Original Article

Non–Skin Related Symptoms Are Common in Chronic Spontaneous Urticaria and Linked to Active and Uncontrolled Disease: Results From the Chronic Urticaria Registry

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What is already known about this topic? Patients with chronic spontaneous urticaria often have recurrent, unexplained, non–skin related symptoms such as fever, joint, bone, and muscle pain, and malaise. The rate of these symptoms and causes (urticaria or other conditions manifesting in wheals) are unknown.

What does this article add to our knowledge? One third of patients had one or more non–skin related symptoms, correlating with infection and food as trigger factors. These symptoms were associated with wheals of 24 hours or more duration, higher disease activity, longer disease duration, angioedema, worse quality of life, and poorer disease control.

How does this study impact current management guidelines? In patients with chronic spontaneous urticaria and non–skin-related symptoms, disease control should be evaluated. Additional investigations such as skin biopsy, evaluation of inflammatory markers, and, rarely, genetic testing should be considered to rule out urticarial vasculitis and urticarial autoinflammatory disorders. Furthermore, it is important to consider and address any comorbidities early on.

BACKGROUND: Chronic spontaneous urticaria (CSU) can present with non–skin related symptoms (NSRS), including recurrent unexplained fever, joint, bone, or muscle pain (JBMP), and malaise, which also occur in other conditions that manifest with wheals (eg, urticarial vasculitis or autoinflammatory disorders) or without wheals (eg, infection).

OBJECTIVE: We sought to determine the rate of patients with CSU affected by fever, JBMP, and malaise, their trigger factors, links with clinical and laboratory characteristics, and their impact on everyday life and treatment responses.

METHODS: We analyzed baseline data from the Chronic Urticaria Registry of 2,521 patients with CSU who were aged 16 years or older.

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Abbreviations used
aOR- Adjusted odds ratio
CRP- C-reactive protein
CSU- Chronic spontaneous urticaria
CU-Q_2oL- Chronic Urticaria Quality of Life Questionnaire
CURE- Chronic Urticaria Registry
DLQI- Dermatology Life Quality Index
ESR- Erythrocyte sedimentation rate
GI- Gastrointestinal
JBMP- Joint, bone, and muscle pain
NSRS- Non−skin related symptoms
QoL- Quality of life
UAS7- Weekly Urticaria Activity Score
UCT- Urticaria Control Test
UV- Urticarial vasculitis

RESULTS: One third of CSU patients (31.2%; 786 of 2,521) had one or more NSRS, including recurrent fever (5.3%), JBMP (19.1%), and/or malaise (18.6%). In a multivariable analysis, having one or more of these NSRS correlated with food and infection as trigger factors of urticaria (adjusted odds ratio [aOR] = 1.7 and 1.5), wheals of 24 hours or greater duration (aOR = 2.5), sleep disturbance (aOR = 2.4), anxiety (aOR = 2.8), comorbid atopic dermatitis (aOR = 2.1), gastrointestinal disease (aOR = 1.8), elevated leukocytes (aOR = 1.7) and erythrocyte sedimentation rate (aOR = 1.5). In a bivariate analysis, these NSRS were additionally associated with higher disease activity (weekly Urticaria Activity Score, median: 21 vs 14; $P = .009$), longer disease duration (years, median: 2 vs 1; $P = .001$), the presence of angioedema (74.6% vs 58.7%; $P < .001$), worse quality of life (Chronic Urticaria Quality of Life Questionnaire, median: 42 vs 29; $P < .001$) and more frequent poor control of CSU (78% vs 69%; $P < .001$).

CONCLUSIONS: The presence of NSRS in a subpopulation of patients with CSU points to the need for better control of the disease, exclusion of comorbid conditions, and/or exclusion of urticarial vasculitis and urticarial autoinflammatory diseases. **(J Allergy Clin Immunol Pract 2024;12:1890-9)**

Key words: *Chronic spontaneous urticaria; Non−skin related symptoms; Malaise; Fever; Joint; bone; and muscle pain*

INTRODUCTION

Chronic spontaneous urticaria (CSU) presents with itchy wheals, recurrent angioedema, or both for over 6 weeks with no

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identifiable trigger.[1,2] CSU is an increasingly common skin disease with an estimated global point prevalence of 1% to 3%,[3-5] which disproportionately affects young and middle-aged women.[6] Patients experience severely compromised health-related quality of life (QoL) and emotional well-being,[7,8] and impairments associated with disease activity, notably sleep interference and daily activities.[5] In addition to the direct burden of CSU, patients often have several comorbidities, including atopic diseases and autoimmune and psychiatric disorders,[9] further impairing QoL. Histamine has a key role in CSU pathogenesis; second-generation antihistamines are the first-line treatment. However, up to around 60% of patients are refractory to second-generation antihistamines administered at the standard dose. The success rate increases to about 70-80% when the dose is increased fourfold, leaving many patients requiring alternative biologic therapies.[10]

Nonresponse to conventional treatment in CSU patients has been linked to different factors, including the presence of systemic or non−skin related symptoms (NSRS) in a subpopulation of patients.[5,11] Doong et al[11] reported higher numbers of emergency department visits and oral corticosteroid use in patients with NSRS than in those without these problems. An epidemiologic study found that NSRS exist in more than one third of patients affected by CSU,[12] including fever, joint, bone, and muscle pain (JBMP) and malaise. For example, patients with CSU can experience episodes of articular swelling and joint pain, which develop predominantly during urticarial flares of whealing and/or angioedema.[13] This suggests that the consequences of mast cell activation may not be limited to the skin. These NSRS are also common in other diseases that present with wheals, such as autoinflammatory diseases and urticarial vasculitis (UV)[11,13] or without wheals (eg, autoimmune diseases, gastrointestinal [GI] diseases and infections).[11,14-16]

The reasons and frequency of fever, JBMP, and general recurrent discomfort (malaise) in CSU are largely unknown, as are whether these NSRS affect demographic parameters, disease characteristics, and QoL. In the current analysis, we evaluated the rates of recurrent unexplained fever, JBMP, and malaise in patients with CSU and their association with baseline clinical and laboratory characteristics, comorbidities, disease control, and QoL.

