İSTANBUL UNIVERSITY PRESS

The Turkish Journal of Ear Nose and Throat,
Tr-ENT 2025

https://doi.org/10.26650/Tr-ENT.2025.1634723

Submitted: 15.02.2025
Revision Requested: 22.08.2025
Last Revision Received: 23.08.2025
Accepted: 04.09.2025
Published Online 22.09.2025

The Turkish Journal of Ear Nose and Throat

Research Article

Open Access

Relationship Between Serum Inflammatory Markers and Olfactory Function in Polypoid and Non-Polypoid Chronic Rhinosinusitis

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Abstract

Objective: This study aimed to investigate the association between serum inflammatory markers, particularly the Systemic Immune-Inflammatory Index (SII), and disease severity and olfactory function in patients with chronic rhinosinusitis (CRS).

Materials and Methods: A total of 59 CRS patients and 29 healthy controls were included. Patients were categorised as CRSsNP (n=30) or CRSwNP (n=29). Olfactory function was assessed with the Sniffin' Sticks test, whereas disease severity was evaluated using the Lund–Kennedy endoscopic and Lund–Mackay radiological staging systems. Quality of life was measured using the SNOT-22 questionnaire. Inflammatory indices, including NLR, PLR, ELR, and SII, as well as eosinophil counts and total serum IgE levels, were analysed.

Results: Compared with controls, CRSwNP patients demonstrated significantly higher eosinophil counts and ELR values ($p<0.001$). No significant differences were observed for IgE, NLR, PLR, or SII levels between the groups ($p=0.248$). Olfactory scores showed a significant negative correlation with both radiological and endoscopic staging. Importantly, systemic inflammatory indices such as SII and NLR were not associated with olfactory dysfunction, suggesting their limited diagnostic utility in CRS.

Conclusion: While most systemic inflammatory indices did not correlate with olfactory performance or disease severity, ELR and eosinophil counts were markedly elevated in patients with CRSwNP, highlighting the potential disease-specific relevance of ELR in CRS-related olfactory dysfunction.

Keywords Loss of smell · chronic rhinosinusitis · nasal polyp · systemic immune-inflammatory index · sniffin sticks

Citation: Amca A, Evrim Tuna E, Cayonu M, Paksoy ZB. Relationship Between Serum Inflammatory Markers and Olfactory Function in Polypoid and Non-Polypoid Chronic Rhinosinusitis The Turkish Journal of Ear Nose and Throat 2025; Advance Online Publication. DOI: 10.26650/Tr-ENT.2025.1634723

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INTRODUCTION

As per the EPOS 2020 guidelines, chronic rhinosinusitis is defined as a long-lasting condition requiring the occurrence of a minimum of two symptoms. These often involve nasal blockage, nasal drainage, pressure or discomfort in the face, and a diminished or absent sense of smell. The diagnosis necessitates that these symptoms persist for more than 12 weeks (1).

Chronic rhinosinusitis is a frequently encountered condition, affecting 9.9% of individuals aged 15 years or older who visit outpatient departments (2). The reported prevalence rates are as high as 16% in the United States and 19.7% in Europe (3, 4).

Multiple elements-including local, host-specific, and environmental factors-play a role in the disease's etiopathogenesis. Identifying new biomarkers that can shed light on the course and severity of the disease is crucial for an effective treatment plan.

The systemic immune-inflammatory index (SII), originally developed as a prognostic tool in hepatocellular carcinoma, has since been investigated in a wide range of chronic inflammatory and autoimmune diseases (5). SII reflects the balance between host immune and inflammatory responses, being calculated from platelet, neutrophil, and lymphocyte counts. Elevated SII values have been associated with increased disease severity and unfavourable clinical outcomes (6-8).

Indices of systemic inflammation, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and SII, have been proposed as potential markers of disease activity in CRS. Recently, given the known role of eosinophilic inflammation in the pathophysiology of CRS, the eosinophil-to-lymphocyte ratio (ELR) has attracted attention as a potential biomarker.

