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The Role of Systemic Inflammatory Ratios in Refractory Chronic Spontaneous Urticaria Patients with Gastroesophageal Reflux Disease

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Abstract

Background: Refractory chronic spontaneous urticaria (R-CSU) is characterized by systemic mast-cell-driven inflammation, which may present with extra-cutaneous conditions such as gastroesophageal reflux disease (GERD). The utility of simple blood-derived inflammatory ratios that characterize this systemic inflammation is currently limited. We investigated the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), and platelet-to-lymphocyte ratio (PLR) as potential inflammatory markers in patients with R-CSU, both with and without GERD.

Methods: A retrospective case-control study was conducted involving 116 patients with recurrent chronic spontaneous urticaria (R-CSU) between 2023 and 2024 at Ali ibn Abi Talib Hospital in Zahedan. Among these patients, 58 were diagnosed with GERD, while the remaining 58 were not. Initially, GERD was clinically confirmed, after which complete blood count (CBC) parameters were utilized to calculate the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), and platelet-to-lymphocyte ratio (PLR). Group differences were analyzed using Mann–Whitney U tests and multivariate regression, adjusted for potential confounders. Receiver operating characteristic (ROC) analysis was employed to assess diagnostic accuracy.

Results: NLR was significantly higher in R-CSU patients with GERD compared to those without GERD (NLR: 2.05 ± 1.7 vs 1.05 ± 0.91, $P = 0.041$; ELR: 0.26 ± 0.18 vs 0.21 ± 0.11, $P = 0.084$). In contrast, PLR did not differ significantly ($P = 0.500$). In the multivariate analysis, NLR remained an independent predictor of GERD comorbidity after adjustment ($\beta = 0.41$, $P < 0.001$). ROC analysis identified an NLR cut-off of 1.24, demonstrating 81% sensitivity and 64% specificity for distinguishing R-CSU with GERD.

Conclusion: Elevated NLR and ELR indicate systemic inflammation in patients with refractory CSU and GERD. These findings support the hypothesis that systemic inflammation contributes to extracutaneous symptoms in this population. Routine, readily available CBC-derived ratios may serve as cost-effective markers for identifying systemic inflammatory activity in R-CSU.

Keywords: Chronic spontaneous urticaria, Refractory urticaria, Gastroesophageal reflux disease, Systemic inflammation, Neutrophil-to-lymphocyte ratio, Eosinophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Mast cell activation

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Introduction

Chronic spontaneous urticaria (CSU) is a prevalent skin condition characterized by recurrent wheals, angioedema, or both, lasting more than 6 weeks without identifiable external triggers. It affects approximately 1% of the global population and can significantly diminish quality of life (1). Additionally, refractory chronic spontaneous urticaria (R-CSU) is defined as the persistence of symptoms despite the administration of maximum tolerated doses of non-sedating antihistamines (2).

Mast cell degranulation is a hallmark of R-CSU patho-

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↑What is "already known" in this topic:
Chronic spontaneous urticaria (CSU) is frequently associated with systemic inflammation and immune dysregulation. However, the relationship between refractory CSU and gastrointestinal comorbidities, such as gastroesophageal reflux disease (GERD), remains inadequately defined.

→What this article adds:
This study demonstrates that patients with refractory CSU and GERD exhibit elevated neutrophil-to-lymphocyte ratios (NLR), indicating the presence of systemic inflammation and suggesting a potential bidirectional interaction between allergic and gastrointestinal pathways.

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physiology, primarily due to histamine release, which causes vasodilation and swelling (3). Biopsies from wheal sites have confirmed the presence of eosinophils, neutrophils, lymphocytes, and monocytes, which accumulate around small venules (4). These immune cells promote inflammation by releasing mediators such as IL-1, IL-6, IL-24, and TNF-alpha, along with other pro-inflammatory cytokines (5). Additionally, leukotriene D4 (LTD4), released by eosinophils, further stimulates histamine release from basophils and mast cells. This inflammatory state is particularly evident in antihistamine-refractory CSU, characterized by higher relapse rates and systemic symptoms (6-8). Beyond the skin, approximately one-quarter of systemic symptoms are related to gastrointestinal issues, with gastroesophageal reflux disease (GERD) being the most prevalent; the prevalence of GERD was four times higher in patients with urticaria compared to those without (9). Studies have shown that R-CSU patients treated for GERD experienced improvements in their wheals and a reduction in mast cell activation (10).

