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Does COVID-19 Really Exacerbate Urticaria? A Survey of 166 Patients in China

Qian Yang [1,†], Zihao Zou [1], Wei Cao [1,†], Yunzhou Shi [1], Xianjun Xiao [1], Sijue Chen [1] and Ying Li [2,*]

[1] Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu 610044, China; yangqian2021@stu.cdutcm.edu.cn (Q.Y.); zouzihao@stu.cdutcm.edu.cn (Z.Z.); weicao@stu.cdutcm.edu.cn (W.C.); shiyunzhou@stu.cdutcm.edu.cn (Y.S.); xiaoxianjun@cdutcm.edu.cn (X.X.); chensijue@stu.cdutcm.edu.cn (S.C.)
[2] Graduate School, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China
* Correspondence: liying@cdutcm.edu.cn; Tel.: +86-137-0809-5607
† These authors contributed equally to this work.

Abstract: The COVID-19 pandemic significantly disrupted global healthcare systems. The impacts of SARS-CoV-2 infection on urticaria and its management are unknown. This study aimed to collect information about patients with urticaria infected with SARS-CoV-2 and to investigate the impact of SARS-CoV-2 infection on urticaria severity, course, and treatment to better support recovery. This was a questionnaire-based study of patients with urticaria infected with SARS-CoV-2. Changes in urticaria severity (measured with the urticaria activity score (UAS)), course, and treatment were assessed before, during, and after SARS-CoV-2 infection. The mean (±SD) UAS scores were 5.17 ± 1.67, 4.23 ± 1.98, and 4.37 ± 1.93 before, during, and after SARS-CoV-2 infection, respectively ($F = 8.839$, $p < 0.01$). The median (IQR) wheal score was 0.464 (0.464, 0.763), 0.464 (0.138, 0.763), and 0.464 (0.138, 0.763) before, during, and after infection, respectively (Kruskal–Wallis H-test, $H = 12.230$, $p = 0.02$). The median (IQR) pruritus score was 0.695 (0.395, 0.695), 0.394 (0.123, 0.695), and 0.394 (0.123, 0.695) before, during, and after infection, respectively (Kruskal–Wallis H-test, $H = 21.001$, $p < 0.01$). Within the limitations of a questionnaire study, urticaria appears to improve during SARS-CoV-2 infection and worsens slightly after recovery, and the frequency of Western medicine use increases.

Keywords: urticaria; SARS-CoV-2 infection; COVID-19 pandemic; mast cells

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1. Introduction

Urticaria, one of the most common dermatological diseases [1,2], is characterized by wheals, pruritus, and/or angioedema. Urticaria is present in 1–30% of the global population (~23% of the Chinese population), with no racial or age distinction, its incidence mainly influenced by environmental and other factors such as sex (male-to-female ratio of about 1:2). The condition is classified into spontaneous and induced urticaria based on the patient's clinical history and physical examination, with urticaria lasting < 6 weeks considered acute spontaneous urticaria and urticaria lasting > 6 weeks with at least two episodes per week considered chronic spontaneous urticaria. Urticaria has many triggers which, after removal, resolves the condition [3–5].

Active urticaria can be debilitating, significantly impacting quality of life and representing a significant global economic burden [1,2,6]. There are several theories about the pathogenesis of urticaria, mainly involving autoinflammation and the release of mediators from cutaneous mast cells (MCs) [7], the main effector cells in urticaria. MCs are usually activated by autoimmune mechanisms, resulting in the release of histamine and other pro-inflammatory cytokines, which in turn lead to sensory nerve activation, vasodilation, plasma extravasation, and cell recruitment. MC degranulation is a central event in the development of urticarial skin lesions, with raised histamine levels detected in skin biopsy samples [8]. MCs are strategically sited at locations interfacing with the external environment (such as the skin, lungs, and intestines), allowing them to act as sentinels for tissue damage and pathogen

invasion. The association between MCs and blood vessels is optimal for enhancing the rapid recruitment of effector cells from the bloodstream into neighboring lesions [9].

The first report of a virus-associated pneumonia of unknown origin was reported in Wuhan, China, in November 2019 [10]. The International Committee on Taxonomy of Viruses (ICTV) subsequently identified the virus as a novel coronavirus strain and designated it "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), with the World Health Organization (WHO) officially naming the associated disease "coronavirus disease 2019" (COVID-19) [11]. COVID-19 was the most significant global public health crisis since the influenza pandemic over 100 years ago [12], and it presented a major challenge to global healthcare systems. As of August 2023, the number of confirmed COVID-19 cases had approached 700 million, with over 6 million recorded deaths attributed to the disease [13–15].

The pathogenesis of severe COVID-19 is characterized by elevated levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), and chemokine (C-C-motif) ligand 2 (CCL2) [16], many of which are produced and released by MCs. Indeed, SARS-CoV-2 activates MCs [17] in addition to other immune cells such as basophils, neutrophils, monocytes/macrophages, and natural killer cells, leading to a "storm" of cytokines (or cytokine release syndrome) [18]. MCs can identify and respond to the virus via several different receptors, including Toll-like receptors, retinoic acid-inducible gene I-like receptors, FcεRI, complement, and IL-1 receptors. The activation of these receptors leads to mast cell activation and degranulation together with the de novo synthesis of many cytokines, chemokines, and growth factors [19]. MC activation in response to viral infection can protect the host by aiding the immune system or by directly fighting the infection. However, if there is extensive MC activation and prolonged or excessive release of inflammatory cytokines and chemokines, this can worsen the inflammation and contribute to severe disease [16].

