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*Review Article*

# Biomarkers of chronic spontaneous urticaria

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## ABSTRACT

Chronic spontaneous urticaria (CSU) is a distressing skin condition that is characterized by the daily or nearly daily appearance of pruritus and wheals of more than 6-week duration. CSU is now believed to have two endotypes, namely, the more common auto-allergic type and the more recalcitrant autoimmune type. It is often difficult to treat the disorder and various treatment modalities are recommended for symptom control, including second-generation non-sedative antihistamines, cyclosporin, and omalizumab. To track the progression of the disease and the efficacy of treatment, certain biomarkers play a key role. Biomarkers identified for CSU include some major ones such as Interleukin (IL)-6, IL-17, and IL-31 and minor ones such as periostin and oncostatin-M. Not only do they may serve as important prognostic tools for proper diagnosis of the disease, but they have also been utilized in several clinical studies to track the progression of the disease, which underlines their importance in the clinical setting.

**Keywords:** Chronic spontaneous urticarial biomarkers, Biomarkers, Cytokines, Interleukins

## INTRODUCTION

Chronic spontaneous urticaria (CSU) is a distressing skin condition that is characterized by the daily or nearly daily appearance of pruritus and wheals of more than 6-week duration.[1]

Over the last decade, scientists have worked to better understand what causes CSU and how it progresses so that they may better utilize biomarkers to measure illness severity, track its course over time, and forecast how well treatments will work for individual patients. It is also crucial for the doctor providing treatment to have access to clinical biomarkers helpful for predicting the future progression of the illness and the most probable response to therapy when a new patient suffering from CSU is identified [Figure 1]. Clinical and laboratory indicators have been suggested for the evaluation of CSU severity and thus can be employed in the treatment plan to keep track. Although mast cells in the skin play a crucial role in the pathophysiology of CSU, little is known about the underlying mechanisms of their activation. Since systemic immunoglobulin G (IgG) autoantibodies directed to thyroid antigens and/or to immunoglobulin E (IgE) or to its IgE receptor (FcεRI) have been detected in a substantial subset of patients, autoimmunity seems to play a role in the etiology of CSU.[2,3] Nonetheless, the fact that autoantibodies are undetectable in a sizable proportion of CSU patients indicates that additional processes are likely involved in the development of the illness, paving the door for the discovery of biomarkers outside autoantibodies.[4]

## CLINICAL PRESENTATION OF URTICARIA

Presentation of CSU varies markedly in disease severity, presence or absence of angioedema, presence or absence of flare with inducing factors, quality of life impairment, course of the disease, and clinical response to treatment. CSU is now believed to have two endotypes, namely, the more common auto-allergic type and the more recalcitrant autoimmune type. More than one-third of CSU patients have IgG antibodies against the FcεRI alpha subunit of the high-affinity IgE receptor,[5] whereas 5–10% demonstrate the generation of IgG toward IgE antibodies;[6] furthermore, up to one-third of CSU patients have anti-thyroid autoantibodies[7] [Figure 2]. CSU is presently diagnosed more clinically and there are no disease-specific biomarkers available to use in the diagnosis. Recent research by Schmetzer *et al.* found a substantial connection between the existence of anti-interleukin (IL)-24 IgE and CSU, and although the results are limited, they are encouraging.[8] That research also shows that IL-24 is more expressed in the serum of CSU patients in comparison with healthy controls, indicating that it is an auto-antigen of IgE. Despite several studies documenting biomarker-based subgroup distinctions among CSU patients, only a few factors are potentially useful phenotypic or endotypic biomarkers. For example, low basophil numbers, high C-reactive protein (CRP), low

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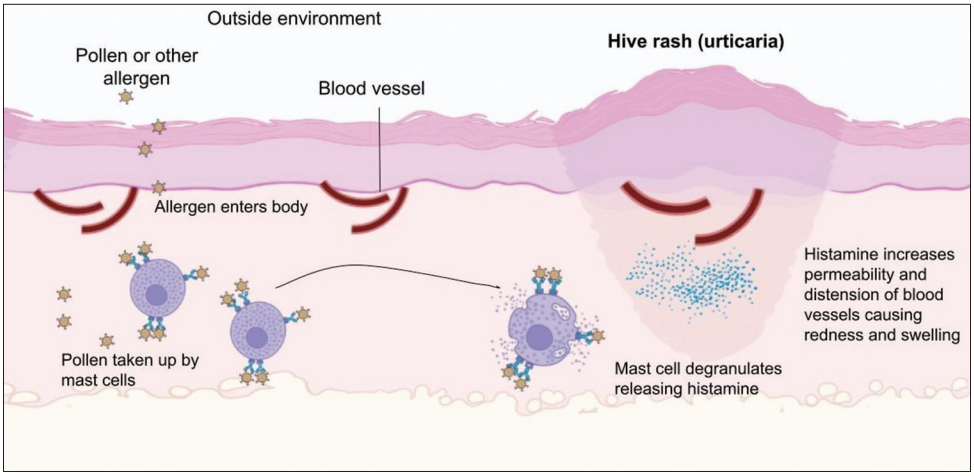


**Figure 1:** Pathophysiology of urticarial.

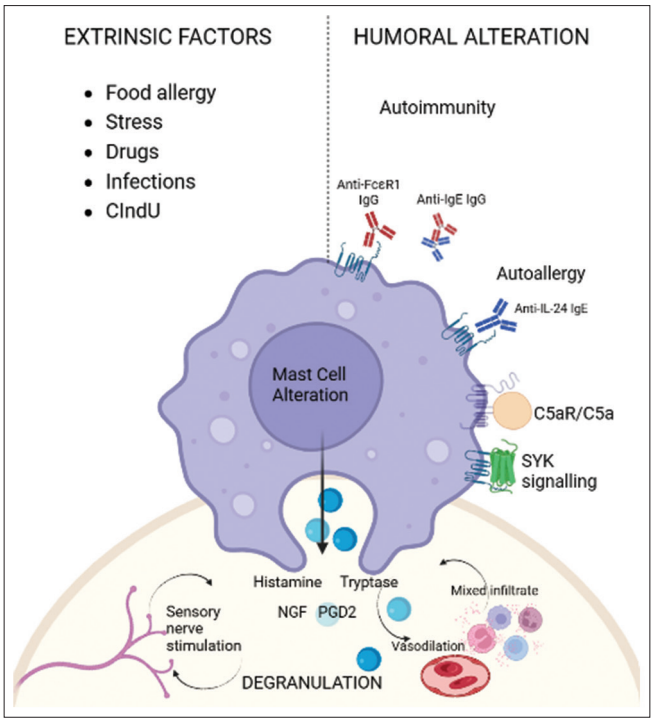


**Figure 2:** Mast cell activation.

IgE, and the presence of anti-thyroid peroxidase antibodies (TPO) may be associated with Type 2B autoimmune CSU, with a recalcitrant course.[9]

## SERUM BIOMARKERS IN URTICARIA

### C-Reactive Protein (CRP)

CRP has been shown to rise in CSU patients, particularly those with positive autologous serum skin test (ASST), and to have a high association with other inflammatory indicators (such as erythrocyte sedimentation rate, blood leukocyte/neutrophil counts, and IL-6 serum levels) and with disease activity in a number of clinical investigations.[10,11] CRP has been suggested as a biomarker of response to medication, which is an interesting development in the dynamic landscape of personalized healthcare. Recent research suggests that a high CRP level may indicate an inadequate response to antihistamines but an adequate response to oral cyclosporin.[12,13] CRP is a widely used biomarker for inflammatory and autoimmune disorders, although it is important to note that CRP levels in individuals with CSU are quantitatively lesser when compared to those identified in other conditions.

