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# Evaluation of Vitamin B12 Levels in Chronic Spontaneous Urticaria Patients and Correlation with Severity of Disease

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*ABSTRACT*

***Background:*** *Chronic spontaneous urticaria (CSU) is a condition with an unclear etiology, which is characterized by recurring hives and/or angioedema. Evidence suggests a potential role of vitamin B12 in modulating immune responses and disease severity. This study explores the relationship between vitamin B12 levels, CSU severity and autoimmunity markers such as autologous serum skin test (ASST) positivity.*

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***Methods:*** *A cross-sectional study of 57 CSU patients was conducted. Participants' demographic and clinical characteristics, vitamin B12 levels and ASST positivity were assessed. Symptom severity was measured using urticaria activity scores (UAS), wheal/flare duration and pruritus severity. Associations between vitamin B12 levels, symptom severity and ASST positivity were analysed.*

***Results:*** *Participants had a mean age of 36 years, with a higher share of female subjects. Vitamin B12 deficiency (<200 pg/mL) was observed in 15.7% of patients, while 78.9% had normal levels. A significant negative correlation was found between vitamin B12 levels and wheal/flare duration (p=0.04). Patients with low vitamin B12 levels had longer wheal/flare duration and trends toward higher pruritus severity compared to those with normal levels. Autologous serum skin test positivity was observed in 21% of participants and was associated with more severe symptoms.*

***Conclusion:*** *This study highlights a potential role for vitamin B12 in modulating CSU severity. Assessing vitamin B12 levels in patients with severe or refractory symptoms could aid in personalized management strategies. Further research is needed to validate these findings and explore the role of supplementation in improving CSU outcomes.*

**Keywords**: chronic spontaneous urticaria, vitamin B12, symptom severity, autoimmunity, autologous serum skin test.

## INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous occurrence of hives and pruritus lasting six weeks or more without an identifiable external trigger (1). It may be accompanied by angioedema – swelling of non-dependent areas such as eyelids, lips, genitals, or larynx – which is typically painful rather than itchy. The etiology of CSU is multifactorial and incompletely understood, with contributions from autoimmunity, infections and systemic diseases. In autoimmune urticaria, autoantibodies target the high-affinity IgE receptor (FcεRI) or IgE itself, triggering mast cell and basophil activation with subsequent histamine release (2).

Vitamin B12 (cobalamin) is a water-soluble vitamin essential for hematological, neurological, and immune functions. Deficiency can cause megaloblastic anemia, neuropsychiatric disorders, and impaired immune responses. Beyond its classical roles, B12 supports nervous system integrity and immune regulation (3). Several mechanisms may link B12 status to CSU. Firstly, B12 deficiency may impair immune function and exacerbate autoimmune disease – important since many CSU cases are autoimmune in origin. Secondly, B12 participates in the methionine synthase pathway, regulating homocysteine levels; elevated homocysteine is pro-inflammatory (4). Thirdly, mast cells – central to CSU pathophysiology – release histamine and other mediators; hence, B12 may contribute to immune regulation and mast cell-mediated inflammatory pathways, potentially influencing mast cell degranulation and urticaria symptoms (5). Fourth, B12 is important for neurotransmitter synthesis, including serotonin, which influences stress and potentially urticaria severity.

Only a few studies have explored B12 levels in CSU. A 2004 Turkish study of 33 CSU patients and 27 controls found that 33.3% of subjects had B12 deficiency (6). A 2015 UK study on 282 patients reported lower B12 levels compared to the general population, though still within the normal range (7). A 2023 Canadian study of 100 CSU patients identified B12 deficiency in 27% (8). While these suggest a possible link, evidence remains limited – especially in the Indian population, where vegetarian diets and gastrointestinal disorders increase deficiency.

Given this paucity of data, the present cross-sectional study was designed to evaluate serum B12 levels in CSU patients and examine correlations with disease severity and autoimmunity. This work is part of a larger randomized controlled trial assessing the effect of combining histaglobulin with antihistamines in CSU (9). By investigating these associations, we aim to clarify whether B12 deficiency contributes to CSU pathogenesis and severity, and whether B12 supplementation might serve as a beneficial adjunct

in management – particularly in autoimmune cases. Such findings could have implications for clinical care and expand understanding of how nutritional factors interact with immune and inflammatory skin disorders.

