

Could peripheral Eosinopenia be Used as a Prognostic Biomarker for Chronic Spontaneous Urticaria?

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ABSTRACT

Background: Chronic spontaneous urticaria (CSU) is a chronic, sometimes debilitating skin disorder characterized by the appearance of wheals, angioedema, or both for a period of more than 6 weeks. Many biomarkers were explored for severity evaluation such as d dimer and C Reactive Protein.

Objectives: The aim of the current study is to assess the usefulness of peripheral eosinopenia as a valuable and an applicable biomarker for CSU severity.

Patients and methods: A case control study was conducted on 60 CSU patients. Patients were divided into 30 patients with mild UAS7 score <15 representing the controls and 30 patients with severe UAS7 score >28 representing the cases. Eosinophils count and other variables were compared.

Results: Severe cases demonstrated significantly higher age (median 34 vs. 29 years, $P = 0.043$), CRP (14 vs. 2 mg/L, $P < 0.001$) and positive ASST (56.7% vs. 23.3%, $P = 0.008$). In contrast, severe cases demonstrated significantly lower eosinophilic count (median 21 vs. 123 cell/mm³, $P < 0.001$), basophilic count (median 5 vs. 25 cell/mm³, $P < 0.001$), and total IgE (median 93 vs. 221.5 IU/ml, $P < 0.001$). The eosinophilic count showed a significant-excellent AUC of 0.954. The best cutoff point was ≤ 70 , at which sensitivity and specificity were 96.7% and 86.7%, respectively.

Conclusion: Peripheral eosinophils are significantly lower count in severe urticarial patients (P value <0.001) and this could be used as a simple and accessible tool for monitoring urticaria activity.

Keywords: Eosinopenia, chronic spontaneous urticaria, biomarker, case control study, Benha University.

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a chronic, sometimes debilitating skin disorder, characterized by the appearance of wheals, angioedema, or both for a period more than 6 weeks⁽¹⁾.

Although the advance in understanding the pathophysiology and classification of chronic spontaneous urticaria, there are still many patients who do not respond efficiently to treatment, so their quality of life was greatly impaired⁽²⁾.

Many urticaria scores and questionnaires were developed to ensure optimum patient evaluation such as Urticaria Activity Score (UAS7), Chronic Urticaria Quality of Life Questionnaire (CU - Q2 OL) and some of them with translated Arabic version⁽³⁻⁷⁾.

Urticaria can be classified according to its duration into acute urticaria which lasts less than 6 weeks and chronic urticaria that extends beyond 6 weeks duration. Thereafter chronic urticaria is subdivided by its triggering factors into chronic spontaneous and chronic inducible one. With advance in urticaria pathophysiology understanding, different CSU subsets were known. Of them CSU type IIb which have the higher activity score, autoimmune diseases associated, longer persistence and lower responsiveness to 2nd generation antihistamines^(8,9).

Many biomarkers were explored for severity evaluation such as d dimer, C reactive Protein and ESR⁽¹⁰⁾.

While eosinophils were considered a defense against parasitic infection, they also had many other physiological and pathological properties as they regulate body thermogenesis^(11,12) activate mast cells and share in allergic diseases development⁽¹³⁾. Peripheral eosinopenia is one of the important biomarkers that might be used as an applicable prognostic marker in chronic urticaria⁽¹⁴⁾.

The aim of the current study is to assess the usefulness of peripheral eosinopenia as a valuable and an applicable biomarker for CSU severity.

PATIENTS AND METHODS

A case control study was conducted at Benha University Hospitals, Qalyubia Governorate, Egypt. Patient was recruited from June 2022 to October 2022.

A total of 60 CSU patients were selected; Patients were divided into 30 patients with mild UAS7 score <15 representing the controls and 30 patients with severe UAS7 score >28 representing the cases.

Inclusion criterion was recently diagnosed CSU and exclusion criteria were patients with malignancy, active autoimmune disease, or recent steroid use.

For each patient's file, the following variables were fulfilled; detailed medical history including demographic data such as age and gender, medication use, duration of illness atopic diseases or associated induced urticaria.

For each patient, these investigations were requested; CBC with 5 differential WBC counts, Total Ig E, thyroid peroxidase antibodies (TPO), ESR and CRP. Autologous Serum Skin Test (ASST) was also done.

Although no universal determination of Peripheral eosinopenia cutoff value, many studies previously used a count below 50 cells/ mm^3 for its definition ^(15,16) also peripheral basopenia is defined when the count below 10 cells/ mm^3 ⁽¹⁷⁾.