### Complement system

The activation of the complement system is critical to the etiology and progression of CSU because its components may activate mast cells. Few studies have found that C3 and C4 levels are much higher in CSU patients than in healthy individuals and that their concentrations strongly correlate with CRP in chronic urticaria (CU) patients, but not in healthy ones. However, only a subset of patients with severe illness (up to 5–10%) show evidence of a rise in C3 and C4 levels, reducing their significance as indicators of disease activity.[14] Some authors suggested that an increased liver production of C3 and C4 may occur in response to pro-inflammatory cytokines such as IL-1, IL-6, or tumor necrosis factor.[15] In addition, the anaphylatoxin C3a is expressed on a wide variety of cells involved in urticarial inflammatory processes, such as mast cells, neutrophils, basophils, monocytes, and, eosinophils.[16] It also appears that C5a, C3a-like, is necessary for IgG-dependent activation of mast cells in CU.[17] These findings suggests that the complement system plays a role in the pathogenesis of CSU, either directly, by causing mast cell degranulation, or indirectly, by intensifying the autoimmune response.

### Interleukins

Since IL-6 plays a crucial role in generating inflammatory responses, it shows promise as a biomarker in CSU. In

individuals with CSU, greater concentrations of IL-6 were found with CRP; the concentration of IL-6 seems to differentiate between more severe and milder form of the illness, as well as between the active and quiescent stages of urticaria.[11,18,19] IL-6 can be therefore considered as a potent stimulator, serving as an inducer of the most acute-phase proteins, including CRP, and controlling the extent of the local and systemic inflammatory responses. Hence, this cytokine has been proposed as a biomarker of disease activity. Pathogenesis of CSU has been also linked to other IL-1 family cytokines like IL-18. Although there is some evidence that IL-18 levels are elevated in the blood of people with CSU by attracting and stimulating eosinophils in inflamed tissue and setting up a feedback loop that promotes the production of IL-8, its involvement in the disease process still remains unclear.[20-22] It has been postulated that the IL-23/IL-17 axis and tumor necrosis factor alpha (TNF-α) have a similar pathogenic function in CSU as IL-1 family cytokines. Several autoimmune disorders rely heavily on IL-17A-producing CD4 T cells (Th17). The capacity to generate IL-17F, IL-21, IL-22, IL-6, and TNF-α, as well as their dependence on the pro-inflammatory cytokine IL-23, has allowed for their identification.[23] Mast cells along with additional inflammatory cells in the skin are known to generate TNF-α, lending credence to its participation in the etiology of urticarial lesions as IL-17 promotes mast cell proliferation by triggering stem cell factors in keratinocytes.[24] There is a substantial correlation between the levels of IL-17, IL-23, and TNF-α in CSU patients and the disease activity score, suggesting that these cytokines may serve as biomarkers for disease progression.[25] Important in the production of chronic inflammation of the skin, IL-31 is mainly generated by primed Th2 lymphocytes, skin-homing CD45R0 CLA+T cells, and mast cells. Serum IL-31 levels were shown to be higher in CSU patients; however, this was unrelated to illness severity.[26]

### Adipokines

Adipokines are pro-inflammatory or anti-inflammatory cytokines and other proteins (e.g., leptin, adiponectin, resistin, IL-6, and TNF-α1) that are secreted by the adipose tissue. A discrepancy between pro- and anti-inflammatory adipokines has been hypothesized as a source of inflammatory mediators in the development and clinical context of CSU. Lipocalin-2 (LCN2) levels were shown to rise in CSU patients, but adiponectin levels fell.[27] Additional investigations revealed an intriguing correlation between LCN2 concentrations and disease activity, showing that individuals who had elevated LCN2 values were more likely to benefit from AH treatment. These findings together suggest that adipokines' pro- and anti-inflammatory components may be valuable as biomarkers for monitoring disease activity and the efficacy of various treatments in the clinic.

### Vascular endothelial growth factor (VEGF)

VEGF, the most powerful pro-angiogenic mediator, had been implicated to the findings that patient suffering from CSU has new blood vessels.[28,29] Confocal imaging with the lectin Ulex europaeus agglutinin 1 verified the enhanced vascularity and showed that the lesional tissue contained greater numbers of CD31-positive endothelial cells compared to the surrounding normal skin.[30] CSU patients have been shown to have elevated levels of VEGF.[30] Not only can inflammatory cells such as mast cells, eosinophils, and basophils produce VEGF, but they may also be the intended recipients of VEGF.[31]

### Endostatin (ES) and thrombospondin-1 (TSP-1)

Endogenous anti-angiogenic intermediaries, including ES and TSP-1, are mostly responsible for controlling the physiological function of VEGF. ES and TSP-1 concentrations in the serum of CSU patients are found to be elevated, but it was unrelated to the severity.[32] Therefore, these anti-angiogenic mediators may play a role in the etiology of CSU by performing different roles in the inflammatory process. TSP-1 contributes to cutaneous vasodilation and subsequent escape of plasma by destabilizing connections between endothelial cells. The proteolytic fraction of ES has an effect on endothelial cells through nitric oxide production, making it a vasoactive facilitator.[33,34] Consequently, vessel leakage in the skin of patients, which leads to the onset of CSU's clinical symptoms including wheals and flare development, may be influenced by both ES and TSP-1. In spite of these mediators being elevated in CSU patients' blood, but they are not an useful biomarkers since they have no association with disease progression or severity.

### Matrix metalloproteinase-9 (MMP-9)

A few members of MMPs are also found to be elevated in the blood of CSU patients.[35] MMP-9 is upregulated in the peripheral bloodstreams of both adult and pediatric CSU patients, and its influence on the remodeling of tissues is hypothesized to contribute to CSU pathogenesis.[36,37] Inflammatory cells such as macrophages, neutrophils, T cells, and mast cells generate MMP-9.[38,39] There are conflicting reports on the correlation between MMP-9 levels in plasma and disease progression.[37,40] Thus, further research is needed before MMP-9 may be considered as a biomarker in the activity and development of CSU.[41]

### Leukocyte adhesion molecules

Enhanced production of leukocyte adhesion molecules including intercellular adhesion molecule (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin is an effect of VEGF during the angiogenesis process.[42] Elevated levels of soluble ICAM-1 and VCAM-1 in the blood and skin biopsies of CSU patients seem to represent a pro-inflammatory endothelial phenotype, which is commonly employed as an indicator of impaired endothelial

function.[43,44] Increased expression of VCAM-1 and ICAM-1 contributes to the pathophysiology of wheal development by increasing vascular permeability. Patients with CSU have elevated levels of soluble vascular endothelial (sVE)-cadherin, a soluble form of VE-cadherin found between endothelial cells. The severity of CSU is correlated with sVE-cadherin levels, indicating its potential for prognosis. Histamine production contributes to increased sVE-cadherin, which can be mitigated by AH medications.[45]

**D-dimer**

Patients with CSU exhibit elevated levels of factor VIIa, prothrombin fragment 1+2, and D-dimer. This is significant due to the potential role of thrombin in increasing blood vessel permeability and stimulating mast cell degranulation. The concentrations of prothrombin fragment 1+2 and D-dimer are also associated with the prevalence and severity of CSU. However, further research is needed to establish the specificity of increased D-dimer levels in CSU. D-dimer has been proposed as a measure of AH resistance, response to omalizumab treatment, and monitoring of clinical response to cysclosporin.[46-54]

**Mean platelet volume (MPV)**

Due to its correlation with inflammation, MPV has been investigated as a diagnostic measure of active disease and its progression in CSU.[55,56] Patients with a positive ASST had a statistically significant relationship between the CSU severity score and MPV, but those with a negative ASST did not.[57] MPV may be a measure of the activity of the disease and may have a part in the inflammatory processes causing CSU. Unfortunately, subsequent research did not replicate these encouraging findings.[58] Serum CRP concentration was found to be positively correlated with platelet count.[58]

**Vitamin D**

Woo *et al*. examined vitamin D levels as a potential indicator of disease severity in CSU. Their study revealed lower Vitamin D levels in CSU patients compared to healthy controls, with CSU patients exhibiting the lowest levels. A negative correlation was found between CSU activity score and disease progression. Vitamin D supplementation was recommended for improved CSU prognosis, but its use as a biomarker for the condition requires further investigation.[59-61]

