 4,988); and (c) an assessable disease activity over 3 months (n = 4,552). Finally, 4,552 patients with CU were selected for analysis.

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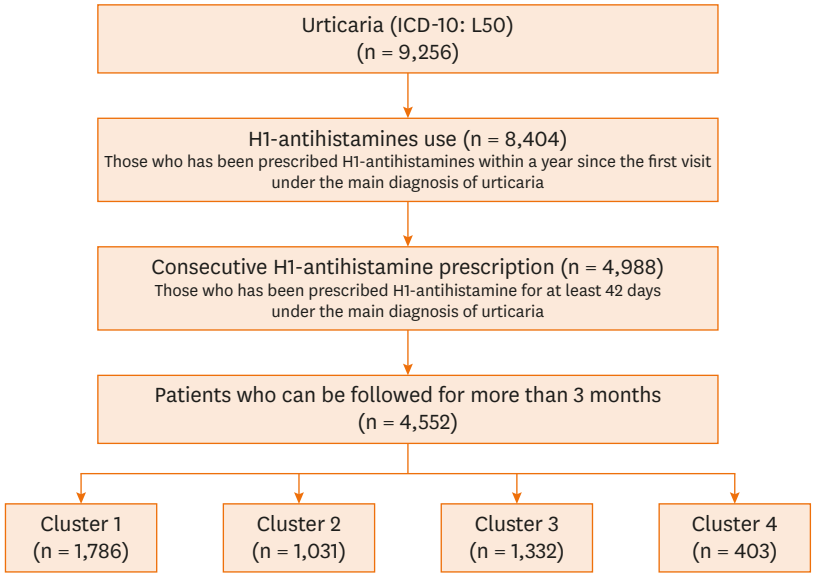

Fig. 1. Scheme of study subject selection.
ICD-10, the 10th version of International Classification of Disease.

Longitudinal medication score assessment

To quantify the trajectories of disease activity, we employed medication scores for each prescription as described in a previous report.[11] Score assessment was divided into 10 categories according to drug dosage and substances. Each point reflected guidelines for urticaria treatment steps and a prior report.[2,9,10] H_1-antihistamine doses were described as equivalent doses of loratadine (mg/day): a daily mean H_1-antihistamine dose of ≤ 20 mg/day was scored 2 points and one > 20 mg/day was scored 4 points (see **Supplementary Table S1** in the online repository). Regarding systemic corticosteroid, 28 days of continuous prescription were 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 point, and we confirmed CU remission for the patient. Daily doses of medication were averaged over the first 3 months. Missing values were replaced using linear interpolation methods.

Cluster generation

We applied K-medoids clustering analysis on trajectory medication scores over the first 3 months using the R package "cluster."[11] Known as partitioning around medoids, K-medoids is utilized to build a set of partitions in data, and each partition represents a cluster.[11,12] Monthly medication scores (0–70) over the first 3 months for all 4,552 patients with CU were the object of clustering. To evaluate inter- and intra-cluster distances, the silhouette method was applied.[13]

CU remission according to clustering and other clinical factors

Survival analysis was conducted to identify differences in CU remission rates among the clusters observed. The treatment duration of CU was defined as the interval from the first

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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. Among the CU clusters, we compared demographics, such as age, sex, and treatment duration, as well as laboratory test results, including total immunoglobulin E (IgE) and specific IgE to house dust mites (HDMs), peripheral blood cell counts, C-reactive protein (CRP), erythrocyte sedimentation ratio, and routine chemistry.

The 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.

Statistical analysis

Welch's analysis of variance was used to compare continuous variables among the CU clusters, and the χ^2 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 0.05 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).

RESULTS

Clinical characteristics of the study subjects

Of the 4,552 patients included in the present study, 2,637 (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 H_1-antihistamines, over the first 3 months of treatment, H_2-antihistamines were prescribed for 1,553 patients (34.1%), leukotriene receptor antagonist for 1,013 patients (22.3%), hydroxychloroquine for 430 patients (9.4%), cyclosporine for 205 patients (4.5%), omalizumab for 203 patients (4.5%). Systemic corticosteroid treatment for 4 weeks or longer was identified in 311 patients (6.8%). 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%).

