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Original Article

Chronic Spontaneous Urticaria in Hong Kong: Clinical Characteristics, Real-World Practice and Implications for COVID-19 Vaccination

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ABSTRACT

Purpose: The real-world management and clinical characteristics of chronic spontaneous urticaria (CSU) in Hong Kong and its implications for coronavirus disease 2019 (COVID-19) vaccination are unknown. We investigated the clinical characteristics of patients with CSU and the role of an immunologist-led Urticaria Clinic as well as the impact of CSU on COVID-19 vaccine uptake in Hong Kong.
Methods: Longitudinal clinical data of 257 CSU patients were collected and analyzed. Association analyses were performed to identify the relationships between variables and factors associated with COVID-19 vaccine uptake.
Results: After the immunologist review, the Weekly Urticaria Activity Score (UAS7) was significantly lower than baseline (median: 0.00 vs. 12.0, $P < 0.001$). Changes in UAS7 were significantly greater among patients with baseline UAS7 ≥ 16 compared to those with UAS7 < 16 (median: −24.0 vs. −2.00, $P < 0.001$). CSU patients had lower COVID-19 vaccination rates than the general population with only 176 (68.5%) and 165 (65.0%) receiving at least one dose and 2 doses of vaccination, respectively. The presence of concomitant suspected drug allergy was associated with lower COVID-19 vaccine uptake (odds ratio [OR], 0.47; $P = 0.010$), while regular pharmacological treatment was associated with higher COVID-19 vaccine uptake among CSU patients (OR, 3.79; $P = 0.010$).
Conclusions: A dedicated immunologist-led Urticaria Clinic may effectively improve CSU management and outcomes in Hong Kong.

Keywords: Chronic spontaneous urticaria; Hong Kong; COVID-19; vaccines; drug hypersensitivity

INTRODUCTION

Chronic urticaria is a common, yet often under-recognized condition characterized by the presence of wheals and/or angioedema for more than 6 weeks. Chronic spontaneous urticaria (CSU), defined as chronic urticaria in the absence of any definite trigger, is the predominant subtype.[1] CSU is postulated to be an autoimmune condition and subclassified into 2 types

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Disclosure

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with reference to the modern Gell-Coombs classification of hypersensitivity reactions: (1) Type I involving immunoglobulin (Ig)E autoantibodies against self-antigens and (2) Type IIb involving IgG and/or IgM autoantibodies against IgE or high-affinity IgE receptors (FcεRI) on mast cells.[1,2]

CSU patients experience symptoms that severely affect their mental health and quality of life.[3-6] Disease activity is often measured by the Weekly Urticaria Activity Score (UAS7), with a score of ≥ 16 defined as moderate-to-severe.[7-9] CSU is also associated with significant comorbidities such as other autoimmune disorders as well as misdiagnoses of various food or drug allergies. However, the clinical characteristics, burden of comorbidities, and drug allergy labels vary widely among countries and regions.[3-6,10-12] Similarly, the characteristics and consequences of CSU in Hong Kong and among Chinese patients have seldom been studied.

According to the international guidelines, the mainstay pharmacological treatment for CSU has been recommended as a 4-step algorithm (**Supplementary Table S1**).[1,13] Use of first-generation H_1-antihistamines and systemic corticosteroids specifically for CSU is inappropriate and associated with significant adverse drug reactions.[1,14-19] Angiotensin-converting enzyme inhibitors (ACEi) are also relatively contraindicated in patients with a history of spontaneous angioedema.[20] Despite clear international guidance, the real-world practice and management of CSU remain highly variable.[21] Furthermore, treatment beyond antihistamines (*e.g.*, omalizumab or cyclosporin) is usually limited to specialist-level care. This is a great concern in Hong Kong, given the severe shortage of immunologists/allergists in our locality. The Urticaria Clinic was, therefore, established by the Hong Kong Hospital Authority in 2018 and is the first immunologist-led clinic dedicated to CSU patients, receiving referrals from the entire territory. However, its capacity remains severely limited, and many patients with uncontrolled CSU do not have access to specialist assessment and appropriate treatment.

