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**ORIGINAL ARTICLE**

# Overweight and obesity in chronic spontaneous urticaria – a retrospective cohort study

## *Excesso de peso e obesidade na urticária crónica espontânea – estudo de coorte retrospetivoin*

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## Abstract

**Objectives:** This study aims to assess the prevalence of excess weight in chronic spontaneous urticaria (CSU) patients and its associations with treatment response and disease course. CSU affects 0.5-1.5% of the population and many patients remain uncontrolled despite the available treatments. Patient-reported outcomes (PROs) are used to monitor disease activity and treatment response. Obesity is a highly prevalent condition that shares inflammatory pathways with CSU; however, links between them remain poorly understood. **Methods:** This retrospective cohort study was conducted at the Dermatology Department of the Coimbra University Hospital and included adults (≥ 18 years) with CSU diagnosis. Collected data included demographics, body mass index (BMI) at CSU onset and at first urticaria consultation, age at onset, disease duration, type of treatment, treatment duration, and response. Variables were compared across BMI categories (normal weight, overweight, and obese), with $p < 0.05$ considered significant. Treatment response, the primary outcome, was defined as an ordinal variable using validated PROs cut-offs (Urticaria Activity Score over 7 days, Urticaria Control Test, and Dermatology Life Quality Index). Ordinal logistic regression analyses were performed. **Results:** The study included 90 patients (83.3% female), with a median age of 48 years. Mean BMI at onset was 27.80 ± 5.24 kg/m$^2$ (72.2% of patients with excess weight) and 28.10 ± 5.41 kg/m$^2$ at first consultation (68.9% excess weight). Treatment response differed significantly across BMI categories ($p = 0.007$), with complete response (CR) decreasing from 46.4% (normal weight group) to 6.5% (obese group). In ordinal logistic regression models, obesity was associated with worse treatment outcomes ($p < 0.001$, odds ratio = 7.63). In adjusted models, other variables showed no association. Age at CSU onset differed between normal weight and overweight patients (Bonferroni $p = 0.025$), with overweight patients presenting later disease onset. Disease duration, type of treatment, and duration did not differ across BMI. **Conclusions:** The patients' profile was consistent with previous CSU literature, reinforcing the high BMI prevalence. This study suggests that obesity is associated with a lower probability of achieving CR, emerging as an independent predictor of worse treatment outcomes. The findings support considering weight management as part of the CSU approach, warranting prospective studies.

***Keywords:*** Urticaria. Body mass index. Obesity. Treatment outcome. Patient-reported outcome measures.

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## Resumo

**Objetivos:** Este estudo tem como objetivo avaliar a prevalência de excesso de peso em doentes com Urticária Crónica Espontânea (UCE) e associações com a resposta ao tratamento e curso da doença. A UCE afeta 0.5-1.5% da população e muitos doentes permanecem não controlados apesar dos tratamentos. Os resultados reportados pelos doentes (PROs) são utilizados para monitorizar a atividade da doença e resposta ao tratamento. A obesidade é altamente prevalente e partilha vias inflamatórias com a UCE; contudo, as ligações entre elas permanecem pouco compreendidas. **Métodos:** Este estudo de coorte retrospetivo foi realizado no Serviço de Dermatologia do Hospital da Universidade de Coimbra e incluiu adultos com UCE. Os dados recolhidos incluíram características demográficas, índice de massa corporal (IMC) no início da UCE e na primeira consulta de urticária, idade de início, duração da doença, tipo de tratamento, duração e resposta ao mesmo. As variáveis foram comparadas entre categorias de IMC, considerando $p < 0.05$ como estatisticamente significativo. A resposta ao tratamento foi definida como variável ordinal utilizando pontos de corte de PROs validados (Urticaria Activity Score over 7 days, Urticaria Control Test, Dermatology Life Quality Index). **Resultados:** O estudo incluiu 90 doentes (83.3% do sexo feminino) com idade mediana de 48 anos. O IMC mostrou 72.2% e 68.9% de doentes com excesso de peso ou obesidade, no início da doença e primeira consulta, respetivamente. A resposta ao tratamento diferiu significativamente entre categorias de IMC ($p = 0.007$), com Resposta Completa a diminuir de 46.4% (grupo de peso normal) para 6.5% (grupo obeso). No modelo de regressão logística ordinal, obesidade associou-se a piores resultados terapêuticos ($p < 0.001$, OR = 7.63). Nos modelos ajustados, as restantes variáveis não mostraram associação significativa. A idade de início da UCE diferiu entre doentes de peso normal e excesso de peso (Bonferroni $p = 0.025$), sendo mais tardia nos doentes com excesso de peso. **Conclusões:** O perfil de doentes foi consistente com literatura previamente publicada. Este estudo sugere que a obesidade está associada a menor probabilidade de resposta completa, constituindo um preditor independente de piores resultados terapêuticos. Estes resultados apoiam a inclusão da gestão do peso como parte da abordagem terapêutica da UCE.


***Palavras-chave:*** Urticária. Índice de massa corporal. Obesidade. Resultado do tratamento. Medidas de resultados reportados pelos doentes.