Cluster profile

Four distinct clusters of medication scores were identified (**Fig. 2**): patients with consistently low disease activity (cluster 1, n = 1,786), those with medium-to-low disease activity (cluster 2, n = 1,031), those with consistently medium disease activity (cluster 3, n = 1,332), and those with consistently high disease activity (cluster 4, n = 403). The mean medication scores among clusters 1, 2, 3, and 4 were significantly different at initial diagnosis (2.37 ± 0.65 vs. 6.32 ± 1.98 vs. 7.83 ± 2.68 vs. 13.46 ± 4.46, $P < 0.001$). The mean silhouette width of the 4 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.

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Table 1. Clinical characteristics of the study subjects according to the 4 clusters

Characteristics	Overall population	Cluster 1 (n = 1,786)	Cluster 2 (n = 1,031)	Cluster 3 (n = 1,332)	Cluster 4 (n = 403)	*P* value	*P* values for cluster 4 vs.		
							1	2	3
Female (%)	2,637 (57.9)	1,026 (57.4)	635 (61.6)	758 (56.9)	218 (54.1)	0.030	1.000	0.067	1.000
Age (yrs)	38.6 ± 14.6	36.4 ± 14.9	38.4 ± 14.6	40.3 ± 14.1	42.8 ± 13.5	< 0.001	< 0.001	< 0.001	0.007
< 20	510 (11.2)	293 (16.4)	114 (11.1)	91 (6.8)	12 (3.0)	< 0.001	< 0.001	< 0.001	0.036
20–39	1,907 (41.9)	754 (42.2)	431 (41.8)	556 (41.7)	166 (41.2)	0.982	1.000	1.000	1.000
40–59	1,763 (38.7)	620 (34.7)	407 (39.5)	563 (42.3)	173 (42.9)	< 0.001	0.014	1.000	1.000
≥ 60	372 (8.2)	119 (6.7)	79 (7.7)	122 (9.2)	52 (12.9)	< 0.001	< 0.001	0.016	0.215
CU duration (mon)	31.7 ± 42.6	31.2 ± 42.5	31.7 ± 43.7	30.3 ± 40.8	39.3 ± 45.4	0.004	0.006	0.023	0.002
Medication use (%)									
H1AH	4,552 (100)	1,786 (100)	1,031 (100)	1,332 (100)	403 (100)	NA	NA	NA	NA
H2AH	1,553 (34.1)	313 (17.5)	371 (36.0)	604 (45.3)	265 (65.8)	< 0.001	< 0.001	< 0.001	< 0.001
LTRA	1,013 (22.3)	182 (10.2)	322 (31.2)	347 (26.1)	162 (40.2)	< 0.001	< 0.001	0.009	< 0.001
Hydroxychloroquine	430 (9.4)	13 (0.7)	40 (3.9)	196 (14.7)	181 (44.9)	< 0.001	< 0.001	< 0.001	< 0.001
Cyclosporine	205 (4.5)	0 (0.0)	4 (0.4)	47 (3.5)	154 (38.2)	< 0.001	< 0.001	< 0.001	< 0.001
Omalizumab	203 (4.5)	20 (1.1)	49 (4.7)	93 (7.0)	41 (10.2)	< 0.001	< 0.001	0.001	0.275
Corticosteroid	311 (6.8)	10 (5.6)	18 (1.7)	90 (6.8)	193 (47.9)	< 0.001	< 0.001	< 0.001	< 0.001
Laboratory test									
WBC (10^3/μL)	7.6 ± 3.4	7.0 ± 2.7	7.9 ± 3.8	7.8 ± 3.4	8.9 ± 4.1	< 0.001	< 0.001	< 0.001	< 0.001
Neutrophil (%)	59.3 ± 11.5	57.4 ± 10.5	60.2 ± 12.0	60.0 ± 11.5	63.1 ± 12.2	< 0.001	< 0.001	< 0.001	< 0.001
