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The effect of psychological stress on c-reactive protein and peripheral blood cells count in chronic idiopathic urticaria

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ABSTRACT

Background: Chronic idiopathic urticaria (CIU) is the most common type of chronic urticaria. Studies suggested that psychosocial factors have a role in the development and exacerbation of CIU. This study was carried out to investigate the correlation of psychological stress, C-reactive protein (CRP) and peripheral blood counts with CIU.

Methods: This was a case-control study. The study participants were patients aged 14 to 65 years old at the Dermatology outpatient clinic in Sanglah Hospital. The case group consisted of CIU patients and the control group consisted of acute urticaria patients. A structured interview based on Holmes-Rahe stress scale was used to assess the psychological stress level. Blood samples were also collected from the subjects, to obtain the blood cells count and CRP level. The severity was assessed by using urticaria activity score (UAS).

Results: Fifty two patients participated in this study; 25 patients with CIU and 27 patients with acute urticaria. Stress was found to be a significant risk factor (OR = 5.04; CI 95%: 1.5-16.4). There was a positive correlation between stress index and the severity of CIU lesion ($R^2 = 0.086$). The mean basophil count of case group was $0.21\times10^3\pm0.15\times10^3/\mu L$, lower than the control group ($p < 0.05$). While mean stress index and mean blood level CRP of the case group were 146.6±19.1% and 5.5±3.25 mg/dL, respectively. The differences between case group and control group were found to be significant ($p < 0.05$).

Conclusion: Psychological stress was a risk factor of CIU, which gave risk for having CIU 5.04 times higher than the control group. The mean basophil count is lower in CIU, while the mean stress index and CRP level are higher in CIU.

Keywords: chronic idiopathic urticaria, psychological stress, CRP, peripheral blood cells count.

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INTRODUCTION

Urticaria is a vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated erythematous papules or plaques (wheals) and often accompanied by severe pruritus.[1] The triggers of urticaria are unknown in around half of all cases.[1] One of the identified triggers is allergic reactions towards food and/or environmental factors such as pollen and dust mites. This reaction is commonly based on type I hypersensitivity reaction. Most cases of urticaria are self-limited and of short duration.[2] Almost 90% of the population has experienced urticaria with or without pruritus.[2] The pathogenesis of chronic urticaria (CU) is not completely understood. However, mast cell degranulation and histamine release are thought to play a central role. Chronic idiopathic urticaria (CIU) is the most common type of chronic urticaria. In 7 out of 10 cases of CU, the cause or trigger cannot be identified; therefore, it is diagnosed as CIU. In patients with CIU, there are no specific triggers or any other causes that activate the mast cells can be identified.[1-3]

Acute urticaria is defined as the presence of evanescent wheals which completely resolve within six weeks while chronic urticaria is defined as the presence of evanescent wheals which persist for more than six weeks.[3] An urticaria that is recurrent and lasts more than 6 weeks is categorized as chronic urticaria, and if the triggering factor cannot be identified, it is considered as a chronic idiopathic urticaria.[3-5] In CIU, the cause is generally difficult to identify and it is often recurrent, hence it will lower the patients' quality of life. Many factors are related to CIU; including drugs, foods, infections, systemic diseases, inhalant allergens, contact allergens, insects bites, physical agents, psychological stress, and genetic factors.[6] Those factors induce urticaria through either immunologic or non immunologic mechanism. The immunopathogenesis of urticaria is type I hypersensitivity reaction, where allergen (antigen) which enters the body will attach to immunoglobulin E (IgE) on the surface of mast cell through a specific receptor which will trigger the mast cell degranulation and release various inflammatory mediators.[6,7] There are two types of mediators released; preformed (secretory granule-associated) and newly synthesized mediators after cellular activation including the

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biogenic amine and macromolecules.[8] Included in preformed mediators are histamine, proteoglycans (heparin, chondroitin sulfate E), serotonin, proteases (such as tryptase, chymase, β-hexosaminidase, β-glucuronidase, β-D-galactosidase, cathepsin G, and carboxypeptidase), some cytokines (tumor necrosis factor [TNF]-α), and basic fibroblast growth factor.[8] The major mediator is histamine, while the other mediators are the slow reacting substance of anaphylaxis (SRS-A), serotonin, bradykinin, and prostalglandin.[8] Their concert of action will cause an increase in vascular permeability leading to vasodilatation and extravasations of blood components to surrounding tissue resulted in clinical manifestation. Non-immunological factors, which directly induce histamine release from mast cell and basophil, are chemical agents, several drugs (such as morphine and codeine), bacterial toxins, physical traumas, and also psychological stress.[8]