METHODS

Study design and patients

The Chronic Urticaria Registry (CURE) is an ongoing, prospective, international, multicenter observational registry.[17] Physician-reported and patient-reported questionnaires are used to collect data around every 6 months. Inclusion criteria for the registry have been described elsewhere.[18] For this analysis, baseline entries were extracted from CURE and patients were required to have physician-verified CSU, be aged 16 years or older, have CSU documented as the predominant urticaria diagnosis with or without angioedema, and have documented information on the presence of fever, JBMP, and malaise. Data for CURE were collected from 53 centers across Europe, Asia, the Middle East, Africa, Oceania, and Latin America; most were GA^{2}LEN Urticaria Centers of Reference and Excellence.

Data extraction and analysis

Baseline questionnaires collected information on patient demographics, disease history, symptoms, factors that can make urticaria worse or can cause an exacerbation (further mentioned as trigger factors), risk factors, comorbidities, inflammation markers, treatments, and disease control, assessed using the Urticaria Control Test (UCT). Moreover, CURE included disease activity levels for some patients using the weekly Urticaria Activity Score (UAS7).

Data from CURE were included as of September 2022; the total number of entries was 5,007, of which 2,521 were included in the current analysis. In total, 2,486 patients were excluded, reasons for which included a lack of information regarding NSRS symptoms (n = 960), predominant chronic inducible urticaria (n = 997), missing data (n = 260), isolated or exclusive angioedema (n = 180), age less than 16 years (n = 79), and errors in data entry (eg, CSU predominant plus another CSU) (n = 10) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Outcome measures

The rates of fever, JBMP, and malaise were assessed from baseline patient questionnaires or data included by physicians directly to CURE. Question 15 asked patients to "Please state if, in addition to wheals and/or angioedema, you are also suffering from the symptoms below: a. fever; b. JBMP; c. general recurrent discomfort (malaise)." Patients could answer yes or no to each NSRS, supplying information about the rates of individual symptoms. The associations among these symptoms, clinical and laboratory characteristics, and disease control were also assessed. Along with the UAS7 and UCT to measure levels of disease activity and control, respectively, the QoL assessment with the Chronic Urticaria QoL questionnaire (CU-Q_2oL) and Dermatology Life Quality Index (DLQI) were available to many patients. In addition, further baseline characteristics included age, disease duration, sex, family history of chronic urticaria, trigger factors (such as infection, medication, or food), wheal duration, sleep disturbance, anxiety, depression, thyroid disease, GI disease, allergic rhinitis, atopic dermatitis, asthma, food allergy, nonsteroidal anti-inflammatory drug hypersensitivity, hypertension, autoimmune disease, current medication, elevated leukocytes, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Statistical analysis

We analyzed the collected data using Statistical Package for Social Sciences software (version 28.0, IBM, Chicago, USA), R (R Foundation for Statistical Computing, RStudio, Indianapolis, USA), and GraphPad Prism (GraphPad Software, version 8.0, San Diego, CA, USA). For descriptive analysis, we used frequency and percentage for categorical variables and medians and interquartile ranges (IQRs) for quantitative variables. For the bivariate analysis of continuous variables, Mann-Whitney and the Kruskal-Wallis tests were used to compare two groups and three groups, respectively. After Kruskal-Wallis significance testing, we conducted *post hoc* analysis using Bonferroni adjustment for pairwise comparisons. In all cases, P less than .05 was considered significant.

Because the dependent variables were dichotomous, many logistic regressions were used for the multivariable analysis. The adequacy of the model was checked using the Hosmer-Lemeshow test. Independent variables introduced in the models were those of potential clinical interest, considering the maximum number of variables allowed to be included given the sample size; thus, sociodemographic and other independent variables were included in the model using the ENTER method. The adjusted odds ratio (aOR), 95% CIs, and related P values are reported.

TABLE I. Baseline demographics and disease characteristics in patients without and with one or more non−skin related symptoms

		Non−skin related symptoms			
Parameters/variables		**0**	**≥1**	***P***	**Total**
Patients,% (n/total)		68.8 (1,735/2521)	31.2 (786/2,521)	—	2,521
Age, y, median (IQR)		45 (33-57), n = 1,735	43 (33-54), n = 786	.010	44 (33-56), n = 2,521
Female, % (n/total)		73.7 (1,279/1,735)	78.6 (618/786)	.008	75.2 (1,897/2,521)
White, % (n/total)		77.5 (1,345/1,735)	59.0 (464/786)	<.001	71.8 (1,809/2,521)
Body mass index, median (IQR)		25 (22-29), n = 1,534	26 (23-30), n = 742	.002	26 (22-30), n = 2,276
Family history of chronic urticaria, % (n/total)		7.2 (113/1,577)	12.1 (85/704)	<.001	8.7 (198/2,281)
Manifestation factor, % (n/total)	Medication	12.1 (210/1,735)	16.2 (128/786)	.004	13.4 (338/2,521)
	Infection	8.9 (154/1,735)	15.8 (124/786)	<.001	11.0 (278/2,521
	Food	12.9 (223/1,735)	25.1 (197/786)	<.001	16.7 (420/2,521)
Presence of angioedema, % (n/total)		58.7 (1,018/1,735)	74.6 (586/786)	<.001	63.6 (1,604/2,521)
Disease duration, y, median (IQR)		1 (0-5), n = 1,715	2 (0-6), n = 769	.001	1 (0-6), n = 2,484
Concomitant chronic inducible urticaria, % (n/total)		26.4 (456/1,726)	24.4 (189/775)	.283	25.8 (645/2,501)
Urticaria Control Test, median (IQR)		8 (5-12), n = 1,416	7 (4-11), n = 719	<.001	8 (5-12), n = 2,135
Weekly Urticaria Activity Score, median (IQR)		14 (3-26), n = 960	21 (7-35), n = 478	.009	15 (4-28), n = 1,438
Chronic Urticaria QoL Questionnaire, median (IQR)		29 (14-44.6), n = 651	42 (26-58), n = 418	<.001	35 (18-50), n = 1,069
Dermatology Life Quality Index, median (IQR)		5 (2-11), n = 572	11 (5-15), n = 307	<.001	7 (2-13), n = 879
Wheal duration ≥24 h, % (n/total)		5.9 (102/1,735)	20.2 (159/786)	<.001	10.4 (261/2,521)
Sleep disturbance, % (n/total)		35.1 (545/1,551)	64.9 (485/747)	<.001	44.1 (1,030/2,337)
Anxiety, % (n/total)	Total	6.4 (106/1,664)	23.0 (172/748)	<.001	11.1 (278/2,500)
	Active	5.4 (90/1,664)	19.4 (145/748)		9.7 (235/2,412)
Depression, % (n/total)	Total	5.0 (84/1,665)	12.2 (90/737)	<.001	7.0 (174/2,500)
	Active	3.7 (62/1,665)	8.1 (60/737)		5.1 (122/2,402)
Atopic dermatitis, % (n/total)	Total	3.6 (60/1,686)	6.7 (50/748)	.001	4.5 (110/2,434)
	Active	1.3 (22/1,686)	3.2 (24/748)		1.9 (46/2434)
Allergic rhinitis, % (n/total)	Total	18.3 (307/1,681)	20.0 (150/751)	<.001	18.8 (457/2432)
	Active	9.8 (164/1,681)	14.8 (111/751)		11.3 (275/2,432)
Asthma, % (n/total)	Total	9.5 (160/1,685)	12.8 (97/758)	.048	10.6 (257/2,443)
	Active	6.3 (106/1,685)	8.4 (64/758)		7.0 (170/2,443)
Thyroid disease, % (n/total)	Total	19.8 (302/1,521)	24.3 (174/717)	.053	20.3 (476/2,340)
	Active	15.6 (238/1,521)	19.5 (140/717)		16.9 (378/2,238)