Lymphocyte (%)	31.0 ± 9.8	32.6 ± 9.2	30.2 ± 10.1	30.4 ± 9.8	28.0 ± 10.4	< 0.001	< 0.001	0.002	< 0.001
Eosinophil (%)	2.3 ± 2.3	2.5 ± 2.4	2.4 ± 2.5	2.2 ± 2.1	2.0 ± 2.4	0.001	0.002	0.056	0.328
Basophil (%)	0.5 ± 0.3	0.6 ± 0.4	0.5 ± 0.3	0.5 ± 0.3	0.4 ± 0.2	< 0.001	< 0.001	< 0.001	< 0.001
Platelet (10^3/μL)	256.6 ± 62.0	253.9 ± 61.6	260.9 ± 61.1	254.9 ± 61.2	263.0 ± 67.5	0.007	0.091	0.995	0.204
ESR (mm/hr)	11.2 ± 10.5	10.6 ± 10.0	11.6 ± 11.1	11.2 ± 10.4	12.8 ± 10.9	0.003	0.004	0.427	0.112
BUN (mg/dL)	12.6 ± 3.9	12.3 ± 3.4	12.7 ± 4.2	12.6 ± 4.1	13.0 ± 4.4	0.012	0.027	0.699	0.341
Creatinine (mg/dL)	2.1 ± 13.6	2.3 ± 16.0	2.3 ± 13.8	1.6 ± 9.5	1.8 ± 12.9	0.415	0.982	0.993	1.000
Uric acid (mg/dL)	4.8 ± 1.4	4.8 ± 1.4	4.7 ± 1.4	4.75 ± 1.42	4.8 ± 1.4	0.222	0.909	1.000	1.000
Total protein (g/dL)	7.3 ± 0.4	7.3 ± 0.4	7.3 ± 0.5	7.26 ± 0.43	7.2 ± 0.5	< 0.001	< 0.001	0.207	0.571
Total bilirubin (mg/dL)	0.7 ± 0.4	0.7 ± 0.4	0.7 ± 0.3	0.79 ± 0.3	0.7 ± 0.4	0.152	0.978	0.997	0.999
Total IgE (kU/L)	249.6 ± 410.3	226.8 ± 361.5	248.1 ± 418.2	249.7 ± 383.0	345.9 ± 603.5	0.006	0.005	0.049	0.045
IgE to HDM < 3.5 kU/L	2,496 (77.3)	967 (78.1)	570 (76.6)	728 (76.6)	231 (78.3)	0.768	1.000	1.000	1.000
IgE to HDM ≥ 3.5 kU/L	732 (22.7)	271 (21.9)	174 (23.4)	223 (23.4)	64 (21.7)	0.768	1.000	1.000	1.000
ALT (U/L)	26.0 ± 38.4	26.7 ± 53.5	24.8 ± 25.6	25.4 ± 23.5	27.6 ± 24.1	0.238	0.996	0.319	0.507
AST (U/L)	24.2 ± 29.0	25.4 ± 40.1	23.7 ± 26.0	23.2 ± 11.5	23.6 ± 16.4	0.224	0.658	1.000	0.999
Complement 3 (mg/dL)	115.0 ± 25.0	113.4 ± 23.8	114.0 ± 23.8	115.2 ± 25.0	123.05 ± 30.2	< 0.001	< 0.001	< 0.001	< 0.001
Complement 4 (mg/dL)	26.86 ± 8.9	26.0 ± 8.3	26.4 ± 8.7	27.3 ± 9.1	29.1 ± 9.9	< 0.001	< 0.001	< 0.001	0.024
ANA positivity (%)	459/2,348 (19.5)	154/897 (17.2)	104/510 (20.4)	143/701 (20.4)	58/240 (24.2)	0.071	0.104	1.000	1.000
Comorbidities									
Gastritis	339 (7.4)	111 (6.2)	79 (7.7)	108 (8.1)	41 (10.2)	0.027	0.040	0.906	1.000
Allergic rhinitis	289 (6.3)	133 (7.4)	86 (8.3)	53 (4.0)	17 (4.2)	< 0.001	0.163	0.055	1.000
Drug allergy	154 (3.4)	70 (3.9)	43 (4.2)	28 (2.1)	13 (3.2)	0.017	1.000	1.000	1.000
Asthma	149 (3.3)	59 (3.3)	45 (4.4)	29 (2.2)	16 (4.0)	0.023	1.000	1.000	0.426
Thyroid diseases	146 (3.2)	59 (3.3)	27 (2.6)	45 (3.4)	15 (3.7)	0.643	1.000	1.000	1.000
Hypertension	109 (2.4)	41 (2.3)	28 (2.7)	27 (2.0)	13 (3.2)	0.477	1.000	1.000	1.000
Diabetes mellitus	77 (1.7)	26 (1.5)	18 (1.7)	25 (1.9)	8 (2.0)	0.777	1.000	1.000	1.000