Patients were classified into 2 groups according to UAS7 score which can be calculated daily of wheals number and itching severity over 7 consecutive days.

The Wheals scored from 0 to 3. 0 means no wheels, 1 means that wheals count is below 20, 2 means wheals count is over 20, and 3 means that wheals count over 50 or large areas communicating with each other. Itching is also calculated from 0 to 3. 0 means no itching, 1 means annoying itching, 2 means bothersome that doesn't affect daily activities and 3 means intense affecting sleep. Mild activity is considered when UAS7 is between 0 and 15, whereas high activity is considered when UAS7 is between 28 and 42.

ETHICAL CONSIDERATIONS

The study was approved by Benha Medical Ethics Committee of Benha faculty of Medicine (Study no.: Rs. 34.2022). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 28 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) and inter quartile range for non-parametric data, and mean and standard deviation (SD) for parametric data after testing normality using Kolmogorov-Smirnov test. Chi-Square test was used for comparison of 2 or more groups. Fischer exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5.

Student's t-test/ Mann-Whitney U test was used to compare 2 independent groups. Receiver Operating Characteristic (ROC) curve analysis: The diagnostic performance of a test, or the accuracy of a test to discriminate diseased cases from non-diseased cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis.

Sensitivity and Specificity were detected from the curve and PPV, NPV and accuracy were calculated through cross tabulation. P value ≤ 0.05 was considered significant.

RESULTS

General and clinical characteristics:

Severe cases demonstrated significantly higher age, positive TPO, and positive ASST. In contrast, severe cases demonstrated significantly lower WBC count, eosinophilic count, basophilic count, and total IgE. No significant differences were observed regarding sex, duration, atopic history, induced urticaria, and ESR (Table 1, Figure 1).

Table 1. General and clinical characteristics of the studied groups.

Variable	Urticaria severity		P-value
	Mild (n = 30)	Severe (n = 30)	
Age (years)	29 (13 - 56)	34 (14 - 64)	0.043
Sex			
Males	11 (36.7)	12 (40)	0.791
Females	19 (63.3)	18 (60)	
Duration (weeks)	21 (6 - 40)	22 (6 - 54)	0.641
Atopic History			
Allergic rhinitis	6 (20)	9 (30)	0.814
Asthma	3 (10)	4 (13.3)	
Both	1 (3.3)	1 (3.3)	
No atopic history	20 (66.7)	16 (53.3)	
Induced urticarial	11 (36.7)	12 (40)	0.791
WBC Count ($10^3 / mm^3$)	7.66 \pm 1.82	6.45 \pm 1.92	0.016
Eosinophilic count (cell / mm^3)	123 (20 - 367)	21 (0 - 79)	<0.001
Basophil (cell / mm^3)	25 (0 - 136)	5 (0 - 100)	<0.001
CRP (mg/L)	2 (0 - 8)	14 (1 - 32)	<0.001
ESR (mm/h)	18 (4 - 62)	21 (0 - 42)	0.976
Total Ig E (IU/ml)	221.5 (70 - 720)	93 (14 - 320)	<0.001
Positive TPO	4 (13.3)	14 (46.7)	0.005
Positive ASST	7 (23.3)	17 (56.7)	0.008

Data are presented as mean \pm SD, median (min-max), or number (percentage) medians and ranges were used for non-parametric distribution data; TPO: Thyroid peroxidase antibody; ASST: Autologous serum skin Test; Significant P-values are marked in bold.

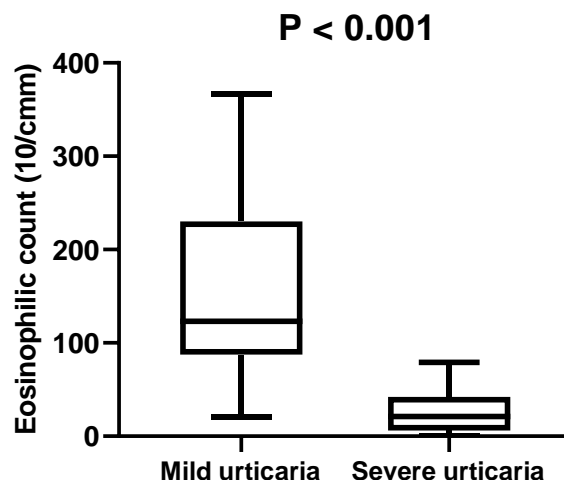


Figure (1) Eosinophilic count in the studied groups of the studied groups.