Psychological stress activates hypothalamus to release corticotropin releasing hormone (CRH) through hypothalamic-pituitary-adrenal (HPA) axis. It is known that CRH receptor is found on the surface of mast cells, which are located close to the free nerve ending, therefore the released CRH binds immediately to mast cell and triggers degranulation.[9] Stress also activates neuropeptide system, particularly P substance and vasoactive intestinal polypeptide (VIP), both neuropeptides are a potent trigger of mast cell degranulation. Many previous studies state that psychological stress plays role chronic urticaria.[9,10] Hunkin's and Ben-Shohan's studies found that psychological stress activated basophil migration from peripheral blood to the affected tissue in chronic urticaria, thus reducing the absolute number of basophil due to its migration to the urticaria lesion in the skin.[11] Several other studies also proved that stress is linked with the function of basophil, eosinophil, and neutrophil in the peripheral blood.[12,13] Likewise, stress also influenced C-reactive protein (CRP), an inflammation mediator, therefore stress could further exaggerate and induce inflammation throughout many organs.[14]

Table 1 **Characteristic of the study subjects**

	Case Group n = 25 (48.1 %)	Control Group n = 27 (51.9 %)	Total
Sex			
Male (%)	13 (25.0)	10 (19.2)	23 (44.2)
Female (%)	12 (23.1)	17 (32.7)	29 (55.8)
Age			
14 – 20 (%)	9 (17.3)	7 (13.5)	16 (30.8)
>20 – 35 (%)	12 (23.1)	15 (28.8)	27 (51.9)
> 35 (%)	4 (7.7)	5 (9.6)	9 (17.3)
Lesion location (dominant)			
Face (%)	3 (5.8)	4 (7.7)	7 (13.5)
Arm/Body (%)	2 (3.8)	5 (9.6)	7 (13.5)
Body (%)	4 (7.7)	6 (11.5)	10 (19.2)
Mixed (%)	16 (30.8)	12 (23.1)	28 (53.8)
Clinical pattern			
Gutatta (%)	6 (11.5)	7 (13.5)	13 (25.0)
Geographic (%)	16 (30.8)	13 (25.0)	29 (55.8)
Linear pattern (%)	3 (5.8)	7 (13.5)	10 (19.2)
Severity (Total lesion)			
Mild (%)	7 (13.5)	8 (15.4)	15 (28.9)
Moderate (%)	12 (23.1)	15 (28.8)	27 (51.9)
Severe (%)	6 (11.5)	4 (7.7)	10 (19.2)

METHODS

This was an analytic case-control study about the psychological stress and its correlation with acute urticaria and CIU, in relation to CRP and peripheral blood cells profile. The case group was patients with CIU and control group was patients with acute urticaria. Study subjects were patients aged 14 to 65 years old, in the outpatient clinic of Dermatology Department, Sanglah Hospital Denpasar from January 2014 to December 2015, who had not received any medical treatments. Urticaria was diagnosed based on specific clinical features. The urticaria was classified according to its pattern; guttatta, geographic (confluence), and linear. The severity of urticaria was assessed by using urticaria activity score (UAS) from Kiran V Gose, which categorized it into 3 different caterogies; 1 (mild), < 20 urticaria lesions; 2 (moderate), 20 – 50 urticaria lesions; 3 (intense/severe), if there is a confluence lesion.[15]

Stress index scale was determined by in depth interview based on Holmes and Rahe questionnaire which consists of 43 questions of life events during the last 3 to 6 months, i.e. the death of a spouse has the highest score (100) and minor violation of the law has the lowest score (11). If the total score is ≥ 150, it suggests that the individual is prone to psychological stress with clinical manifestation.[7,8,9] Informed consent was given before the patients participated in this study. Peripheral blood samples were obtained from the cubital vein in the morning for measuring CRP and blood cells count.

