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# Prospective analysis of clinical evolution in chronic urticaria: Persistence, remission, recurrence, and pruritus alone

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## ABSTRACT

**Background:** Population and study's methodology heterogenicity became clinical evolution of chronic spontaneous urticaria (CSU) highly variable.

**Objective:** In a prospective cohort, we evaluated the different pathways of clinical evolution of CSU and identified possible risk factors.

**Methods:** A total of 685 CSU patients (>12 years) were prospectively followed over 5 years. Diagnosis and follow-up of urticaria were based on medical evaluation and photographic records. Remission was defined as at least 6 months without symptoms (hives, angioedema, or pruritus) and medication. The follow-up included at least 2 visits per year, with photographic registration and clinical evaluation. Predefined clinical and paraclinical variables were included in the regression analyses.

**Results:** We identified four clinical evolution pathways; The cumulative prevalence of remission at 5 years was 59.1%, recurrence was 17.1%, persistence was 11.6%, and chronic pruritus without hives or angioedema was 12.2%. The probability of persistence increased with hypothyroidism diagnosis (HR 0.425, 95% CI 0.290–0.621) and each point in the UAS7 (HR 0.931 95% CI 0.918–0.945).

**Conclusion:** Chronic urticaria has different evolutions. Disease activity and hypothyroidism predict persistence and remission. Recurrence and chronic pruritus phenotypes require further study to evaluate their causality and prognosis.

**Keywords:** Chronic pruritus, Persistence, Remission, Recurrence, Urticaria

## INTRODUCTION

Chronic urticaria (CU) is a disease with a high socioeconomic impact.[1–3] Over time, many patients seem to experience spontaneous remission of the disease, so the patient stops treatment and resumes activities that were previously restricted. The few studies that have evaluated the duration of urticaria suggest that remission of the disease occurs in 10%–50% of patients at the first year, and

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40%–80% at 5 years.[4–7] The high variability in the frequency of remission presented in various studies may be due to characteristics of each population, but also to the different methodological approaches used in the studies; most were based on retrospective data without structured follow-up, so there was a high risk of selection bias and measurement bias. As Goncalo et al mentioned,[8] the published information of disease duration may be biased as many studies reported Kaplan-Meyer curves for patients who still had CU at the time of assessment, and many calculations on disease duration consider the first consultation as the disease start, which is not reflective of the true CU onset. The diagnosis tended to be based on self-report and hives or angioedema was not always objectified, so overdiagnosis is possible and the definition of remission varies between studies, making it difficult to compare the results.

Recurrence of urticaria has been less studied than persistence or remission.[9,10] Two studies suggested that 13%–15% of patients suffer a reappearance of urticaria during the first two years without drug treatment, generating anxiety. For some patients, hives or angioedema do not occur again, but chronic pruritus persists and there is not information about the prevalence of this evolution. In this study, we aimed to evaluate the different clinical evolutions of patients with urticaria, reducing possible selection and measurement biases through strict patient follow-up and objective evaluation of the lesions. Following the recommendations of the Prognosis Research Strategy (PROGRESS) series for prognostic model investigations,[11] we carried out an exploration of predictive factors that could help with the future construction of a predictive model of remission or recurrence.

## METHODS

### Study design

This was a prospective cohort study followed-up over 5 years. Outcomes from CSU were defined as follows: "Remission" was defined as at least 6 months without medication, hives, and angioedema, and an itchy activity score (ISS) for 7 days of less than 3 points, with a maximum per day of 1 point. "Recurrence" was defined as the presence of hives, angioedema, and itching (ISS for 7 days over 3 points) after a remission period. "Pruritus only" was defined as the absence of hives for at least 6 months but with persistence of itching at least 2 days a week, with an ISS7 greater than 3 points.

The reduction and suspension of drug therapy was according to medical criteria when 1) the patient had at least 3 months without itching and no record of hives or angioedema, and 2) the patient had at least 6 months without photographic record of hives or angioedema, independent of the presence of pruritus.

### Study population

Patients were recruited from centers located in 2 cities in Colombia. Some had participated in other studies,[12–14] but participation in these previous studies did not influence the outcomes of interest (remission and duration of urticaria), and therefore did not constitute a selection bias.