Several studies have investigated blood cell–derived indices, including the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), and platelet-to-lymphocyte ratio (PLR), as systemic inflammatory markers (11). To the best of our knowledge, elevated NLR and PLR are associated with disease activity in conditions such as psoriasis, atopic dermatitis, and lupus (12,13).

Furthermore, it has been demonstrated that ELR is linked to allergic and eosinophilic inflammation (14). However, it is important to note that data regarding their role in R-CSU remain limited, and the findings are still uncertain (15).

Although CBC-derived inflammatory ratios are routinely available, no study to date has directly compared NLR, ELR, and PLR in R-CSU patients with and without GERD. Therefore, this study aimed to compare these markers among R-CSU patients with and without GERD. We sought to determine whether these inflammatory markers could serve as indicators of systemic inflammation in R-CSU patients with gastrointestinal comorbidities.

Methods

Study Design

This retrospective case-control study was conducted between 2023 and 2024 at the allergy and asthma clinic of Ali ibn Abi Talib Hospital in Zahedan. R-CSU was diagnosed by allergists and immunologists based on clinical presentations of recurring urticarial lesions persisting for more than six weeks without identifiable external triggers. Gastroesophageal reflux disease (GERD) was diagnosed by gastroenterologists based on common symptoms such as frequent heartburn and acid reflux, and patients had received prior PPI (proton pump inhibitor) treatment for four weeks or more (16, 17). Refractory CSU may also require systemic immunosuppressive therapies (e.g., cyclosporin, dupilumab, methotrexate, mycophenolate mofetil, or omalizumab) or hospitalization for disease control. Patients were selected into the R-CSU with GERD (case group) and R-CSU without GERD (control group), matched by age and gender.

Study Population and Sample Size

The study included patients with R-CSU who were referred to the allergy and asthma clinic at Ali ibn Abi Talib Hospital. Inclusion criteria required patients to provide informed consent, possess comprehensive case data, and have available laboratory test results. Based on previous studies, the sample size was calculated using the NLR standard deviation, with a type I error of 0.05 and a power of 80%, resulting in a minimum of 58 patients per group. Patients with co-occurring acute infections, such as gastroenteritis or pneumonia, individuals with any gastrointestinal disease other than GERD, those unwilling to continue participation, and individuals lacking complete data or adequate laboratory testing were all excluded.

Data Collection

Data were acquired through structured patient interviews, clinical examinations, and a comprehensive review of available medical records. The collected information included demographic data, family history of urticaria, occupational status, and exposure to family smoking. Complete blood count (CBC) and differential counts—comprising neutrophils, eosinophils, lymphocytes, and platelets—were obtained from existing records. The differential counts were manually analyzed to calculate inflammatory markers, including NLR, ELR, and PLR. Only patients confirmed to have R-CSU and evaluated by a dermatologist were included as cases. The classification of R-CSU adhered to dermatological criteria, defining patients as refractory if symptoms persisted despite maximum tolerated doses of standard H1-antihistamines for 4 weeks or if systemic immunosuppressive therapy was required or there was a previous history of hospitalization (18). All collected data were coded and entered into SPSS version 22 software for detailed statistical analysis. The study protocol received institutional ethics committee approval (IR.ZAUMS.REC.1403.157), and all participants provided informed consent.

Statistical Analysis

Statistical analyses were conducted using SPSS version 22, with a significance threshold set at $p < 0.05$. Continuous variables were expressed as means ± standard deviations, while categorical variables were presented as frequencies and percentages. For group comparisons, independent t-tests or Mann–Whitney U tests were employed, depending on the normality of the data, as determined by the Kolmogorov–Smirnov test. Chi-square or Fisher's exact tests were utilized for categorical variables. Univariate and multivariate logistic regression models, accounting for confounders such as age, sex, and smoking status, were employed to analyze associations between inflammatory ratios (NLR, ELR, PLR) and R-CSU with GERD. The diagnostic accuracy of these markers was evaluated using receiver operating characteristic (ROC) curve analysis, which reports the area under the curve (AUC).