## Introduction

Chronic spontaneous urticaria (CSU) is an inflammatory skin disease characterized by recurrent wheals and/or angioedema for longer than 6 weeks, with no identifiable trigger.[1] It affects approximately 0.5-1.5% of the global population.[2] Disease duration is highly variable, ranging from months to several years. Remission within the 1st year occurs in about 20-75% of patients and within 5 years in 30-55%.[3] CSU negatively impacts patients' quality of life (QoL) through symptom unpredictability, psychological distress, sleep impairment, and decreased productivity.[3-5] It imposes a significant economic burden on healthcare systems and patients.[3,5,6] The 2022 guidelines recommend four lines of symptomatic treatment.[1] However, real-life evidence shows that over 25% of cases are refractory to first- and second-line treatments, and one third of these are resistant to third and fourth lines.[2,3] The fluctuating nature of CSU complicates disease monitoring and treatment. Patient-reported outcomes (PROs) help to overcome this problem by monitoring CSU activity, symptom control, and impact on patients' QoL.[1] The use of PROs is also recommended in Portuguese patients, in whom these tools have proved to be practical and effective in clinical practice.[6-8] Some examples include the Urticaria Activity Score (UAS), Urticaria Control Test (UCT), and Dermatology Life Quality Index (DLQI).[9]

The mechanism behind CSU is not entirely understood. Mast cells (MCs) are the main effector cells in urticaria.[1] Signs and symptoms are caused by MCs' degranulation, activation of peripheral sensory nerves, vasodilation, increased vascular permeability, and recruitment of inflammatory cells.[10] The complex MC activation in CSU is thought to have an endogenous origin, with several proposed mechanisms,[10,11] mostly linked to autoimmunity.[12] Many non-autoimmunity-related causes have been proposed as additional triggers, such as infections, vitamin D deficiency, coagulation cascade, neurogenic, and genetic factors.[11-14] However, there are still many uncharacterized CSU cases.[10] Autoimmune, psychiatric, and cardiometabolic diseases are frequent comorbidities reported in chronic urticaria.[3,15,16] Metabolic syndrome, overweight, and obesity appear to be more common in CSU patients compared to healthy controls[17-19] and may influence treatment response.[20]

Obesity is defined by excessive adipose tissue within the body, impairing health.[21] According to the World Health Organization (WHO), in 2022, 1 in 8 people in

the world were obese and 43% of adults were overweight.[21] The diagnosis relies on body mass index (BMI): with BMI ≥ 25 kg/m$^2$ considered overweight, and ≥ 30 kg/m$^2$ as obese.[21]

White adipose tissue is an important endocrine organ, composed of adipocytes that secrete adipokines, pro-inflammatory cytokines, and chemokines, interacting with the immune system.[22,23] Adiponectin upregulates the anti-inflammatory interleukin (IL)-10 secretion from adipocytes and macrophages, helping to maintain immunological tolerance.[22] Its levels appear decreased in obese patients.[22,24] On the contrary, pro-inflammatory cytokines (e.g., IL-6 and tumor necrosis factor alpha [TNF-α]) and leptin levels are increased in obese patients.[22] Similar findings were reported in CSU patients: increased levels of IL-6 and TNF-α and decreased levels of adiponectin.[25]

CSU and obesity share a low-grade inflammatory state[24,26] and overlapping inflammatory pathways. Obesity's inflammatory mechanisms may alter immune cell functioning, including MCs, creating a conducive environment for diseases such as CSU. Further research into a deeper understanding of the disease and the bidirectional links with obesity may contribute to improving patient management. The present study aims to evaluate the prevalence of excess weight in CSU patients and to explore potential associations with treatment response and disease course.

## Methods

This observational, retrospective cohort study conducted at the Dermatology Department of the Coimbra University Hospital included patients followed in the outpatient urticaria consultation. Eligible patients were ≥ 18 years old with a medically confirmed diagnosis of CSU. Exclusion criteria included < 18 years of age, inability to provide informed consent, and pregnancy. Patients with CSU and other concomitant diseases were not excluded. The study received approval from the Ethics Committee of the Faculty of Medicine, University of Coimbra, Portugal. Informed consent was obtained from all patients included in the study.

Recruitment was conducted in consultations and through phone/email. Data were collected from medical records and complemented by patient interviews by phone/email. Relevant data collected included age, sex, weight, and height (at disease onset and at the first urticaria consultation in this department), age at CSU onset, disease duration, type of treatment, treatment duration, and response. Concomitant comorbidities including smoking, arterial hypertension, diabetes mellitus, dyslipidemia, depression, and anxiety disorders were also registered. BMI was calculated as weight divided by height squared (kg/m$^2$).