The study population comprised patients aged 12–50 years with a clinical diagnosis of CSU.[15] The age range was selected because, based on previous observations,[12–14] we suspect that patients who begin symptoms after 50 years of age may have a different endophenotype. The recruited patients were less than 18 months from the onset of urticaria, to avoid memory biases. Challenge tests were performed for physical triggers (dermographism, cold, exercise, water, and pressure) or non-steroidal anti-inflammatory drugs (NSAIDs) in patients with self-reported reactions without a clear clinical history. The challenge test protocols have been described in previous studies,[14,16] and were based on international guidelines.[17] Patients with CSU and inducible urticaria were included, but patients with only inducible urticaria were excluded. Patients with any other comorbidity that could confuse the diagnosis of CSU were excluded.

### Statistical analyses

Analyses were performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp, Armonk, New York). The mean and SDs (standard deviation) were reported for descriptive variables after evaluation of the distribution. Differences between proportions were analyzed using the Pearson chi-square test. Correlations were assessed with the Spearman coefficient (R) when it was necessary to

compare nominal variables. Multivariate analyses with clinical and demographic variables were included in the Cox regression. These variables were defined before the study start.

The crude risk (odds ratio [OR]) and adjusted risk (adjusted OR) were reported with a 95% CI (Confidence Interval). We adjusted by sex and age. Given the reported frequency of remission in previous studies, we considered that a sample of at least 400 patients would be adequate to detect at least 20% of patients with the primary outcome measure (remission).

## RESULTS

### Patient's characteristics

A total of 948 patients with previous diagnosis of CSU were evaluated to participate in the study (Fig. 1) but 222 patients did not meet the selection criteria; 163 reported itching but did not have a photographic record of hives or angioedema despite not using urticaria treatment for at least 2 weeks during eligibility follow-up (6 months), and 59 patients, according photographic records, were diagnosed with keratosis pilaris (n = 38), dermatitis (n = 12), and scabies (n = 9). Therefore, 726 patients were included and 49 (5.7%) patients were censored because loss of contact. The general characteristics of the patients who had the 5 years follow-up (n = 685) are presented in Table 1. Censored patients they did not present sociod-emographic or paraclinical characteristics different from those included in statistical analysis.

### Clinical evolution of chronic urticaria

Additional to persistence, three types of clinical evolution pathways were identified in patients with CSU: remission, only pruritus, and recurrence (Fig. 2). In the first year, only 9.5% of the patients reached remission, but in the fifth year the cumulative prevalence of remission was 59.2%

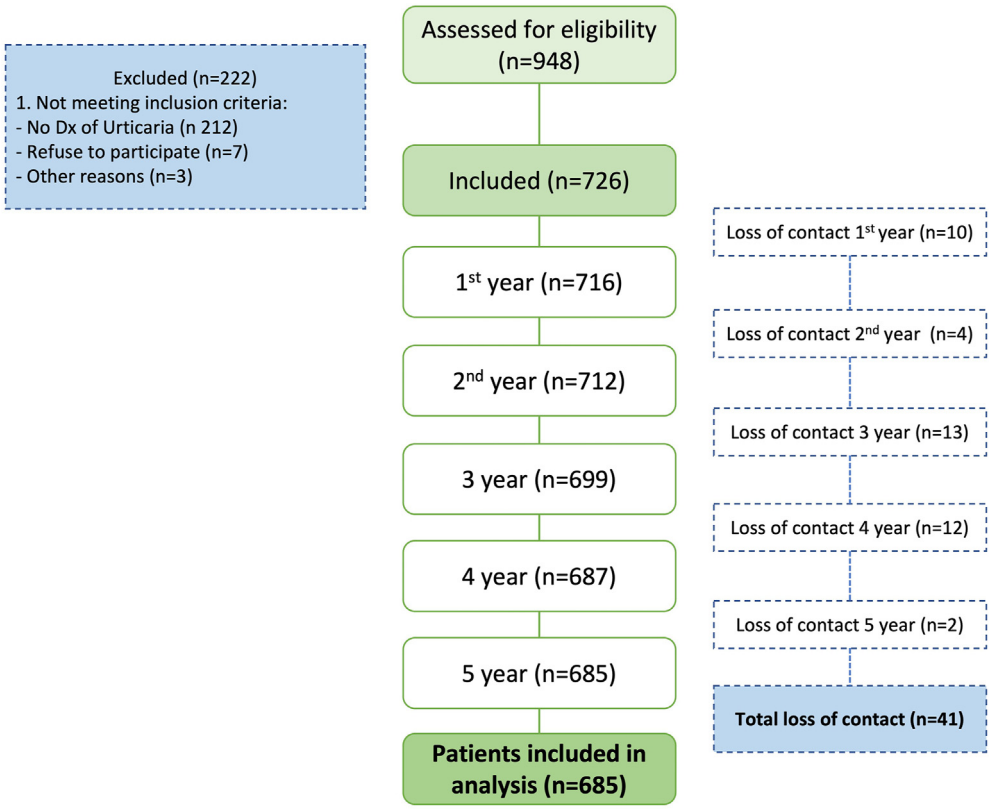



**Fig. 1 Chronic spontaneous urticaria cohort flowchart**. Most of the patients who were not included did not have urticaria. A total of 44 patients were censored.