(continued)

TABLE I. *(Continued)*

Parameters/variables		Non−skin related symptoms 0	Non−skin related symptoms ≥1	*P*	Total
Gastrointestinal disease, % (n/total)	Total	21.5 (357/1,661)	33.0 (245/743)	<.001	24.1 (602/2,500)
	Active	12.8 (212/1,661)	23.4 (174/743)		16.1 (386/2,402)
Elevated inflammation markers*, % (n/total)	Leukocytes	7.6 (104/1,363)	14.5 (85/586)	<.001	9.7 (189/1,949)
	C-Reactive protein	26.4 (291/1,104)	32.9 (171/519)	.006	28.5 (462/1,623)
	Erythrocyte sedimentation rate	15.9 (165/1,038)	22.4 (85/380)	.005	17.6 (250/1,418)

IQR, interquartile range.
*During the course of chronic spontaneous urticaria.

Ethics

The CURE was approved in 2014 by the Ethics Committee of the Charité−Universitätsmedizin Berlin, Germany (Reference EA1/146/14). All participating centers obtained ethics committee approval before joining the registry.

RESULTS

About one third of patients with CSU have recurrent fever, JBMP, and/or malaise

Across 2,521 patients with CSU (of 5,007 assessed for eligibility [see the Consolidated Standards of Reporting Trials flow diagram Figure E1]), median age was 44 years (IQR = 33-56 years), 75.2% were female and median disease duration was 1 year (IQR = 0-6 year) (Table I). Almost one third (31.2%; 786 of 2,521) had one or more NSRS, such as recurrent and unexplained fever (5.3%; n = 134), JBMP (19.1%; n = 482), and/or malaise (18.6%; n = 470). One third of patients had at least one NSRS; 532 (21.1%) experienced a single symptom, 208 (8.2%) had two symptoms, and 46 (1.8%) presented with all three (Figure 1).

Recurrent fever, JBMP, and malaise are linked to trigger factors in CSU, higher disease activity and duration, longer wheal duration, and the presence of angioedema

In multivariable analyses (Figure 2), having one or more NSRS in patients with CSU was correlated with trigger factors in CSU such as food (aOR = 1.7), infection (aOR = 1.5), medication (only for JBMP and fever; aOR = 2.3 and 2.2), and wheal duration of 24 or more hours (aOR = 2.5). In a bivariate analysis, the presence of one or more NSRS was additionally linked to higher disease activity (UAS7, median: 21 vs 14; $P = .009$), longer disease duration (2 vs 1 year; $P = .001$), and the presence of angioedema (74.6% vs 58.7%; $P < .001$) compared with patients without NSRS (Table I and Figures 3 and 4). Similar significant results for angioedema were identified for patients with JBMP and malaise compared with those without these NSRS (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). In a multivariable analysis, wheal duration of 24 hours or more was strongly correlated with a subset of patients with CSU with each NSRS: fever (aOR = 5.2), JBMP (aOR = 3.5) or malaise (aOR = 3.2) (Figure 2).

Recurrent fever, JBMP, and malaise are linked to lower QoL and sleep disturbance

Sleep disturbance was correlated with having one or more NSRS in patients with CSU (aOR = 2.4) and with fever (aOR = 2.9), JBMP (aOR = 3.6), or malaise (aOR = 3.7) (Figure 2). The presence of one or more NSRS was also linked to worse QoL (CU-Q_2oL, median: 42 vs 29; $P < .001$; DLQI, median: 11 vs 5; $P < .001$) (Table I and Figure 3) compared with patients with no NSRS.

Recurrent fever, JBMP, and malaise are associated with concomitant diseases

Concomitant anxiety (aOR = 2.8), atopic dermatitis (aOR = 2.1), GI disease (aOR = 1.8), and thyroid disease (aOR = 1.9, only for malaise) were correlated with having one or more NSRS in patients with CSU identified by multivariable analyses (Figure 2). In addition, bivariate analysis identified that the presence of one or more NSRS was linked to depression (12.2% vs 4.9%; $P < .001$), anxiety (23.0 vs 6.1; $P < .001$), sleep disturbance (64.9 vs 35.1; $P < .001$), and GI disease (33.0 vs 20.6; $P < .001$) compared with patients with no NSRS (Table I and Figure 4).

Recurrent fever, JBMP, and malaise are associated with elevated inflammation markers

Elevated leukocytes (aOR = 1.7) and ESR (aOR = 1.5) were also correlated with having one or more NSRS in patients with CSU when they were studied by multivariable analysis (Figure 2). When each NSRS was assessed individually, leukocytosis was shown to correlate with JBMP (aOR = 2.4) and malaise (aOR = 2.0), whereas elevated ESR was correlated only with fever (aOR = 5.0) (Figure 2).

Bivariate analysis also showed that the presence of one or more NSRS is associated with a higher frequency of elevated CRP levels (32.9% vs 26.4%; $P = .006$) compared with patients without NSRS (Table 1 and Figure 4). It was true when comparing patients with and without fever or JBMP but not with and without malaise (Table E1).