In addition, basophils also participate in the pathogenesis of COVID-19 and urticaria. COVID-19 patients have been reported to have a reduced number of basophils, similar to patients with chronic spontaneous urticaria [20]. The effective treatment of COVID-19 normalizes blood basophil counts [21]. These associations and effects of MCs and basophils might explain several reports of urticaria and angioedema associated with COVID-19 infection, with urticaria-like lesions ranked the second most common cutaneous manifestation of COVID-19 infection, reported to be present in 19% of patients in a Spanish cohort [22].

Due to the potential impact of SARS-CoV-2 on systemic inflammation and MCs, here, we studied patients with urticaria infected with SARS-CoV-2 and investigated the impact of SARS-CoV-2 infection on urticaria severity, course, and management to provide better support for recovery.

2. Materials and Methods

2.1. Study Participants and Inclusion Criteria

A questionnaire was administered to the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine between 29 March and 5 June 2023, using the online anonymous QuestionStar platform. Participants were patients who had been infected with SARS-CoV-2 and suffered from urticaria and were included in the study after meeting eligibility criteria and consenting to participate. The questionnaire was designed to obtain basic information about patients with urticaria infected with SARS-CoV-2, the severity of SARS-CoV-2 infection, and the severity of urticaria to investigate the relationship between SARS-CoV-2 infection and urticaria.

The inclusion criteria were age ≥18 years; history of urticaria and SARS-CoV-2 infection; ability to complete the questionnaire independently; and voluntary participation in the survey. Exclusion criteria were patients who had not been infected with SARS-CoV-2; non-urticaria patients; and patients who could not complete the questionnaire.

To ensure survey quality, we discussed the questionnaire several times, based on which we improved the questionnaire design and developed questions that prohibited repeat answers to ensure data accuracy.

2.2. Survey Content

The questionnaire had 22 questions (see Table S1). The survey consisted of three parts: general information about urticaria patients and their vaccination status; symptoms experienced during the COVID-19 pandemic and the use of medications; and the severity of urticaria and the impact of COVID-19 pandemic on urticaria.

2.2.1. General Questions

Data were collected on participants' socio-demographic characteristics including sex; age; medical history; COVID vaccination status; and, if vaccinated, the type of vaccine.

2.2.2. COVID-19 Questions

Data were collected on whether COVID-19 was formally diagnosed, how the diagnosis was made, the main symptoms experienced, overall self-perception during the period of infection, specific treatments after infection, and the time elapsed between symptom onset and recovery.

2.2.3. Urticaria Characteristics and Symptomatic Variation

Data were gathered on the urticaria characteristics; disease activity before, during, and after SARS-CoV-2 infection; and medication use. Urticaria characteristics, such as contributing factors, disease duration, and time of first episode, were documented. Disease activity before, during, and after SARS-CoV-2 infection was assessed using the urticaria activity score (UAS), which evaluates the number of wheals and pruritus. For wheals, patients counted the number of wheals, which were evaluated on a scale from 0 to 3 (0 = absent, $1 \leq 20$ wheals over 24 h, 2 = 20–50 wheals over 24 h, and $3 \geq 50$ wheals over 24 h). Pruritus was analyzed on a scale from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, and 3 = severe) retrospectively for 24 h. Medication use (both Western drug use and traditional Chinese medicine) was recorded with respect to specific urticaria treatments before, during, and after recovery from SARS-CoV-2 infection.

2.3. Statistical Analysis

Data were tabulated in Microsoft Excel v2310, and statistical analyses were performed in IBM SPSS Statistics for Windows v25.0 (IBM Statistics, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation ($x \pm s$) for those conforming to a normal distribution and as median (interquartile range, IQR) for those that do not. Categorical variables are expressed as frequency (%). Continuous variables were analyzed using one-way analysis of variance (ANOVA) or non-parametric rank-sum tests depending on the data characteristics. Ridit analyses and nonparametric rank sum tests were used for ranked variables. The Mann–Whitney U test was used to compare two groups of data, and the Kruskal–Wallis H test was used for three groups of data. A p-value < 0.05 was deemed statistically significant.

3. Results

3.1. General Information Data

A total of 198 patients with urticaria were surveyed. Thirty-six ineligible questionnaires (not infected with SARS-CoV-2) were excluded, giving a response rate of 83.8%. The characteristics of the study respondents are presented in Table 1. Of the 166 patients investigated, 49 (29.5%) were male and 117 (70.5%) were female, with a mean age of 33.45 ± 12.72 years (range: 14–67 years). One hundred and twenty-three patients (71.90%) had no past medical history of note, while thirty-one patients (18.10%) had a history of allergic diseases (e.g., allergic rhinitis, allergic asthma, and atopic dermatitis), 4 patients (2.30%) had a history of

hypertension, 1 patient (0.60%) had diabetes mellitus, and 12 patients had other unspecified diseases (7.0%). The ratio of vaccinated to unvaccinated patients was 9:1. Eighty-eight (53%) patients had received three doses of the COVID-19 vaccine (recombinant protein vaccine), sixty patients (36.1%) had received two doses of the vaccine (inactivated vaccine), and four patients (2.4%) had received one dose of the vaccine (adenovirus carrier vaccine).

Table 1. Demographic characteristics of the patients in our study group.