**Serotonin (5-hydroxytryptamine, 5-HT)**

The skin 5-HT transporter levels in CU patients with anxiety were substantially greater compared to healthy controls, and it was positively linked to the severity of anxiety, suggesting that the 5-HT transporter might be considered a particular biomarker and an unusual pharmaceutical target.[62-64]

**Platelet-activating factor (PAF)**

Patients with CSU and those with low H1 receptor sensitivity had significantly greater blood PAF levels compared to controls.[65,66] Rupatadine, a dual antagonist of H1-histamine, and PAF receptor, is used in the management of CSU.[67,68]

**Oncostatin M (OSM)**

OSM, a cytokine belonging to the IL-6 family, plays a crucial role in inflammatory reactions and metabolic disorders. T-lymphocytes in the skin release OSM. The physiological effects of OSM are mediated by its receptor gene, OSM receptor (OSMR), which binds to gp130. A study on CSU revealed that OSMR is overexpressed in CSU patients, leading to increased expression of genes involved in the Janus Kinase/Signal Transducers and Activators of Transcription 3 (JAK/STAT3) signaling pathway. Inhibiting OSMR resulted in reduced eosinophils, inflammatory cytokines, and gene expression related to the JAK/STAT3 pathway. OSMR expression was primarily observed in the superficial and middle dermis, as well as surrounding blood vessels.[69-71]

**Periostin**

It was shown that the periostin levels correspond with the severity of CSU. Serum periostin levels were lower in CSU patients than in healthy controls. In addition, individuals with CSU who were classified as having a severe to very severe case of CSU had considerably lower serum periostin levels in comparison to those who had mild to moderate disease. It is of utmost necessity for more research into fibroblast activity in CSU, because it is generally known that fibroblasts are key producers of periostin.[72]

**Serum amyloid A (SAA)**

SAA is an acute-phase protein produced in the liver by monocytes and macrophages.[73] Higher SAA levels were seen in CSU patients, suggesting a correlation between SAA levels and the development of urticaria.[74]

**LIGHT (homologous to lymphotoxins, exhibiting inducible expression, and competing with herpes simplex virus [HSV] glycoprotein D)**

Moderate-to-severe CSU is associated with higher plasma concentrations of soluble LIGHT, a pro-inflammatory protein belonging to the TNF superfamily. LIGHT has been linked to autoimmune diseases and T lymphocyte activation. Exposure to LIGHT can trigger the release of IL-8 and other inflammatory cytokines. The presence of soluble LIGHT suggests its malfunctioning in CSU, impacting the immune system's response. Severe CSU symptoms correlate with higher levels of soluble LIGHT, potentially indicating its involvement in other inflammatory conditions. LIGHT may contribute to the development of severe manifestations in CSU.[75,76]

## CELLULAR BIOMARKERS IN URTICARIA

**Basophils and basophil activation markers**

Grattan demonstrated that a decrease in the overall quantity of basophil in the peripheral blood was associated with the

activity of CSU. Basophils are attracted to skin lesion sites, which may explain why this group found an unfavorable linear connection between basophil counts and Urticaria activity score (UAS) in untreated CSU patients.[77-80] Ye *et al.* found a correlation between CD203c-expressing basophils and clinical indicators of intensity in 82 patients with urticaria. Severe urticaria patients exhibited higher levels of CD203c-expressing basophils compared to those with milder symptoms and healthy controls.[81] CD203c on the basophil membrane confirms cellular stimulation and can serve as a marker for severe CSU, guiding treatment approaches. Histamine production through FcεRI activation has been used as a biomarker to indicate basophil involvement in CSU development.[82-85]

### Mast cell-related biomarkers and mediators

Heparin, stored in mast cell granules, affects vessel permeability and muscle contraction. It is rapidly released on cellular stimulation.[86] Heparin is associated with mast cell collections in urticaria pigmentosa lesions and can cause hemorrhagic complications in severe mast cell proliferation diseases. However, most patients of CSU maintain normal coagulation times.[87,88]

Tryptase is highly expressed in basophils and retained in human mast cells. The active tetrameric form of mature β-tryptase is exclusively secreted by active mast cells. In contrast, the low levels of the monomeric form of tryptase, produced by resting mast cells, represent baseline serum levels (ranging from 1 ng/mL to 11 ng/mL). The increase in serum tryptase levels indicates mast cell degranulation and can be used potentially as a biomarker of CSU.[89-91]

## BIOMARKERS PREDICTING TREATMENT RESPONSE OR RELAPSE

### Antihistamines

Second-generation non-sedating antihistamines are the primary treatment for CSU. Clinical trials have demonstrated that higher doses of antihistamines are more effective and well-tolerated compared to standard doses or combined use of different antihistamines.[92,93]

However, a significant number of CSU patients show inadequate improvement despite updosing of AHs. Factors predicting positive treatment response are not well understood. Refractory CSU has been linked to coexistent morbidities such as atopic asthma, rhinitis and rhinosinusitis, thyroid disease, and hypertension.[94]

Patients with antihistamine resistant CSU exhibit higher levels of complement C5a in the serum, longer duration of wheals, and increased positivity in ASST.[95] Furthermore, patients with CU who test positive for ASST or the basophil activation test (BAT) are less likely to benefit from antihistamine therapy.[96,97] Asero *et al.* recommended that high plasma D-dimer concentrations be used as a biomarker for CSU that has developed resistance to antihistamines. Patients with higher D-dimer levels are more likely to be unresponsive to cetirizine.[98] CSU patients show imbalances in pro- and anti-inflammatory adipokines, with lower levels of adiponectin and higher levels of TNF-α, IL-6, and IL-10 in their serum. Higher blood IL-6 levels are observed in refractory CSU patients. LCN2 correlates with UAS7 and was suggested to be as a biomarker to predict clinical outcomes after antihistamine therapy.[99]

### Omalizumab

The basophil histamine release assay (BHRA) is used to detect autoantibodies against cell-bound IgE or empty FcεRI. Studies showed BHRA-positive individuals typically exhibit a delayed response to omalizumab, with an average response duration of 29 days, whereas BHRA-negative patients respond within 2 days. The ASST was also used to examine this concept. A positive ASST response may be a predictor of a sluggish reaction.[100,101] Slow response to omalizumab treatment is predicted by a positive BHRA, suggesting that omalizumab's effect is mediated via the downregulation of FcεRI production in such individuals. IgG antibodies to unoccupied IgE receptors have been hypothesized to stimulate mast cell mediator release, resulting in a delayed response to omalizumab.

Only basophils, mast cells, and CD34 progenitor cells in the peripheral circulation express the ectoenzyme CD203c (ectonucleotide pyrophosphatase/phosphodiesterase). The specificity and sensitivity of CD203c make it a promising basophil activity indicator.[102,103]

An absence of basophil CD203c-upregulating function in the serum of CSU patients corresponds to an excellent outcome after receiving omalizumab.[103-105] Eighteen of the 41 participants had upregulating activity for CD203c. Only nine of the 18 individuals with CD203c-upregulating activity responded well to omalizumab in terms of symptomatic recovery. Conversely, omalizumab was clinically effective for 20 out of 23 (87%) patients who did not exhibit CD203c-upregulating function ($P$ = 0.02, Fisher's exact test). Age, gender, or the existences of thyroid autoantibodies were not shown to be related to effectiveness. Overall, 71% of CSU patients indicated that omalizumab had benefited them, which is a little higher than the success rate reported in the previous trials.[106-108] The existence of autoantibodies against IgE and/or FcεRIα was shown to indicate a reduced chance of a good response, and the basophil CD203c-upregulating activity might indicate this.

Patients with CSU have been shown to have considerably greater blood IL-31 levels compared to healthy controls.[109] A recent study found that omalizumab dramatically lowered IL-31 levels in individuals with CSU, but a placebo had no such effect. However, IL-31 was not associated with urticaria activity score, wheal score, or itch score.[110] Researchers concluded that further study is needed to determine how

IL-31 contributes to CSU's pathogenesis and the severity of its symptoms.