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Results

Demographic and Clinical Characteristics

A total of 116 patients with R-CSU participated in the study. Among them, 58 patients had GERD (R-CSU +GERD), while 58 patients did not have GERD (R-CSU -only). The mean age was 38.6 ± 10.2 years for the R-CSU with GERD group and 37.9 ± 9.8 years for the R-CSU without GERD group, with no significant difference between the groups (P = 0.620). Females comprised 65.5% of the total population, and the gender distribution did not differ significantly (P = 0.440). The overall mean age was 33.12 ± 9.14 years, with a range of 14 to 67 years. Females accounted for 62.9% (n = 73), while males accounted for 37.1% (n = 43). A positive family history of urticaria was documented in 41% of the participants overall, with a statistically significantly higher prevalence in the non-GERD group (P = 0.024). No significant differences were found between the groups concerning age, gender distribution, maternal employment status, smoking exposure, or number of children (P > 0.05) (Table 1).

Values are presented as numbers (%) or means ± standard deviation. The variables include age (years), sex distribution (n, %), maternal occupation (n, %), smoking exposure (n, %), family history of urticaria (n, %), and number of children (mean ± SD).

Systemic Inflammatory Profile of R-CSU Patients

In univariate analyses (Table 2), the neutrophil-to-lymphocyte ratio (NLR) and eosinophil-to-lymphocyte ratio (ELR) differed significantly between patients with refractory chronic spontaneous urticaria (R-CSU) who had gastroesophageal reflux disease (GERD) and those who did not, while the platelet-to-lymphocyte ratio (PLR) showed no significant differences. The distributions of these markers were non-normal; therefore, non-parametric Mann-Whitney U tests were employed. The NLR was significantly higher in the GERD group compared to controls (2.05 ± 1.7 vs. 1.5 ± 0.91; P = 0.041). The ELR and PLR did not differ significantly (P = 0.084 and P=0.5, respectively) (Table 2).

Values are presented as mean ± standard deviation (unitless ratio), along with median, minimum, and maximum values. The mean NLR was significantly higher in patients with R-CSU and GERD (2.05 ± 1.7) compared to R-CSU-only patients (1.5 ± 0.91, P < 0.001). The median NLR was 2.95 (IQR 2.2–3.8) in the GERD group and 1.9 (IQR 1.4–2.6) in the non-GERD group (Table 2).

The ELR did not differ significantly between R-CSU patients with GERD (0.26 ± 0.18) and R-CSU-only patients (0.21 ± 0.11, p = 0.084). The median ELR was 0.25 (IQR 0.17–0.33) for the GERD group compared to 0.20 (IQR 0.14–0.26) for the non-GERD group (Table 2). The PLR also demonstrated no significant difference between the two groups (8.2 ± 3.3 vs 7.7 ± 5.7, P = 0.500) (Table 2).

Multivariate and Adjusted Regression Analyses

After adjusting for age, sex, and family history of urticaria, multivariate regression analysis identified NLR as an independent predictor of GERD in patients with R-CSU (β = 0.41, SE = 0.11, P < 0.001). ELR demonstrated a weaker yet significant association (β = 0.58, SE = 0.29, P = 0.047), while PLR did not achieve statistical significance (P = 0.48).

Diagnostic Performance and ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis confirmed the diagnostic value of NLR in distinguishing between R-CSU patients with and without GERD. The area under the curve (AUC) was 0.61 (95% CI: 0.74–0.88, P = 0.038), and a cut-off value of 1.24 yielded a sensitivity of 81% and a specificity of 69% (Figure 1). ELR demonstrated a limited ability to discriminate, with an AUC of 0.64 (Figure 2), while PLR was uninformative, exhibiting an AUC of 0.58 (Figure 3).

Table 1. Demographic characteristics of patients with refractory chronic spontaneous urticaria (R-CSU) with and without gastroesophageal reflux disease (GERD).

Variable	GERD+ (n=58)	GERD− (n=58)	*P*-value
Female, n (%)	34 (58.6)	39 (67.2)	0.120
Male, n (%)	24 (41.4)	19 (32.8)	
Maternal occupation*			0.300
- Homemaker	31 (59)	35 (70)	
- Employed	21 (40)	15 (30)	
Smoking exposure*			0.210
- Yes	37 (68)	35 (60)	
- No	17 (31)	23 (40)	
Family history of urticaria	19 (33)	32 (55)	0.024
Mean age (years)	33.03 ± 13.4	34.8 ± 12.8	0.400
Mean number of children*	2.2 ± 0.9	2.1 ± 0.8	0.800

Values are presented as numbers (%) or means ± standard deviation. The variables include age (years), sex distribution (n, %), maternal occupation (n, %), smoking exposure (n, %), family history of urticaria (n, %), and number of children (mean ± SD).