Parameter		n (%)
Sex	Male	49 (29.5%)
	Female	117 (70.5%)
Age *		33.45 ± 12.72
Past basic diseases	No basic disease	123 (71.9%)
	Hypertension	4 (2.3%)
	Diabetes mellitus	1 (0.6%)
	Allergic diseases	31 (18.1%)
	Other	12 (7%)
COVID-19 vaccine	Yes	152 (91.6%)
	No	14 (8.4%)
Several doses of the COVID-19 vaccine	One dose of New Crown Vaccine (adenovirus vector vaccine)	4 (2.4%)
	Two doses of New Crown Vaccine (inactivated)	60 (36.1%)
	Three doses of New Crown Vaccine (recombinant protein vaccine)	88 (53%)
Diagnostic modalities	Nucleic acid testing	40 (24.1%)
	Antigen detection	76 (45.78%)
	Suspected symptoms, not tested	50 (30.12%)

* Data are expressed as mean ± SD. Significance $p < 0.05$.

3.2. COVID-19 Disease-Related Information

Nearly half of the respondents were diagnosed with infection by antigen testing (n = 76, 45.8%), nearly a quarter were diagnosed by nucleic acid testing (n = 40, 24.1%), and the remainder with suspected symptoms were not tested (n = 50, 30.1%). High fever (n = 120, 72.44%), fatigue (n = 110, 66.3%), and sore throat (n = 108, 65.1%) were the most common symptoms. Headache (n = 88), muscle ache (n = 80), and nasal congestion (n = 74) were reported in 53.0%, 39.6%, and 44.6% of participants, respectively (Figure 1). Over half of the patients described their symptoms as "moderate" (n = 90, 54.2%), nearly a quarter described them as "mild" (n = 40, 24.1%), and 21.69% reported "severe" symptoms (n = 36, 21.7%). Ninety-five patients took symptomatic treatments (57.2%), and seventy-one patients (42.8%) received no treatment. Treatments were diverse and were mainly Western medicines (e.g., antipyretics, cough suppressants, expectorants, etc.; n = 84, 88.4%) and proprietary Chinese medicines (such as Lianhua Qingdian capsules, Banlangen granules, Niu Huang Shangqing pills, etc.; n = 37, 39.0%) (Figure 2). The average number of days from symptom onset to recovery was 11.5 ± 16.0 days (range: 1 to 140) (Table 2).

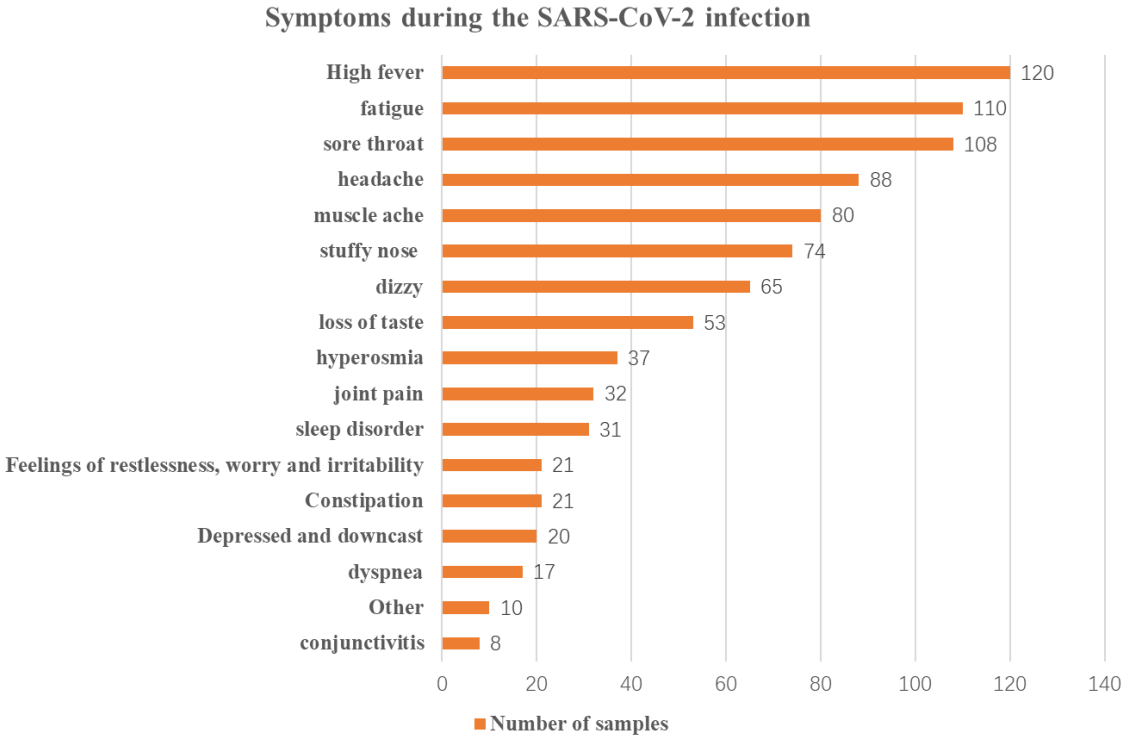

Figure 1. The main symptoms of infection with SARS-CoV-2 infection.