Statistical analysis

Chi square test was used to see if there is a correlation between two variables. To determine the mean differences between two groups, student T test was used. Linear regression analysis was used to determine the correlation between two variables.

Table 2 Correlation of several variables with acute urticaria and CIU

	Case Group n = 25 (48.1 %)	Control Group n = 27 (51.9 %)	p value
Family history			
Yes (%)	10 (19.2)	6 (11.5)	p > 0.05
No (%)	15 (28.8)	21 (40.4)	
Atopic history			
Yes (%)	6 (11.5)	8 (15.4)	p > 0.05
No (%)	19 (36.5)	19 (36.5)	
Environmental factors			
Yes (%)	9 (17.3)	18 (34.6)	p < 0.05*
No (%)	16 (36.5)	9 (17.3)	
Food allergy			
Yes (%)	7 (13.5)	17 (32.7)	p > 0.05
No (%)	18 (34.6)	10 (19.2)	
Stress level			
Stress index≥ 150 (%)	17 (32.7)	8 (15.4)	OR = 5.04
Stress index< 150 (%)	8 (15.4)	19 (36.5)	CI 95 % (1.5-16.4)
Mean quantitative CRP (mg/dL)	5.5 ± 3.25	3.87 ± 1.54	p < 0.05*
Mean stress index	146.6 ± 19.14	89.6 ± 43.42	p < 0.05*
Mean peripheral blood cells count			
Eosinophil (10^3/µL)	1.76 ± 0.12	1.16 ± 0.24	p > 0.05
Basophil (10^3/µL)	0.21 ± 0.15	0.75 ± 0.12	p < 0.05*
Neutrophil (10^3/µL)	5.15 ± 0.14	4.95 ± 0.21	p > 0.05

*statistically significant

RESULTS

During 6 months of the study period, there were 52 patients who participated in this study, which consisted of 25 patients (48.1%) with CIU as the case group and 27 patients (51.9%) with acute urticaria as the control group. The general characteristic of the patients is described in table 1.

In Table 1, it is showed that out of 52 study subjects, 25 (48.1%) had CIU; 13 were males (25.0%) and 12 were females (23.1%). The most common age group was 20 to 35 years old with 27 subjects (51.9%). The most frequent location of the urticaria was all over the body with 28 subjects (53.8%). The geographic pattern was the most observed pattern; 29 out of 52 subjects (55.8%). According to the urticaria severity, there were 15 subjects (28.9%) with mild cases, 27 subjects (51.9%) with moderate cases, and 10 subjects (19.2%) with severe cases (Table 1).

In table 2, several urticaria risk factors are shown. The family history of urticaria was described as parents and/or siblings with urticaria. In this study, 16 patients (30.8%) have a family history and as much as 14 cases (26.9%) have an atopic history (Table 2). Food allergy was found in 24 patients (46.2%), but the percentage in the control group is higher than the case group (Table 2). Environmental factors in this study were house dust, pets dust, and dust exposure related to occupation, such as farmer, factory worker, and so on. Analysis showed that there was a correlation between the environmental factors and acute urticaria ($p < 0.05$) (Table 2). There were no statistically significant correlations between CIU and the other factos.

The mean CRP level in case group was 5.5 ± 3.25 mg/dL, higher when compared to the control group (3.87 ± 1.54 mg/dL) (Table 2). Mean stress index was also higher in case group (146.6 ± 19.1%) when compared to the control group (89.6 ± 5.3%). The differences were found to be statistically significant ($p < 0.05$). For the peripheral blood count, the mean basophil count in case group is $0.21\times10^3 \pm 0.15\times10^3$/µL, which is lower when compared to mean basophil count in the control group ($0.21\times10^3 \pm 0.15\times10^3$/µL) (Table 2). This difference was statistically significant, unlike the differences of mean eosinophil count and neutrophil count between the two groups. Analysis showed that psychological stress was a risk factor of CIU, which gave risk for having CIU 5.04 times higher than the control group (OR = 5.04; CI 95%; 1.5 – 16.4) (Table 2).

On the correlation test between the levels of CRP with the stress index, CRP with CIU severity and correlation between stress and severity index with CIU scatter plot shown in the picture below.