This study aimed to investigate the association between systemic inflammatory indices (SII, NLR, and ELR) and olfactory dysfunction in patients with chronic rhinosinusitis (CRS), with particular focus on ELR as a potentially disease-specific biomarker.

MATERIALS AND METHODS

This study was conducted as a prospective, cross-sectional investigation in the Department of Otolaryngology at Ankara Bilkent City Hospital. Approval for this research was obtained from the Institutional Ethics Committee of Ankara Bilkent City Hospital (Date: 19.10.2022, No: E1-22-2964). All procedures followed the ethical principles outlined in the Declaration of Helsinki, and all participants signed written informed consent forms.

Patient selection

Participants aged 18 to 75 years with a diagnosis of chronic rhinosinusitis who attended the clinic from October 2021 to May 2022 were enrolled in the study. Participants were classified into three groups according to their nasal polyp status and overall health: the CRSwNP group (chronic rhinosinusitis with nasal polyps), the CRSsNP group (chronic rhinosinusitis without nasal polyps), and a healthy control group. Patients with systemic conditions that might influence systemic inflammatory parameters (such as diabetes mellitus, a history of oncological or haematological disorders, rheumatological conditions, etc.), recent use of systemic steroids that could suppress active inflammation, and smokers were excluded from the study.

Clinical and laboratory evaluation

Patients identified as having CRSwNP or CRSsNP through detailed endoscopic evaluations and paranasal CT scans were recruited for the study. Following the initial evaluation, the Turkish version of the The SNOT-22 questionnaire and Sniffin' Sticks test for olfactory evaluation tests were applied (9). All patients underwent olfactory testing using Sniffin' Sticks tests at the time of admission.In addition, endoscopic staging (Lund Kennedy) and paranasal CT staging (Lund Mackay) were conducted (10, 11). .

Complete blood count, serum total IgE levels, and inflammatory parameters calculated using complete blood count data-including the ratios of neutrophils, platelets, and eosinophils to lymphocytes (NLR, PLR, ELR), and systemic inflammatory index (SII)-were recorded.

Olfactory testing

Sniffin' Sticks olfactory tests were applied in accordance with the literature. Typically, olfactory function is expressed as a TDI score, which is derived from three separate tests of odour discrimination (OD), threshold (OT), and identification (OI).In this study, TDI values under 16.5 were interpreted as functional anosmia, values exceeding 30.3 were regarded as normosmia, and those within the range of 16.5 to 30.3 were defined as hyposmia (12-14).

Statistical analysis

Analysis was performed using version 11.5 of the Statistical Package for the Social Sciences (SPSS) software on a Windows platform (SPSS Inc., Chicago, IL, USA). To compare quantitative variables across more than two independent groups, such as olfactory function groups and chronic rhinosinusitis versus control groups, the Kruskal-Wallis test was employed. Categorical data were evaluated with the chi-square test.

When significant differences were identified among the groups, pairwise comparisons were performed. Correlations among the quantitative variables were analysed through Spearman's correlation test. A p-value 0.05 was considered statistically significant.

RESULTS

A total of 59 CRS patients (29 CRSwNP, 30 CRSsNP) and 29 healthy controls were included (47 males, 41 females; age range 18–75 years). Gender distribution was similar across the groups, whereas age showed a significant difference. Among the participants, 29 (33%) had CRS with nasal polyps (CRSwNP), 30 (34%) had CRS without nasal polyps (CRSsNP), and 29 (33%) were healthy controls.

The olfactory function, assessed by the Sniffin' Sticks test (OT, OD, OI, and TDI), was significantly lower in the CRSwNP group compared to both the CRSsNP and controls ($p<0.05$). Multivariate general linear model analysis confirmed that age did not confound the olfactory test results ($p=0.9$).