### Cyclosporin A

Cyclosporin A is the second medication that has demonstrated potential for individuals with CSU resistant to therapy.[111-113] Patients with CSU who have a positive BAT had more favorable responses to cyclosporin therapy.[111] Another research provided more evidence for this observation, reporting that the results of a positive BHRA suggested a greater chance of response in individuals treated with cyclosporin.[114] A positive response to cyclosporin therapy is also predicted by a shorter duration of illness and greater initial severity.[115]

There is a strong inverse connection between baseline D-dimer levels and cyclosporin responsiveness.[54] Therefore, baseline D-dimer can prove to be a helpful index of disease progression in most individuals with CSU and may be used to track the therapeutic effect of cyclosporin.[116]

## PROGNOSTIC BIOMARKERS FOR LONG-TERM OUTCOMES

Various clinical indicators of the degree of severity, responsiveness to therapy, and relapse rates have been shown to be beneficial in CSU research. Patients <19 year old had a far greater rate of improvement than adults, and there is some evidence that suggests a negative correlation between age and illness severity.[117,118] The CU-Q2oL is a disease-specific quality of life instrument, and it seems that older individuals with CSU fare worse on this scale than younger ones. Patients under the age of 40 showed the most impairment in terms of functionality and pruritus, while those above the age of 40 showed the greatest impairment in terms of sleep and eating.[118] Epidemiological investigations have shown that women between the ages of 20 and 59 make up the majority of those diagnosed with CSU and that being a woman seems to be a predictor of an extended period of remission and a worse quality of life.[119,120] Despite the fact that research is lacking, sex hormones may have a role as catalysts in a minority of individuals.[121] The majority of the women in the study did not develop CU until after puberty. Other pregnant women reported their symptoms being worse, and others found that using hormonal birth control made their CU worse.[121] Patients with CSU also had lower amounts of dehydroepiandrosterone sulfate in their blood compared to those who were asymptomatic or in remission.[121,122] A further indicator of illness severity is the length of affliction.[119] Patients experiencing urticaria for less than a year have been shown to benefit more from therapy than those with longer-lasting symptoms.[118] Angioedema and anti-thyroid antibody positivity were also linked to longer illness duration.[123] Patients with CSU who also exhibit simultaneous angioedema have a more severe course and a later remission point than those without.[123]

## BIOMARKERS IN URTICARIA SUBTYPES AND COMORBIDITIES

### Specific biomarkers in physical urticarias

Several studies have identified promising biomarkers associated with different types of physical urticarias. For instance, in cold urticaria, the presence of cryoglobulins and cold-induced histamine release has been observed, providing insights into the disease process.[124] Similarly, heat urticaria is associated with elevated levels of heat-shock proteins and cytokines, indicating the involvement of immune and inflammatory pathways.[125] In pressure urticaria, mast cell activation markers and eosinophil cationic protein have shown relevance, highlighting the role of mast cells and eosinophils in the condition.[126] These specific biomarkers not only aid in accurate diagnosis but also hold the potential for targeted therapeutic interventions.

### Autoimmune urticaria

Autoimmune urticaria, a subset of chronic urticaria, is characterized by dysregulated immune responses leading to recurrent and persistent hives. Extensive research has shed light on the autoimmune mechanisms underlying this condition and identified a range of biomarkers associated with autoimmune urticaria. Autoantibodies targeting specific components of the skin, such as IgE receptors (e.g., anti-FcεRI) and complement proteins (e.g., anti-C1q), have been detected in patients with autoimmune urticaria.[127,128] These autoantibodies serve as crucial biomarkers, indicative of immune dysregulation, and provide insights into the pathogenesis of the disease. In addition to autoantibodies, elevated levels of inflammatory mediators have also been implicated as biomarkers of autoimmune urticaria. For instance, increased histamine release and elevated levels of cytokines (e.g., IL-6, IL-17) and chemokines (e.g., CCL5, CXCL8) have been observed in the affected individuals.[129] These biomarkers reflect the inflammatory processes and immune activation associated with autoimmune urticaria. The identification and validation of these biomarkers not only contribute to the accurate diagnosis of autoimmune urticaria but also hold promise for the development of targeted therapies aimed at modulating the autoimmune response [Table 1].

## FUTURE PERSPECTIVES AND CHALLENGES

Recent years have witnessed a surge in research on the possibilities of identifying novel biomarkers helpful for predicting treatment response and monitoring CSU activity and treatment effectiveness.

Heat shock proteins (Hsps) have recently gained attention for their role in inflammation and the immune system. In patients with CSU, higher levels of Hsp70 and anti-Hsp70 antibodies have been found in the bloodstream. The

**Table 1:** Prospective biomarkers and their role in the disease prediction.

| Biomarkers | Prognosis and severity predictive ability |
|---|---|
| Clinical markers | |
| Age | Young patients have a better prognosis. |
| Sex | Females patients have a poorer prognosis and more severe symptoms. |
| Duration of the disease | Disease duration more than 1 year is linked to a poorer outcome. |
| Presence of Angioedema | Presence of angioedema is associated with a poorer prognosis. |
| Aggravation on NSAID consumption | When NSAID consumption leads to aggravation, a poor prognosis is often demonstrated. |
| Molecular markers | |
| IL-6 | Elevated levels are associated with poor outcome.[11,18,19] |
| IL-18 | Elevated levels are associated with poor outcome.[20] |
| MMP-9 | Elevated levels are associated with poor outcome.[36,37] |
| CRP | Elevated levels are associated with poor outcome.[12,13] |
| D-dimer | Elevated levels are associated with poor outcome.[49-52] |
| F1+2 | Elevated levels are associated with poor outcome.[46,47] |
| Vitamin D | Lower levels are associated with poor outcome.[61] |
| MPV | Higher values are associated with poorer outcome.[57] |
| Basophil counts | Lower counts have been associated with disease progression.[77] |
| CD203c basophils | Increased numbers have been associated with worsening of symptoms.[81] |

NSAID: Nonsteroidal anti-inflammatory drug, IL: Interleukin, MMP-9: Matrix metalloproteinase-9, CRP: C-reactive protein, MPV: Mean platelet volume

exact cause and clinical relevance of this finding in CSU are still unclear. Hsp70 can have both pro-inflammatory and protective effects, while anti-Hsp70 antibodies may stimulate pro-inflammatory processes. Increased plasma concentrations of Hsp70 and anti-Hsp70 antibodies have been observed in CSU patients, regardless of disease severity. Further research is needed to understand the role of Hsp70 and anti-Hsp70 antibodies in CSU and their potential as biomarkers.[130,131]

Environmental stressors in CSU may alter enzyme activity and trigger the generation of pro-inflammatory cytokines, indicating an imbalance in antioxidant defense systems. Nettis *et al*. found that advanced oxidation protein products (AOPPs) are significantly higher in CSU patients, while advanced glycation end products are not elevated, suggesting AOPPs as potential oxidative stress biomarkers.[132]

Epigenetic research in skin diseases like urticaria has shed light on gene regulation processes. Micro-ribonucleic acids (miRNAs) play a crucial role in silencing genes by binding to specific locations on messenger RNA. In CSU, five miRNAs (2355-3p, 4264, 2355-5p, 29c-5p, and 361-3p) were found at significantly higher levels. These miRNAs may serve as biomarkers for chronic autoimmune urticaria, as they target genes involved in various cellular processes, including inflammation and leukocyte response.[133]

In addition, reverse transcription-quantitative polymerase chain reaction was used to verify the expression of upregulated or downregulated miRNA in CSU patients. During the active phase of the illness, miR-125a-5p and CCL17 expression rates were found to be considerably elevated in the serum of these people. Still, they were dramatically reduced during the remission period.[134]

A biomarker for illnesses such as cancer and skin disorders is a single-nucleotide polymorphism, or SNP, which is a variation in a deoxyribonucleic acid sequence that occurs as a result of a change in only one nucleotide at the genomic level.[135] Many genes have been identified to have polymorphisms that are strongly correlated with urticaria and may be used as markers to predict disease severity or the impact of pharmacological therapy.