Recently, coronavirus disease 2019 (COVID-19) vaccination programs have been implemented across the globe to control the pandemic. However, given the novelty of these vaccines, there had been initial concerns about CSU imposing a risk to COVID-19 vaccinations.[22] Although several authorities have advocated the safety of COVID-19 vaccines for CSU patients, vaccine hesitancy and misdiagnosis of vaccine-related 'allergy' remain, especially among CSU patients with vaccine-triggered CSU attacks.[22-25] The impact of CSU on COVID-19 vaccine uptake, albeit likely significant, remains unknown.

In view of these shortcomings, we conducted this study to investigate the clinical characteristics and real-world management of CSU by immunologists and non-immunologists in Hong Kong. We also investigated the effectiveness of a dedicated immunologist-led Urticaria Clinic in disease management and factors associated with COVID-19 vaccination rates among CSU patients.

MATERIALS AND METHODS

Anonymized data from the Hospital Authority Clinical Management Systems were retrieved to identify patients who attended the Urticaria Clinic of the Hong Kong West Cluster between 2018 and 2021. Since 2018, the Hong Kong West Cluster has been the only referral center with formal Immunology and Allergy services under the Hospital Authority, receiving referrals from across the entire territory. Therefore, its patients represented the general population of

Hong Kong referred for immunologist care of chronic urticaria. Only patients fulfilling the diagnostic criteria of CSU according to the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline were included in this study.[1] Patients with only ACEi-induced angioedema and no concomitant CSU were excluded. Patients with missing demographic, clinical, or disease activity data were excluded. The study protocol was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (UW 22-197). Informed consent was waived as all data were anonymized and collected retrospectively.

Demographic and clinical data, including past medical history, age of onset of urticaria and age at presentation to the Urticaria Clinic, other medical comorbidities, and details of drug allergy labels (*i.e.*, physician-reported), were obtained. The duration of follow-up at the Urticaria Clinic was defined as that between the first and latest follow-up visits to the Urticaria Clinic (as of December 2021). The disease duration was defined as the period between the onset of urticaria and the latest follow-up visit to the Urticaria Clinic (as of December 2021). Prior prescriptions used for the treatment of CSU, including regular first-generation H_1-antihistamines, second-generation H_1-antihistamines, systemic corticosteroids, omalizumab, cyclosporin, and other immunosuppressants, were obtained. Specialist-level treatment was defined as third- or fourth-line treatment for CSU (**Supplementary Table S1**). A proportion of patients had persistent low disease activity, self-declined regular pharmacological treatment, and opted to take second-generation H_1-antihistamine 'as needed.' These patients were categorized as having 'no regular pharmacological treatment.' The use of ACEi following the onset of spontaneous angioedema was recorded. Prescriptions of regular first-generation H_1-antihistamines, systemic corticosteroids, and ACEi after spontaneous angioedema were considered inappropriate.[1,20]

CSU disease activity is regularly assessed during patient visits to the Urticaria Clinic using the validated UAS7 (ranging from 0 to 42).[7-9] UAS7 < 16 was classified as 'hive-free-to-mild urticaria activity,' whereas UAS7 ≥ 16 was classified as 'moderate-to-severe urticaria activity.'[9] Patients' COVID-19 vaccination status, including the number of doses received, the type of COVID-19 vaccine received, and any significant adverse events or allergic reactions after vaccination, were also obtained. Significant adverse events were defined as serious or unexpected adverse events following immunization of COVID-19 vaccines defined by the Hong Kong Department of Health according to the World Health Organization guideline.[26,27] UAS7 scores at the first visit to the Urticaria Clinic were described as 'baseline.' UAS7 scores 'after immunologist review' were measured during the latest follow-up visit to the Urticaria Clinic (as of December 2021). 'Immunologist review' referred to the assessment, diagnosis, and management (including pharmacological and non-pharmacological treatment) by a specialist in Immunology and Allergy.