Age, weight, and height were treated as numeric variables. Weight and height values considered at onset corresponded to those recorded closest to the date of disease onset (within an approximate 2-year period). For 33 patients, weight and height at onset were self-reported due to the absence of recorded measures. Anthropometrics recorded at the first urticaria consultation were also collected and used to calculate BMI at the first urticaria consultation, considered the primary exposure variable. BMI was considered both a numeric and an ordinal variable, divided into four categories following the WHO classification.[21] For patients aged ≥ 20 years, BMI was classified as underweight (< 18.50 kg/m$^2$), normal weight (18.50-24.99 kg/m$^2$), overweight (25.00-29.99 kg/m$^2$), and obese (≥ 30.00 kg/m$^2$). For patients aged 5-19 years (at onset or at first consultation), BMI categories were defined according to the WHO BMI-for-age reference standards, with underweight corresponding to < −2 standard deviation (SD), normal weight defined as ≥ −2 to ≤ +1 SD, overweight > +1 SD, and obesity defined as > +2 SD, for age and sex.[27]

Age at disease onset and disease duration were considered numeric variables. The former was considered the age of first CSU symptoms. Disease duration was defined as the time interval, in years, between the date of initial symptoms and the date of study inclusion or of medical discharge from urticaria consultation, whichever occurred first.

Treatment line was coded as an ordinal variable, from 1 to 6, following the international guidelines:[1] 1 – second-generation H1 antihistamines (AH), standard dose; 2 – AH, up-dosing up to fourfold; 3 – omalizumab (OMZ) 300 mg; 4 – OMZ 450 mg; 5 – OMZ 600 mg; and 6 – ciclosporin (Cy). It was considered the highest treatment line reached for each patient during the consultation period. However, in real-life practice, treatment escalation did not always follow the guidelines' recommended sequence, as patients with suspected type IIb autoimmune CSU were treated with cyclosporin before OMZ, when no contraindication was present.[28] Treatment duration was recorded as a numeric variable, in years. Treatment response was categorized into four groups: Complete response (CR), good response (GR), partial response (PR), and no response (NR), with PROs used to define the categories' thresholds. UAS over 7 days (UAS7), UCT, and DLQI were the approved instruments used to define response groups.[9]

UAS is used to assess CSU activity and treatment response.[9] It evaluates daily intensity of itch and wheals, resulting in a daily score of 0-6. UAS7 is a 7-day sum of the daily score, 0-42 points, usually used in clinical practice.[9] Even though cut-offs are not globally defined, 0 corresponds to no active disease. A score ≤ 6 corresponds to minimal disease activity or well-controlled disease, 7-15 as mild disease activity, 16-27 as moderate, and 28-42 indicating severe disease activity.[9]

UCT is used in clinical practice to assess CSU control. It is a retrospective 4-week score with four questions: symptom severity, effect on QoL, how often treatment failed to control symptoms, and how often they were under control. UCT of ≥ 12 indicates well-controlled CSU, ≤ 11 indicates poor disease control.[9]

DLQI is not CSU-specific, but a skin-specific score used to assess patients' health-related QoL in several dermatological diseases. The score addresses symptoms, social activities, treatment problems, work, and personal relationships. Score ≤ 1 indicates no impact on QoL and 21-30 indicates a very great negative effect on QoL.[9]

The last score before treatment was considered the baseline. Treatment response was defined based on the score after approximately 3-6 months of therapy or at the next follow-up consultation available, as timelines were not always matched.

CR was defined as improvement in all PRO scores compared to baseline, with UAS7 = 0, UCT = 16, and DLQI ≤ 1. GR was defined as improvement in scores compared to baseline, with 1 ≤ UAS7 ≤ 6, 12 ≤ UCT ≤ 15, and 2 ≤ DLQI ≤ 5, indicating "well controlled" UAS7 and minimal to small QoL impairment. PR was defined as mild-to-moderate activity, with 7 ≤ UAS7 ≤ 27, UCT < 12, and 6 ≤ DLQI ≤ 10, provided that the scores showed improvement from baseline. NR was defined as the absence of clinically meaningful improvement (a reduction of < 50% from baseline in UAS7), or as UAS7 ≥ 28, UCT < 12, and DLQI > 10, indicating severe or uncontrolled CSU with moderate to severe QoL impairment. Treatment response categories are summarized in table 1. The thresholds are compatible with the current literature.[29-31] The use of three PROs was necessary to overcome misalignment of medical records. In cases where the three scores were not all available in the record, treatment response was defined based on the available one or two scores, applying the same thresholds. In cases where the scores fell in different response groups, the rule was to assign the patient to the least favorable group (based on the "worst" score).

**Table 1.** Treatment response categories based on PRO thresholds

| Response category | UAS7 | UCT | DLQI | Improvement from baseline |
|---|---|---|---|---|
| CR | 0 | 16 | ≤ 1 | Yes |
| GR | 1-6 | 12-15 | 2-5 | Yes |
| PR | 7-27 | < 12 | 6-10 | Yes |
| NR | ≥ 28 | < 12 | > 10 | No (reduction of < 50%) |

PRO: patient-reported outcomes; UAS7: urticaria activity score over 7 days; UCT: urticaria control test; DLQI: dermatology life quality index; CR: complete response; GR: good response; PR: partial response; NR: no response.