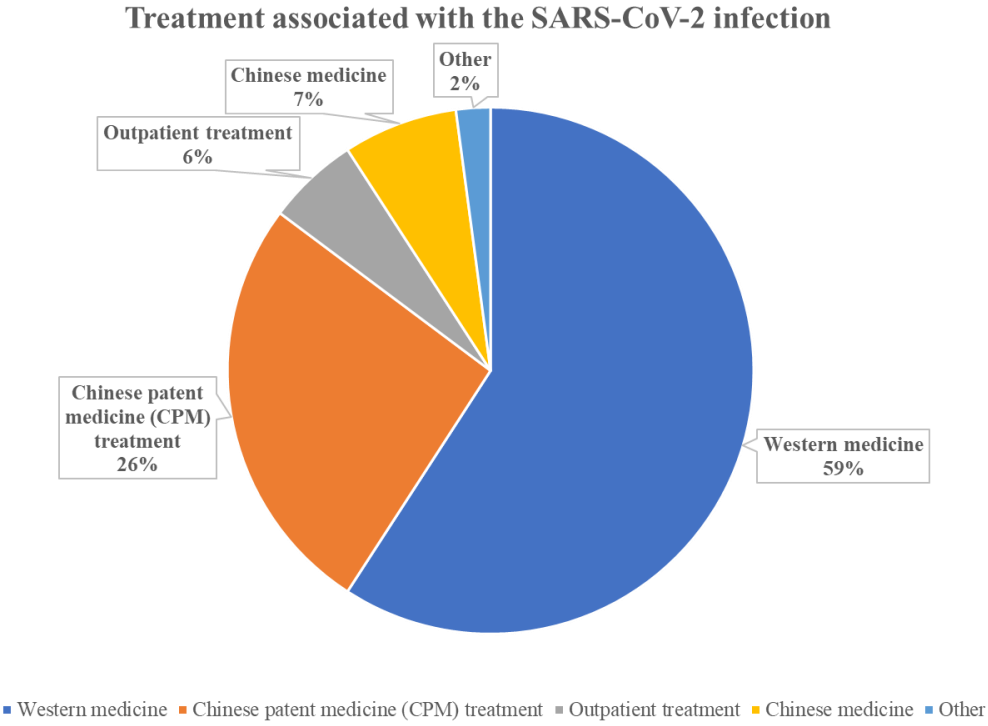

Figure 2. Treatment associated with SARS-CoV-2 infection.

Table 2. COVID-19 disease-related information.

Parameter		n (%)
Main symptoms of SARS-CoV-2 infection	High fever	120 (13.4%)
	Constipation	21 (2.3%)
	Stuffy nose	74 (8.3%)
	Sore throat	108 (12.1%)
	Headache	88 (9.8%)
	Dizziness	65 (7.3%)
	Fatigue	110 (12.3%)
	Conjunctivitis	8 (0.9%)
	Joint pain	32 (3.6%)
	Muscle ache	80 (8.9%)
	Dyspnea	17 (1.9%)
	Loss of taste	53 (5.9%)
	Hyperosmia	37 (4.1%)
	Depresion and feeling downcast	20 (2.2%)
	Feelings of restlessness, worry, and irritability	21 (2.3%)
	Sleep disorder	31 (3.5%)
	Other	10 (1.1%)
Symptoms of SARS-CoV-2 infection—overall self-perception	Mild symptoms	40 (24.1%)
	Moderate symptoms	90 (54.2%)
	Severe symptoms	36 (21.7%)
Whether SARS-CoV-2 infection was treated	Yes	95 (57.2%)
	No	71 (42.8%)
What treatment was given for SARS-CoV-2 infection	Western medicine	84 (88.4%)
	Chinese patent medicine (CPM) treatment	37 (39.0%)
	Outpatient treatment	10 (10.5%)
	Chinese medicine	8 (8.4%)
	Other	3 (3.2%)
Onset to recovery *		11.54 ± 16.027
Course of disease	Less than 6 weeks	25 (15.1%)
	6~2 years	51 (30.7%)
	2~5 years	44 (26.5%)
	Over 5 years	46 (27.7%)
When did the hives first flare up	Before SARS-CoV-2 infection	115 (69.3%)
	During SARS-CoV-2 infection	3 (1.8%)
	After SARS-CoV-2 infection	15 (9%)
	Resolved before SARS-CoV-2 infection	33 (19.9%)
Flare-ups of urticaria after administration of medication to alleviate the symptoms of SARS-CoV-2 infection	Aggravating	9 (7.6%)
	Alleviate	13 (11%)
	Unaffected	96 (81.4%)

* Data are expressed as mean ± SD. Significance $p < 0.05$.

3.3. Urticaria Characteristics and Symptomatic Variation

The main known triggers for patients with urticaria were no discernible trigger (n = 95, 57.2%), exercise or post-exercise (n = 40, 24.1%), eating hot or cold substances (n = 36, 21.7%), and emotional stimuli (n = 30, 18.1%) (Figure 3). Over 80% of urticaria patients had chronic urticaria, while only 15.1% (n = 25) had acute urticaria; 69.3% of patients experienced their first urticaria episode before SARS-CoV-2 infection (n = 115), 19.9% had a history of urticaria that had resolved before SARS-CoV-2 infection (n = 33), 9.0% had their first episode following the SARS-CoV-2 infection (n = 15), and 1.8% had their first episode during SARS-CoV-2 infection (n = 3). Most patients who took medications to alleviate SARS-CoV-2 symptoms reported no impact of medication use on their urticaria attack (n = 96, 81.4%), although 13 patients (11.0%) experienced symptom relief while taking medications and a few patients experienced worsening of symptoms (n = 9, 7.6%).