Data are expressed as a mean ± standard deviation for continuous variables and as a number (%) for categorical variables. Welch's analysis of variance for continuous variables, Pearson's χ^2 test for categorical variables, Fisher's exact test. Multiple comparisons were corrected by Dunnett's test and Bonferroni correction for categorical and continuous variables, respectively.

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; IgE, immunoglobulin E; HDM, house dust mites; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ANA, antinuclear antibody; NA, not applicable.

Demographic data and laboratory test results stratified by the 4 CU clusters

Table 1 summarizes the clinical characteristics of the study subjects in the 4 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 4 clusters ($P < 0.001$). 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% ($P = 0.03$). There was a larger number of male patients in cluster 4 than in

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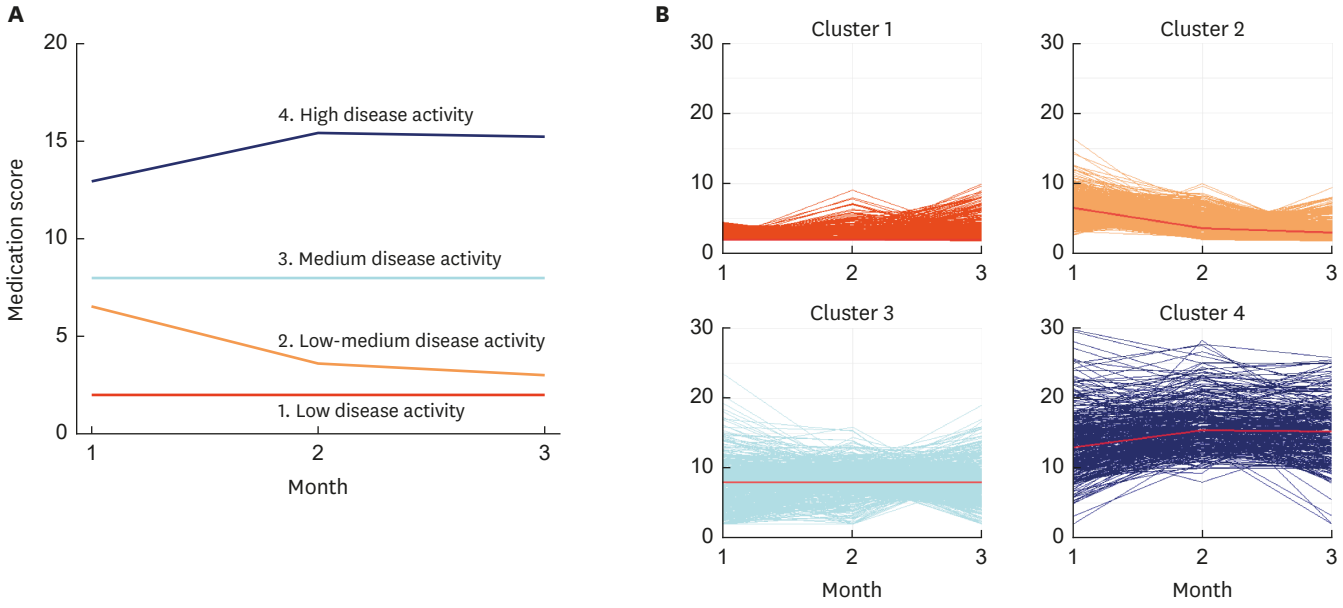