Statistical analysis was performed using Jamovi statistical software (version 2.7). Numeric variables were summarized as mean ± SD or median and interquartile range (IQR), while categorical variables were summarized as percentages. BMI at the first urticaria consultation was considered the primary exposure variable in treatment-related analysis, as treatment response occurs during the consultation period. Therefore, it better reflects the patient's metabolic status at the time of treatment included in the study. BMI at onset was included in secondary analyses to explore potential disease course associations as it better reflects metabolic status at disease onset. For categorical variables, comparisons across BMI categories were performed using Fisher's exact test. For numeric variables, comparisons were made using analysis of variance or Kruskal-Wallis, depending on whether normal distribution was accepted or rejected based on the Shapiro–Wilk test, respectively. A $p < 0.05$ was considered statistically significant. Treatment response was considered the primary outcome of interest in the study, compared across BMI categories using Fisher's exact test. *Post hoc* residuals allowed identification of the drivers of the association, and Cramér's V was calculated to assess its magnitude. In addition, ordinal logistic regression models were fitted to evaluate the association between treatment response and BMI categories, with adjustment for potential confounders.

## Results

### *Sample characteristics*

The study enrolled 90 patients, including 75 females (83.3%) and 15 males (16.7%) aged 18-86 years (median age 48 years, IQR 39-57).

BMI at CSU onset ranged from 18.90 to 43.80 kg/m$^2$, with a mean of 27.80 ± 5.24 kg/m$^2$. Considering BMI

categories, 30 patients were obese, 35 were overweight, 25 were of normal weight, and no patients were underweight. This resulted in 65 patients (72.2%) with excess weight (obese or overweight). BMI at first urticaria consultation ranged from 18.90 to 44.60 kg/m$^2$, with a mean of 28.10 ± 5.41 kg/m$^2$. Considering these categories, 31 patients were obese, 31 were overweight, and 28 were of normal weight, with none underweight. This resulted in 62 patients (68.9%) with excess weight at the first urticaria consultation. The demographic and clinical characteristics are presented for the overall study population and stratified by BMI categories in table 2. Comorbidities were common in the cohort. The most prevalent was depression or anxiety disorder, present in 45.6% of the patients. Dyslipidemia was present in 34.4%, arterial hypertension in 28.9%, smoking in 14.4%, and diabetes mellitus in 13.3%.

**Table 2.** Demographic and clinical characteristics of the overall study population and stratified by BMI category

| Variables in the study population | Statistic | Minimum-Maximum |
|---|---|---|
| Age (years) | | |
| Overall | 48 [39; 57] | 18-86 |
| Normal weight | 43 [25; 50] | 18-69 |
| Overweight | 53 [44; 58] | 23-80 |
| Obese | 48 [44; 58] | 19-86 |
| BMI at onset (kg/m$^2$) | | |
| Overall | 27.80 (5.24) | 18.90-43.80 |
| Normal weight | 22.10 (1.69) | 18.90-24.80 |
| Overweight | 27.00 (1.92) | 25.00-29.80 |
| Obese | 33.70 (3.67) | 30.00-43.80 |
| BMI at first urticaria consultation (kg/m$^2$) | | |
| Overall | 28.10 (5.41) | 18.9-44.6 |
| Normal weight | 22.00 (1.79) | 18.90-24.90 |
| Overweight | 27.70 (1.57) | 25.30-29.90 |
| Obese | 34.00 (3.29) | 30.10-44.60 |
| Age at onset (years) | | |
| Overall | 42 [28; 50] | 9-78 |
| Normal weight | 33 [19; 45] | 14-66 |
| Overweight | 46 [34; 52] | 9-65 |
| Obese | 42 [30; 51] | 16-78 |
| Disease duration (years) | | |
| Overall | 6 [3; 9] | 1-28 |
| Normal weight | 5 [3; 9] | 1-20 |
| Overweight | 6 [2; 8] | 1-22 |
| Obese | 8 [3; 15] | 1-28 |
| Treatment duration (years) | | |
| Overall | 1.5 [1.0; 3.0] | 0.2-8.0 |
| Normal weight | 1.5 [1.0; 3.0] | 0.2-7.0 |
| Overweight | 1.5 [0.8; 4.0] | 0.2-7.0 |
| Obese | 1.2 [1.0; 2.0] | 0.2-8.0 |

Statistics are presented as mean (standard deviation) or median [interquartile range].
BMI: body mass index; CSU: chronic spontaneous urticaria.

## *Associations with BMI at CSU onset (secondary exposure)*

Age at CSU onset ranged from 9 to 78 years, with a median of 42 years and IQR 28-50. Across BMI categories, using the Kruskal-Wallis test, there was a significant difference in age at onset (p = 0.026). The *post hoc* comparisons revealed a difference between normal weight and overweight patients (Bonferroni p = 0.025), where overweight patients had a later disease onset (median 46 years, IQR 34-52) compared to normal weight patients (median 33 years, IQR 19-45). Obese patients presented intermediate values (median 42, IQR 30-51 years). The distribution of age at CSU onset across BMI categories is illustrated in the boxplot corresponding to (Fig. 1A).