Mast cell degranulation involves a surge of calcium mediated by the ORAI1 gene. Polymorphisms in ORAI1 (rs12320939 and rs3741596) correlate with CU sensitivity and response to non-sedative H1 receptor antagonists, suggesting their potential for personalized treatment. Polymorphisms in FCER1A are associated with responses to non-sedative H1 receptor antagonists and aspirin-intolerant CU. The HNMT gene polymorphism (939A>G) predicts increased histamine release and aspirin-intolerant chronic urticaria. Polymorphisms in CRP (rs3093059) and C5AR1 (−1,330T/G) are linked to poor responses to specific AH.[136-142]

Gremlin1, involved in tissue differentiation and organ development, promotes inflammation in CSU by activating the transforming growth factor beta pathway. Gremlin1 induces the production of pro-inflammatory factors and can be targeted for personalized therapy in CSU.[143]

## CONCLUSION

While researchers are diligently studying various biomarkers, the quest for a single molecule that can truly aid clinicians in the process of diagnosis and treatment decision-making for conditions like CSU remains ongoing. The significance of thoroughly describing and understanding this complex pathological process is amplified by the expanding array of

therapeutic options entering clinical practice. It becomes increasingly clear that a collaborative, multicentric effort is essential to amass the voluminous data necessary to unravel the intricate pathogenesis of CSU and validate valuable biomarkers for accurate diagnosis and prediction of treatment response. This collaborative endeavor holds the key to unlocking the mysteries of CSU, enabling healthcare professionals to offer more effective and personalized care to the patients of CSU.

### Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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### Conflicts of interest

Dr. Abhishek De, Dr. Aarti Sarda, Dr. Sandipan Dhar are on the editorial board of the Journal.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

1. Godse K, Patil A, De A, Sharma N, Rajagopalan M, Shah B, *et al.* Diagnosis and management of urticaria in Indian settings: Skin allergy research society's guideline-2022. Indian J Dermatol 2022;67:732-43.
2. Kaplan AP, Greaves M. Pathogenesis of chronic urticaria. Clin Exp Allergy 2009;39:777-87.
3. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase--a novel pathomechanism of chronic spontaneous urticaria? PLoS One 2011;6:e14794.
4. Kocatürk E, Maurer M, Metz M, Grattan C. Looking forward to new targeted treatments for chronic spontaneous urticaria. Clin Transl Allergy 2017;7:1.
5. Fiebiger E, Maurer D, Holub H, Reininger B, Hartmann G, Woisetschläger M, *et al.* Serum IgG autoantibodies directed against the alpha chain of Fc ε RI: A selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? J Clin Invest 1995;96:2606-12.
6. Hide M, Francis DM, Grattan CE, Hakimi J, Kochan JP, Greaves MW. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. N Engl J Med 1993;328:1599-604.
7. Kikuchi Y, Fann T, Kaplan AP. Antithyroid antibodies in chronic urticaria and angioedema. J Allergy Clin Immunol 2003;112:218.
8. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, *et al.* IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol 2018;142:876-82.
9. Kolkhir P, André F, Church MK, Maurer M, Metz M. Potential blood biomarkers in chronic spontaneous urticaria. Clin Exp Allergy 2017;47:19-36.
10. Kolkhir P, Altrichter S, Hawro T, Maurer M. C-reactive protein is linked to disease activity, impact, and response to treatment in patients with chronic spontaneous urticaria. Allergy 2018;73:940-8.
11. Kasperska-Zajac A, Sztylc J, Machura E, Jop G. Plasma IL-6 concentration correlates with clinical disease activity and serum C-reactive protein concentration in chronic urticaria patients. Clin Exp Allergy 2011;41:1386-91.
12. Ohtsuka T. Response to oral cyclosporine therapy and high sensitivity-CRP level in chronic idiopathic urticaria. Int J Dermatol 2010;49:579-84.
13. Kolkhir P, Pogorelov D, Olisova O. CRP, D-dimer, fibrinogen and ESR as predictive markers of response to standard doses of levocetirizine in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol 2017;49:189-92.
14. Kasperska-Zajac A, Grzanka A, Machura E, Misiolek M, Mazur B, Jochem J. Increased serum complement C3 and C4 concentrations and their relation to severity of chronic spontaneous urticaria and CRP concentration. J Inflamm (Lond) 2013;10:22.
15. Ritchie RF, Palomaki GE, Neveux LM, Navolotskaia O, Ledue TB, Craig WY. Reference distributions for complement proteins C3 and C4: A practical, simple and clinically relevant approach in a large cohort. J Clin Lab Anal 2004;18:1-8.
16. Klos A, Tenner AJ, Johswich KO, Ager RR, Reis ES, Köhl J. The role of the anaphylatoxins in health and disease. Mol Immunol 2009;46:2753-66.
17. Kikuchi Y, Kaplan AP. A role for C5a in augmenting IgG-dependent histamine release from basophils in chronic urticaria. J Allergy Clin Immunol 2002;109:114-8.
18. Streetz KL, Wüstefeld T, Klein C, Manns MP, Trautwein C. Mediators of inflammation and acute phase response in the liver. Cell Mol Biol (Noisy-le-grand) 2001;47:661-73.
19. Kasperska-Zajac A, Grzanka A, Damasiewicz-Bodzek A. IL-6 Transsignaling in patients with chronic spontaneous urticaria. PLoS One 2015;10:e0145751.
20. Tedeschi A, Lorini M, Suli C, Asero R. Serum interleukin-18 in patients with chronic ordinary urticaria: Association with disease activity. Clin Exp Dermatol 2007;32:568-70.
21. Kurt E, Aktas A, Aksu K, Keren M, Dokumacioglu A, Goss CH, *et al.* Autologous serum skin test response in chronic spontaneous urticaria and respiratory diseases and its relationship with serum interleukin-18 level. Arch Dermatol Res 2011;303:643-9.
22. Puxeddu I, Italiani P, Giungato P, Pratesi F, Panza F, Bartaloni D, *et al.* Free IL-18 and IL-33 cytokines in chronic spontaneous urticaria. Cytokine 2013;61:741-3.
23. Sabag DA, Matanes L, Bejar J, Sheffer H, Barzilai A, Church MK, *et al.* Interleukin-17 is a potential player and treatment target in severe chronic spontaneous urticaria. Clin Exp Allergy 2020;50:799-804.
24. Walsh LJ, Trinchieri G, Waldorf HA, Whitaker D, Murphy GF. Human dermal mast cells contain and release tumor necrosis factor alpha, which induces endothelial leukocyte adhesion molecule 1. Proc Natl Acad Sci 2006;103:9891-6.
25. Atwa MA, Emara AS, Youssef N, Bayoumy NM. Serum concentration of IL-17, IL-23 and TNF-α among patients with chronic spontaneous urticaria: Association with disease activity and autologous serum skin test. J Eur Acad Dermatol Venereol 2014;28:469-74.
26. Chaowattanapanit S, Choonhakarn C, Salao K, Winaikosol K, Julanon N, Wongjirattikarn R, *et al.* Increased serum IL-31 levels in chronic spontaneous urticaria and psoriasis with pruritic symptoms. Heliyon 2020;6:e05621.
27. Trinh HK, Pham DL, Ban GY, Lee HY, Park HS, Ye YM. Altered systemic adipokines in patients with chronic urticaria. Int Arch Allergy Immunol 2016;171:102-10.
28. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995;1:27-31.
29. Kay AB, Ying S, Ardelean E, Mlynek A, Kita H, Clark P, *et al.* Elevations in vascular markers and eosinophils in chronic spontaneous urticarial weals with low-level persistence in uninvolved skin. Br J Dermatol 2014;171:505-11.
30. Tedeschi A, Asero R, Marzano AV, Lorini M, Fanoni D, Berti E, *et al.* Plasma levels and skin-eosinophil-expression of vascular endothelial growth factor in patients with chronic urticaria. Allergy 2009;64:1616-22.
31. Puxeddu I, Ribatti D, Crivellato E, Levi-Schaffer F. Mast cells and eosinophils: A novel link between inflammation and angiogenesis in allergic diseases. J Allergy Clin Immunol 2005;116:531-6.
32. Puxeddu I, Rabl SC, Panza F, Pratesi F, Rocchi V, Del Corso I, *et al.* Endostatin and thrombospondin-1 levels are increased in the sera of patients with chronic spontaneous urticaria. Arch Dermatol Res 2014;306:197-200.
33. Isenberg JS, Ridnour LA, Dimitry J, Frazier WA, Wink DA, Roberts DD. CD47 is necessary for inhibition of nitric oxide-stimulated vascular cell responses by thrombospondin-1. J Biol Chem 2006;281:26069-80.
34. Wenzel D, Schmidt A, Reimann K, Hescheler J, Pfitzer G, Bloch W, *et al.* Endostatin, the proteolytic fragment of collagen XVIII, induces vasorelaxation. Circ Res 2006;98:1203-11.