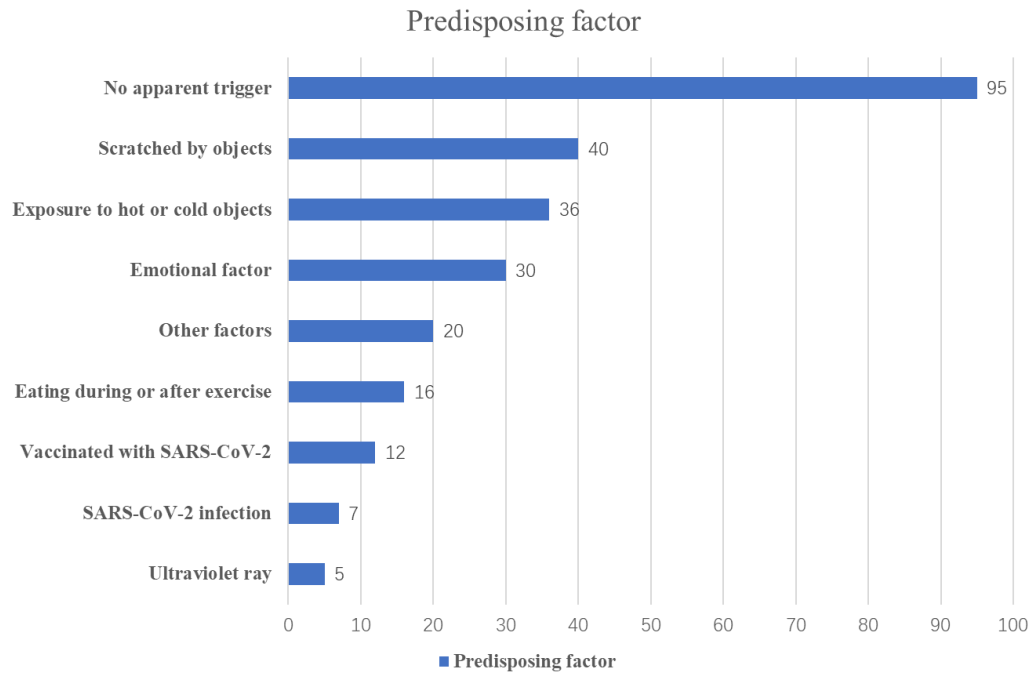

Figure 3. Predisposing factor for the development of urticaria.

Taking the patient's infection with SARS-CoV-2 as the reference, time was categorized into three phases: before SARS-CoV-2 infection, during SARS-CoV-2 infection, and during recovery from SARS-CoV-2 infection (having turned negative). UAS scores were significantly different before infection, during infection, and after infection at 5.17 ± 1.67, 4.23 ± 1.98, and 4.37 ± 1.93, respectively (F = 8.839, $p < 0.01$; Table 3). Pairwise comparisons similarly showed that UAS scores were significantly different before and during SARS-CoV-2 infection, and UAS scores before SARS-CoV-2 infection were significantly higher than UAS scores during the recovery period ($p < 0.01$). When considering wheals alone, the mean (IQR) of the wheal score before infection, during infection, and during recovery were 0.464 (0.464, 0.763), 0.464 (0.138, 0.763), and 0.464 (0.138, 0.763), respectively (Kruskal–Wallis H-test, H = 12.230, $p = 0.02$; Table 4). Wheal scores before infection were significantly higher than during infection and during the recovery stage. Similarly, mean (SD) pruritus scores were significantly different pre-infection, during infection, and during recovery at 0.695 (0.395, 0.695), 0.394 (0.123, 0.695), and 0.394 (0.123, 0.695), respectively (Kruskal–Wallis H Test, H = 21.001, $p < 0.01$; Table 5). Pairwise comparisons showed that there was a statistically significant difference in pruritus scores before SARS-CoV-2 infection, during infection, and during recovery ($p < 0.01$), with pruritus scores significantly higher in the pre-infection period than during infection and during recovery.

Table 3. Comparison of UAS scale scores before, during, and after SARS-CoV-2 infection.

Variables	Number of Samples	Mean ± Standard Deviation	F	*p* **	LSD
1	115	5.17 ± 1.67	8.84	<0.01	1 > 2, 1 > 3
2	118	4.23 ± 1.98			
3	166	4.37 ± 1.93			

Notion: ** $p < 0.01$, 1 = before SARS-CoV-2 infection, 2 = during SARS-CoV-2 infection, 3 = after SARS-CoV-2 infection. Significance values have been adjusted for multiple tests using Bonferroni correction.

Table 4. Comparison of the wheal scores in the UAS scale before, during, and after SARS-CoV-2 infection.

Variables	Number of Samples	M (P25, P75)	H	*p* *
1	115	0.464 (0.464, 0.763)	12.23	<0.05
2	118	0.464 (0.138, 0.763)		
3	166	0.464 (0.138, 0.763)		

Notion: * $p < 0.05$, 1 = before SARS-CoV-2 infection, 2 = during SARS-CoV-2 infection, 3 = after SARS-CoV-2 infection, M = median value. Significance values have been adjusted for multiple tests using Bonferroni correction.

Table 5. Comparison of the pruritus scores in the UAS scale before, during, and after SARS-CoV-2 infection.

Variables	Number of Samples	M (P25, P75)	H	*p* **
1	115	0.695 (0.395, 0.695)	21.001	<0.01
2	118	0.394 (0.123, 0.695)		
3	166	0.394 (0.123, 0.695)		

Notion: ** $p < 0.01$, 1 = before SARS-CoV-2 infection, 2 = during SARS-CoV-2 infection, 3 = after SARS-CoV-2 infection, M = median value. Significance values have been adjusted for multiple tests using Bonferroni correction.