Disease duration ranged from 1 to 28 years (median 6 years, IQR 3-9). In contrast with age at onset, there was no significant global difference in disease duration (p = 0.178). *Post hoc* comparisons were non-significant between all the groups, showing no trend towards shorter or longer disease duration in any BMI category. The distribution of disease duration across BMI at onset categories is illustrated in the boxplot corresponding to (Fig. 1B).

## *Associations with BMI at first urticaria consultation (primary exposure)*

Regarding treatment, the highest therapeutic line reached for most patients was OMZ 300 mg (third-line treatment), used in 40 patients (44.4%). No patient remained on a standard dose of second-generation H1 AHs (first-line treatment). A total of 25 patients were treated with higher doses of second-generation H1 AHs (second line), 5 patients were treated with subcutaneous OMZ 450 mg, 2 patients with OMZ 600 mg, and 18 patients with oral ciclosporin 2.5-3 mg/kg/day (considered off-label fourth-line treatment). Patients treated with up-dosing of OMZ up to 450 mg belonged to the overweight and obese groups (2 and 3 patients, respectively); up-dosing up to 600 mg was needed in 2 obese patients. Of the 18 ciclosporin-treated patients, 3 had to suspend treatment after a few months due to adverse effects. 10 out of 18 patients (55.6%) on ciclosporin had never been treated with the previous line of treatment (OMZ), deviating from the guideline-recommended sequence. The type of treatment did not differ significantly (with Fisher's

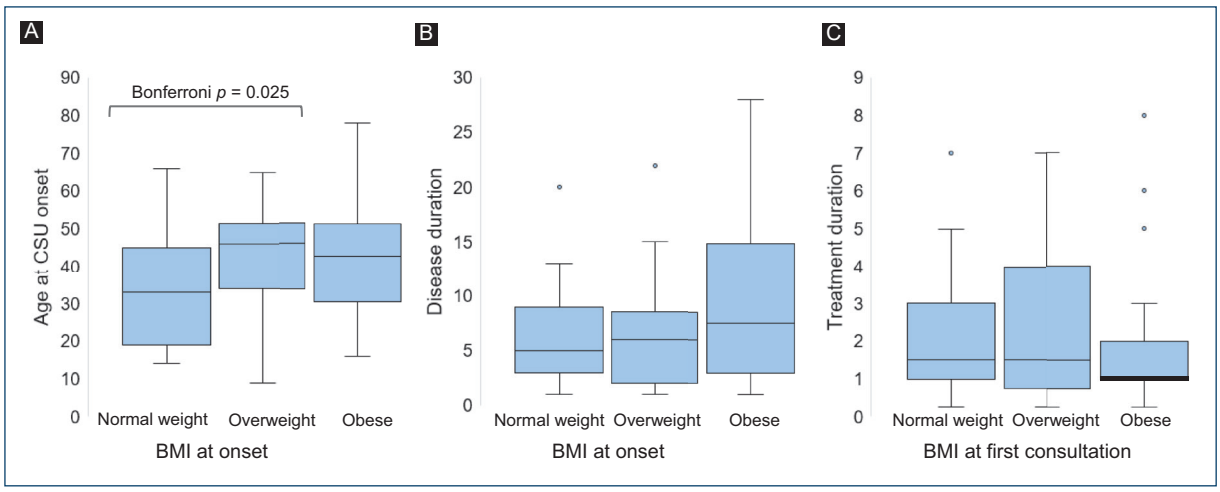



**Figure 1.** Boxplots presenting median, interquartile range, extreme values, and outliers. **A:** boxplot of age at CSU onset across BMI at onset categories (normal weight, overweight, and obese). Kruskal-Wallis p = 0.026, statistically significant difference between normal weight and overweight groups in *post hoc* comparisons (p = 0.025). **B:** boxplot of disease duration across BMI at onset categories. Kruskal-Wallis p = 0.178, without a statistically significant difference. **C:** boxplot of treatment duration across BMI at the first consultation categories, with no significant difference (p = 0.905). CSU: chronic spontaneous urticaria; BMI: body mass index.

exact p = 0.545). This distribution across BMI categories can be found in the bar chart of figure 2.

Treatment duration ranged from 0.2 years (or 3 months) to 8.0 years (median 1.5 years and IQR 1.0-3.0). Across BMI categories, there was no significant difference (with Kruskal-Wallis p = 0.905). The distribution of treatment duration across BMI categories is illustrated in the boxplot corresponding to (Fig. 1C).