COVID-19 vaccination rate and rate of significant adverse events after COVID-19 vaccination of the general Hong Kong population were obtained for comparison with the CSU cohort.[28-30]

Statistical analysis

All the data were analyzed using IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.2 (http://www.r-project.org; R Foundation, Vienna, Austria). Categorical variables are presented as numbers (percentages); continuous variables are presented as mean ± standard deviation or median (25th to 75th percentiles) for non-parametric variables as determined by the Shapiro-Wilk test. Student's *t*-test for parametric continuous variables, the Mann-Whitney *U* test for non-parametric continuous variables, and the χ^2 test or Fisher

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exact test (if > 5% of the cells have expected count < 5) for categorical variables were used to examine the distribution of data faceted by baseline urticaria activity. The Wilcoxon sign-ranked test was used to compare UAS7 values between at baseline and after immunologist review at the Urticaria Clinic, faceted by baseline urticaria activity. The binomial test was used to compare the COVID-19 vaccination rates between the CSU patients and the general Hong Kong adult population. Multivariable logistic regression analysis was performed to identify variables associated with COVID-19 vaccination status. Variables included in the multivariable logistic regression model were the ones with a *P* value < 0.1 in the univariate analysis. Two-sided *P* values < 0.05 were considered significant in all the statistical tests.

RESULTS

Demographics and clinical characteristics

Out of 346 patients who attended the Urticaria Clinic during the study period, a total of 257 were recruited (**Fig. 1**). Their demographics and clinical characteristics are summarized in **Table 1**. The median follow-up at the Urticaria Clinic was 1.06 years (interquartile range [IQR], 0.60, 1.68).

At baseline, 157 (61.1%) of patients had 'hive-free-to-mild urticaria activity' (UAS7 < 16), while 100 (38.9%) had 'moderate-to-severe urticaria activity' (UAS7 ≥ 16). For urticaria manifestations, 254 (98.8%) patients experienced wheals, 168 (65.4%) experienced angioedema, and 165 (64.2%) experienced both wheals and angioedema. Thirty-seven (14.8%) patients had a history of at least one autoimmune comorbidity; Graves' disease (n = 15, 5.8%), Hashimoto's thyroiditis (n = 4, 1.6%), and lupus erythematosus (n = 4, 1.6%) were the most common autoimmune diseases. Other diseases are listed in **Supplementary Table S2**. More