Fig. 2. Chronic urticaria clustering with the K-medoids algorithm. Centroids (A) and line plot (B) of clustered groups.

the other clusters. Urticaria treatment duration was longer in cluster 4 (39.3 ± 45.4 months) than the other 3 clusters (31.2 ± 42.5, 31.7 ± 43.7, and 30.3 ± 40.8 months, respectively) (P = 0.004). 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 3 clusters received steroid treatment. The use of cyclosporine was recorded for 38.2% of cluster 4. Except for 14.7% of the patients in cluster 3, less than 5% of patients in clusters 1 and 2 were treated with cyclosporine. In clusters 3 and 4, respectively, 7.0% and 10.2%, were found to have received omalizumab.

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

Serum total IgE levels were significantly higher in cluster 4 patients than in patients in clusters 1, 2, and 3 (226.8 ± 361.5 vs. 248.1 ± 418.2 vs. 249.7 ± 383.0 vs. 345.9 ± 603.5, P = 0.006). Levels of complement 3 and complement 4 were higher in the sera from cluster 4 patients than in patients in the other 3 clusters. Rates of HDM sensitization, determined by levels of specific IgEs to D1 (*Dermatophagoides pterygium*) and D2 (*Dermatophagoides farina*), were not different among the 4 clusters. Other laboratory parameters, such as creatinine, aspartate aminotransferase, alanine aminotransferase, total bilirubin, and uric acid, were not different among the 4 clusters.

The prevalence of hypertension, diabetes mellitus, or thyroid disease was not different among the 4 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.

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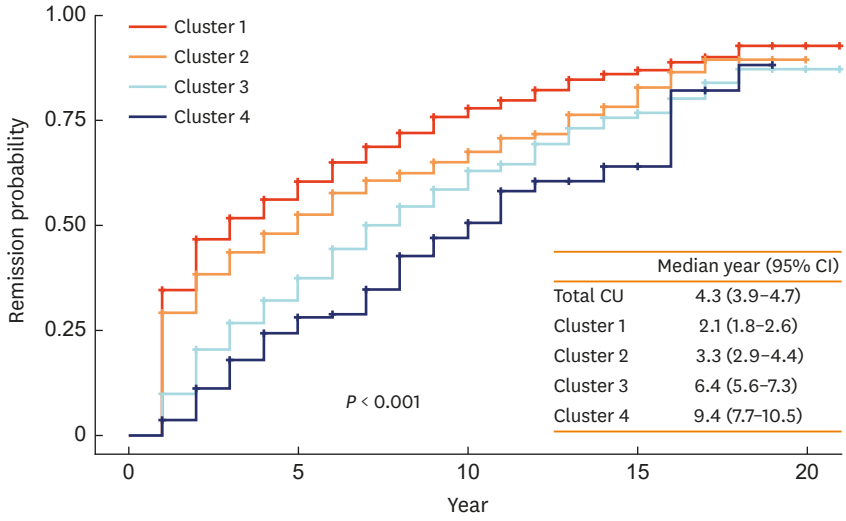

Fig. 3. Kaplan-Meier survival curves for remission from CU among the 4 CU clusters.
CU, chronic urticaria; CI, confidence interval.