Recurrent fever, JBMP, and malaise are linked to worse control of disease

Patients with CSU with one, two, or three NSRS had worse disease control than did patients without NSRS (median UCT: 8, 7, or 5 vs 8; $P < .001$). A higher number of patients with CSU with one or more NSRS had poor control of the disease (defined

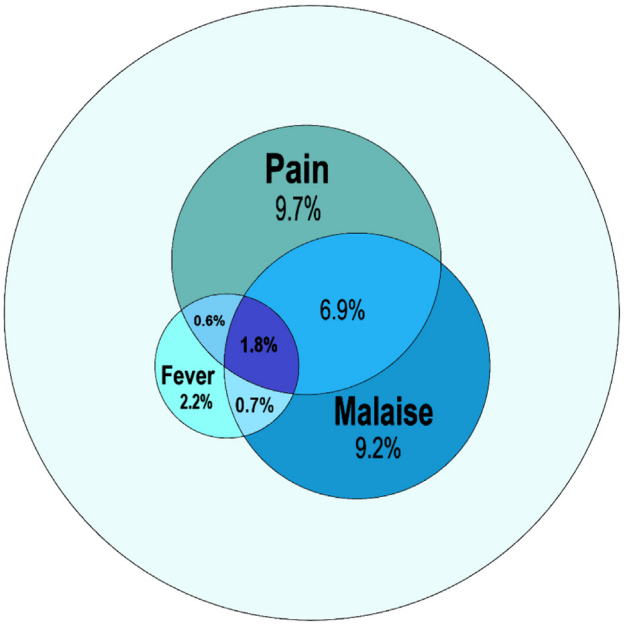

FIGURE 1. Venn diagram showing the overlap of patients with fever, joint, bone, and muscle pain (JBMP), and malaise among all patients with chronic spontaneous urticaria being analyzed. A total of 31.2% patients (786 of 2,521) experienced one or more of these three non–skin related symptoms (NSRS). Of the 21.1% of patients who had any one NSRS (532 of 2,521), 46.1% (245 of 587) had JBMP, 43.6% (232 of 587) had malaise, and 10.3% (55 of 585) had fever. Of the 8.2% of patients who had any two NSRS (208 of 2,521), 84.1% (175 of 208) had JBMP and malaise, 8.2% (17 of 208) had fever and malaise, and 7.7% (16 of 208) had JBMP and fever. The external circle represents all analyzed patients with CSU.

as a UCT of 0 to <12) compared with those without NSRS (78% vs 69%; $P < .001$).

DISCUSSION

The current CURE analysis demonstrates that one third of patients with CSU had any of the three NSRS investigated (fever, JBMP, or malaise). From a clinical viewpoint, these results show the importance of further investigations in patients who have wheals and NSRS before giving them the diagnosis of CSU. The presence of systemic symptoms can point to other disorders and is essential for defining the best treatment options. Understanding the cause of systemic symptoms in CSU may be helpful in predicting the response to mast cell–targeted therapy in patients with CSU.

This proportion is lower than in the literature reported by Doong et al,[11] in which as many as two thirds had NSRS. Together, these data suggest a prevalence range of 33% to 66% of NSRS in patients with CSU. In addition, joint pain or swelling was previously reported to exist in around 55% of patients with CSU,[11] but the current patient cohort had a lower incidence at 19%. These notable differences may be partly due to the number of patients in each study; the current robust, large-scale analysis included 2,521 patients from global centers, and the study by Doong et al included only 155 patients from one university allergy clinic.

There are several reasons why patients with CSU have NSRS. First, it could be because of CSU itself (eg, mast cell activation and the production of mediators and/or other drivers of CSU pathogenesis, such as autoantibodies, which are linked to severe CSU skin symptoms, such as angioedema and poor disease control). The presence of one or more NSRS in the current study was related to significantly higher disease activity, a higher rate of angioedema, signs of inflammation such as elevated CRP, ESR, and leukocytes, and worse response to treatment compared with patients with no NSRS. Whether better control of CSU is associated with the absence of systemic symptoms should be further investigated. Patients with severe CSU experience angioedema more frequently, and this has a significant impact on their QoL.[19,20] One study showed that patients with severe daily joint pain experience angioedema but no wheals. As such, physicians can misdiagnose patients with arthritis and therefore administer inappropriate therapies.[13] C-Reactive protein is a sensitive marker of inflammation, and its levels are reportedly linked to urticaria activity, positive autologous skin serum tests, and nonresponse to antihistamines.[21] Elevated CRP levels were found in one third of patients with CSU, and levels correlated with disease activity and QoL.[21,22] Rates in the current study corresponded to this, ranging from 26.4% (no NSRS) to 32.9% (one or more NSRS).

In CSU pathogenesis, there is a close interplay between autoimmunity and inflammation.[1] The presence of angioedema, increased disease activity with CRP elevation, thyroid disease, and worse response to treatment are all features of autoimmune CSU mediated by mast cell–activating IgG autoantibodies.[23,24] This suggests that NSRS might appear more often in patients with this autoimmune endotype, which should be investigated in further studies. One such study is the international Urticaria Center of Reference and Excellence CSU plus study, which is ongoing and will address this.[25]

Second, NSRS could be a sign of other diseases. Indeed, we observed that patients with concomitant diseases such as anxiety, depression, GI disease, thyroid disease, and atopic diseases had significantly higher rates of NSRS compared with no symptoms. Gastrointestinal diseases, including Crohn's and celiac disease, are known to cause fatigue, pain, and periods of fever,[26] and it is well documented that thyroid disease, such as hypothyroidism, can cause fatigue and general feelings of malaise.[27] More research is needed to determine whether NSRS in patients with CSU are caused by concomitant conditions or the presence of CSU itself. Research showed that patients with CSU experience anxiety and depression,[28] which can be triggered by pruritus and sleep disturbance, creating a negative feedback loop in which one exacerbates the other. In addition to dealing with the cutaneous symptoms of CSU, these patients must navigate potentially more burdensome physical symptoms affecting the whole body, consequently lowering the overall QoL.