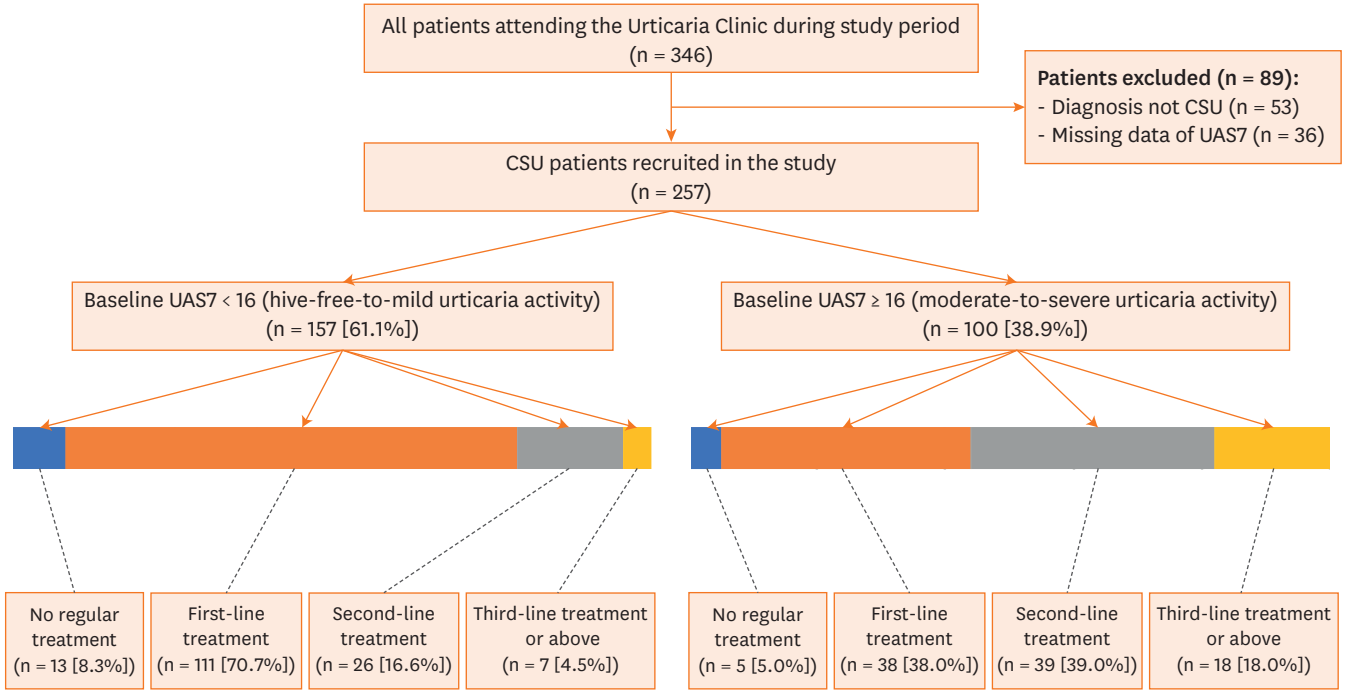

Fig. 1. Breakdown of patient recruitment, disease activity, and lines of treatment after immunologist review.
CSU, chronic spontaneous urticaria; UAS7, Weekly Urticaria Activity Score.

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Table 1. Clinical characteristics and comparison between chronic spontaneous urticaria patients with baseline UAS7 < 16 and ≥ 16

Parameters	All patients (n = 257)	Baseline UAS7 < 16 (n = 157)	Baseline UAS7 ≥ 16 (n = 100)	*P* value
Female	189 (73.5)	117 (74.5)	72 (72.0)	0.655
Age of onset (yr)	33.00 (19.50, 52.50)	30.00 (18.00, 52.50)	35.50 (23.50, 52.30)	0.193
Age at first clinic visit (yr)	49.40 (34.80, 58.70)	49.80 (34.70, 58.30)	47.50 (35.00, 59.70)	0.653
Duration of disease (yr)	5.69 (3.22, 18.00)	6.82 (3.30, 23.00)	4.70 (3.03, 14.50)	0.050
Follow-up duration at the Urticaria Clinic (yr)	1.06 (0.60, 1.68)	1.11 (0.57, 1.53)	0.97 (0.62, 2.03)	0.878
Autoimmune comorbidity	38 (14.8)	20 (12.7)	18 (18.0)	0.247
Drug allergy label	102 (9.7)	66 (42.0)	36 (36.0)	0.335
Urticaria manifestations				0.035
Wheals only	89 (34.6)	46 (29.3)	43 (43.0)	
Angioedema only	3 (1.2)	3 (1.9)	0 (0.0)	
Wheals and angioedema	165 (64.2)	108 (68.8)	57 (57.0)	
Disease activity				
Baseline UAS7	12.00 (2.00, 28.00)	4.00 (0.00, 8.00)	32.50 (24.30, 42.00)	N/A
Change in UAS7 after immunologist review	−6.00 (−18.00, 0.00)	−2.00 (−6.00, 0.00)	−24.00 (−34.00, −10.30)	< 0.001
UAS7 = 0 at baseline	56 (21.8)	-	-	N/A
UAS7 = 0 after immunologist review	153 (59.5)	-	-	N/A

Continuous data were presented as median (25th to 75th percentiles). Categorical data were presented as numbers (percentages).
UAS7, Weekly Urticaria Activity Score; N/A, not available.

than a third (n = 102, 39.7%) of patients had at least one drug allergy label, and 47 (18.3%) had multiple drug allergy labels. Drug allergy labels to non-steroidal anti-inflammatory drugs (NSAIDs) (n = 43, 16.7%) and beta-lactam antibiotics (n = 20, 7.8%) were the most common among the patients (**Supplementary Table S3**).

Inappropriate prescriptions for CSU prior to immunologist review

Prior to immunologist review, 171 (66.5%) patients had received inappropriate treatment for CSU. Eighty-one (31.9%) and 129 (50.2%) patients had been prescribed regular first-generation H_1-antihistamines and systemic corticosteroids for CSU, respectively. Out of the 168 patients with a history of spontaneous angioedema, 16 (9.5%) had been prescribed an ACEi following their onset of angioedema. All (100%) of these inappropriate prescriptions were stopped after attending the Urticaria Clinic.