CU remission according to clustering and other clinical factors

Moving from clusters 1 to 4, times to CU remission became longer (**Fig. 3**). 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 < 0.001). 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 (**Fig. 2**). After 5 years of maintenance treatment, the cumulative incidences of CU remission for clusters 1, 2, 3, and 4 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; 95% CI, 0.698–0.902; P < 0.001) than cluster 1 as a reference. Compared to cluster 1, clusters 3 (HR, 0.463; 95% CI, 0.401–0.534; P < 0.001) and 4 (HR, 0.340; 95% CI, 0.265–0.436; P < 0.001) also showed markedly lower probabilities of CU remission. Along with CU clusters, female sex was found to be an independent prognostic factor for remission in CU patients (HR, 0.886; 95% CI, 0.795–0.988; P = 0.029). Additionally, sensitization to

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

Variables	HR (95% CI)	*P* value
Age (yrs)	0.998 (0.995–1.002)	0.371
Female	0.886 (0.795–0.988)	0.029
Cluster		
Cluster 1	Reference	Reference
Cluster 2	0.794 (0.698–0.902)	< 0.001
Cluster 3	0.463 (0.401–0.534)	< 0.001
Cluster 4	0.340 (0.265–0.436)	< 0.001
Total IgE (kU/L)	1 (1.000–1.000)	0.542
Specific IgE to house dust mites (kU/L)		
< 3.5	Reference	Reference
≥ 3.5	0.731 (0.632–0.847)	< 0.001

HR, hazard ratio; CI, confidence interval; IgE, immunoglobulin E.

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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; 95% CI, 0.632–0.847; $P < 0.001$). Serum total IgE levels and age in CU patients showed no influence on CU remission.

Relapse of CU according to clustering

Among 2,385 patients who had ever achieved CU remission at least once, 470 (19.7%) experienced relapses, 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, $P = 0.880$) 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, $P = 0.600$) were not different among clusters 1, 2, 3, and 4 (**Fig. 4**). Compared to patients who did not experience relapses, those who did were found to be of younger age at diagnosis and to have frequently used medications other than H_1-antihistamines. Sex, presence of allergic diseases, steroid use, total IgE, and HDM sensitization did not differ between these patient groups (**Table 3**).