Figure 4 shows the urticaria treatments used by patients before the pandemic. The majority of patients (n = 74, 41.3%) were treated with Western medicines, some (n = 45, 25.1%) took traditional Chinese medicines, and the remainder (n = 40, 22.3%) were treated with acupuncture. A small number of patients (n = 18, 10.1%) did not receive any urticaria treatment due to factors such as high medical costs or extremely stubborn urticaria. Two patients (1.1%) used topical medication and medicated baths, respectively. In urticaria patients infected with SARS-CoV-2, the proportion of patients treated with western medicines decreased significantly (n = 46, 34.1%), as did the proportion of patients treated with traditional Chinese medicines (n = 15, 11.1%). Only nine (6.7%) received acupuncture due to the patient's health and family isolation, while the number of patients who did not receive any treatment increased significantly (n = 64, 44.4%). Only one patient did not use any of the above treatments (0.70%). Therefore, the treatment preferences of patients with urticaria during the COVID-19 pandemic showed a significant reduction in medication use and a preference for no treatment.

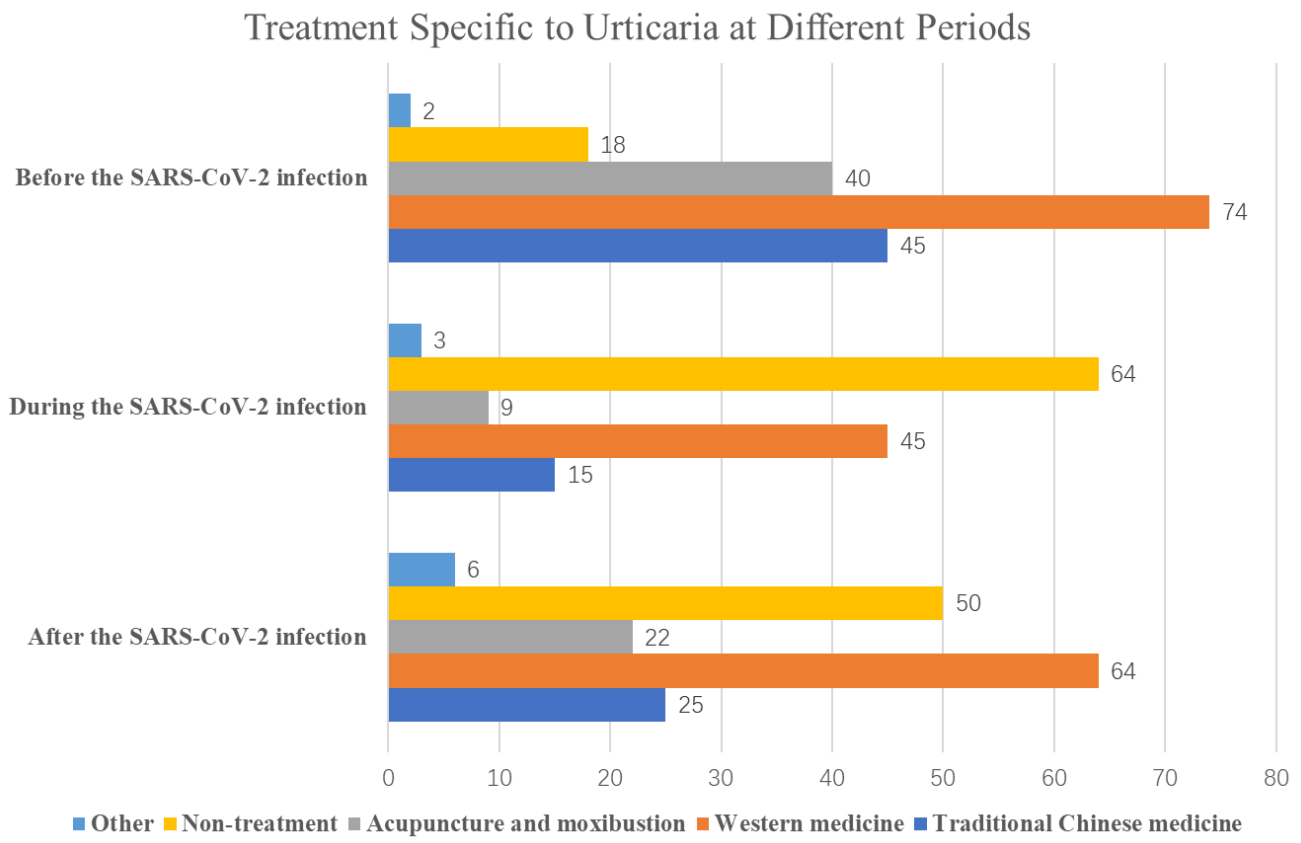

Figure 4. Description of specific treatments for different stages of urticaria.

The proportion of patients who received Western medicines increased significantly from 39.30% during the epidemic to 48.9% (n = 65) after patients with urticaria had fully recovered from SARS-CoV-2. The proportion of patients treated with traditional Chinese medicines also increased from 12.80% to 18.8% (n = 25), and the proportion of patients treated with acupuncture increased from 7.7% to 16.54% (n = 22). By contrast, there was a decrease in the proportion of patients who did not receive treatment (50, 37.60%). Six patients (4.50%) used other treatments. We analyzed the frequency of western drug use and showed that the mean (IQR) frequency of Western drug use was 0.482 (0.482, 0.482) during SARS-CoV-2 infection and 0.820 (0.248, 0.820) after infection, which was significantly different (Z = 3.377, p = 0.01; Table 6).

Table 6. The frequency of western drug use during SARS-CoV-2 infection compared with after the infection.