Significant improvements in disease activity after immunologist review

Over a median follow-up of 1.06 years, median UAS7 significantly improved after immunologist review (12.00 [IQR, 2.00, 28.00] vs. 0.00 [IQR, 0.00, 6.00], $P < 0.001$), with the proportion of patients with UAS7 score of 0 increasing from 56 (21.8%) to 153 (59.5%). Improvements in UAS7 were consistent for patients with baseline UAS7 < 16 (4.00 [IQR, 0.00, 8.00] vs. 0.00 [IQR, 0.00, 2.00], $P < 0.001$) and those ≥ 16 (32.50 [IQR, 24.30, 42.00] vs. 4.00 [IQR, 0.00, 15.00], $P < 0.001$). However, changes in UAS7 were significantly greater among patients with baseline UAS7 ≥ 16 (−24.00 [IQR, −34.00, −10.30]) compared to those with baseline UAS7 < 16 (−2.00 [IQR, −6.00, −0.00]) ($P < 0.001$) (**Table 1**).

Significantly better CSU control among moderate-to-severe CSU patients with access to specialist-level treatment

Thirty-two (12.5%) patients had UAS7 ≥ 16 at baseline and persistent uncontrolled urticaria despite second-line treatment; among these patients, 18 (56.3%) escalated to specialist-level treatment (*i.e.*, third- or fourth-line), while the remaining 14 (43.8%) were unable to escalate due to drug intolerance or financial restrictions. UAS7 scores at baseline and after immunologist review are shown in **Fig. 2**. Improvements in UAS7 were significantly greater among those with access to specialist-level treatment (−26.00 [IQR, −33.30, −7.00]) compared to those without (−3.50 [IQR, −7.00, 0.00]) ($P < 0.001$).

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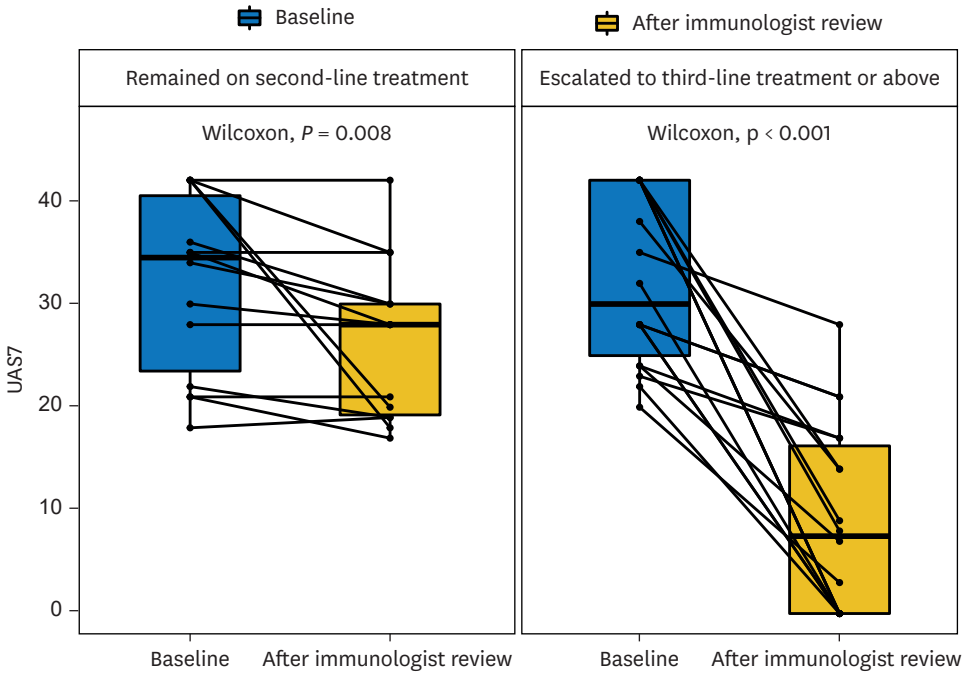

Fig. 2. Longitudinal UAS7 of patients with moderate-to-severe baseline disease activity (UAS7 ≥ 16) despite second-line treatment with or without access to specialist-level treatment.
UAS7, Weekly Urticaria Activity Score.