35. Tedeschi A, Asero R, Lorini M, Marzano AV, Cugno M. Plasma levels of matrix metalloproteinase-9 in chronic urticaria patients correlate with disease severity and C-reactive protein but not with circulating histamine-releasing factors. Clin Exp Allergy 2010;40:875-81.
36. Kolkhir P, Pogorelov D, Olisova O, Maurer M. Comorbidity and pathogenic links of chronic spontaneous urticaria and systemic lupus erythematosus--a systematic review. Clin Exp Allergy 2016;46:275-87.
37. Kessel A, Bishara R, Amital A, Bamberger E, Sabo E, Grushko G, *et al.* Increased plasma levels of matrix metalloproteinase-9 are associated with the severity of chronic urticaria. Clin Exp Allergy 2005;35:221-5.
38. Ram M, Sherer Y, Shoenfeld Y. Matrix metalloproteinase-9 and autoimmune diseases. J Clin Immunol 2006;26:299-307.
39. Belleguic C, Corbel M, Germain N, Léna H, Boichot E, Delaval PH, *et al.* Increased release of matrix metalloproteinase-9 in the plasma of acute severe asthmatic patients. Clin Exp Allergy 2002;32:217-23.
40. Dilek F, Ozceker D, Ozkaya E, Tamay Z, Yazici M, Kesgin S, *et al.* Plasma levels of matrix metalloproteinase-9 in children with chronic spontaneous urticaria. Allergy Asthma Immunol Res 2016;8:522-6.
41. Folci M, Heffler E, Canonica GW, Furlan R, Brunetta E. Cutting edge: Biomarkers for chronic spontaneous urticaria. J Immunol Res 2018;2018:5615109.
42. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246:1306-9.
43. Puxeddu I, Panza F, Pratesi F, Bartaloni D, Rabl SC, Rocchi V, *et al.* CCL5/RANTES, sVCAM-1, and sICAM-1 in chronic spontaneous urticaria. Int Arch Allergy Immunol 2013;162:330-4.
44. Lee KH, Kim JY, Kang DS, Choi YJ, Lee WJ, Ro JY. Increased expression of endothelial cell adhesion molecules due to mediator release from human foreskin mast cells stimulated by autoantibodies in chronic urticaria sera. J Invest Dermatol 2002;118:658-63.
45. Chen T, Lin ZW, Zhang YQ, Chen WF, Zhong YS, Wang Q, *et al.* Submucosal tunneling endoscopic resection vs thoracoscopic enucleation for large submucosal tumors in the esophagus and the esophagogastric junction. J Am Coll Surg 2017;225:806-16.
46. Asero R, Tedeschi A, Riboldi P, Griffini S, Bonanni E, Cugno M. Severe chronic urticaria is associated with elevated plasma levels of D-dimer. Allergy 2008;63:176-80.
47. Asero R, Tedeschi A, Marzano AV, Cugno M. Chronic spontaneous urticaria: Immune system, blood coagulation, and more. Expert Rev Clin Immunol 2016;12:229-31.
48. Relvas M, Silva J, Matos AL, Alves F, Gonçalo M. Concomitant evaluation of d-dimer and C-reactive protein in chronic spontaneous urticaria may show divergent values. Eur Ann Allergy Clin Immunol 2022; doi: 10.23822/EurAnnACI.1764-1489.259. Epub ahead of print.
49. Tedeschi A, Kolkhir P, Asero R, Pogorelov D, Olisova O, Kochergin N, *et al.* Chronic urticaria and coagulation: Pathophysiological and clinical aspects. Allergy 2014;69:683-91.
50. Takeda T, Sakurai Y, Takahagi S, Kato J, Yoshida K, Yoshioka A, *et al.* Increase of coagulation potential in chronic spontaneous urticaria. Allergy 2011;66:428-33.
51. Triwongwaranat D, Kulthanan K, Chularojanamontri L, Pinkaew S. Correlation between plasma D-dimer levels and the severity of patients with chronic urticaria. Asia Pac Allergy 2013;3:100-5.
52. Wang D, Tang H, Shen Y, Wang F, Lin J, Xu J. Activation of the blood coagulation system in patients with chronic spontaneous urticaria. Clin Lab 2015;61:1283-8.
53. Asero R, Marzano AV, Ferrucci S, Cugno M. D-dimer plasma levels parallel the clinical response to omalizumab in patients with severe chronic spontaneous urticaria. Int Arch Allergy Immunol 2017;172:40-4.
54. Asero R. Plasma D-dimer levels and clinical response to ciclosporin in severe chronic spontaneous urticaria. J Allergy Clin Immunol 2015;135:1401-3.
55. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: Associations found in a large population study. J Allergy Clin Immunol 2012;129:1307-13.
56. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm 2019;2019:9213074.
57. Magen E, Mishal J, Zeldin Y, Feldman V, Kidon M, Schlesinger M, *et al.* Increased mean platelet volume and C-reactive protein levels in patients with chronic urticaria with a positive autologous serum skin test. Am J Med Sci 2010;339:504-8.
58. Kasperska-Zając A, Grzanka A, Jarzab J, Misiołek M, Wyszyńska-Chłap M, Kasperski J, *et al.* The association between platelet count and acute phase response in chronic spontaneous urticaria. Biomed Res Int 2014;2014:650913.
59. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, *et al.* Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 2000;164:4443-51.
60. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
61. Woo YR, Jung KE, Koo DW, Lee JS. Vitamin D as a marker for disease severity in chronic urticaria and its possible role in pathogenesis. Ann Dermatol 2015;27:423-30.
62. Thorslund K, Amatya B, Dufva AE, Nordlind K. The expression of serotonin transporter protein correlates with the severity of psoriasis and chronic stress. Arch Dermatol Res 2013;305:99-104.
63. Qin G, Zhang Y, Yao SK. Serotonin transporter and cholecystokinin in diarrhea-predominant irritable bowel syndrome: Associations with abdominal pain, visceral hypersensitivity and psychological performance. World J Clin Cases 2020;8:1632-41.
64. Zabolinejad N, Molkara S, Bakhshodeh B, Ghaffari-Nazari H, Khoshkhui M. The expression of serotonin transporter protein in the skin of patients with chronic spontaneous urticaria and its relation with depression and anxiety. Arch Dermatol Res 2019;311:825-31.
65. Pałgan K, Bartuzi Z. Platelet activating factor in allergies. Int J Immunopathol Pharmacol 2015;28:584-9.
66. Ulambayar B, Yang EM, Cha HY, Shin YS, Park HS, Ye YM. Increased platelet activating factor levels in chronic spontaneous urticaria predicts refractoriness to antihistamine treatment: An observational study. Clin Transl Allergy 2019;9:33.
67. Potter P, Mitha E, Barkai L, Mezei G, Santamaría E, Izquierdo I, *et al.* Rupatadine is effective in the treatment of chronic spontaneous urticaria in children aged 2-11 years. Pediatr Allergy Immunol 2016;27:55-61.
68. Hide M, Suzuki T, Tanaka A, Aoki H. Efficacy and safety of rupatadine in Japanese adult and adolescent patients with chronic spontaneous urticaria: A double-blind, randomized, multicenter, placebo-controlled clinical trial. Allergol Int 2019;68:59-67.
69. Boniface K, Diveu C, Morel F, Pedretti N, Froger J, Ravon E, *et al.* Oncostatin M secreted by skin infiltrating T lymphocytes is a potent keratinocyte activator involved in skin inflammation. J Immunol 2007;178:4615-22.
70. Hong IK, Eun YG, Chung DH, Kwon KH, Kim DY. Association of the Oncostatin M receptor gene polymorphisms with papillary thyroid cancer in the Korean population. Clin Exp Otorhinolaryngol 2011;4:193-8.
71. Luo XY, Liu Q, Yang H, Tan Q, Gan LQ, Ren FL, *et al.* OSMR gene effect on the pathogenesis of chronic autoimmune Urticaria via the JAK/STAT3 pathway. Mol Med 2018;24:28.
72. Bae Y, Izuhara K, Ohta S, Ono J, Hong GU, Ro JY, *et al.* Periostin and interleukin-13 are independently related to chronic spontaneous urticaria. Allergy Asthma Immunol Res 2016;8:457-60.
73. Eklund KK, Niemi K, Kovanen PT. Immune functions of serum amyloid A. Crit Rev Immunol 2012;32:335-48.
74. Lu W, Chen B, Wang C, Yang X, Zhou C. Serum amyloid A levels in acute and chronic urticaria. An Bras Dermatol 2019;94:411-5.
75. Wang J, Fu YX. The role of LIGHT in T cell-mediated immunity. Immunol Res 2004;30:201-14.
76. Lim SG, Suk K, Lee WH. Reverse signaling from LIGHT promotes pro-inflammatory responses in the human monocytic leukemia cell line, THP-1. Cell Immunol 2013;285:10-7.
77. Grattan CE. Basophils in chronic urticaria. J Investig Dermatol Symp Proc 2001;6:139-40.
78. Grattan CE, Dawn G, Gibbs S, Francis DM. Blood basophil numbers in chronic ordinary urticaria and healthy controls: Diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. Clin Exp Allergy 2003;33:337-41.
79. Yamaguchi M, Hirai K, Nakajima K, Ohtoshi T, Takaishi T, Ohta K, *et al.* Dexamethasone inhibits basophil migration. Allergy 1994;49:371-5.
80. Charlesworth EN, Kagey-Sobotka A, Schleimer RP, Norman PS, Lichtenstein LM. Prednisone inhibits the appearance of inflammatory mediators and the influx of eosinophils and basophils associated with the cutaneous late-phase response to allergen. J Immunol 1991;146:671-6.