Variables	Number of Samples	M (P25, P75)	Z	p *
a	45	0.482 (0.482, 0.482)	3.737	<0.05
b	64	0.820 (0.248, 0.820)		

Notion: * $p < 0.05$, a = the frequency of western drug use during SARS-CoV-2 infection, b = the frequency of western drug use after SARS-CoV-2 infection, M = median value. Significance values have been adjusted for multiple tests using Bonferroni correction.

4. Discussion

Urticaria, especially chronic urticaria, is a disease that has a serious impact on the lives of patients, and it can incur a significant health and financial cost. It is usually characterized by fluctuating disease activity, and many patients have severe symptoms that are resistant to treatment with antihistamines. Therefore, access to specialized urticaria centers is crucial. This is the first study to examine the effect of SARS-CoV-2 infection on the severity, course,

and treatment of patients with urticaria in China. Our findings suggest that SARS-CoV-2 infection has a significant impact on urticaria and influences how they are treated. Our results also indicate that COVID-19 is linked to urticaria, often improving it.

The ratio of male to female participants with urticaria in this study was approximately 3:7, with a mean age of 33.45 ± 12.72 years (range 14–67 years). These findings are consistent with data from previous studies on the epidemiology of urticaria [23]. About 18% of our cohort suffered from prior allergic diseases, including allergic rhinitis, allergic asthma, and atopic dermatitis, which are known to be associated with urticaria. Allergic rhinitis is a type I allergic disease characterized by an imbalance in helper T-lymphocyte 1/helper T-lymphocyte 2 (Th1/T2) immunity [24,25], which manifests as a significantly higher number of circulating Th2 than Th1 cells and elevated immunoglobulin E (IgE) [26,27]. Recent studies have suggested that the Th1/Th2 imbalance also plays an important role in the occurrence and development of chronic urticaria [28]. It has been suggested that chronic urticaria is stimulated by specific allergens, which stimulate a Th2-dominated immune response and consequent allergic reaction. Patients with urticaria have significantly lower total T cell counts, CD4 T cells, and IL-2 and IFN-γ levels but increased IL-4, characteristic of the Th2 phenotype [29,30]. The pathogenesis of allergic rhinitis is very similar to that of urticaria [31], explaining their co-existence.

In our study, all participants were vaccinated, nearly 60% with three doses of recombinant protein vaccine and nearly 40% with two doses of inactivated vaccine. Vaccination coverage in China appears to be very extensive, with near total population coverage.

During the pandemic, the large number of patients infected with SARS-CoV-2 resulted in an extreme shortage of antigen detection kits and a substantial increase in their price. As a result, 30% of patients had symptoms suggestive of COVID-19 but had not been formally tested for antigens or antibodies to confirm the diagnosis. High fever, malaise, and sore throat were reported as the three most common COVID-19 symptoms, as expected, which were generally self-perceived as mild to moderate and only one-fifth perceiving their symptoms as severe. Despite most patients experiencing their disease as asymptomatic or mild, there is increasing evidence that many patients who either recovered from or had mild symptoms after COVID-19 exhibit diffuse, multiorgan symptoms months after the infection, known as the adult multisystem inflammatory syndrome, or "long COVID" [32]. The clinical picture of long COVID is diverse and includes symptoms such as malaise, myalgia, chest tightness, brain fog, and other neuropsychiatric symptoms similar to those of patients with mast cell activation syndrome [33]. During the COVID-19 pandemic, nearly 60% of patients infected with SARS-CoV-2 were treated with neocoronaviral therapy for various reasons such as home isolation, ill-health, and scarce medication. Among the 95 patients who took treatments for SARS-CoV-2 infection, 84 patients took symptomatic Western medicines (e.g., antipyretics, cough suppressants, and expectorants) and 37 patients used proprietary Chinese medicines (e.g., Lianhua Qingdian capsules, Panlangen granules, Niu Huang Shangqing pills, etc.) to alleviate their symptoms. Ten patients went to outpatient clinics, and eight patients were treated with traditional Chinese medicines (e.g., Chinese herbs, acupuncture, gua sha, and cupping). Although there were many different treatment options, most patients chose to buy over-the-counter medications and very few patients sought medical help.

Over 80% of our urticaria patients had chronic urticaria and over half had spontaneous urticaria. Nearly 90% of patients first developed their urticaria before SARS-CoV-2 infection, with nearly 20% were symptom-free before SARS-CoV-2 infection, and the rest developed urticaria for the first time during or after SARS-CoV-2 infection. In 80% of patients, the onset of urticaria was unaffected by the use of medications to relieve the symptoms of SARS-CoV-2. Therefore, a large proportion of patients in our study had chronic spontaneous urticaria. In a small number of patients, the first urticaria episode started during SARS-CoV-2 infection or after the period of recovery, and it has been demonstrated that urticaria is the second most common skin disease seen with SARS-CoV-2 infection. Hence, infection with SARS-CoV-2 is likely to induce urticaria flare-ups [34].