COVID-19 vaccination rate and associated factors

Within the study period, 176 (68.5%) patients had received at least one dose of the COVID-19 vaccine, which was significantly lower than that of the general Hong Kong adult population (75.2%) (P = 0.009); 165 (65.0%) had completed their primary series of COVID-19 vaccination (*i.e.*, at least 2 doses of COVID-19 vaccine), which was also significantly lower than that of the general Hong Kong adult population (73.2%) (P = 0.002). Among patients who had received at least one dose of the COVID-19 vaccine, 111 (63.1%) had received the Fosun-BioNTech Comirnaty mRNA COVID-19 vaccine, and 65 (36.9%) had received the SinoVac CoronaVac inactivated COVID-19 vaccine. No patients reported any significant adverse events or allergic reactions to the vaccines which required medical attention.

Compared to those unvaccinated, CSU patients who received COVID-19 vaccination had a younger age of CSU onset, were less likely to carry drug allergy labels, and were more likely to be on regular pharmacological therapy (data not shown). Upon multivariable logistic regression, the presence of concomitant suspected drug allergy (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.26, 0.83; P = 0.010) and regular pharmacological treatment after immunologist review (OR, 3.79; 95% CI, 1.37, 10.50, P = 0.010) remained significant in a model adjusted for age of CSU onset and delay in presentation to the Urticaria Clinic (**Table 2**).

DISCUSSION

In this study, we demonstrated the beneficial role of an immunologist-led Urticaria Clinic dedicated to CSU patients in Hong Kong. Alarmingly, two-thirds of patients were prescribed inappropriate treatment for CSU (namely, regular first-generation H_1-antihistamines and systemic corticosteroids as well as ACEi following the onset of angioedema) prior to

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Table 2. Multivariable logistic regression analysis showing the associations of demographic and clinical variables with COVID-19 vaccination status

Parameters	Unvaccinated	Received at least 1 dose of the COVID-19 vaccine	Adjusted odds ratio (95% CI)	*P* value
Patients	81 (31.5)	176 (68.5)		
Age of onset (yr)	34.00 (26.00, 58.00)	31.00 (19.00, 49.00)	0.99 (0.97, 1.01)	0.349
Delay in presentation to the Urticaria Clinic (yr)	3.53 (1.23, 13.20)	5.08 (1.84, 19.20)	1.02 (0.99, 1.05)	0.218
Drug allergy label	41 (50.6)	61 (34.7)	0.47 (0.26, 0.83)	0.010
Treatment regimen				
No regular pharmacological treatment	11 (13.6)	7 (4.0)	Referent	
Regular pharmacological treatment	70 (86.4)	169 (96.0)	3.79 (1.37, 10.5)	0.010

Continuous data are presented as median (25th to 75th percentiles). Categorical data are presented as numbers (percentages).
CI, confidence interval; COVID-19, coronavirus disease 2019.

immunologist review. This reflected the poor adherence of non-immunologists to the CSU guidelines and highlighted the importance of future physician education.

Optimization of CSU management at the Urticaria Clinic was not just limited to discontinuation of inappropriate treatment. Overall, there was a significant improvement in longitudinal UAS7 scores observed in CSU patients after immunologist review, with a substantial increase in the proportion of patients achieving complete remission of urticaria symptoms (*i.e.*, UAS7 =0). Moreover, we identified that CSU patients with baseline UAS7 ≥ 16 had significantly greater improvement in urticaria activity compared to those with lower baseline UAS7. Given the scarcity of immunologists in Hong Kong, we propose that 'persistent UAS7 ≥ 16' may be used as a recommended criterion for immunologist referral in the future to prioritize patients who benefit the most from specialist input.