| | Total patients (n = 685) |
|---|---|
| Female n (%) | 527 (76.9%) |
| Age median | 28 years (SD 8.3 range 38) |
| CSU Age | 27 years (SD 8.3 range 37) |
| Only CSU | 468 (62.3%) |
| CSU and Inducible urticaria | 217 (37.7%) |
| Angioedema | 237 (34.6%) |
| NSAIDs reaction | 99 (14.5%) |
| Respiratory distress | 154 (22.5%) |
| Hypothyroidism | 100 (14.6%) |
| Autoimmune disease | 154 (22.5%) |
| UAS7 | 26 points (SD 6.9) |
| DLQI | 17,6 (SD 5.5) |
| Basophil | 16,5 (SD 14.9) |
| Eosinophil | 117,7 (SD 51) |

**Table 1.** Patients' characteristics. *Clinical and sociodemographic characteristics of the patients at the beginning of the study. SD, standard deviation*

(n = 398). Recurrence of urticaria was 17.1%, and pruritus without hives was 12.2%.

### Risk factors associated with persistence

Hypothyroidism reduced the chance of remission in the first 5 years of the disease (HR 0.425, 95% CI 0.290–0.621). For each point on the UAS7, the probability of remission was reduced (HR 0.931 95% CI 0.918–0.945). We observed that those with less than 18 points had a probability of remission in the first year of 29.7% and in the fifth of 79.7%, while those with a UAS7 over 28 points had a probability of remission of only 28% (Fig. 3).

Patients who achieved good control with antihistamines with conventional or higher doses had a net increase of 16.6% in the frequency of remission compared with patients using omalizumab or cyclosporine (60.8% antihistamines vs 44.2% omalizumab/cyclosporine group chi$^2$ 10.6 p 0.001). Angioedema was significantly higher in the remission group, but the association disappeared in adjusted model.

We did not evaluate the hazard ratio in the pruritus group and recurrence group, since the number of patients in these groups did not allow this analysis. However, we explore the frequency of the predefined variables in each group (Table 2), and none of them had a higher prevalence in the recurrence group or only pruritus group.

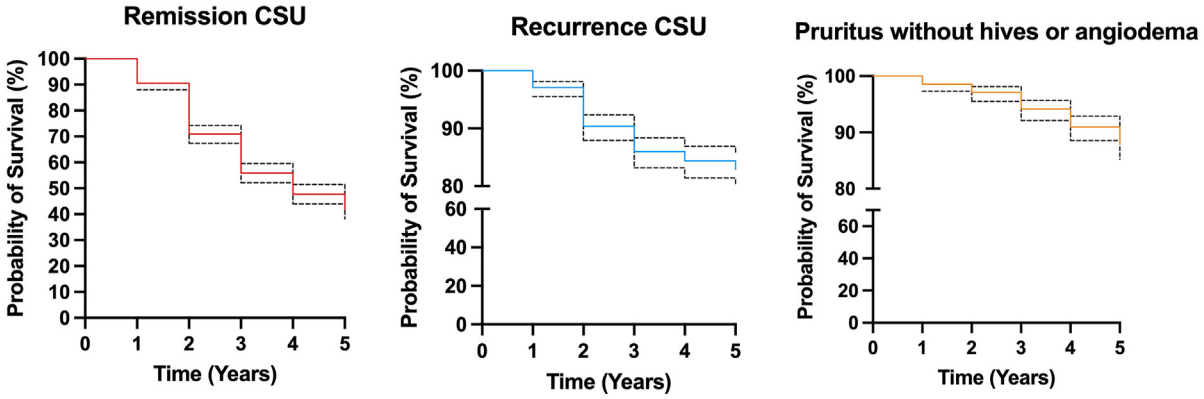
## DISCUSSION

Duration and frequency of remission of urticaria over time appears to be variable among populations.[5–7,18–20] Furthermore, although the concepts of "remission" and "recurrence" have been widely used, there are no unified criteria for their definition.