81. Ye YM, Yang EM, Yoo HS, Shin YS, Kim SH, Park HS. Increased level of basophil CD203c expression predicts severe chronic urticaria. J Korean Med Sci 2014;29:43-7.
82. Greaves MW, Plummer VM, McLaughlan P, Stanworth DR. Serum and cell bound IgE in chronic urticaria. Clin Allergy 1974;4:265-71.
83. Kern F, Lichtenstein LM. Defective histamine release in chronic urticaria. J Clin Invest 1976;57:1369-77.
84. Luquin E, Kaplan AP, Ferrer M. Increased responsiveness of basophils of patients with chronic urticaria to sera but hypo-responsiveness to other stimuli. Clin Exp Allergy 2005;35:456-60.
85. Sabroe R, Francis D, Barr R, Black A, Greaves M. Anti-Fc∈RI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. J Allergy Clin Immunol 1998;102:651-8.
86. Metcalfe DD, Lewis RA, Silbert JE, Rosenberg RD, Wasserman SI, Austen KF. Isolation and characterization of heparin from human lung. J Clin Invest 1979;64:1537-43.
87. Metcalfe DD, Soter NA, Wasserman SI, Austen KF. Identification of sulfated mucopolysaccharides including heparin in the lesional skin of a patient with mastocytosis. J Invest Dermatol 1980;74:210-5.
88. Sucker C, Mansmann G, Steiner S, Gattermann N, Schmitt-Graeff A, Loncar R, *et al.* Fatal bleeding due to a heparin-like anticoagulant in a 37-year-old woman suffering from systemic mastocytosis. Clin Appl Thromb Hemost 2008;14:360-4.
89. Pallaoro M, Fejzo MS, Shayesteh L, Blount JL, Caughey GH. Characterization of genes encoding known and novel human mast cell tryptases on chromosome 16p13.3. J Biol Chem 1999;274:3355-62.
90. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. Immunol Allergy Clin North Am 2006;26:451-63.
91. Sverrild A, van der Sluis S, Kyvik KO, Garvey LH, Porsbjerg C, Backer V, *et al.* Genetic factors account for most of the variation in serum tryptase--a twin study. Ann Allergy Asthma Immunol 2013;111:286-9.
92. Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Treatment of recalcitrant chronic urticaria with nonsedating antihistamines: Is there evidence for updosing? J Investig Allergol Clin Immunol 2013;23:141-4.
93. Sánchez-Borges M, Ansotegui I, Jimenez JM, Rojo MI, Serrano C, Yañez A. Comparative efficacy of non-sedating antihistamine updosing in patients with chronic urticaria. World Allergy Organ J 2014;7:33.
94. Borges MS, Tassinari S, Flores A. Epidemiologic features in patients with antihistamine-resistant chronic urticaria. Rev Alerg Mex 2015;62:279-86.
95. Huilan Z, Bihua L, Runxiang L, Jiayan L, Luyang L, Zhenjie L. Features of antihistamine-resistant chronic urticaria and chronic urticaria during exacerbation. Indian J Dermatol 2015;60:323.
96. Staubach P, Onnen K, Vonend A, Metz M, Siebenhaar F, Tschentscher I, *et al.* Autologous whole blood injections to patients with chronic urticaria and a positive autologous serum skin test: A placebo-controlled trial. Dermatology 2006;212:150-9.
97. Ye YM, Park JW, Kim SH, Ban GY, Kim JH, Shin YS, *et al.* Prognostic factors for chronic spontaneous urticaria: A 6-month prospective observational study. Allergy Asthma Immunol Res 2016;8:115-23.
98. Asero R, Tedeschi A, Cugno M. Heparin and tranexamic Acid therapy may be effective in treatment-resistant chronic urticaria with elevated d-dimer: A pilot study. Int Arch Allergy Immunol 2010;152:384-9.
99. Adamczyk K, Wcislo-Dziadecka D, Zbiciak-Nylec M, Brzezinska-Wcislo L, Brzoza Z. Does adiponectin play a role in the pathogenesis of chronic spontaneous urticaria? Cent Eur J Immunol 2020;45:56-9.
100. Baysak S, Kecici AS, Dogan B. Long-term follow-up effect of omalizumab in chronic spontaneous urticaria and its association with serum C-reactive protein levels. Dermatol Ther 2020;33:e13663.
101. Konstantinou GN, Asero R, Maurer M, Sabroe RA, Schmid-Grendelmeier P, Grattan CE. EAACI/GA2LEN task force consensus report: The autologous serum skin test in urticaria. Allergy 2009;64:1256-68.
102. Bühring HJ, Streble A, Valent P. The basophil-specific ectoenzyme E-NPP3 (CD203c) as a marker for cell activation and allergy diagnosis. Int Arch Allergy Immunol 2004;133:317-29.
103. Palacios T, Stillman L, Borish L, Lawrence M. Lack of basophil CD203c-upregulating activity as an immunological marker to predict response to treatment with omalizumab in patients with symptomatic chronic urticaria. J Allergy Clin Immunol Pract 2016;4:529-30.
104. Yasnowsky K, Dreskin S, Efaw B, Schoen D, Vedanthan PK, Alam R, *et al.* Chronic urticaria sera increase basophil CD203c expression. J Allergy Clin Immunol 2006;117:1430-4.
105. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, *et al.* Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. J Allergy Clin Immunol 2013;132:101-9.
106. Beck LA, Marcotte GV, MacGlashan D Jr., Togias A, Saini S. Omalizumab-induced reductions in mast cell FcεRI expression and function. J Allergy Clin Immunol 2004;114:527-30.
107. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis. J Dermatol Sci 2014;73:57-62.
108. MacGlashan DW, Bochner BS, Adelman DC, Jardieu PM, Togias A, McKenzie-White J, *et al.* Down-regulation of FcεRI expression on human basophils during *in vivo* treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
109. Raap U, Wieczorek D, Gehring M, Pauls I, Ständer S, Kapp A, *et al.* Increased levels of serum IL-31 in chronic spontaneous urticaria. Exp Dermatol 2010;19:464-6.
110. Altrichter S, Hawro T, Hänel K, Czaja K, Lüscher B, Maurer M, *et al.* Successful omalizumab treatment in chronic spontaneous urticaria is associated with lowering of serum IL-31 levels. J Eur Acad Dermatol Venereol 2016;30:454-5.
111. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, *et al.* Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. Br J Dermatol 2000;143:365-72.
112. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P, Neo-I-30 Study Group. Cyclosporine in chronic idiopathic urticaria: A double-blind, randomized, placebo-controlled trial. J Am Acad Dermatol 2006;55:705-9.
113. Doshi DR, Weinberger MM. Experience with cyclosporine in children with chronic idiopathic urticaria. Pediatr Dermatol 2009;26:409-13.
114. Iqbal K, Bhargava K, Skov PS, Falkencrone S, Grattan CE. A positive serum basophil histamine release assay is a marker for ciclosporin-responsiveness in patients with chronic spontaneous urticaria. Clin Transl Allergy 2012;2:19.
115. Hollander SM, Joo SS, Wedner HJ. Factors that predict the success of cyclosporine treatment for chronic urticaria. Ann Allergy Asthma Immunol 2011;107:523-8.
116. Baek YS, Jeon J, Kim JH, Oh CH. Severity of acute and chronic urticaria correlates with D-dimer level, but not C-reactive protein or total IgE. Clin Exp Dermatol 2014;39:795-800.
117. Hiragun M, Hiragun T, Mihara S, Akita T, Tanaka J, Hide M. Prognosis of chronic spontaneous urticaria in 117 patients not controlled by a standard dose of antihistamine. Allergy 2013;68:229-35.
118. Chuamanochan M, Kulthanan K, Tuchinda P, Chularojanamontri L, Nuchkull P. Clinical features of chronic urticaria in aging population. Asian Pac J Allergy Immunol 2016;34:201-5.
119. Gregoriou S, Rigopoulos D, Katsambas A, Katsarou A, Papaioannou D, Gkouvi A, *et al.* Etiologic aspects and prognostic factors of patients with chronic urticaria: Nonrandomized, prospective, descriptive study. J Cutan Med Surg 2009;13:198-203.
120. Młynek A, Magerl M, Hanna M, Lhachimi S, Baiardini I, Canonica GW, *et al.* The German version of the Chronic Urticaria Quality-of-Life Questionnaire: Factor analysis, validation, and initial clinical findings. Allergy 2009;64:927-36.
121. Amsler E, Augey F, Soria A, Boccon-Gibod I, Doutre MS, Mathelier-Fusade P, *et al.* Chronic urticaria and hormones: Is there a link? J Eur Acad Dermatol Venereol 2016;30:1527-30.
122. Kasperska-Zajac A, Brzoza Z, Rogala B. Lower serum concentration of dehydroepiandrosterone sulphate in patients suffering from chronic idiopathic urticaria. Allergy 2006;61:1489-90.
123. Kasperska-Zajac A, Brzoza Z, Rogala B. Lower serum dehydroepiandrosterone sulphate concentration in chronic idiopathic urticaria: A secondary transient phenomenon? Br J Dermatol 2008;159:743-4.
124. Maltseva N, Borzova E, Fomina D, Bizjak M, Terhorst-Molawi D, Košnik M, *et al.* Cold urticaria - What we know and what we do not know. Allergy 2021;76:1077-94.
125. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, *et al.* Clinical and laboratory parameters in predicting chronic urticaria duration: A prospective study of 139 patients. Allergy 2004;59:869-73.
126. Ensina LF, Cusato-Ensina AP, Cardona R. Advances in the pathogenesis representing definite outcomes in chronic urticaria. Curr Opin Allergy Clin Immunol 2019;19:193-7.