Third, NSRS could result from other conditions and main differential diagnoses of CSU such as UV, or an urticarial autoinflammatory disease such as Schnitzler syndrome, cryopyrin-associated periodic syndrome and Still disease. Urticarial vasculitis is a rare chronic and debilitating disease defined by leukocytoclastic vasculitis on skin biopsy.[29] UV presents with wheals, which makes it clinically challenging to distinguish from CSU.[30] However, in patients with UV, wheals usually last 24

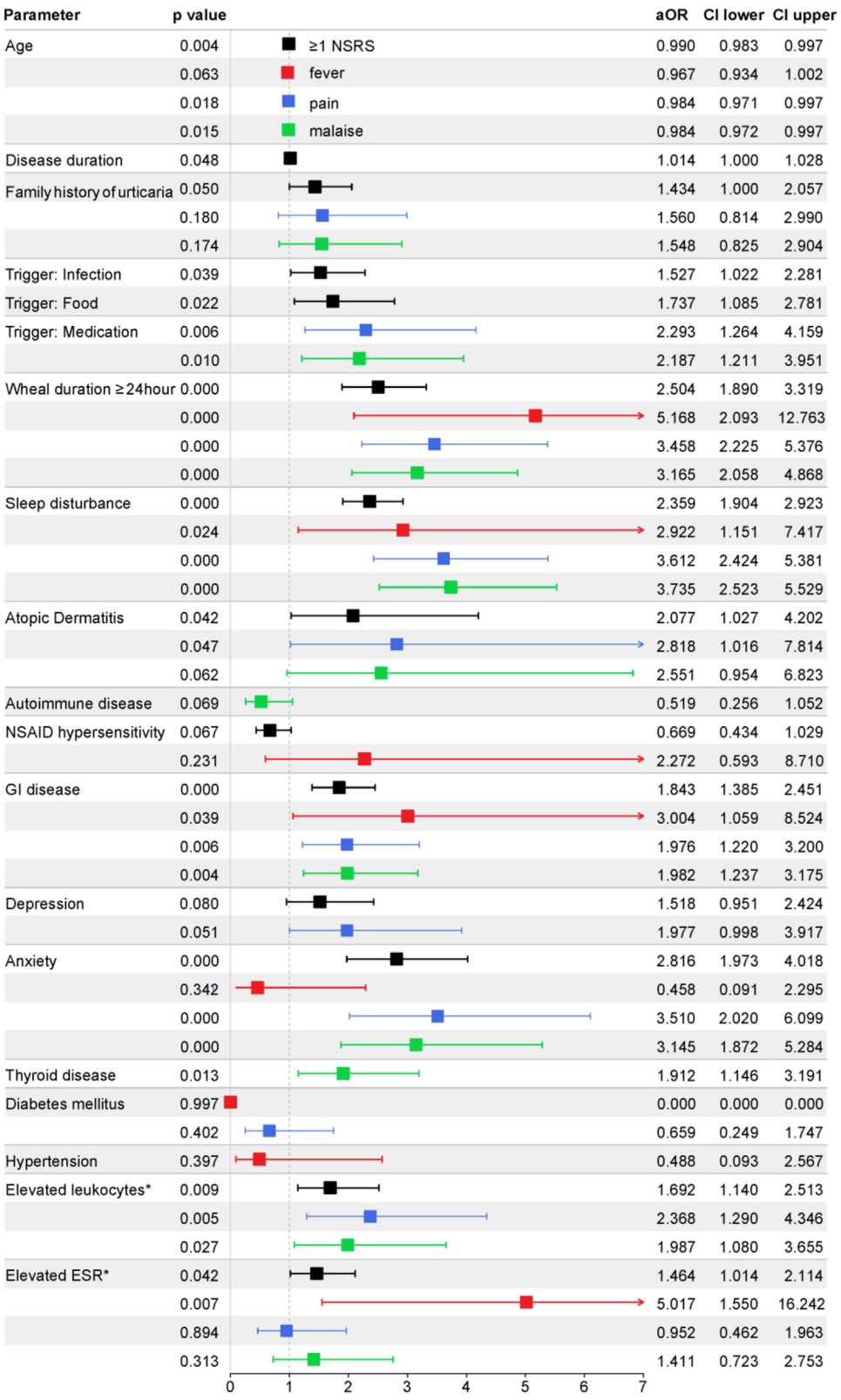

FIGURE 2. *Horizontal lines* represent CIs and mean adjusted odd ratios (ORs) are shown as *squares*. When the OR is more than 1, it can be assumed that there is an association between the investigated parameter and having one or more of non–skin related symptom (NSRS) (*black*), fever (*red*), joint, bone, and muscle pain (*blue*), and malaise (*green*). Mean adjusted OR (aOR) of 1 is represented by the *vertical dashed line*. *During the course of chronic spontaneous urticaria. Trigger relates to manifestation factor for chronic spontaneous urticaria. *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal; *NSAID*, nonsteroidal anti-inflammatory drugs.