We describe the clinical evolution of urticaria using objective evaluation methods (photographic records, medical interviews), avoiding some bias detected in other studies, and we found some interesting results. 1) Misdiagnosis was frequent, 2) 4 possible clinical evolution pathways were identified, and 3) some factors were associated with persistence of the disease.

### Misdiagnosis was frequent

The unpredictable nature of the appearance of hives and angioedema make urticaria diagnosis usually based on patient report. Photos are a useful diagnostic tool in urticaria. We observed that 222 (23.5%) patients had an incorrect diagnosis. The most frequent differential diagnosis was chronic pruritus without primary hives or angioedema (also known as pruritus sine *materia* or pruritus of unknown origin). For at least 6 months we followed these patients, and we did not obtain photographic records suggestive of urticaria, so we ruled out this diagnosis with high certainty. An error in diagnosis misfocus attention and generating unnecessary expenses of time and money for the patient.



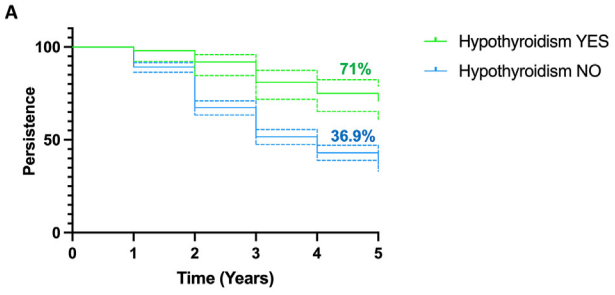

| | Remission | Recurrence | Pruritus |
|---|---|---|---|
| 1st year | 9,5% (SD 1.9 - 2,4) | 3% (SD 1 – 1.56) | 1.6%(SD 0.6 – 1.2) |
| 2nd year | 29.1% (SD 3.2 - 3.5) | 9.7% (SD 1.9 – 2.4) | 3% (SD 1 – 1.5) |
| 3rd year | 44.1% (SD 3.6 - 3.8) | 14.1% (SD 2.3 – 2.8) | 5.9% (SD 1.52 – 2) |
| 4th year | 52.3% (SD 3.6 – 3.7) | 16.7% (SD 2.5 - 2.9) | 9.1% (SD 1.9 – 2.4) |
| 5th year | 59.2% (SD 3.6 – 3.7) | 17.1% (SD 2.6 - 3) | 12.2% (SD 2.2 – 2.6) |

**Fig. 2 Chronic spontaneous urticaria cohort *Cox* regression analysis**. Additional to persistence the follow-up of the patients showed three groups; remission, recurrence and only pruritus without hives or angioedema. SD, standard deviation; CSU, Chronic spontaneous urticaria.

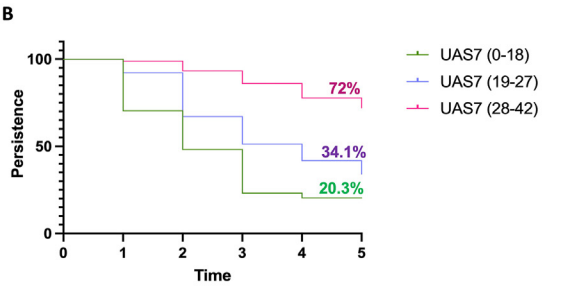
## Clinical evolution pathways

Remission of urticaria improves the quality of life of patients. Additionally, it can have direct and indirect positive economic effects for the patient and society.[3,8] After a thorough review between 2001 and 2019, we found that less than ten articles were published where the main objective was to evaluate the clinical evolution of urticaria.[5-7,18-26] In these articles, the definition of "remission" ranged between 1 to 12 months without urticaria, and some articles did not clarify it as a complete suspension of drug pharmacotherapy. Additionally, only 3 studies conducted a follow-up for more than 4 years, and virtually all data were based on medical records, which can generate measurement bias because, for example, the onset of the disease is defined by the memory of the patient.