In terms of urticaria activity, our cohort reported more severe disease before SARS-CoV-2 infection compared with during infection and recovery. Also, the severity of wheals and pruritus was worse before infection than during infection and after recovery. Overall, urticaria flare-ups improved considerably during infection with SARS-CoV-2 and worsened slightly during the recovery period, in contrast to some other studies. The pandemic appears to have significantly altered the treatment of urticaria patients: before SARS-CoV-2 infection, patients were primarily treated with Western medications, traditional Chinese medicine, and acupuncture, and only a small proportion of patients did not receive any treatment. However, over half of the patients opted out of treatment during the pandemic, leading to a significant decrease in the use of Western medicines and only a small number of patients receiving Chinese medicine or acupuncture treatment. After SARS-CoV-2 infection and recovery, patients increasingly received Western medicines, Chinese medicines, and acupuncture, albeit at lower levels than before COVID-19 infection. Additionally, the proportion of patients receiving no treatment decreased but remained higher than pre-infection levels. It is reasonable to hypothesize that the main reason for the significant increase in the proportion of patients not receiving treatment and the significant decrease in the proportion of patients taking Western treatments was because patients isolated at home did not feel well during their COVID-19 illness, decreasing their ability to buy medications or to attend clinics. In addition, since urticaria disease activity decreased and flare-ups improved during SARS-CoV-2 infection, this may have reduced the need for treatment.

The frequency of Western medication use in patients with urticaria increased after SARS-CoV-2 infection compared with during infection, which was also reflected in the worse UAS scores of patients with urticaria after SARS-CoV-2 infection compared with during infection and explaining why more medication was needed. It is reasonable to hypothesize that the immune–inflammatory response is high after COVID-19, and there is heightened sensitivity to environmental triggers which, coupled with low autoimmunity, promotes an immune response and enhances urticaria [6].

Our data suggest that SARS-CoV-2 does not necessarily exacerbate urticaria. Urticaria patients had a decrease in wheal and pruritus scores and a significant decrease in overall UAS scores during SARS-CoV-2 infection. We hypothesize that antiviral treatment is the main trigger for improvements in urticaria, but more data on its incidence and associations are needed. Previous studies have shown that 5 of 12 patients with chronic urticaria had complete remission after treatment with acyclovir, which reappeared after discontinuation of acyclovir. Because these patients had high herpes simplex virus or Epstein–Barr virus antibody titers, it was concluded that acyclovir exerts its therapeutic effect by inhibiting circulating viral antigens [35]. It has been shown that raltegravir, a retroviral integrase inhibitor, may have an effect on chronic idiopathic urticaria by directly inhibiting its expression. Patients with CIU completely resistant to histamine and steroids experienced complete remission of all symptoms and remained completely urticaria-free for three months without the need for oral corticosteroids, with a significant improvement in their quality of life [36]. The proposed mechanism was that aspartic or glutamic acid residues on the retroviral integrase fold together in the retroviral integrase to form a magnesium-binding site known as the "DDE site", which is present in the RAG-1 (recombination activating gene) protein required for the generation of acquired immunity through somatic recombination of immunoglobulin and T cell receptor genes. The DDE recombinase utilizes this conserved mechanisms to break and reattach nucleic acid molecules [37]. RAG-1, which is required to generate the acquired immune reserve, shares a similar DDE site, so some drugs that target the DDE enzyme-retroviral integrase inhibitors, such as raltegravir, may block B and T cell production and act as anti-inflammatory or immunosuppressive drugs. Thus, antiviral therapy plays a therapeutic role in autoimmune inflammatory responses such as urticaria [38].

The limitations are threefold, beginning with this survey being a single-center survey study and the data potentially having geographical selection bias. The data we collected at the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine included

patients with urticaria which may not be fully representative of the broader population of patients with urticaria in China or globally. The urticaria patients at this hospital may have some geographic characteristics that make their urticaria symptoms or treatment responses different from patients in China or other parts of the world. In the future, we will further expand the sample size by adopting a multi-center, multi-region, or even multi-country format in order to improve the apparent credibility of the questionnaire results. Expanding the study to include patients from multiple hospitals or medical centers in different cities/regions of China or even other countries will capture the epidemiological credibility of the questionnaire results, and expanding the study to include centers from different cities/regions in China or even other countries will capture a more diverse patient population. The findings will then be more generalizable and representative, meaning that the data and results of this study are more likely to reflect the experiences of the overall global population of patients with urticaria. Second, this study was a retrospective data study relying on self-report. The raw data in the questionnaire were all derived from the subjective feelings and self-assessment of the urticaria patients, and there was a lack of objective data support (e.g., the results of objective laboratory test indicators). Therefore, in future studies, the questionnaire should be supplemented and improved to enhance the objectivity and credibility of the overall data. Finally, the use of online questionnaires by elderly patients is low, so the study population is more inclined toward young and middle-aged patients; therefore, we should increase the distribution of questionnaires for elderly patients, and it is suggested that paper questionnaires be used, distributed in outpatient clinics.

5. Conclusions

Our findings help to explain the condition, course, and treatment of urticaria pallidum during the COVID-19 pandemic and may serve as a supplement to previous studies of urticaria disease during the COVID-19 pandemic, as well as a reference and guideline for future epidemiologic studies incorporating dermatologic conditions. The results of this study, in the form of an online questionnaire, will allow healthcare professionals to better understand the impact of urticaria disease during the COVID-19 pandemic and to better respond to real-world unmet medical needs related to urticaria care.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/covid3120118/s1, Table S1: Questionnaire survey of urticaria patients infected with the SARS-CoV-2.

Author Contributions: Q.Y. collected the data, performed the preliminary analyses, interpreted the data, and drafted the first draft. Z.Z. and W.C. commented on, proofread, reviewed, and revised the manuscript. Y.S. commented on and reviewed the manuscript. X.X. and S.C. were involved in the study conceptualization and design, discussion of the details, and review and revision of the manuscript. Y.L. provided the final review and evaluation of articles. All authors have read and agreed to the published version of the manuscript.

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