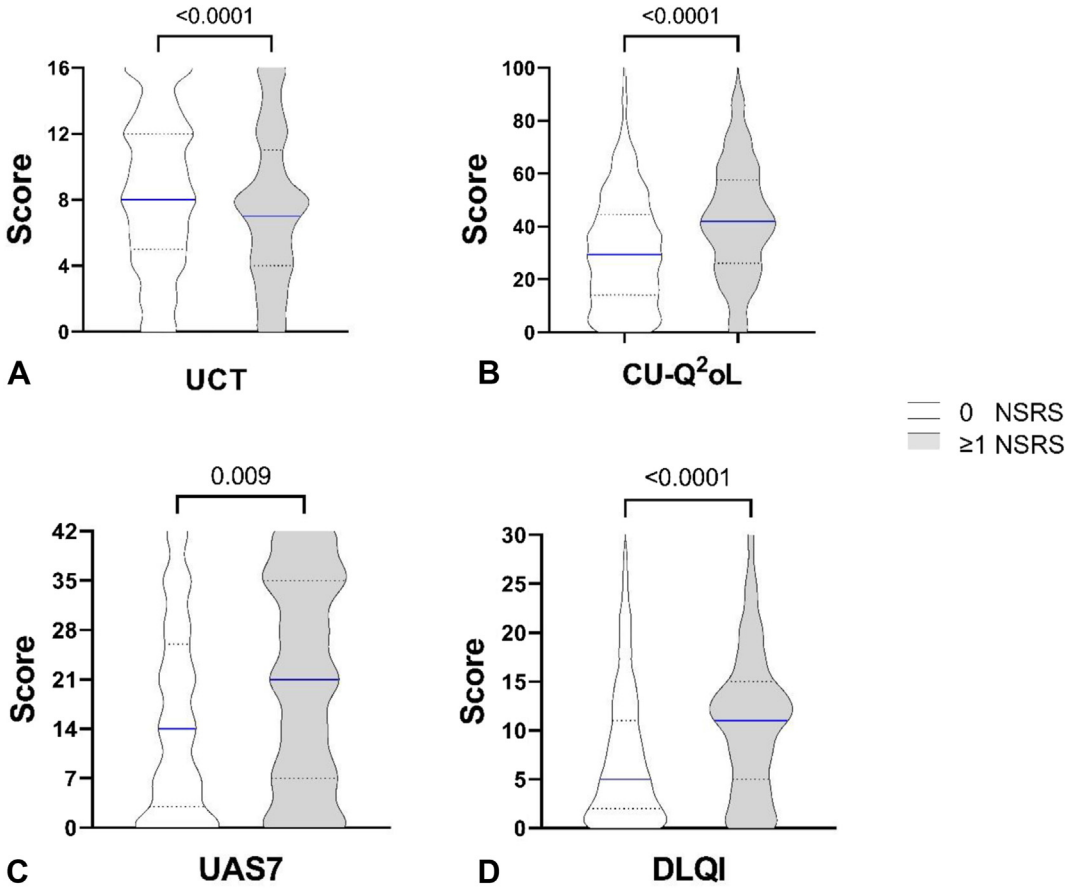

FIGURE 3. Baseline parameters regarding disease control, activity, and quality of life in patients with chronic spontaneous urticaria with no and with one or more non–skin related symptoms (NSRS). *CU-Q$_2$oL*, Chronic Urticaria Quality of Life Questionnaire; *DLQI*, Dermatology Life Quality Index; *UAS7*, Weekly Urticaria Activity Score; *UCT*, Urticaria Control Test.

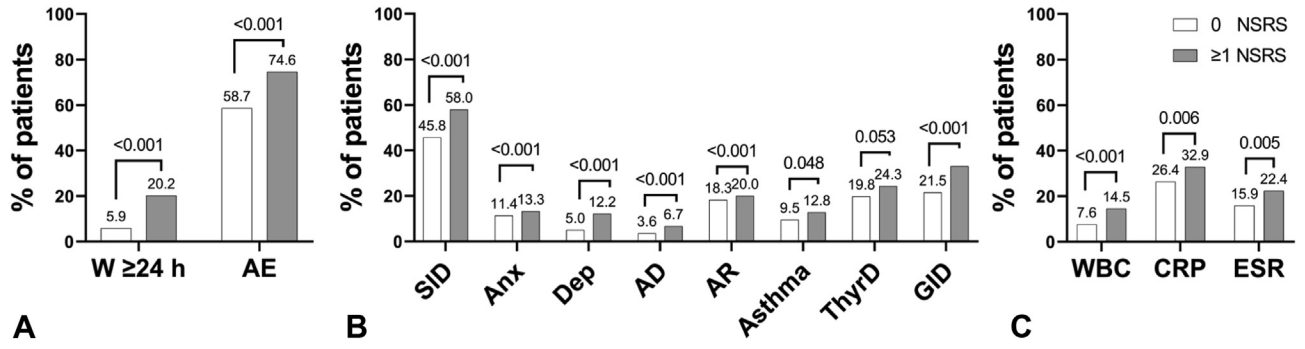

FIGURE 4. Baseline parameters regarding (**A**) clinical features, (**B**) comorbidities, and (**C**) elevated inflammatory blood markers in patients with chronic spontaneous urticaria with no and with one or more non–skin related symptoms (NSRS). *AR*, allergic rhinitis; *AD*, atopic dermatitis; *AE*, angioedema; *Anx*, anxiety; *CRP*, C-reactive protein; *Dep*, depression; *ESR*, erythrocyte sedimentation rate; *GID*, gastrointestinal disease; *SID*, sleep disturbance; *ThyrD*, thyroid disease; *WBC*, white blood cells/leukocytes; *W ≥24h*, wheal duration ≥24 hours.

hours or longer, and other systems are often involved, such as musculoskeletal, renal, pulmonary, GI, and ocular. In addition, significantly higher levels of CRP and ESR are observed.[31,32] In the current study, every fifth patient with one or more NSRS had a wheal duration of 24 hours or longer, significantly higher than those without NSRS. In line with the international urticaria guidelines,[2] we recommend including UV and autoinflammatory conditions in the differential diagnosis of patients with CSU and NSRS, because patients with these diseases benefit from the administration of timely, appropriate treatment regimens

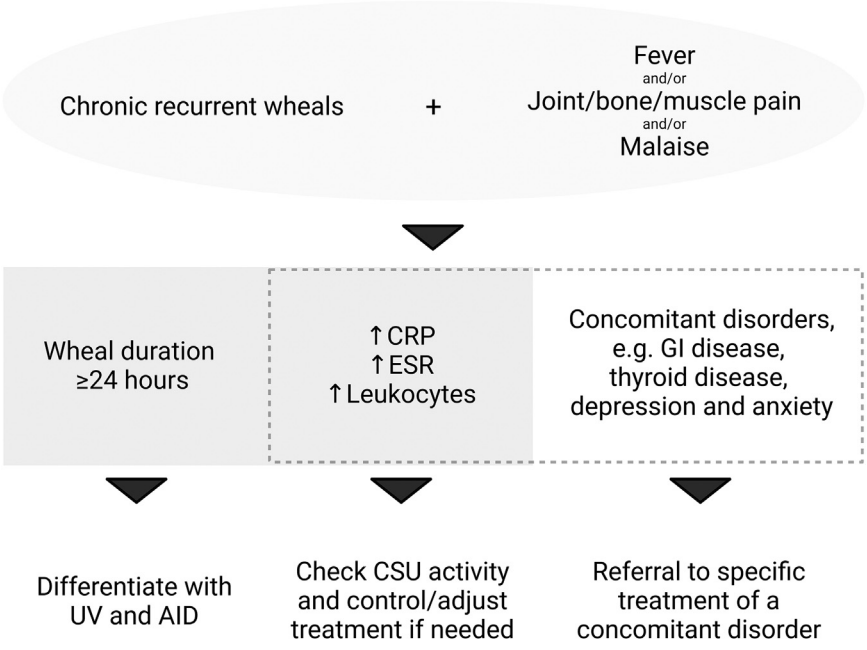

FIGURE 5. Steps for arriving at a diagnosis for and treating patients with wheals and no−-skin related symptoms. *AID*, autoinflammatory diseases; *CRP*, C-reactive protein; *CSU*, chronic spontaneous urticaria; *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal; *UV*, urticarial vasculitis.