127. Kroegel C, Matthys H. Platelet-activating factor-induced human eosinophil activation. Generation and release of cyclo-oxygenase metabolites in human blood eosinophils from asthmatics. Immunology 1993;78:279-85.
128. Sabroe RA, Fiebiger E, Francis DM, Maurer D, Seed PT, Grattan CE, *et al.* Classification of anti-FcepsilonRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. J Allergy Clin Immunol 2002;110:492-9.
129. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: What we know and what we do not know. J Allergy Clin Immunol 2017;139:1772-81.e1.
130. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy 2017;72:519-33.
131. Kasperska-Zając A, Damasiewicz-Bodzek A, Bieniek K, Skrzypulec-Frankel A, Tyrpien-Golder K, Grzanka A. Elevated circulating heat shock protein 70 and its antibody concentrations in chronic spontaneous urticaria. Int J Immunopathol Pharmacol 2018;31:0394632017750440.
132. Nettis E, Distaso M, Saitta S, Casciaro M, Cristani M, Saija A, *et al.* Involvement of new oxidative stress markers in chronic spontaneous urticaria. Postepy Dermatol Alergol 2017;34:448-52.
133. Lin CE, Kaptein JS, Sheikh J. Differential expression of microRNAs and their possible roles in patients with chronic idiopathic urticaria and active hives. Allergy Rhinol (Providence) 2017;8:67-80.
134. Zhang L, Qi R, Yang Y, Gao X, Chen H, Xiao T. Serum miR-125a-5p and CCL17 upregulated in chronic spontaneous urticaria and correlated with treatment response. Acta Derm Venereol 2019;99:571-8.
135. Gong Y, Zhao W, Jia Q, Dai J, Chen N, Chen Y, *et al.* IKBKB rs2272736 is associated with gastric cancer survival. Pharmgenomics Pers Med 2020;13:345-52.
136. Cao H, Yang S, Yu X, Xi M. Correlation between heparanase gene polymorphism and susceptibility to endometrial cancer. Mol Genet Genomic Med 2020;8:e1257.
137. Li J, Guo A, Chen W, Bin L, He Y, Zhu W, *et al.* Association of ORAI1 gene polymorphisms with chronic spontaneous urticaria and the efficacy of the non sedating H1 antihistamine desloratadine. J Allergy Clin Immunol 2017;139:1386-8e9.
138. Honda T, Nomura T, Kabashima K. Advances in atopic dermatitis and urticarial in 2016. J Allergy Clin Immunol 2017;140:369-76.
139. Bae JS, Kim SH, Ye YM, Yoon HJ, Suh CH, Nahm DH, *et al.* Significant association of FcepsilonRIalpha promoter polymorphisms with aspirin-intolerant chronic urticaria. J Allergy Clin Immunol 2007;119:449-56.
140. Kim SH, Kang YM, Kim SH, Cho BY, Ye YM, Hur GY, *et al.* Histamine N-methyltransferase 939A>G polymorphism affects mRNA stability in patients with acetylsalicylic acid-intolerant chronic urticaria. Allergy 2009;64:213-21.
141. Yan S, Chen W, Peng C, Zhu W, Chen M, Zhang J, *et al.* C-reactive protein (CRP) rs3093059C predicts poor mizolastine response in chronic spontaneous urticaria patients with elevated serum CRP level. Exp Dermatol 2019;28:240-6.
142. Yan S, Chen W, Wen S, Zhu W, Guo A, Chen X, *et al.* Influence of component 5a receptor 1 (C5AR1) −1330T/G polymorphism on non sedating H1-antihistamines therapy in Chinese patients with chronic spontaneous urticaria. J Dermatol Sci 2014;76:240-5.
143. Qu S, Liu Z, Wang B. Down-regulation of Gremlin1 inhibits inflammatory response and vascular permeability in chronic idiopathic urticaria through suppression of TGF-β signaling pathway. Gene 2020;756:144916.

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