DISCUSSION

Chronic idiopathic urticaria is the most common subtype of urticaria. The exact prevalence of CIU is difficult to determine. A study in Thailand reported that CIU accounted for about 75% of all CU cases.[1] Greater awareness of CIU may be attributable to an increased number of studies and a more accurate identification of CIU patients. Immunologic or allergic reactions, infections, systemic diseases, drugs and psychological stress have been identified as risk factors. The pathogenesis of CIU is not fully understood yet.[1,2]

According to Hans Selye, "the father of stress," stress is a non specific response of the body to any demand for change. The symptoms of stress complained by the patient are predominated by somatic (physical) symptoms, but can also be followed by psychological symptoms. Not all stress

are negative (distress), some are positive which described as eustress.[17] Since the era of Selye, the research about the stress hormones secreted by organs in the human body when having biological stress had grown rapidly. A broader and more acceptable concept states that emotional, physical, biological, or social stressors (source of stress) will lead to a cellular stress. This condition will be perceived by the cerebral cortex as stress-perception, and then it will be sent to the limbic system in the hypothalamus. This system will react by releasing stress hormones, among others, corticotrophin releasing hormone (CRH). Subsequently, this hormone will cause mast cell degranulation through the CRH receptor on the surface of the mast cell. This pathway is known as HPA axis. Norepinephrine, another neuropeptide, also increases under stressful condition, which will directly affect the non-immunologic mechanism of mast cell degranulation.[9,18]

Among other characteristics, environmental factor was the only one that had a correlation. There is a trend that subjects in the control group are affected more by the environmental factors when compared to subjects with CIU. In acute urticaria, environtmental factors (which are allergens) might induce the histamine release from mast cells through an allergic reaction, particularly type 1 reaction. The patients must have been sensitized to the specific environmental factor and contact with the allergen induces this reaction. There are also patients who did not come in contact with the environtmental factors. It is possible that the inducing factors in this group of patients must be another allergen not including in the definition of environmental factors or any other allergens beside house dust, pets dust, and dust exposure related to work.

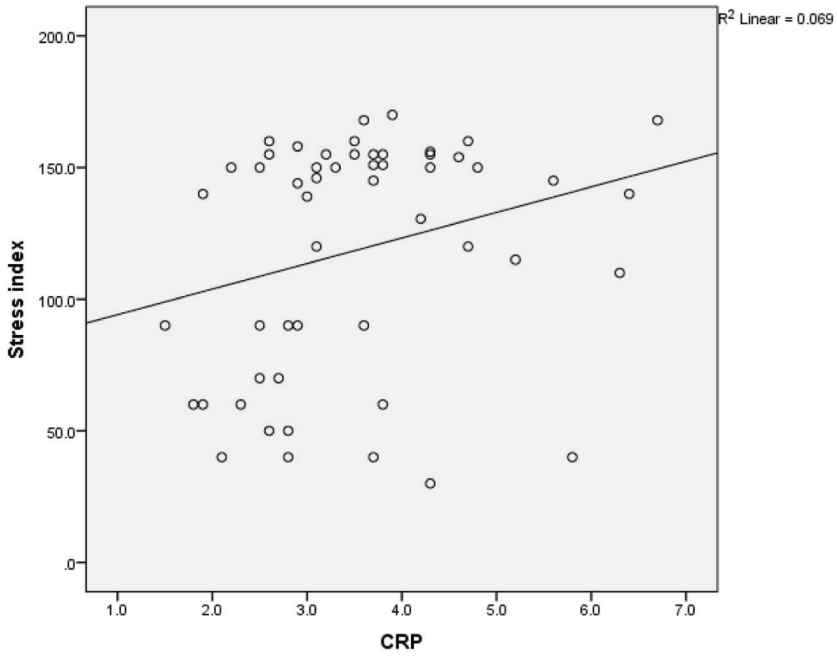

Figure 1 Scatter plot of CRP and stress index

This study found that the level of blood CRP and stress index was higher in the study group when compared to control group, and this difference is statistically significant ($p < 0.05$). C-reactive protein is predominantly synthesized in the liver in response to pro-inflammatory cytokines, especially IL-6, IL-1β, and TNF. It has been observed that CRP level is increased in CU, along with some other cytokines.[8,18] As for stress, it has been proposed that psychological stress has a role in CIU. This finding was also observed in several other researches.[5,7,9,10]