(Figure 5). Additional investigations should be considered, such as a skin biopsy, evaluation of inflammatory markers, and genetic testing to rule out these disorders.

The presence of one or more NSRS was linked to significantly worse QoL and higher rates of sleep disturbance compared with patients without NSRS. Doong and coworkers[11] also noticed more prominent QoL impairment in CSU patients with systemic problems. Sleep interference in patients with CSU is well documented,[33] the incidence of which is almost double that of age- and sex- matched controls without CSU.[34] Sleep disturbance also correlates with disease activity[33] and is generally worse during high urticaria disease activity.[35] This is consistent with our results in which higher disease activity, measured by UAS7, and worse QoL, assessed by CU-Q2oL and DLQI, were identified in patients with one or more NSRS. Addressing CSU symptoms, especially pruritus, can directly affect sleep in patients with CSU, as was shown by an improvement in sleep after treatment with ligelizumab.[33]

This study was limited by the analysis of only three NSRS based on patient-reported data, which might be inaccurate or biased by patients' subjective opinions. Data are lacking on the severity of NSRS and its link to the onset and exacerbation periods in CSU. Furthermore, although we conducted a multivariable analysis with multiple potential confounders, the possibility of residual confounding exists. Finally, cross-sectional studies such as this cannot establish causation or track changes over time and the findings may be influenced by selection bias and recall bias. Further prospective studies that consider these weaknesses are necessary to confirm findings from the current study.

As many as one third of patients with CSU had recurrent fever, JBMP, and/or malaise. The presence of these NSRS was linked to higher disease activity, longer wheal duration, the presence of angioedema, worse QoL, sleep impairment, elevated inflammatory blood markers, increased rates of concomitant diseases, and worse disease control. Recognizing additional NSRS in CSU could be a key prognostic marker to determine the relevant treatment. This CSU patient group may need alternative therapies to address NSRS. Our results indicate the need for the better diagnosis and management of CSU when NSRS are present, including the differential diagnosis of UV and urticarial autoinflammatory diseases and early diagnosis and treatment of concomitant disorders (Figure 5).

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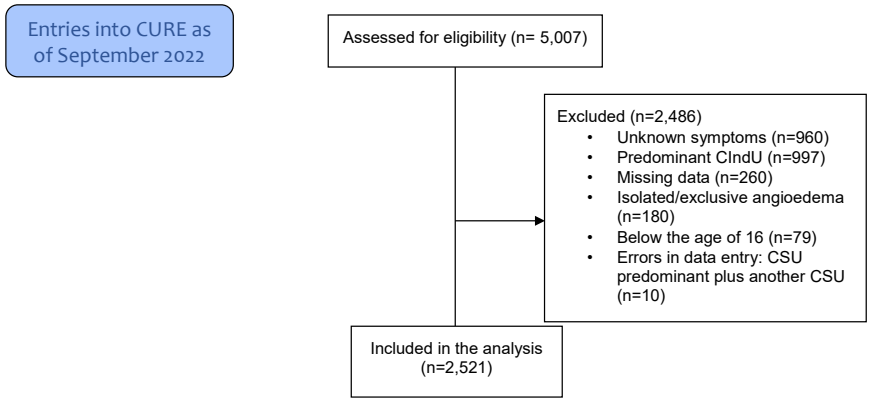

FIGURE E1. Consolidated Standards of Reporting Trials flow diagram showing the number of patients assessed for eligibility and reasons for exclusion from the study. *CIndU*, chronic inducible urticaria; *CSU*, chronic spontaneous urticaria; *CURE,* Chronic Urticaria Registry.

TABLE E1. Demographics and disease characteristics of patients with chronic spontaneous urticaria with and without non–skin related symptoms