## METHODOLOGY

### Study design and setting

The study was initiated after obtaining Institutional Ethics Committee (IEC) approval. Patients who met the eligibility criteria were voluntarily recruited from the dermatology department between September 2023 and August 2024.

### Eligibility criteria

Inclusion criteria comprised patients aged >18 years of both genders; CSU symptoms for more than six weeks; and willingness to participate in the study.

Exclusion criteria comprised the following: infective foci or dental implants; use of steroids, immunosuppressants, or drugs affecting vitamin B12 levels (e.g., metformin, phenytoin, phenobarbitone, proton pump inhibitors, H2 blockers); known cases of vitamin B12 deficiency or chronic autoimmune conditions; pregnant and lactating women; and physical urticaria (e.g., cold-induced, pressure, heat-contact, solar, dermographic, vibratory, aquagenic, cholinergic, drug-induced).

### Sample size

Although the optimal sample size for a prevalence study on vitamin B12 deficiency in the general population was calculated as 383 (based on 47% prevalence in India) (10), this analysis focuses on the specific CSU population. In our randomized controlled trial investigating the effects of histoglobulin in CSU patients, we initially calculated a sample size of 62 participants based on the mean urticaria activity score (UAS) (11), which was the primary study endpoint. In this paper, we are reporting serum vitamin B12 levels in the subset of 57 participants who completed all assessments, as a cross-sectional study within this trial. Convenient sampling was employed during the study period. Data was collected from the enrolled participants.

### Data collection

Demographic details such as age, sex, occupation and education and disease characteristics (duration of CSU, diurnal variation of lesions, presence of angioedema, medication details), drug name and dosage regimen (dose, frequency, duration and formulation) and comorbidities were collected.

The severity of urticaria was measured using UAS 1 (one day UAS) that takes into consideration the severity of pruritus and number of hives. This simple validated tool is based on scoring the wheal and itch separately on the scale of 0-3. A wheal score 0 represents no wheal, wheal score 1 means < 20 wheals over 24 hours, wheal score 2 means 20-50 wheals over 24 hours and wheal score 3 means more than 50 wheals over 24 hours. An itch score 0 represents no itch, itch score 1 means itch present but not troublesome or annoying, itch score 2 means troublesome itch but does not interfere with normal daily activity or sleep and itch score 3 means severe itch sufficiently troublesome to interfere with normal daily activity or sleep. The final score was calculated by adding together. In our study, the score was collected only once and it were categorized into five disease states: urticaria free (UAS=0), well- controlled urticaria (UAS=1-6), mild-activity urticaria (UAS=7-15), moderate-activity urticaria (UAS=16-27) and severe-activity urticaria (UAS=28-42) (12)

### Laboratory investigations

Later, 10 millilitres of blood were collected for investigations including red blood cell count (RBC), white blood cell count (WBC), platelet count, serum creatinine, serum TSH, serum IgE, absolute eosinophil count (AEC) and vitamin B12. Autologous serum skin test was performed with 0.05 mL of serumaccording to the standard procedure. It was injected intradermally into each patient's left flexor forearm and 0.05 mL of sterile normal saline was injected into the right forearm as a negative control. After 30 minutes and one hour, the wheal was examined and its diameter was measured. The result is interpreted as those patients with a wheal diameter of ≥1.5 mm greater than that of controls with erythema will be considered as ASST positive (13).

Serum vitamin B12 levels were quantified using the vitamin B12 Quanti Microliza kit, a microwell ELISA immunoassay. It is a microwell ELIZA immunoassay for the quantitative detection of vitamin B12 in human serum. The results have been calculated automatically using curve

regression mode. Results were read as normal if levels of vitamin B12 were between 200 and 835 pg/mL, deficient/low if they were lower than 200 pg/mL.

### Statistical analysis

Data analysis was conducted using Graph Instat. Continuous variables, such as age, wheal/flare duration and lab parameters, were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution. Categorical variables, including gender, education level, occupation, wheal/flare severity and the presence of diurnal variation, were summarized using frequencies and percentages.

Group comparisons were performed between patients with low versus normal vitamin B12 levels to assess differences in clinical parameters. Independent samples t-tests or Mann-Whitney U tests were applied for continuous variables based on data normality, which was evaluated using the Shapiro-Wilk test. Chi-square or Fisher's exact tests were used for categorical comparisons, depending on sample size. Spearman's correlation coefficients were calculated to assess associations between vitamin B12 levels and clinical variables (e.g., CSU duration, wheal/flare severity, pruritus duration). Statistical significance was set at $p < 0.05$.