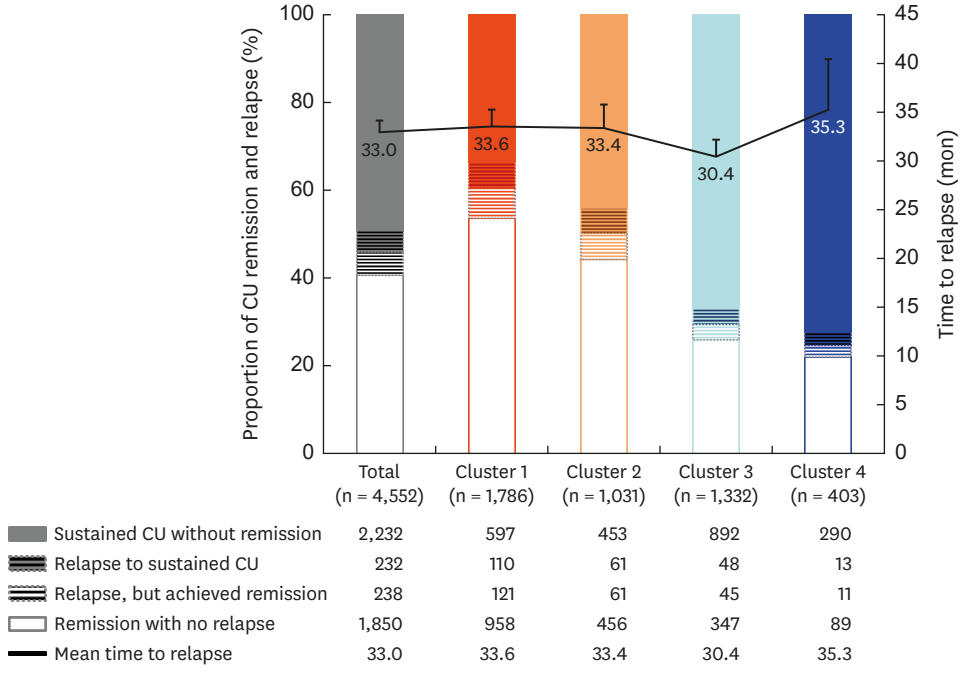

Fig. 4. Proportions of relapsed patients with CU and times to the relapse (mean ± standard error) among the 4 CU clusters.
CU, chronic urticaria.

Table 3. Clinical characteristics and medication use according to CU relapse

Variables	Subjects achieving CU remission once		*P* value
	Relapsed (n = 470)	Not relapsed (n = 1,915)	
Age	36.9 ± 13.4	38.7 ± 14.8	0.012
Female (%)	281 (59.8)	1,104 (57.7)	0.400
Combined allergic diseases (%)	50 (10.6)	183 (9.6)	0.479
Use of medications other than H1AH (%)*	264 (56.2)	955 (49.9)	0.014
Systemic steroid use (%)	34 (7.2)	125 (6.5)	0.582
Serum total IgE (kU/L)	217.3 ± 318.8	230.3 ± 386.4	0.555
HDM sensitization ≥ class 3	74 (20.8)	283 (18.2)	0.252

Data are shown as mean ± standard deviation or number (%).
CU, chronic urticaria; H1AH, H1-antihistamines; IgE, immunoglobulin E; HDM, house dust mites.
*Medications including omalizumab, cyclosporine, montelukast, H2-antihistamines, and hydroxychloroquine.

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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, we noted 4 distinct clusters of CU patients with discernible differences in disease activity. Moreover, we found that CU clusters, based on daily medication scores for the initial 3 months of treatment, were useful in predicting long-term treatment outcomes.

Studies describing the natural course of CU are rare, and those which are available report varying results. Differences in study population, design, and period as well as definitions of outcomes may account for the variability in the results. Observational studies have reported 5-year CU remission rates of 29%–86%.[14,15] The lowest remission rate was noted in a retrospective study conducted between 1968 and 1990,[14] and therein 5- and 10-year remission rates were 29% and 44%, respectively.[16] Toubi *et al.*,[9] however, reported relatively higher 2- and 5-year remission rates of 48% and 86%, respectively, in their prospective study performed between 1998 and 2003.

Epidemiological studies have reported remission rates for CU within 3 months ranging from 12.0% to 50%[5-7] and 5-year remission in about 90% of CU patients.[5,6] In the present study, we found that the proportion of patients who achieved CU remission differed significantly among the 4 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 epidemiological studies for Korea,[6,7] while those for clusters 3 and 4 were remarkably lower. We believe that because the 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 to 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.[15] In the current study, female sex was identified as an indicator predictive of difficulty in 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 (CSU).[16,17] Considering that estradiol enhances histamine release from mast cell lines,[18] changes in the 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, erythrocyte sedimentation rate, complement 3 and 4, and peripheral basopenia and neutrophilia were observed for cluster 4, compared to the other clusters. Kessel *et al.*[19] suggested that elevated total IgE could be a marker for urticaria severity and duration. 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.[20] Highly cytokinergic IgE antibodies against thyroid autoantigens[21,22] or interleukin (IL) 24[23] and those against staphylococcal enterotoxins[24] have been suggested as potential causes of CSU in a subpopulation of patients. Moreover, previous results have