It has been observed that the basophil count in peripheral blood of those with CU is low. The same finding was observed in this study, which was not observed in the other cells (eosinophil and neutrophil). The role of basophils in the CU pathogenesis is unclear. There are several similarities between basophil and mast cell granules; both are metachromatic and containing heparin and histamine. Like mast cells, certain antigens can induce basophils to release its granule contents which will elicit an allergic reaction, causing urticaria.[19] Basopenia is well documented in CU and basophil numbers are inversely related to urticaria severity. A possible explanation of this basopenia is that the basophils migrate to and remain in the tissue, decreasing the peripheral basophil number.[11] Basopenia has also been linked with disease activity and the serum histamine-releasing activity (HRA). However, the number of basophils recruited is similar between the lesional and non-lesional skin site, whether the patients are presenting or lacking HRA.[20] The data on the correlation between serum HRA and serum immunoreactivity to FcεRIα are conflicting. It has been showed that sera (which contain HRA) from patients with CU, which shows a positive autologous skin serum test (ASST), induced basophil histamin release when administered. In the other hand, in patients with upregulated CD63 and CD203c basophils (markers of basophil activity), there is a lack of association between serum HRA and serum immunoreactivity to FcεRIα.[20] It has been proposed that autoimmune reaction may also have a role since a specific IgG antibody directed to the alpha subunit of IgE receptor (FcεRIα) might activate the receptor and induce histamine release in patients with CU.[8] Another explanation is that there is imbalances in the molecules regulate the histamin release of basophils, including spleen tyrose kinase (Syk) and src homology 2 (SH2) containing inositol phosphatases (SHIP-1 and SHIP-2).[8]