## *Treatment response (primary outcome)*

Regarding treatment response across BMI at first consultation categories, there was a statistically significant difference (Fisher's exact test p = 0.007). This indicated an association between BMI categories and treatment response, with worse outcomes observed in higher BMI categories. A total of 25.6% of patients achieved CR, 53.3% GR, 20.0% PR, and 1.1% NR. The association between treatment response and BMI categories was of moderate magnitude, with Cramér's V = 0.295. *Post hoc* residuals indicated that the association was mostly driven by the CR, where in the normal weight group, CR was higher than expected (standardized residual = +2.18), and in the obese group, there was a deficit of CR (less than expected, standardized residual = –2.10). With increasing BMI, the percentage of patients achieving CR decreased from 46.4% (normal weight group) to 25.8% (overweight group) and 6.5% (obese group); whereas

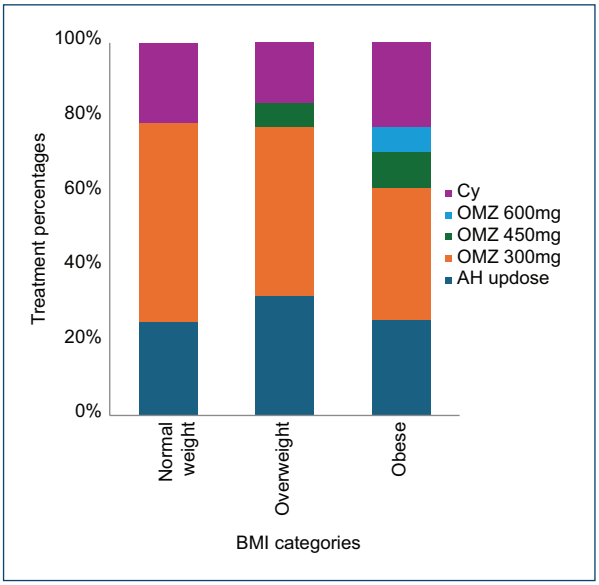



**Figure 2.** Bar chart of the highest treatment line reached in chronic spontaneous urticaria patients across BMI at first consultation category (normal weight, overweight, and obese), including AH updose, OMZ, and Cy.
AH: antihistamines; OMZ: omalizumab; Cy: ciclosporin; BMI: body mass index.

GR and PR increased in frequency. NR was observed in only one patient, belonging to the obese group. The highest percentage in the normal weight group was in CR (46.4% or 13 patients), in the overweight and obese

groups was GR (58.1% or 18 patients in both groups). figure 3 illustrates treatment response percentages in the BMI categories. *Post hoc* power analyses suggested overall adequate power to detect clinically relevant associations, with 86.1% regarding the primary outcome, and 77.7%, 84.6%, and 93.9% for regression models 1-3, respectively.

### Regression models

In ordinal logistic regression models, with normal weight as reference, obesity was significantly associated with worse treatment outcomes (odds ratio [OR] of being in a lower treatment response category, from CR to NR). In the unadjusted model or model 1, obese patients presented 7.63-fold higher odds of achieving lower treatment responses ($p < 0.001$, OR = 7.63, 95% confidence intervals 2.64-23.71). Overweight patients presented 2.33-fold higher odds; however, the effect was non-significant ($p = 0.104$). In the adjusted model (model 2), obesity remained associated with worse outcomes ($p = 0.001$, OR = 6.40). Overweight ($p = 0.246$) and covariables (age at onset and disease duration) showed no association ($p = 0.229$ and $p = 0.313$, respectively). Representation of the regression models is presented in figure 4. A third regression model was performed, adjusted for treatment line and the concomitant comorbidities analyzed (smoking, arterial hypertension, diabetes, dyslipidemia, and depression/anxiety disorders), with obesity remaining the only associated variable ($p = 0.005$, OR = 5.72).

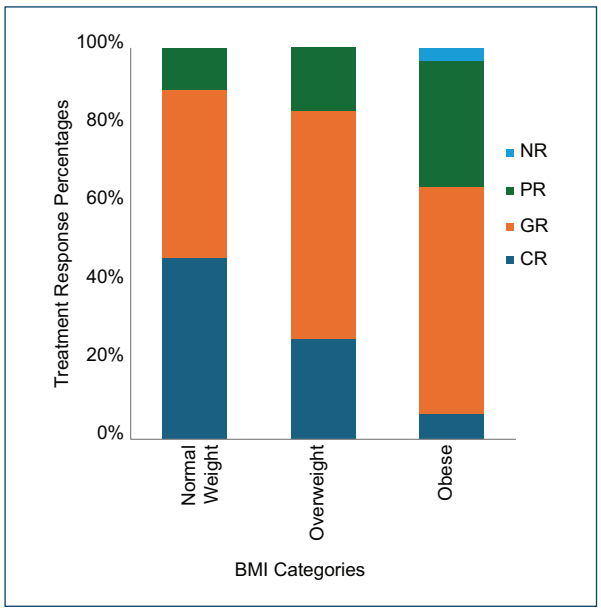



**Figure 3.** Bar chart of treatment response categories (CR, GR, PR, and NR), in percentage, across BMI at first consultation categories (normal weight, overweight, and obese) in chronic spontaneous urticaria patients. Fisher's exact test showed a statistically significant difference ($p = 0.007$). CR: complete response; GR: good response; PR: partial response; NR: no response, BMI: body mass index.