	Fever		Joint, bone, and muscle pain		Malaise		*P*		
Parameters/variables	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**Fever**	**Joint, bone, and muscle pain**	**Malaise**
Patients, % (n/total)	94.7 (2,387/2,521)	5.3 (134/2,521)	90.9 (2,039/2,521)	19.1 (482/2,521)	81.4 (2,051/2,521)	18.6 (470/2,521)	—	—	—
Age, y, median (IQR)	44 (33-56), n = 2,387	44 (33-55), n = 134	44 (33-55), n = 2,039	40 (34-55), n = 482	45 (33-57), n = 2,051	42 (33-53), n = 470	.915	.950	**.004**
Female, % (n/total)	75.3 (1,797/2,387)	74.6 (100/134)	73.9 (1,507/2,039)	80.9 (390/482)	74.8 (1,535/2,051)	77.0 (362/470)	.864	**.001**	.323
White, % (n/total)	72.0 (1,719/2,387)	67.2 (90/134)	73.9 (1,506/2,039)	62.9 (303/482)	76.3 (1,565/2,051)	51.9 (244/470)	.225	**<.001**	**<.001**
Body mass index, median (IQR)	25 (22-29), n = 2,152	26 (23-30), n = 124	25 (22-29), n = 1,821	26 (23-31), n = 455	25 (22-29), n = 1,833	26 (23;30), n = 443	**.021**	**<.001**	**.014**
Family history, % (n/total)	8.5 (183/2,159)	12.3 (15/122)	8.1 (149/1,849)	11.3 (49/432)	8.1 (151/1,868)	11.4 (47/413)	.183	**.030**	**.034**
Manifestation factor, % (n/total)									
Medication	13.4 (321/2,387)	12.7 (17/134)	12.3 (251/2,039)	18.0 (87/482)	12.7 (260/2,051)	16.6 (78/470)	.897	**<.001**	**.025**
Infection	6.5 (154/2,387)	9.0 (12/134)	5.8 (118/2,039)	10.0 (48/482)	6.4 (131/2,051)	7.4 (35/470)	.256	**<.001**	.403
Food	4.4 (105/2,387)	6.0 (8/134)	4.0 (82/2,039)	6.4 (31/482)	4.0 (83/2,051)	6.4 (30/470)	.392	**.021**	**.027**
Presence of angioedema, % (n/total)	64.4 (1,508/2,340)	71.6 (96/134)	61.4 (1,224/1,992)	78.8 (380/482)	62.1 (1,245/2,004)	76.4 (359/470)	.090	**<.001**	**<.001**
Disease duration, y, median (IQR)	1 (0-5), n = 2,346	2 (0-7), n = 133	1 (0-5), n = 2,013	2 (0-6), n = 466	1 (0-5), n = 2,015	2 (0-6), n = 464	**.032**	**.034**	**.004**
Concomitant chronic inducible urticaria, % (n/total)	25.9 (613/2,369)	24.2 (32/132)	25.8 (522/2,024)	25.8 (123/477)	26.8 (547/2,038)	21.2 (98/463)	.676	.998	**.012**
Urticaria Control Test, median (IQR)	8 (5-12), n = 2,008	7 (3-9), n = 127	8 (5-12), n = 1,691	7 (4-11), n = 444	8 (5-12), n = 1,698	7 (4-11), n = 437	**<.001**	**<.001**	**<.001**
Weekly Urticaria Activity Score, median (IQR)	15 (4-28), n = 1,355	21 (7-30), n = 83	14 (4-28), n = 1,156	21 (7-35), n = 282	14 (4-27), n = 1,137	21 (8-35), n = 301	**.046**	**<.001**	**<.001**
Chronic Urticaria QoL Questionnaire, median (IQR)	35 (17-49), n = 996	42 (26-62), n = 73	33 (16-47), n = 798	42 (25-59), n = 271	30 (15-46), n = 810	45 (33-62), n = 259	**<.001**	**<.001**	**<.001**
Dermatology Life Quality Index, median (IQR)	7 (2-13), n = 828	8 (4-17), n = 51	6 (2-12), n = 688	11 (5-15), n = 191	6 (2-12), n = 689	12 (7-15), n = 190	.063	**<.001**	**<.001**
Wheal duration ≥24 h, % (n/total)	9.7 (231/2,387)	22.4 (30/134)	8.2 (168/2,039)	19.3 (93/482)	7.5 (154/2,051)	22.8 (107/470)	**<.001**	**<.001**	**<.001**
Atopic dermatitis, % (n/total)									
Total	4.4 (101/2,305)	7.0 (9/129)	4.1 (81/1,981)	6.4 (29/453)	3.9 (77/1,991)	5.2 (23/443)	.291	.066	**<.001**
Active	1.8 (42/2,305)	3.1 (4/129)	1.6 (32/1,981)	3.1 (14/453)	1.4 (27/1,991)	4.3 (19/443)	.291	.066	**<.001**
Allergic rhinitis, % (n/total)									
Total	18.9 (436/2,302)	16.2 (21/130)	18.3 (362/1,977)	20.9 (95/455)	18.8 (373/1,986)	18.8 (84/446)	.264	**.003**	**.002**
Active	11.3 (259/2,302)	12.3 (16/130)	10.4 (205/1,977)	15.4 (70/455)	10.6 (210/1,986)	14.6 (65/446)	.264	**.003**	**.002**

(continued)

TABLE E1. *(Continued)*

	Fever		Joint, bone, and muscle pain		Malaise		*P*		
Parameters/variables	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**Fever**	**Joint, bone, and muscle pain**	**Malaise**
Asthma, %(n/total)									
Total	10.5 (243/2,313)	10.8 (14/130)	9.4 (186/1,983)	15.4 (71/460)	10.2 (204/1,992)	11.8 (53/451)	.946	**<.001**	.373
Active	7.0 (161/2,313)	6.9 (9/130)	6.2 (122/1,983)	10.4 (48/460)	6.9 (138/1,992)	7.1 (32/451)	.946	**<.001**	.373
Gastrointestinal disease, % (n/total)									
Total	24.6 (560/2,276)	32.8 (42/128)	22.8 (444/1,947)	34.6 (158/457)	23.2 (457/1,964)	33.0 (145/440)	**.020**	**<.001**	**<.001**
Active	16.0 (364/2,276)	17.2 (22/128)	14.1 (275/1,947)	24.3 (111/457)	14.0 (275/1,964)	25.2 (111/440)	**.020**	**<.001**	**<.001**
Sleep disturbance, % (n/total)	45.8 (954/2,085)	58.0 (76/131)	41.2 (723/1,755)	66.6 (307/461)	40.2 (710/1,764)	70.8 (320/452)	**.006**	**<.001**	**<.001**
Anxiety, % (n/total)									
Total	11.4 (261/2,284)	13.3 (17/128)	8.9 (173/1,953)	22.9 (105/459)	8.4 (166/1,968)	25.2 (112/444)	.166	**<.001**	**<.001**
Active	9.8 (223/2,284)	9.4 (12/128)	7.6 (149/1,953)	18.7 (86/459)	7.0 (137/1,968)	22.1 (98/444)	.166	**<.001**	**<.001**
Depression, % (n/total)									
Total	6.9 (158/2,275)	12.6 (16/127)	5.5 (108/1,951)	14.6 (66/451)	5.7 (112/1,962)	14.1 (62/440)	.051	**<.001**	**<.001**
Active	4.9 (111/2,275)	8.7 (11/127)	3.9 (76/1,951)	10.2 (46/451)	4.1 (80/1,962)	9.5 (42/440)	.051	**<.001**	**<.001**
Thyroid disease, % (n/total)									
Total	21.3 (450/2,113)	20.8 (26/125)	20.2 (362/1,794)	25.7 (114/444)	20.3 (369/1,819)	25.2 (107/419)	.942	**.037**	**.041**
Active	16.9 (358/2,113)	16.0 (20/125)	15.9 (286/1,794)	20.7 (92/444)	15.9 (290/1,819)	21.0 (88/419)	.942	**.037**	**.041**
Elevated inflammatory markers*, % (n/total)									
Leukocytes	9.3 (172/1,848)	16.8 (17/101)	8.4 (133/1,590)	15.6 (56/359)	8.8 (142/1,607)	13.7 (47/342)	**.013**	**<.001**	**.005**
C-Reactive protein	27.8 (429/1,542)	40.7 (33/81)	26.5 (344/1,299)	36.4 (118/324)	27.5 (363/1,320)	32.7 (99/303)	**.012**	**<.001**	.072
Erythrocyte sedimentation rate	16.8 (226/1,348)	34.3 (24/70)	16.0 (192/1,198)	26.4 (58/220)	17.0 (206/1,209)	21.1 (44/209)	**<.001**	**<.001**	.160

IQR, interquartile range.

*During the course of chronic spontaneous urticaria. Statistical significance is indicated by use of bold font.