ROC analysis for the eosinophilic count, and total Ig E:

ROC analyses were done for the eosinophilic count and total IgE to predict severe urticaria. The eosinophilic count showed a significant-excellent AUC of 0.954. The best cutoff point was ≤ 70 , at which sensitivity and specificity were 96.7% and 86.7%, respectively (**Figure 2-A**).

Total Ig E showed a significant-good AUC of 0.847. The best cutoff point was ≤ 127 IU/ml, at which sensitivity and specificity were 76.7% and 83.3%, respectively (**Figure 2-B**).

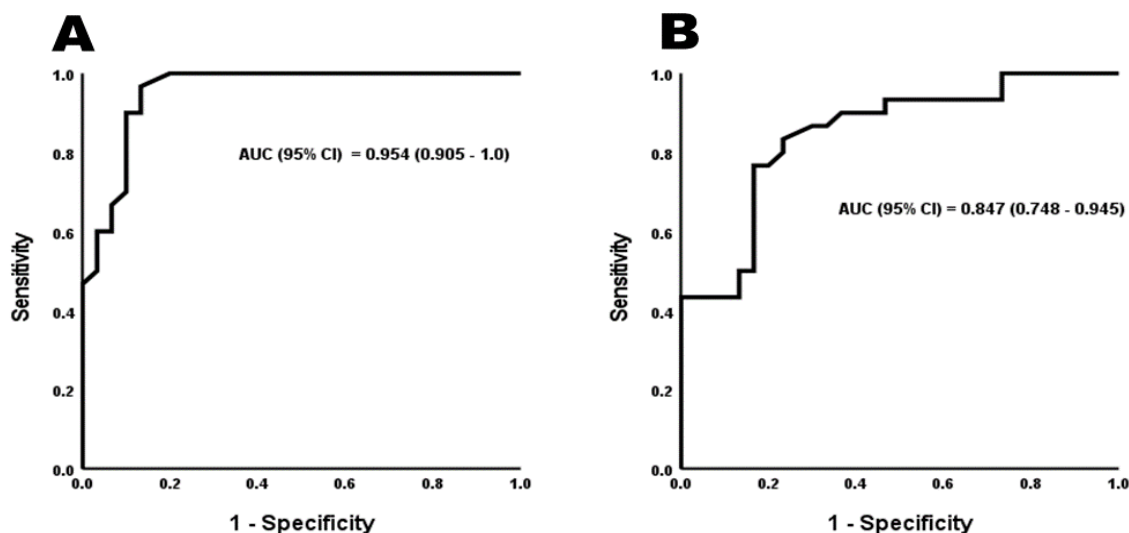


Figure (2) ROC analysis to predict severe urticaria for A) eosinophilic count and B) total IgE

Correlation between UAS7 score and other parameters:

The UAS7 score revealed significant negative correlations with WBC count, eosinophilic count, basophilic count, and total Ig E (**Table 2, Figure 3-A**).

No significant correlations were reported with age ($P = 0.096$), duration ($P = 0.633$), and ESR ($P = 0.693$) (**Table 2**).

Table 2. UAS7 score correlation with other parameters in the studied patients.

Variable	UAS7 Score	
	R	P
Age (years)	0.217	0.096
Duration (weeks)	0.063	0.633
WBC Count ($10^3 / mm^3$)	-.283	0.029
E. Count (cell / mm^3)	-.754	<.001
Basophil (cell / mm^3)	-.373	0.003
ESR (mm/h)	0.052	0.693
Total Ig E (IU/ml)	-.525	<.001

“r”: Correlation coefficient; Significant P-values are marked in bold.