When the systemic inflammatory indices were compared, no significant intergroup differences were observed for IgE, NLR, PLR, or SII ($p > 0.05$) (Table 1). In contrast, eosinophil counts and ELR values were significantly higher in CRSwNP patients compared to both CRSsNP and controls ($p<0.05$). ROC analysis demonstrated the discriminative ability of ELR, yielding an AUC of 0.762 (95% CI: 0.664–0.860, $p<0.001$), which indicates good diagnostic performance of ELR in distinguishing CRSwNP from other groups (Figure 1). Regression analysis showed that age did not influence eosinophil or ELR values ($p=0.13$ and $p=0.075$, respectively).

Correlation analysis revealed no significant association between IgE, NLR, PLR, SII, or ELR and olfactory test scores, endoscopic grade, radiological grade, or SNOT-22 scores (Table 2). However, a strong negative correlation was observed between TDI scores and both the Lund-Kennedy ($r=-0.709$, $p<0.001$) and Lund-Mackay staging systems ($r=-0.718$, $p<0.001$), underscoring the close link between disease severity and olfactory impairment.

DISCUSSION

Our study yielded three key observations: patients with CRSwNP demonstrated significantly higher eosinophil counts and ELR values compared with CRSsNP and controls; systemic inflammatory indices such as SII, NLR, PLR, and IgE were not associated with olfactory function, endoscopic or radiological severity, or SNOT-22 scores; and a strong negative correlation was observed between radiological and endoscopic grading and olfactory performance, particularly TDI scores.

Table 1. Descriptive statistics of the groups depending on the presence of CRS

	Control (n=29)	CRSsNP (n=30)	CRSwNP (n=29)	P Value
Gender (Female/Male)	17/12	12/18	11/18	0.21*
Age	31±8.6	34.9±11.8	47.1±13.5	<0.001*
IgE (IU/mL)	101.24±134.3	135.2±257.8	158.7±259.7	0.318
NLR	1.93±0.63	2.35±1.33	2.42±1.10	0.221
PLR	123.96±47.58	124.58±51.74	116.83±33.16	0.995
ELR	0.08±0.04	0.11±0.06	0.18±0.10	<0.001*
Eozinophil (x10^ 9/L)	0.18±0.10	0.36±0.75	0.40±0.21	0.161
Neutrophil (x10^ 9/L)	4.31±0.95	4.45±1.1	5.1±2.01	0.055
Lymphocyte (x10^ 9/L)	2.38±0.66	2.09±0.55	2.28±0.70	0.209
SII	529.87±203.7	564.56±336.29	607.29±319.29	0.572
Odour threshold	8.88±3.54	8.44±3.93	3.02±2.98	<0.001*A, B
Odour discrimination	11.45±1.90	10.57±2.58	6.55±2.76	<0.001*A, B
Odour identification	11.07±1.67	10.27±1.91	5.66±2.58	<0.001*A, B
TDI	31.3± 4.3	29.28±6.69	15.23±6.61	<0.001*A,B
Lund-Kenedy scores	3.9±1.6	4.8±1.5	10.5±2.3	<0.001*A,B
Lund-Mackay scores	1.3±1.7	9.6±3.8	19.4±3.1	<0.001*A,B

*: p- value <0.05 was considered indicative of statistical significance, KW Test Statistics, A: Normosmia-Hyposmia, B: Hyposmia-Anosmia, N: Number of patients, SD: Standard deviation, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio, SII: Systemic immune-inflammatory index, TDI: Total score threshold, discrimination, identification CRSwNP: Chronic rhinosinusitis with nasal polyp, CRSsNP: Chronic rhinosinusitis without nasal polyp, NLR: neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio, SII: Systemic immune-inflammatory index, TDI: Total score threshold, discrimination, identification, IU/mL: International Unit per milliliter