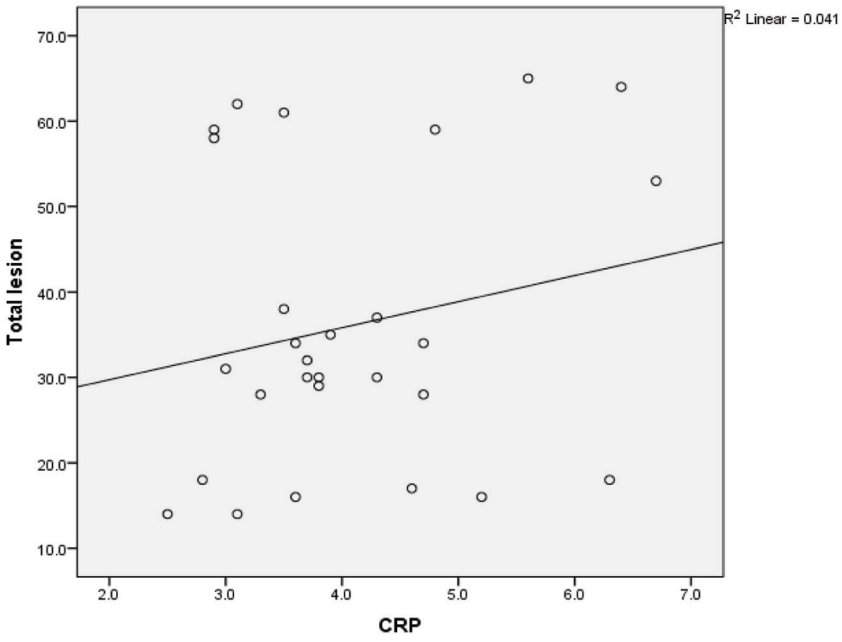

Figure2 Scatter plot of CRP level and Severity (total lesion) of urticaria

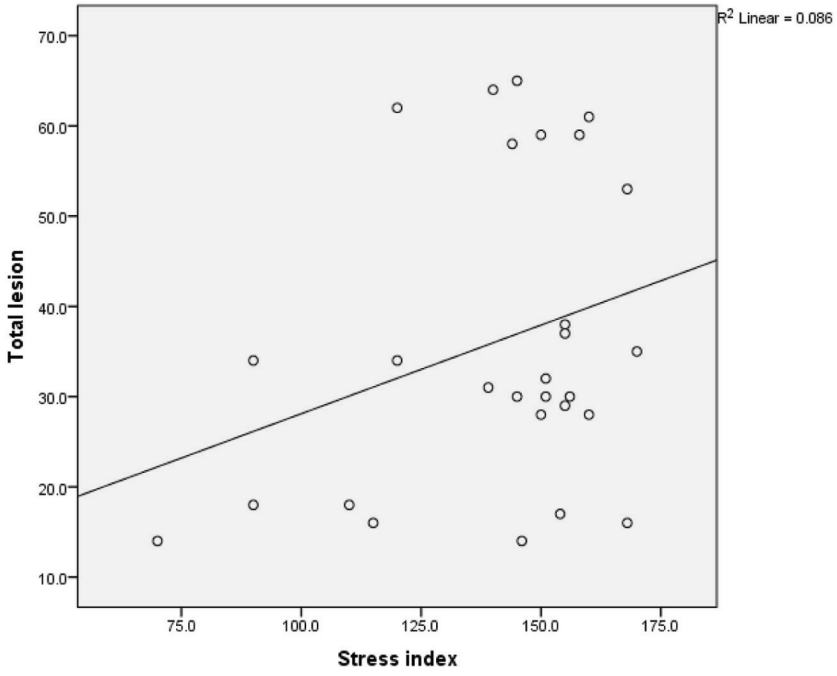

Figure 3 Scatter plot of stress index and urticaria severity (total lesion)

The correlation of stress factor with CIU severity

Psychological stress may play role in CIU recurrence. This study found that psychological stress was a risk factor of CIU, which give risk for having CIU 5.4 times higher than the control group (Table 4). The mean stress level was also higher in case group when compared to control group (Table 2). Several other studies also showed that there is a significant relationship between stress index and severity of CIU. This finding is also consistent with previous studies, that human body gives physiologic responses in a stressful condition. The explanation of this finding is in the stress pathways. Stress will induce hypothalamus to release corticotrophin releasing hormone (CRH) and this hormone can directly affect mast cell, inducing mast cell degranulation.[21] Stress condition may also activate the cutaneous peripheral equivalent of HPA axis. Along with sensory nerve activation, these conditions will induce the local mast cells degranulation because anatomically mast cells are located closely to sensory nerve endings. The nerve cells produce molecules such as substance P, neurotensin, and nerve growth factor that could induce mast cells degranulation.[21] This study is consistent with the previous study by Staubach, in which this study found a positive correlation between the stress level with the CIU severity (total lesion) as shown in the scatter plot (figure 3).[22,23]

The correlation of stress and C–reactive protein level

This study found that there was a positive correlation between stress index and CRP level (R^2 = 0.069) as shown in scatter plot (Figure 1). Mast cells degranulation does not only release histamine, but also pro-inflammatory cytokines. In addition, it has been shown that psychological stress, depression, and other negative emotions will induce the secretion of IL-6, which is produced by both mast cells and basophils.[19,21] A study in mice showed that the stress-induced IL-6 is less observed in mast cells-deficient mice, suggesting that stress-induced IL-6 secretion is mast cell-dependent.[24] These inflammatory mediators will then induce an acute-phase response, triggering inflammation and the production of CRP, increasing the blood CRP level.

The correlation of CIU severity with CRP level

Other than common stress hormones, Konduru also proved that CRP is also a stress biomarker which influences the immune cells. Another research by Aleem *et al.* also discovered that CRP plays role in mast cell degranulation and the occurrence of chronic idiopathic urticaria.[25] It has been demonstrated that circulating CRP concentration is increased in CU and that both CRP and IL-6 concentrations correlate with the disease severity.[19] As an acute phase reactant, CRP may enhance the inflammation process of urticaria and subsequently increase the disease activity in CU. This study found that the severity of CIU (total lesion) had a positive correlation with the increase of CRP level, R^2 = 0.041 (Figure 2), consistent with the previous studies.

CONCLUSIONS

In conclusion, results of this study reveal that psychological stress was found in 32.6% of patients with CIU and environmental factor influenced CIU. The number of basophils was lower in CIU than in acute urticaria, but no difference was detected in eosinophil and neutrophil. Possibly this is because the basophils migrated into the skin tissue. CRP level had a positive correlation with the stress level and CIU severity. Correlation analysis on stress index and acute urticaria (total urticaria lesion) were found to be strongly correlated $r^2 = 0.36$ ($p < 0.05$) which means that the higher the stress is, the more lesions appear.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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