## Discussion

### Clinical and epidemiological profile

The clinical profile described in this study aligns with previously published CSU data. The predominance of female patients, age at onset centered in middle-aged adults (median 42 years), and disease duration of several years is consistent with CSU findings.[3-5,16] Most patients also presented higher BMI values, confirming the high prevalence of excess weight among CSU patients,[17,18,26] although no causal relationship can be inferred.

### Secondary outcomes: chronicity of CSU

Regarding age at CSU onset, overweight patients presented a later disease onset compared to normal weight patients. A similar finding was reported by Zbiciak-Nylec et al.[32] However, in this study, obese patients presented intermediate values without a significant difference, so a clear linear pattern across BMI categories cannot be established.

Disease duration was not significant across BMI categories. This contrasts with the hypothesis that excess weight may be associated with disease persistence (due to chronic inflammation, metabolic comorbidities, or treatment-related side effects).[18,22,25,26] However, the definition of disease duration in this study is constrained by patients' age at inclusion. Some patients presented up to 28 years of CSU, while others were only 18 years old, implying lower and limited disease duration. A fairer comparison would consider the mean duration of flare-ups or active disease, as it may overlook age-related differences; however, such detailed information could not be obtained due to the retrospective design.

Overall, this study did not demonstrate a clear association between BMI and CSU chronicity. Nonetheless, Zbiciak-Nylec et al. have reported an association between later disease onset and higher BMI and a trend in higher BMI patients toward longer disease duration.[32] This should be further clarified in larger cohort studies.

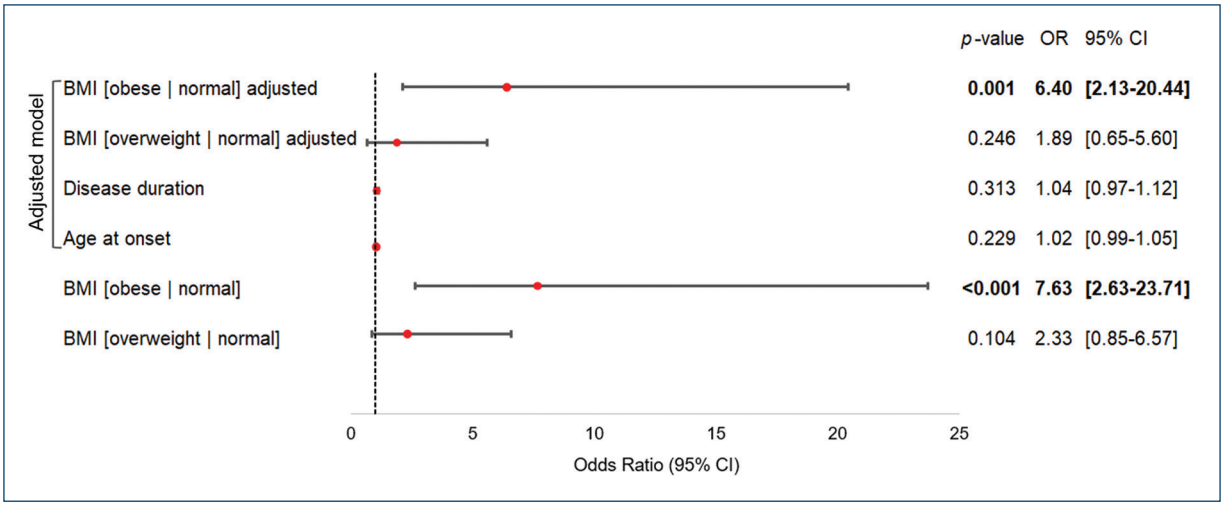



**Figure 4.** Forest plot of OR and 95% CI for achieving poorer treatment response (vs. complete response) in different BMI categories at first consultation and adjusted for covariables. OR: odds ratio; CI: confidence intervals; BMI: body mass index.

## *CSU treatment profile*

Treatment was consistent with real-world CSU data. No patients were treated with first-line treatment alone, as these were followed in a consultation, mostly for refractory cases, and only 27.8% with second-line treatment, reflecting the prevalent AHs-refractory disease.[2,3,5,6] Most patients required OMZ (third line), and yet, CR was not the most prevalent response group (with only 25.6% of patients achieving it). This finding highlights the difficulty in achieving full disease control and the need for novel therapeutic approaches, which have just been included in the recent 2026 guideline.[33]

No difference was observed between BMI categories regarding the type of treatment. Although OMZ was the most prevalent treatment in every group, the few patients requiring higher doses (450 or 600 mg) belonged to the overweight or obese groups, which is in line with another recent study from the same department.[34] Ciclosporin use was observed in all groups; notably, 55.6% of those patients escalated to the fourth line without prior treatment with the third line (OMZ), highlighting a misalignment between real-life practice and the international guideline-recommended sequence. This reflects the local preference for short courses of ciclosporin in patients with suspected type IIb autoimmune subtype of CSU,[28] and some local clinical constraints: OMZ is restricted to hospital use and needs 3-4 weeks waiting for approval before its use, while ciclosporin, although off-label, can be prescribed immediately with little cost for the patients.[1,5,16]

Treatment duration presented a wide time range (0.2-8.0 years), reflecting heterogeneous therapeutic regimens. Comparing treatment duration across different drug classes has limited interpretive value. This may explain the lack of significance across BMI categories, with the benefit of performing separate analyses for each treatment line, considering a larger-scale study.