In our study, cumulative remission in the first year was low (9.5%), but by the second year it was 29.1% and after 5 years it had reached 59.1%.




| Hypothyroidism | Yes | No |
|---|---|---|
| 1st year | 98% (1,4– 5.7) | 89.2% (2.2 – 2.8) |
| 2nd year | 92% (3.9 – 7.3) | 67.3% (3.6 – 3.9) |
| 3rd year | 81% (6.4 – 9.1) | 51.6% (3.9 – 4,1) |
| 4th year | 75% (7.3 – 9.7) | 43% (3.9 – 4) |
| 5th year | 71% (7.8 – 9.9) | 36.9% (3.9 – 3.9) |




| Urticaria Activity Score | UAS7 (0-18) | UAS7 (19-27) | UAS7 (28-42) |
|---|---|---|---|
| 1st year | 70.3% (7.6 – 9.5) | 92.2% (2.2 – 3.1) | 98.8% (0.8 – 3.2) |
| 2nd year | 48.1% (9 - 9.6) | 67% (4.3 – 4.8) | 93.2% (2.8 – 4.7) |
| 3rd year | 23.1% (7.4 – 8.2) | 51.2% (4.7 - 5) | 86% (4.3 – 5.9) |
| 4th year | 20.3% (8 – 6.9) | 41.7% (4.7 – 4.8) | 77.6% (5.4 – 6.8) |
| 5th year | 20.3% | 34.1% (4.6 – 4.8) | 72% (5.9 – 7.1) |

**Fig. 3 Chronic spontaneous urticaria risk factors for persistence**. Hypothyroidism and high urticaria activity were associated with persistence. SD: standard deviation. CSU: Chronic spontaneous urticaria. UAS, Urticaria Activity Score.

| | Persistence (n = 87, 12.7%) | Remission (n = 398, 58.1%) | Recurrence (n = 117, 17.1%) | Only pruritus (n = 83, 12.1%) |
|---|---|---|---|---|
| Female sex | 69 (79.3%) | 300 (75.4%) | 91 (77.8%) | 67 (80.7%) |
| Age (median) | 25 (SD 8) | 29 years (SD 8) | 24 (SD 9) | 29 (SD 8) |
| CSU Age | 23 (SD 8) | 28 years (SD 8) | 24 (SD 9) | 29 (SD 8) |
| CSU and IU | 29 (33.3%) | 138 (34.7%) | 24 (29.5%) | 26 (31.3%) |
| Angioedema | 27 (31%) | 153 (38.4%) | 34 (29.1%) | 23 (27.7%) |
| NSAIDs reactions | 12 (13.8%) | 58 (14.6%) | 20 (17.1%) | 9 (10.8%) |
| Respiratory distress | 20 (23%) | 99 (24.9%) | 16 (13.7%) | 19 (22.9%) |
| Hypothyroidism | 19 (21.8%) | 29 (7.3%) | 40 (34.2%) | 12 (14.5%) |
| UAS7 | 26 (SD 6) | 26 (SD 7) | 28 (SD 6) | 27 (SD 6) |
| DLQI | 18 (SD 5) | 16 (SD 6) | 19 (SD 6) | 18 (SD 5) |
| Basophil | 12 (SD 14) | 12 (SD 16) | 10 (SD 12) | 17 (SD 16) |
| Eosinophil | 120 (SD 51) | 114 (SD 51) | 114 (SD 54) | 111 (SD 48) |

**Table 2.** Patients' variables according to clinical evolution pathway. *Clinical and sociodemographic characteristics of the patients according with the four clinical evolution pathways. SD, standard deviation; CSU, Chronic spontaneous urticaria; IU, Inducible Urticaria*

These results may be useful to define the moment to reduce drug treatment.

The recurrence of urticaria was low in the first year, but increased over time and the cumulative incidence at 5 years was 17.1%. We cannot rule out that it may have been even higher over a longer period. Therefore, in clinical practice, it is recommended that even if the patient has suspended pharmacotherapy due to remission of the urticaria, to continue with sporadic control visits, possibly every year.

Chronic pruritus after urticaria is a clinical evolution pathway that has been little studied, but it has been proposed that it can occur because of a neoinnervation of the skin during a chronic inflammatory process.[27,28] After 5 years, 12.2% of the patients had remission of hives and angioedema, even with the suspension of treatment, but cutaneous itching persisted, for which it was necessary to restart antihistamines, with clinical success in most cases. Another possibility is that chronic pruritus is a very common symptom, affecting up to 20% of the population. Therefore, the pruritus without hives in some patients may not have anything to do with urticaria. Possibly, they have had pruritus for some other reason. Whether this remaining itching can still be called urticaria, or whether it should be considered a new disease, depends on the underlying mechanism.