Table 2. Comparison of the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), and platelet-to-lymphocyte ratio (PLR) between refractory CSU patients with and without GERD.

Marker	GERD+ Mean (SD)	GERD− Mean (SD)	Median (GERD+)	Median (GERD−)	*P*-value
NLR	2.05 ± 1.7	1.5 ± 0.91	1.6	1.4	0.041
ELR	0.26 ± 0.18	0.21 ± 0.11	0.26	0.21	0.084
PLR	8.2 ± 3.3	7.7 ± 5.7	7.6	6.0	0.500

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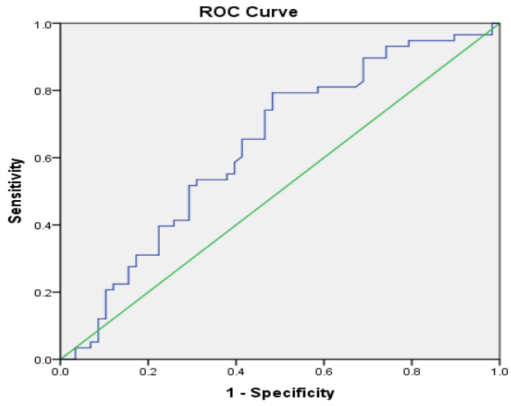

Figure 1. The receiver operating characteristic (ROC) curve illustrates the diagnostic performance of NLR in detecting refractory CSU associated with GERD. The optimal cut-off point of 1.24 provides high sensitivity and moderate specificity.

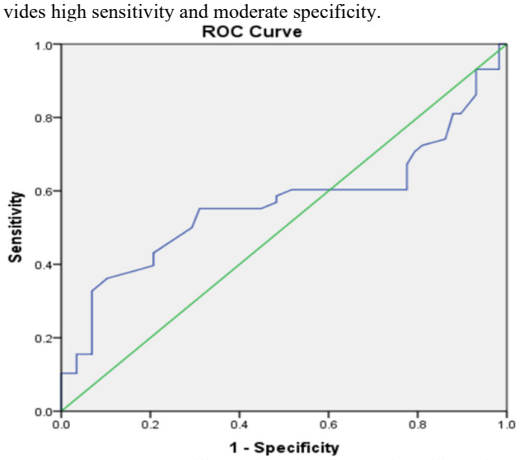

Figure 2. ROC curve illustrating the diagnostic utility of ELR in refractory CSU with GERD, demonstrating limited discriminatory value.

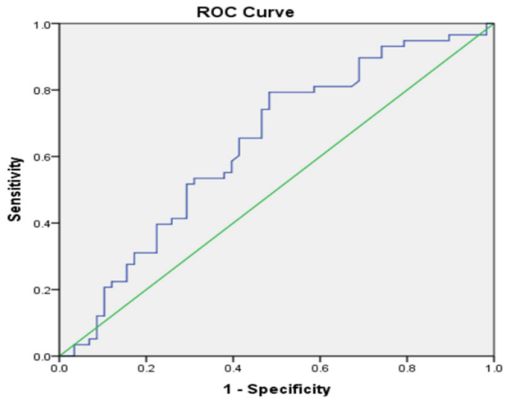

Figure 3. ROC curve analysis of PLR for distinguishing refractory CSU patients with GERD demonstrates modest accuracy (AUC: 0.63) at an optimal cut-off value of 7.55.

Discussion

It is well established that patients with R-CSU experience extracutaneous symptoms more frequently than healthy controls. Gastroesophageal complaints have been identified as the most common, particularly those associated with hypersensitivity symptoms such as heartburn and chest pain, or excessive esophageal acid exposure. As mentioned previously, inflammatory markers such as NLR, ELR, and PLR are readily accessible, available, and can be measured instantaneously, indicating systemic inflammation; however, their role in R-CSU patients who do not respond to first-line therapy or who have R-CSU with gastroesophageal-related hypersensitivity symptoms remains unclear (9, 15).