## RESULTS

The study included 57 CSU patients (mean age 35.1 ± 11.79 years), of whom 24 were males and 33 females. Educational levels ranged from no formal education (10.5%) to secondary education (31.6%). Occupations included homemakers (31.6%), skilled workers (21%) and students (14%) (Table 1).

**TABLE 1.** Demographic characteristics of study participants enrolled between September 2023 and August 2024

| Sno | Characteristics | N | % |
|---|---|---|---|
| 1 | **Total n** | 57 | - |
| 2 | **Age in years** | 35.9±11.2 | - |
| | a) 18-29 | 19 | 33.3% |
| | b) 30-39 | 17 | 29.8% |
| | c) 40-49 | 13 | 22.8% |
| | d) >50 | 8 | 14% |
| 3 | **Sex** | | |
| | a) Male | 24 | 42.1% |
| | b) Female | 33 | 57.8% |
| 4 | **Education** | | |
| | a) Primary education | 6 | 10.5% |
| | b) Secondary education | 18 | 31.6% |
| | c) Higher secondary education | 4 | 7% |
| | d) Degree | 18 | 31.6 % |
| | e) Masters | 5 | 8.8% |
| | f) No formal education | 6 | 10.5% |
| 5 | **Occupation** | | |
| | a) Unskilled worker | 7 | 12.2% |
| | b) Skilled worker | 12 | 21% |
| | c) Student | 8 | 14% |
| | d) Agriculture | 5 | 8.8% |
| | e) Home maker | 18 | 31.6% |
| | f) Self employed | 4 | 7% |
| | g) Professional | 3 | 5.2% |

### Disease-specific clinical features

The median CSU duration was 12 months [interquartile range (IQR) 5–36]. Wheals and flares typically lasted 60 minutes (IQR 30–120), with moderate and severe symptoms equally common (43.8% each). Most patients (59.6%) reported diurnal variation, predominantly worsening at night (85.3%). Pruritus also had a median duration of 60 minutes (IQR 30–120), with aggravating factors identified by 15.8% (e.g., certain foods, constipation more than two days). Angioedema occurred in 31.6% of subjects and 12.3% had a family history of CSU; notably, one family had four affected siblings. Over half (56.1%) of patients had prior medication use, most commonly cetirizine. Autologous serum skin test positivity was seen in 21.1% of subjects, indicating an autoimmune component in some patients. The median UAS score was 25 (IQR 16–38), with 47.3% being classified as severe and 29.8% as moderate (Table 2).

### Laboratory findings

Mean RBC, WBC and platelet counts were 4.81 ± 0.89, 7.73 ± 1.82 and 271.78 ± 65.44, respectively. Serum creatinine and thyroid-stimulating hormone (TSH) were largely normal. Mean IgE was 390.97. Average vitamin B12 level was 422.12 pg/mL, with deficiency (< reference range) being found in 15.7% of subjects. Classification of laboratory results showed normal levels in 24.5% for IgE, 96.5% for AEC and 75.5% for B12 (Table 3). Vitamin B12 distribution is shown in Figure 1.

### Correlation analysis

Vitamin B12 levels had a weak but statistically significant negative correlation with wheal/flare

**TABLE 2.** Character-wise disease details in study participants with chronic spontaneous urticaria

| Sno | Characteristics | Value |
|---|---|---|
| 1 | **Duration of disease in months (median IQR)** | 12 (5-36) |
| 2 | **Wheals and flares** | |
| a | Duration in minutes – median IQR | 60 (30-120) |
| b | Wheal/flare severity | |
| | Mild n (%) | 7 |
| | Moderate n (%) | 25 |
| | Severe n (%) | 25 |
| c | Diurnal variation | |
| | Yes n (%) | 34 (59.6) |
| | No n (%) | 23 (39.4) |
| | Day time more | 5 (15%) |
| | Night time more | 29 (85%) |
| | No diurnal variation | 23 |
| 3 | **Pruritus** | |
| a | Duration in minutes median IQR | 60 (30-120) |
| b | Aggravation factors Yes | 9 |
| c | Aggravation factors No | 48 |
| d | Relieving factors | 0 |
| 4 | **Angioedema (n)** | |
| a | Yes | 18 |
| b | No | 39 |
| 5 | **Family history (n)** | |
| a | Yes | 7 (12.2%) |
| b | No | |
| 6 | **Previous medication history (n)** | |
| | Yes | 32 |
| 7 | **ASST (n)** | |
| a | Positive | 12 (21%) |
| 8 | **Urticaria activity score (one day)** | |
| a | Overall score median IQR | 25 (16-38) |
| b | Well-controlled urticaria (1-6) n (%) | 2 (3.5%) |
| c | Mild disease activity (7-15) n (%) | 11 (19.3%) |
| d | Moderate disease activity (16-27) n (%) | 17 (29.8%) |
| e | Severe disease activity (28-42) n (%) | 27 (47.3%) |