## *Primary outcome: response to treatment*

Regarding the main finding, the study suggests that higher BMI is associated with poorer treatment response. This association is supported by ordinal logistic regression analyses. In the unadjusted regression model, compared to normal weight patients, obese patients had almost eightfold higher odds of belonging to lower response categories. Despite wide confidence intervals, probably due to the modest sample size, the consistent direction of the effect supports a meaningful association. The results suggest that obesity is associated with a significantly decreased probability of achieving CR with the recommended treatments. Overweight patients had over twofold higher odds, even though the effect was non-significant, contrary to the expected. This may be explained by the limited sample size of the study, warranting larger-scale studies.

In the adjusted regression models, obesity remained a significant predictor of poorer treatment response, suggesting an independent effect. Age at onset and disease duration were selected as confounders since

reports have identified associations between them and CSU prognosis and response to treatment.[30,35]

A trend towards worse outcomes with increasing BMI (suggestive of a dose-response pattern) was observed, although statistical significance was only observed in the obese group. This hypothesis- the higher the BMI, the greater the odds of poorer response- may be explained by the obesity-related mechanisms (such as chronic low-grade inflammation, altered cytokine profiles, and frequent metabolic comorbidities) affecting disease control and treatment response.[10,22-25,34] Another potential explanation for this hypothesis is based on pharmacokinetic mechanisms, including the increased volume of distribution and lower serum drug concentrations in obese patients, as previously reported regarding OMZ.[36,37] This may raise the question of whether fixed dosing strategies for AHs and OMZ are optimal across BMI categories or whether dose adjustment could improve treatment response.

### *Clinical implications*

These findings indicate that higher BMI, particularly obesity, may be a predictor of more difficult-to-treat CSU. Clinically, this supports the consideration of weight management as a complementary therapeutic target in CSU patients, alongside current recommended treatments.[15]

### *Considerations*

Both BMI and response to treatment were treated as ordinal variables. Although categorization may reduce sensitivity to small differences, it better reflects real-world clinical reasoning. Clinicians usually reason with the BMI category rather than exact BMI values, and treatment response is often assessed in categories. Given the study's focus on clinically meaningful associations rather than maximal statistical sensitivity, categorization was justified.

BMI was the sole measure of body composition used in the study. This is a simplification, as waist circumference better reflects visceral adiposity, associated with cardiometabolic risk.[38] A multidimensional assessment combining waist circumference, bioimpedance, and BMI would likely provide a more accurate understanding of the relationship between body composition and CSU.[38]

### *Limitations*

This study has multiple limitations. As a single-center study in a tertiary center, it is prone to selection bias (non-severe cases can be followed in primary healthcare centers, leading this study to reflect more severe CSU cases). As a retrospective cohort study, it is prone to information bias, from incomplete medical records and uncontrolled filling of PROs.[9] Self-reported data may introduce recall bias. The categorization of treatment response can lead to low sensitivity but enhances clinical interpretation. Regarding statistical analysis, this study is prone to multiple testing and alpha-spending bias. Although the *post hoc* analyses show adequate statistical power for the main analyses, the small sample size and low frequency of some outcome categories may still limit robustness. In addition, potential confounders such as treatment adherence, immunoglobulin E (IgE) levels, and concomitant systemic diseases were not fully controlled.

## Conclusion

This study suggests that obesity is associated with a significantly reduced likelihood of achieving CR or full disease control with the guideline-recommended treatments. Obesity may act as a clinical modifier of disease rather than a mere comorbidity, associated with limited treatment response in CSU.[17]

Clinically, the findings highlight the need to consider BMI during CSU management. Recognizing obesity as a potential predictor of disease refractoriness may help clinicians consider weight loss and nutritional management as adjunctive therapies, anticipate the need for treatment escalation or dose adjustment, and manage expectations realistically. Further investigation into the relationship between obesity and CSU is essential for a better understanding of the disease and improving patient management with a focus on holistic and personalized approaches. Prospective, multicenter studies with larger sample sizes, considering multidimensional body composition assessment, IgE levels, concomitant diseases, and comorbidities, are warranted to explore causality and determine whether weight-loss intervention improves treatment responsiveness and long-term disease control.

## What does this study add?

Obesity was associated with poorer treatment response in CSU. Obesity may act as an independent predictor of worse therapeutic outcomes. These findings support considering weight management as an adjunct strategy in CSU management.

## Funding

None.

## Conflicts of interest

M. Gonçalo has been an advisor and/or performed lectures for AbbVie, Almirall, Astra-Zeneca, Leo Pharma, Pfizer, Novartis, Sanofi, and Takeda outside the area of this work.

## Ethical considerations

**Protection of human subjects and animals.** The authors declare that no experiments on humans or animals were performed for this research.

**Confidentiality, informed consent, and ethical approval.** The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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