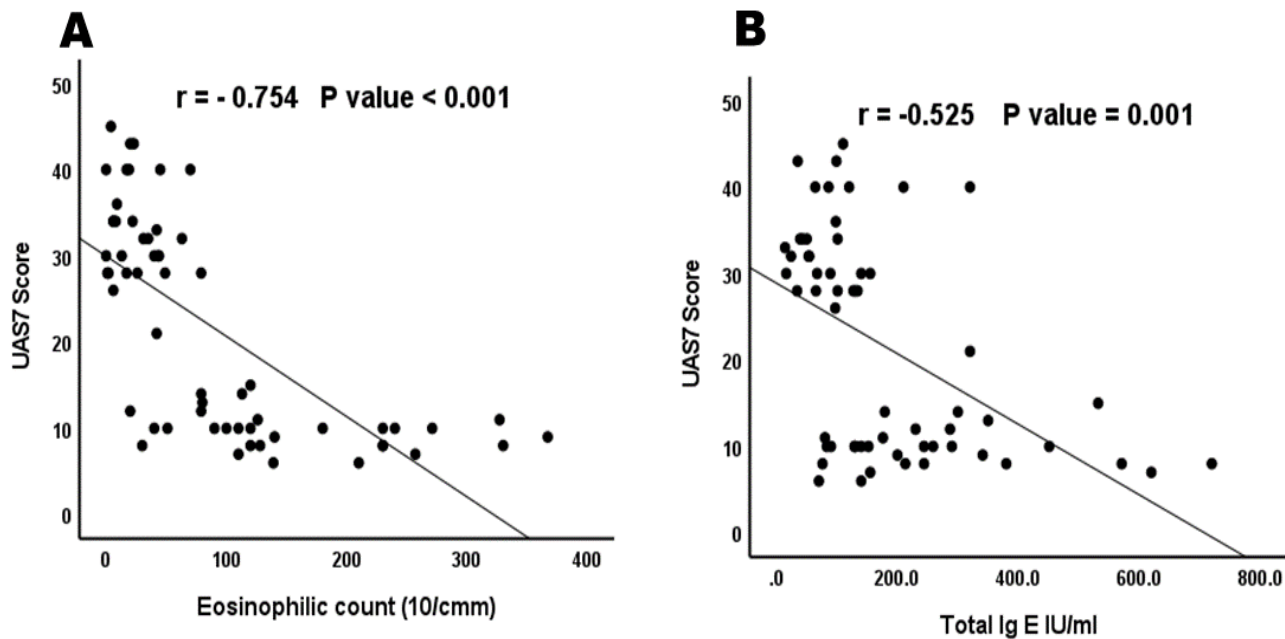


Figure (3) Correlation between UAS7 score and A) eosinophilic count and B) total IgE.

Prediction of severe urticaria

Multivariate logistic regression analysis was explored to predict severe urticaria. The predictors were eosinophilic count, basophilic count, total Ig E, TPO, and ASST, controlling for age, gender, duration, and atopic history (**Table 3**).

Table 3. Multivariate logistic regression analysis to predict severe urticarial.

Variable	OR (95% CI) [†]	P-value
Eosinophilic count	0.915 (0.859 - 0.975)	0.006
Basophilic count	0.973 (0.950 - 0.997)	0.027
Total IgE	0.986 (0.977 - 0.994)	<0.001
TPO	8.863 (2.104 - 37.326)	0.003
ASST	6.369 (1.712 - 23.691)	0.006

[†]Adjusted for age, gender, duration, and atopic history; OR: Odds ratio; 95% CI: 95% confidence interval; TPO: Thyroid peroxidase antibody; ASST: Autologous serum skin Test; Significant P-values are marked in bold

DISCUSSION

Few studies foresighted the peripheral eosinophils count in natural history of urticaria^(14,18), but to our knowledge this article is the first to explore eosinophils count and other variables relations to Urticaria severity with a case control methodology. UAS7 was selected as it had been validated and used in many clinical trials as an important clinical tool for monitoring urticaria severity⁽¹⁹⁾.

Several biomarkers were suggested for monitoring urticaria and deciding the treatment strategies such as ASST, CRP, Total Ig E and TPO but still there is no unifying accepted treatment approach based on these potential markers⁽²⁰⁾. Chronic urticaria is a heterogeneous spectrum of different pathogenesis⁽²¹⁾.

Severe cases showed substantial significant higher CRP ($P < 0.001$), positive TPO ($P = 0.005$), positive ASST ($P = 0.008$) and lower total Ig E ($P < 0.001$) which may reflect distinct type IIb autoimmunity urticaria subtype⁽²²⁾.

Age and gender relation to urticaria severity had a contradictory result between different studies⁽²³⁾. While some showed severity association, others did not find a close interplay between them and urticaria severity like our results which also can be explained by different phenotypes and possible distinctive urticarial pathogenic mechanisms⁽²⁴⁾.

Peripheral eosinophils are significantly lower count in severe urticarial patients with median 21 (0 - 79) cell/mm³ (P value < 0.001) and to our results it could be used as a simple and accessible tool for monitoring the urticaria activity as we showed that UAS7 score had a negative correlations with eosinophilic count ($r = -0.754$, $P < 0.001$), (OR 0.915, 95% CI: 0.859 – 0.975, $P = 0.006$), which is concordant with other studies^(14, 25).

Our study acquires its strength with being the first case control study that explores the peripheral eosinopenia relation to CSU score. The limitation in our study is in its sample size so the need for more cohort and case control studies with larger participants to evaluate the treatment approaches in CSU patients with eosinopenia.

Conflict of Interest: No conflict of interest to declare

Fund: Neither international nor national funds were obtained to set up this project

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