CSU=chronic spontaneous urticaria; IQR=interquartile range

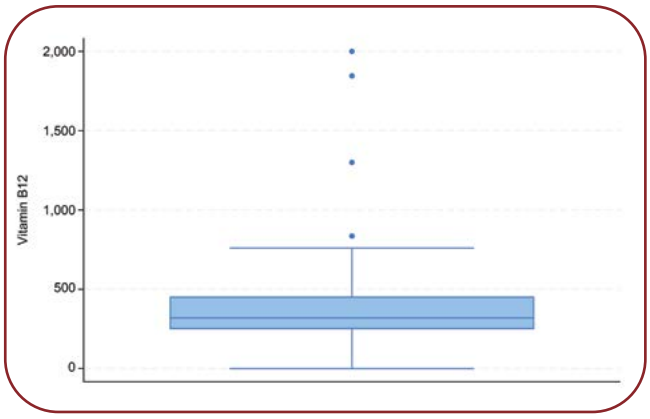


**FIGURE 1.** Box and Whisker plot of vitamin B12 levels among participants with chronic spontaneous urticaria

duration ($r = -0.2703$, $p = 0.04$), suggesting that lower B12 levels were associated with longer episodes. No significant correlations were observed between B12 and CSU duration, severity, pruritus duration, angioedema, UAS, or ASST status ($p > 0.05$) (Table 4).

### Group comparisons by vitamin B12 status

When stratified by B12 status, patients with deficiency had significantly longer wheal/flare durations (median 120 minutes) compared to those with normal B12 (median 60 minutes; $p = 0.02$). A trend toward longer pruritus duration in the deficient group was noted but not statistically significant ($p = 0.06$). Duration of CSU and levels of TSH and IgE showed no significant differences between groups (Table 5). Figure 2 illustrates that severe symptoms were most

**TABLE 3.** Laboratory investigations of study participants with chronic spontaneous urticaria

| Sno | Laboratory parameter | N (%) | Mean ±SD | Median IQR |
|---|---|---|---|---|
| 1 | Red blood cells | 57 (100) | 4.81±0.89 | - |
| 2 | White blood cells | 57 (100) | 7.73±1.82 | - |
| 3 | Platelets | 57 (100) | 271.78±65.44 | - |
| 4 | Serum creatinine | 46 (80) | - | 0.6 (0.4-0.7) |
| 5 | Thyroid stimulating hormone | 49 (86) | - | 1.6 (1.3-2.39 |
| 6 | **Serum IgE n=57** | 57 (100) | - | 219 (113-648) |
| | Normal IgE<100 | 14 (24.5) | | 65 (50-88) |
| | Abnormal IgE> 100 | 43 (75.4) | | 352.7 (169-788) |
| 7 | **Absolute eosinophil count (IU/mL)** | 57 (100) | 177.34±65.81 | - |
| | Normal 30-350 | 55 (96.5) | 168.8±48.4 | |
| | Abnormal >350 | 2(3.5) | 410.5± 55.8 | |
| 8 | **Serum vitamin B12** | 57(100) | - | 319 (248-454) |
| | Low levels (<200) | 9(15.7) | 143.7±76.8 | |
| | Normal (200-835) | 45(78.9) | 387±141.3 | |
| | High (>835) | 3 (5.2) | 1495.4±532.4 | |