Table 2. Correlation analysis of variables in the study

	TDI	SII	NLR	ELR	PLR	IgE	Eosinophil	Lund kennedy	Lund mackay
TDI	1	0.522	0.463	0.226	0.275	0.189	0.171	<0.001*	<0.001*
		r=-0.069	r=-0.79	r=-0.131	r=0.118	r=-0.141	r=0.147	r=-0.709	r<-0.718
SII	0.522	1	<0.001*	0.455	<0.001*	0.237	0.206	0.223	0.392
	r=-0.069		r=0.893	r=-0.81	r=0.727	r=0.127	r=-0.136	r=0.131	r=0.092
NLR	0.463	0.001*	1	0.558	0	0.199	0.196	0.071	0.096
	r=-0.79	r=0.893		r=-0.63	r=0.567	r=0.138	r=-0.139	r=-0.193	r=0.179
ELR	0.226	0.455	0.558	1	0.827	0.486	<0.001*	0.455	0.057
	r=-0.131	r=-0.81	r=-0.63		r=-0.24	r=0.075	r=-0.978	r=0.081	r=0.204
PLR	0.275	<0.001*	<0.001*	0.827	1	0.227	0.22	0.669	0.353
	r=-118	r=727	r=0.567	r=-0.24		r=-0.130	r=-0.132	r=-0.046	r=-0.100
IgE	0.189	0.237	0.199	0.486	0.227	1	0.395	0.493	0.436
	r=-0.141	r=0.127	r=0.138	r=0.75	r=-0.130		r=-0.092	r=0.074	r=0.084
Eosinophil	0.171	0.206	0.196	0.000*	0.22	0.395	1	0.45	0.205
	r=-147	r=-0.136	r=-0.139	r=0.978	r=-0.132	r=0.092		r=0.082	r=0.56
Lund Kenedy	<0.001*	0.223	0.071	0.455	0.669	0.493	0.45	1	<0.001*
	r=-0.709	r=0.131	r=-0.193	r=0.081	r=-0.046	r=0.074	r=0.082		r=0.783
Lund Mackay	<0.001*	0.392	0.096	0.057	0.353	0.436	0.205	<0.001*	1
	r<-0.718	r=0.092	r=0.179	r=0.204	r=-0.100	r=0.084	r=0.56	r=0.783	

*: p-value <0.05 was considered indicative of statistical significance, NLR: neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio, SII: systemic immune-inflammatory index, TDI: Total score threshold, discrimination, identification, NLR: neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, ELR: Eosinophil-lymphocyte ratio, SII:Systemic immune-inflammatory index, TDI: Total score threshold, discrimination, identification

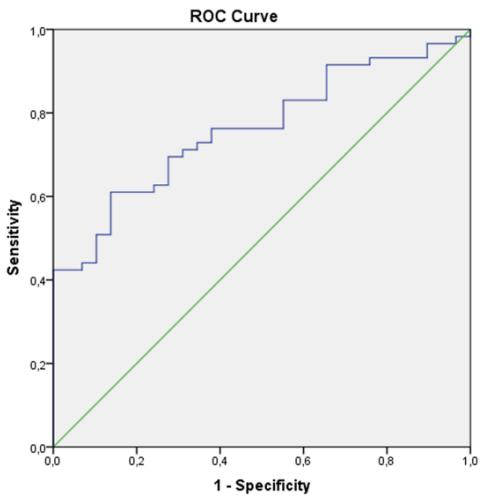


Figure 1. ROC analysis for eosinophils to lymphocyte ratio
The area under the curve (AUC) was 0.762 (95% CI: 0.664–0.860, p<0.001)

Chronic rhinosinusitis is a long-term inflammatory disorder of the sinonasal mucosa that significantly impairs patients' quality of life and represents a major burden for healthcare systems (15, 16). The prevalence of CRS has been reported to reach 19.7% in Europe, and despite considerable advances in the understanding of sinonasal inflammation, the precise pathophysiology remains incompletely defined (16, 17).

Olfactory dysfunction is one of the most prominent symptoms of CRS, affecting 60% – 80% of patients (18). In CRSwNP, this impairment may result from mechanical obstruction of the olfactory cleft as well as from sensorineural alterations caused by chronic mucosal inflammation and epithelial damage (19).