The 4 different clinical evolution pathways suggest that the inflammation associated with urticaria fluctuates over time. We propose two hypotheses for why not all patients have the same evolution: hives, angioedema, and itching could have a common inflammation mechanism that, according to the intensity of the inflammation, could initially generate itching and then angioedema and hives. This is supported by the fact that there were no patients in whom the hives persisted, but the itching disappeared, which suggests that the threshold for itching is lower than the threshold for hives. The second hypothesis is that if the chronic inflammatory process persists, new mechanisms independent of the initial one appears, and may contribute to the persistence of some symptoms for longer than others, as would be the case of neoinnervation in patients with chronic pruritus.[27-30]

Regardless of the mechanism, our results suggest that in patients with urticaria, a "minimal persistent inflammation" could facilitate, in certain

conditions, persistence of symptoms or recurrence, as in other diseases.[31] In the survival curves we indicate the first change that the patients presented. However, 30 patients had additional status changes during follow-up, eg, "persistence" then "remission" then "pruritus without wheals". In future studies it would be interesting to evaluate the factors that could be influencing these changes in state.

### Risk factors for remission

Multiple clinical and paraclinical variables have been studied to evaluate the relationship with the duration of urticaria.[32-35] We studied some variables of easy clinical access. Some studies suggest that levels of basophils or eosinophils could be associated with autoimmune type 2b inflammation[36,37] but in our study there were no significant differences in the levels of basophils or eosinophils in patients with persistence or remission. We observed that angioedema and respiratory distress have a high impact on quality of life but were not associated with urticaria persistence or remission.

Disease activity (by UAS7) was associated with persistence and remission. This is supported by the fact that we also observed that patients with a refractory response to antihistamines had a lower remission rate than patients with good control with conventional or high doses.

Hypothyroidism is a chronic autoimmune inflammatory process. A recent study by Kolkhir et al, suggested that high levels of anti-TPO IgG and low levels of total IgE are associated with a type 2b autoinflammatory response.[38] Our results showed that having hypothyroidism is associated with the persistence of the disease, but we did not observe an association with total IgE, perhaps because the Latin American population has higher levels of total IgE than reported in European countries.[39] Whether type 1 (autoallergy) or type 2b autoimmunity is associated with the persistence or recurrence of urticaria is unknown, but it is a possibility that should be explored, since the chronic recognition of self-antigens by IgE or IgG could explain the persistence of the inflammatory process.

UAS7 and hypothyroidism are easily measured variables that can help predict the evolution of the disease (persistence risk up to 5 times). Patients with UAS7 >28 points and anti-TPO IgG had a risk of urticaria persistence 15 times greater than the rest of the patients; this is the population with the highest risk of persistence. The identification of this population allows long-term health policies to be developed and helps to make the patient aware of the importance of adherence to treatment to make the disease more tolerable. Additionally, the high frequency of hypothyroidism in the population with urticaria also shows the need to evaluate the presence of this disease early, to reduce its clinical impact.

In the exploratory analyses, none of the variables were associated with evolution to chronic pruritus or recurrence; this may be because the sample size to assess risk factors was aimed at assessing persistence/remission, and not the other pathways. Recurrence phenotype, it is likely that variables such as the presence of hypothyroidism would not be associated, because the inflammatory process would not be chronic but intermittent but these assumptions must be confirmed.

Due to the peak incidence of the disease, we had little participation of children (12–18 years); therefore, the results in these age groups could be not reproducible adequately. Another limitation was the prevalence of remission reported in the first year, which could be lower than the real one due to follow-up time to reduce therapy and evaluate control at each step. However, this was according to suggestions by international guidelines and reflects daily practice.

## CONCLUSIONS

CU is a disease that can have different evolutions. Disease activity and hypothyroidism can help us to identify patients with a greater or lesser probability of persistence and remission. Recurrence and chronic pruritus are clinical phenotypes in urticaria that require further study to evaluate their causality and prognosis.

#### Abbreviations

CIU, chronic inducible urticaria; CRP, C-reactive protein; CSU, Chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; ISS, itchy severity score; NSAID, Nonsteroidal anti-inflammatory drugs; UAS, Urticaria Activity Score.

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**Data availability statement**
The datasets generated for this study are available on request to the corresponding author.

**Authors' contribution**
JS contributed the central idea. RC and JS evaluated and collected clinical data from patients. JS, and LA organized the databases. JS, LA and RC analyzed the data. JS, and LA wrote the first draft. All authors were involved in writing, reviewing, and editing the final manuscript.

**Ethical considerations**
This study was approved by the Ethics Committee of the University of Antioquia (Code F-017-00). All participants (or their legal guardian) were asked to sign an informed consent document. No photos were collected that could identify the patients.

**Authors' consent for publication**
All authors have approved the submission of this manuscript. These results have not been previously published in another journal.

**Declaration of competing interest**
The authors have no conflict of interest in this work.

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