IQR=interquartile range; SD=standard deviation

| Sno | Variable | Correlation coefficient (r) | p-value | 95% CI |
|---|---|---|---|---|
| 1. | CSU duration (months) | -0.09387 | 0.48 | -0.3530 to 0.1786 |
| 2. | Wheal/flare duration (hours) | -0.2703 | 0.04* | -0.5019 to-0.0024 |
| 3. | Wheal/flare severity | 0.007081 | 0.95 | -0.2614 to 0.2745 |
| 4. | Pruritus duration (hours) | -0.1962 | 0.14 | -0.4409 to 0.0757 |
| 5. | Angioedema | 0.01912 | 0.30 | -0.1269 to 0.3850 |
| 6. | UAS | 0.05764 | 0.67 | -0.2136 to 0.3206 |
| 7. | ASST positive (Y/N) | -0.1046 | 0.43 | -0.3624 to 0.1680 |
| 8. | Serum IgE | -0.03124 | 0.82 | -0.3015 to 0.2436 |
| 9. | AEC | 0.2053 | 0.12 | -0.06628 to 0.4486 |

*p<0.05 considered as statistically significant. CSU=chronic spontaneous urticaria; ASST=autologous serum skin test; AEC=absolute eosinophil count; UAS=urticaria activity score; CI=confidence interval

**TABLE 4.** Correlation between vitamin B12 levels and clinical parameters in patients with chronic spontaneous urticaria

| Sno | Clinical parameter | Low B12 group (N = 10) | Normal B12 group (N = 44) | p-value | 95 % CI |
|---|---|---|---|---|---|
| 1. | Age (years) | 32.5 ± 11.8 | 35.1 ± 11.8 | 0.52 | -5.676 to 10.949 |
| 2. | CSU duration (months)<br>median IQR | 32.5 ± 26.2<br>30 (6-60) | 39.1 ± 74.3<br>12 (4-36) | 0.33 | |
| 3. | Wheal/flare(duration) | 120 (90-240) | 60 (30-120) | 0.02* | |
| 4. | Pruritus duration (hours) | 120 (60-180) | 60 (30-120) | 0.06 | |
| 5. | TSH | 1.61 (1.31-10.1) | 1.6 (1.28-2.54) | 0.45 | |
| 6. | IgE | 150 (135.7-322.3) | 320 (110-795) | 0.32 | |

*p-value <0.05 considered significant; CI=confidence interval; CSU=chronic spontaneous urticaria; TSH=thyroid stimulating hormone

**TABLE 5.** Comparison of clinical parameters based on vitamin B12 levels

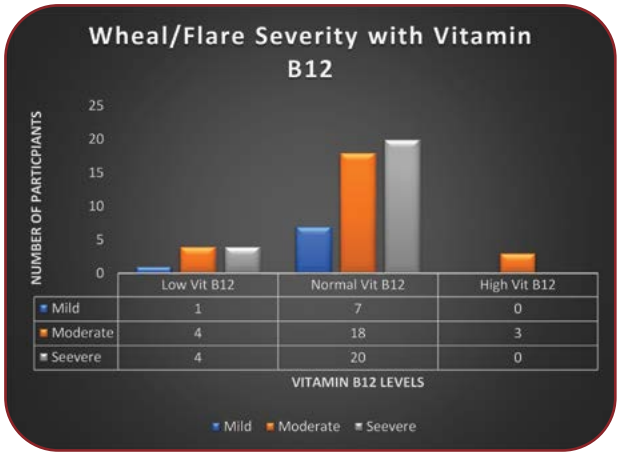


**FIGURE 2.** Wheal/flare severity with vitamin B12 levels in patients with chronic spontaneous urticaria

common among patients with normal B12, whereas no severe cases occurred in the high B12 subgroup.

## DISCUSSION

Our study found that most participants experienced moderate to severe symptoms, with wheals/flares and pruritus episodes lasting a median of 60 minutes. Diurnal variation was reported by 59.6% of subjects, of whom 85% had worsening symptoms at night. Angioedema occurred in 31.5% of cases. A notable finding was the negative correlation between vitamin B12 levels and wheal/flare duration, with deficiency associated with longer symptom episodes and higher severity, while higher B12 levels corresponded to milder symptoms. Autoimmunity was suggested by ASST positivity in 21% of participants.

Participants had a mean age of 36 years, with 60% of them having under 40 years, and women were more frequently affected – a trend consistent with the previous literature linking female sex hormones to increased autoimmune risk (14). Homemakers (31.6%) and skilled workers (21%) were the most common occupational groups, reflecting possible exposure to physical or environmental triggers. Prior research found that 32.9% of CSU patients reported occupational aggravation of symptoms, a trend echoed here (15).