Subgroup analysis also revealed one of the main challenges of CSU management in Hong Kong. One-eighth of CSU patients had persistent uncontrolled disease despite second-line treatment. Although specialist-level treatment (such as omalizumab or cyclosporin) is indicated for these patients, such much-needed medications could not be initiated in nearly half of our CSU patients due to drug intolerance (very occasionally with higher doses of cyclosporin) or financial difficulties for omalizumab (major reason, as omalizumab remains a self-financed item and completely unsubsidized in Hong Kong).[31-41] In contrast to patients with access to specialist-level treatments, our study demonstrated that patients without access had persistent high UAS7 scores despite immunologist review. This also highlighted the urgency of improving accessibility to specialist-level treatments, especially with omalizumab, to those financially restricted patients in Hong Kong.

Interestingly, our study revealed that CSU patients had lower rates of COVID-19 vaccination. Ten months since the launch of our territory-wide vaccination program, only 65% of CSU patients had completed their primary series of COVID-19 vaccination (*i.e.*, 2-doses), which was significantly lower than that among the general adult population (73.2%).[28,29] Vaccine hesitancy might exist among CSU patients because of the fear of disease exacerbation or misconception of possible vaccine-associated anaphylaxis.[23] Although there have been reports of urticaria flares after vaccination, CSU has not been associated with an increased risk of COVID-19 vaccine-associated allergy.[22,42] In this cohort, no patients reported any significant adverse events or allergies to COVID-19 vaccination. The overall rate of significant adverse events in the Hong Kong general population has been reported to be 6.7 events per dose of COVID-19 vaccine administered, according to the Hong Kong SAR Government.[30] We hope our findings can reassure the safety of COVID-19 vaccines among CSU patients.

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The prevalence of concomitant patient-reported drug allergies in CSU patients varied widely across different studies, ranging from 4% to 56%.[4,43,44] Alarmingly, we found that 40% of our CSU patients had a physician-reported drug allergy (*i.e.*, drug allergy label). However, drug allergy labels might be false among CSU patients, especially when coincidental CSU flares upon drug intake were mistaken as drug 'allergy.' NSAIDs were the most commonly implicated drug but may be a misdiagnosis of NSAID-exacerbated cutaneous disease rather than genuine IgE-mediated NSAID allergy.[45] Incorrect allergy labels may lead to unnecessary drug avoidance or accidental re-exposure. Furthermore, we identified concomitant suspected drug allergy to be independently associated with lower COVID-19 vaccine uptake among CSU patients. Again, this may be due to incorrect fear of possible higher risk for excipient allergies (caution for mRNA COVID-19 vaccinations) or COVID-19 vaccine-associated allergies. Unvaccinated individuals carry a significantly higher risk of COVID-19 hospitalization and mortality[46]; hence, it is urged that priority be given to these CSU patients for early management. Given this potentially significant public health impact on COVID-19 vaccination efforts, immunologists should be empowered to play a bigger role in drug allergy de-labeling and optimization of CSU control. Unfortunately, the waiting time for formal drug allergy testing is almost 8 years in Hong Kong at the time of writing—highlighting the urgent need for furthering the accessibility of Immunology and Allergy services in our locality.

There are several limitations in this study. First, CSU disease activity was characterized using UAS7 alone. Although being one of the most widely used patient-reported outcome measurements of CSU, manifestations of angioedema might not be optimally reflected. Secondly, data of UAS7 were only available at 2 time points, one at baseline and the other after immunologist review. It was possible that patients' urticaria activities fluctuated and varied over time. Thirdly, the observational study design did not allow the investigation of causal relationships between various factors.

In conclusion, this is the first study to report the characteristics and real-world practice of management of CSU in Hong Kong as well as investigate COVID-19 vaccination rates and factors associated with vaccine uptake among CSU patients. A dedicated immunologist-led Urticaria Clinic effectively improved CSU management and outcomes in Hong Kong. Patients with higher baseline UAS7 scores benefited the most, but inaccessibility to specialist-level remains a significant barrier to many patients. COVID-19 vaccination rates were lower in CSU patients than in the general population and associated with concomitant suspected drug allergy. Findings from this study highlighted the urgent need for furthering the accessibility of Immunology and Allergy services in Hong Kong.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

Treatment algorithm regarding pharmacological management of chronic spontaneous urticaria

Click here to view

Supplementary Table S2

Prevalence of autoimmune comorbidities among included patients

Click here to view

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Supplementary Table S3

Prevalence of drug allergy labels among included patients

Click here to view

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