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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, there has been few studies to affirm correlations between urticaria duration and total IgE levels, and we found no significant association between serum total IgE levels and CU remission or relapse. The complement system is a central part of the acute phase response (APR). IL-6 and CRP, well-known biomarkers of APR, have been demonstrated to correlate with severity and activity of CU.[25,26] It has also been reported that serum C3 and C4 concentrations were increased in CU patients as compared to the healthy subjects and significant differences were found between patients with mild and severe CU.[25,27] Elevated C3 and C4 may be due to enhanced production in the liver in response to acute phase reactants, such as, IL-6 or tumor necrosis factor, which are increased in active CU and are known to control synthesis of the acute phase reactant protein.[25] Peripheral basopenia and eosinopenia are well-known clinical features of high disease activity in CU patients.[15] Although the clinical relevance of basopenia and eosinopenia in CU is not yet unclear, 2 potential reasons have been suggested. One reason is that since higher numbers of eosinophils and basophils are observed in lesional skin of CU patients than in non-lesional skin, the recruitment of eosinophils and basophils to the skin during active disease can reduce eosinophils and basophils in the blood.[28] The other is immunological destruction of eosinophils in the blood of patients with CU. It is supported by the finding that a complement-dependent IgG-related activity was observed in the serum of a patient with urticaria and complete eosinopenia.[29] Our findings that elevated C3 and C4 levels and decreased peripheral basophils and eosinophils were observed in cluster 4 patients, consistent with previous results showing the same finding in patients with severe CU or refractory to H_1-antihistamine therapy.

In addition to female sex, strong sensitization to HDM was found to be an independent predictor for CU remission, even though proportions thereof did not differ among the 4 clusters. HDMs are major allergens known to induce allergic rhinitis, asthma, and atopic dermatitis.[30] Sensitization to HDM, particularly to *Dermatophagoides*, has increased greatly with rapid industrialization in many countries,[31-34] as in the prevalence of CU.[3,7] There are several reports on the relationships between HDMs and CU.[35-40] Previous studies have described positive skin reactivity and/or serum specific IgE to HDM in 18% to 63% of patients with CU.[35-37,39,40] 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.[33] Song *et al.*[37] reported significantly higher urticaria activity scores in HDM-sensitive CU patients than in patients with a negative skin test to HDM. Furthermore, a clinical benefit from mite immunotherapy has been proven in CU patients with mite hypersensitivity.[38,41]

The release of histamine and inflammatory mediators from activated mast cells are regarded as the primary mechanism for CU.[42,43] Currently, primed mast cells ready to release mediators upon exposure to various stimuli are thought to be at play.[43] 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.[43,44] A prior study described significant increases in tryptase-positive and chymase-negative mast cells (MC_T) in wheals from CSU patients, whereas tryptase- and chymase-positive mast cells, which are the major subtype of skin mast cells, showed no difference from healthy skin.[45] Consequently, as MC_T has been shown to be associated with allergic disease,[46] this would indicate that CU may stand in the line of atopic march, along with asthma, allergic rhinitis, and atopic dermatitis. As HDMs are considered as key players in the progression of atopic march,[47] the presence of specific

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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 in achieving CU remission. Indeed, research has proven that HDMs activate nociceptors to release substance P from sensory neuron,[48] 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.[48] Furthermore, MRGX2 has been found to be highly expressed in CSU skin, particularly in severe CSU,[49] 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 dig a little deeper into 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 al.*[50] 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-antihiatamine 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 to Kim *et al.*'s[50] report, we found the relapse rate in CU patients overall to be 19.7%. Furthermore, we also found the use of immunomodulators to pose a higher risk of CU relapse, similar to a previous study.[50] Considering that relapse rates or mean times to relapse of CU did not differ among the 4 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 H_1-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 4 distinct clusters of CU based on exact medication scores during the first 3 months, and then, a longitudinal cohort covering up to 21 years was established. Secondly, this study did not include information specific to CU, such as urticaria activity score, the presence of autoantibodies, and urticaria subtypes. Thirdly, 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 4 CU clusters reflective of medication scores during the first 3 months of treatment. These 4 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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SUPPLEMENTARY MATERIAL

Supplementary Table S1

Medication score applied for clustering analysis

Click here to view

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