Median disease duration was 12 months, though the range extended from three to 360 months, with three participants reporting durations of 15, 20 and 30 years, respectively. Such variability aligns with studies describing an

unpredictable course of CSU (16). The high prevalence of nocturnal symptom worsening supports findings by Maurer *et al* (17) potentially explained by circadian influences on mast cell activity (18).

A family history of CSU was present in 12% of participants, higher than the percentage of about 4% of patients with a family history of CSU affecting at least one first-degree relative reported elsewhere (19). In one family, four siblings were affected. Among these cases, ASST positivity and high IgE levels were common. Angioedema, characterized by sudden swelling of subcutaneous or submucous membrane areas like lips and eyelids (20), had a prevalence of 31.5%, which was lower than the 40% reported in some studies, possibly reflecting sample characteristics. Its pathogenesis involves mast cell degranulation and mediator release, consistent with CSU mechanisms (21).

Autologous serum skin test positivity (21%) suggests an autoimmune subset, often linked to more severe disease and poorer antihistamine or omalizumab responses (22). A meta-analysis reported higher UAS scores and IgE levels in ASST-positive *versus* ASST-negative CSU, which was consistent with this study's findings (23).

Vitamin B12 deficiency was present in 15.7% of participants, similar to earlier reports but higher than in the general population. Previous studies have demonstrated lower B12 levels in CSU patients compared to controls (24), sometimes correlating with severity. Here, deficiency was associated with longer wheal/flare durations and most deficient patients were female, often with concurrent angioedema, hypothyroidism, or ASST positivity. Four patients had high B12 levels, possibly from recent supplementation – data not collected in this study.

The potential role of vitamin B12 in CSU may involve immune modulation, mast cell stabilization and reduction of oxidative stress (25). Low B12 might exacerbate inflammation through homocysteine elevation or impaired neurotransmitter synthesis, thereby influencing both immune and psychological factors relevant to CSU. This parallels observations for vitamin D, where deficiency has been linked to CSU severity.

Clinically, these findings suggest that B12 assessment in CSU – particularly in severe or long-duration cases – may provide useful information for management. While causality cannot be established from this cross-sectional design, the pattern of milder symptoms with higher B12 levels raises the question of whether supplementation could be a beneficial adjunct. Tailoring treatment to ASST-positive patients, who may require immunosuppressive or biologic therapy, could also improve outcomes.

### Limitations of the study

The main limitations include the small sample size and single-center design, which limit generalizability. The cross-sectional approach precludes causal inferences and unmeasured confounders (*e.g.*, diet, supplementation history, smoking and alcohol use) may influence the results. The study also relied on a subset from an RCT, focusing on vitamin B12 levels without assessing longitudinal changes or treatment response.

### Implications and future directions

Despite these limitations, the study adds to limited data linking vitamin B12 with CSU severity and specific symptom parameters. Larger, prospective studies should investigate whether B12 supplementation reduces symptom burden or alters disease trajectory, particularly in autoimmune-positive cases. Additionally, exploring interactions between multiple micronutrients, immune markers and CSU could enhance understanding of disease mechanisms and open new therapeutic avenues.

## CONCLUSION

This study demonstrated that 17.5% of CSU patients had vitamin B12 deficiency, with a significant negative correlation between vitamin B12 levels and wheal/flare duration. Autologous serum skin test positivity, observed in 21% of participants, highlights an autoimmune component associated with severe symptoms. These findings suggest that vitamin B12 assessment could play a role in managing CSU, particularly for patients with severe or refractory symptoms. Testing vitamin B12 levels in CSU patients, particularly those with refractory symptoms, could provide additional insight into disease management. Even suboptimal levels of vitamin B12 may still influence immune responses and CSU severity. Clinicians may consider vitamin B12 supplementation as a supportive therapy for

CSU patients, though further research is needed to confirm its efficacy. ❑

*Clinical trial registration: This study represents a secondary analysis of baseline data obtained from participants enrolled in a randomized controlled trial evaluating the efficacy of histaglobulin in patients with chronic spontaneous urticaria. The baseline data collected prior to randomization were analyzed to assess serum vitamin B12 levels and their association with clinical characteristics. CTRI: CTRI/2023/08/056841 for RCT study.*

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*Authors' contributions: All authors confirm that the manuscript has been read and approved. Also, all authors meet authorship criteria and stated that the manuscript represents honest work.*

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