In this study, we found that the neutrophil-to-lymphocyte ratio (NLR) was significantly elevated in patients with refractory chronic spontaneous urticaria (R-CSU) who also had gastroesophageal reflux disease (GERD) compared to those with R-CSU without GERD. However, the eosinophil-to-lymphocyte ratio (ELR) and the platelet-to-lymphocyte ratio (PLR) were not significantly different among the three groups. Sarac et al. previously demonstrated that both acute and chronic urticaria patients exhibited higher NLR values than control groups; however, PLR did not differ significantly between groups, which is consistent with our findings. Another study by Weissmann and colleagues indicated that adult patients with chronic spontaneous urticaria (CSU) had higher NLR and PLR compared to those with acute spontaneous urticaria (ASU) or children with CSU. They also reported that these ratios are associated with the severity of urticaria, suggesting that the discrepancies in findings may be attributed to the timing of measurements (19, 20). Similarly, Qiu et al. demonstrated that elevated NLR is associated with a poorer response to H1-antihistamine therapy in patients with chronic spontaneous urticaria, thereby supporting the role of NLR as a systemic inflammatory marker in refractory disease (21).

One possible explanation is that continuous activation of eosinophils and other immune cells at wheal sites in R-CSU patients leads to the release of inflammatory cytokines, including IL-4, IL-13, IL-17, IL-25, IL-33, and IL-17A (22, 23). This activation subsequently drives an inflammatory state mediated by T cells, which recruit mast cells and modify their immunological properties through potential autoimmune mechanisms. As a result, FcεRI expression on their surface becomes upregulated, extending beyond wheal sites (24-26). Consequently, these autoreactive mast cells are distributed throughout the body, including in the esophagus, where reaching a primed state makes even minimal acid exposure sufficient to trigger degranulation and histamine release (27). Tryptase and other cytokines can sensitize nerve endings, leading to visceral hypersensitivity. They may also induce neuroinflammation via the release of substance P, which explains why some studies have found elevated levels of substance P in R-CSU patients (28-31). Clinically, these patients often present with symptoms of reflux hypersensitivity, and treatment with omalizumab or other systemic therapies has been shown to alleviate gastrointestinal complaints (32, 33).

Conclusion

In conclusion, our study highlights the potential value of readily accessible inflammatory markers, such as NLRs,

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in understanding the role of systemic inflammation in R-CSU patients with GERD. Several limitations should be acknowledged. Although none of the patients were receiving systemic immunomodulatory therapies at the time of CBC measurement, prior exposure to these therapies could not be fully controlled. The retrospective, cross-sectional design of the study does not allow for the establishment of a clear cause-and-effect relationship. To minimize bias, patients in the R-CSU groups were matched to controls by age and sex, and multivariate analysis was employed to adjust for potential confounders, including family history of urticaria and smoking exposure. The same results were consistently observed. The ROC analysis yielded a cut-off value of 1.24 for NLR as a predictor of R-CSU with GERD versus R-CSU without GERD, with statistical significance. Moreover, the relatively small sample size restricts the depth of subgroup analysis. Additionally, excluding other inflammatory cytokines, such as TNF-α, IL-1, and IL-6, limits the ability to fully understand the underlying immunopathological mechanisms.

Although this study supports a systemic perspective on skin rash diseases and categorizes the R-CSU patient group based on GERD, it enhances the clinical relevance of the findings. The utilization of routine, cost-effective inflammatory markers strengthens the translational potential in everyday clinical practice. Future research should focus on prospective longitudinal studies with larger cohorts, incorporate standardized endoscopic grading (e.g., Los Angeles classification), ambulatory reflux monitoring, and validated GERD severity scores, and explore the effects of therapeutic interventions targeting systemic inflammation on clinical outcomes in R-CSU patients who do not require additional treatment for GERD. Such studies will be essential for advancing personalized management strategies for this challenging patient population.

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

M.S.B: Conceptualization, data collection, and manuscript drafting. H.A.: Statistical analysis and methodology. E.A: Supervision and final approval. H.S: Supervision and final approval. H.A.K.: conceptualization, project administration, and final approval. S.G.A.: Data interpretation, critical revision, Supervision, and final approval. All authors reviewed and approved the final version of the manuscript.

Ethical Considerations

The current study was approved by the Ethics Committee of Zahedan University of Medical Sciences under the reference code IR.ZAUMS.REC.1403.157.

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Data Availability

The datasets generated and analyzed during the current study are not publicly available due to patient privacy considerations but are available from the corresponding author after requesting.

AI Use Statement

Artificial intelligence-assisted tools were used only for language editing and paraphrasing during the preparation of this manuscript. All scientific content, data, interpretations, and conclusions are under the responsibility for the authors.

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