Our results confirmed that olfactory performance, as measured by Sniffin' Sticks testing, was significantly reduced in CRSwNP patients compared with both CRSsNP and controls. Importantly, we observed a strong negative correlation between TDI scores and both radiological and endoscopic staging, indicating that disease severity is closely linked to olfactory impairment. These findings are consistent with those of Kim et al., who classified olfactory cleft opacification into mild, moderate, and severe categories on CT and demonstrated that postoperative olfactory improvement was limited in patients with severe opacification (>75%) (19).

Other studies further reinforce these observations. Zheng et al. found no significant differences in SNOT-20 scores among CRSwNP, CRSsNP, and controls, but identified a weak yet

significant correlation between SNOT-20 and Lund–Mackay scores within the CRSwNP subgroup (20). In contrast, our results showed a more robust association between disease severity and olfactory performance, suggesting that validated psychophysical olfactory tests, such as the Sniffin' Sticks, may be more sensitive indicators of disease burden than generic quality-of-life questionnaires. Similarly, Litvack et al., in a cross-sectional study of 367 patients, reported that olfactory dysfunction was significantly more common in patients with nasal polyps, whereas septal deviation did not contribute to smell loss (21). These findings align with our results and highlight the central role of polyp-related and inflammatory mechanisms in CRS-associated olfactory impairment.

In our study, systemic inflammatory indices such as SII, NLR, and PLR did not show significant associations with olfactory performance, endoscopic or radiological grading, or quality of life scores. In contrast, both peripheral eosinophil counts and ELR were significantly elevated in CRSwNP patients, and ROC analysis demonstrated good discriminative ability of ELR in differentiating CRSwNP from CRSsNP and controls. These findings suggest that ELR may represent a more disease-specific marker compared with other systemic indices.

Several studies have similarly highlighted the value of eosinophil-based indices in CRS and related airway diseases. Pade et al. demonstrated that elevated serum eosinophil levels were associated with olfactory dysfunction and inversely correlated with odour scores (22). Kara et al. reported significantly higher ELR in CRSwNP compared with controls, with a positive correlation between ELR and Lund–Mackay scores (23). More recently, Bayer et al. showed that both peripheral eosinophil count and ELR were independently associated with the need for revision ESS, suggesting their prognostic utility in predicting surgical outcomes (24). Beyond CRS, ELR has also been associated with therapeutic response: in patients with severe allergic asthma, Merve et al. demonstrated that higher baseline ELR predicted favourable response to omalizumab, with better ACT scores and improved lung function during follow-up (25). Together, these findings consistently point to ELR as a robust and clinically relevant marker of eosinophil-driven inflammation across airway diseases.

In contrast, other systemic indices such as SII and NLR were not significantly associated with CRS severity or olfactory dysfunction in our cohort. This is in line with the study by Erdogan et al., who evaluated SII in asthma and NSAID-exacerbated respiratory disease and found that while SII provided some discriminatory ability, it lacked robust predictive power for differentiating disease phenotypes (26). Similarly, another study demonstrated that NLR was significantly elevated in patients with nasal polyps compared with healthy controls, whereas PLR did not differ significantly (27). However, our findings did not reveal an association between NLR and CRS severity, which may reflect differences in patient selection, sample size, or inflammatory phenotype. Furthermore, systemic inflammatory indices such as SII and NLR have shown stronger associations in diseases characterised by widespread systemic inflammation, including neutrophilic asthma or chronic obstructive pulmonary disease, rather than in conditions dominated by localised eosinophilic mucosal inflammation (28, 29).

Overall, ELR appears to reflect the eosinophilic burden typical of CRSwNP and may provide additional insight into disease severity beyond conventional systemic indices. There is a clear need for larger, multicenter studies to validate these findings and to determine the clinical utility of ELR in CRS management.

CONCLUSION

Our findings revealed no significant correlations between systemic inflammatory indices (IgE, NLR, PLR, and SII) and olfactory test outcomes, endoscopic staging, radiological staging, or SNOT-22 scores. In contrast, ELR was significantly elevated in CRSwNP and showed discriminative potential as a disease-specific biomarker. Future research with larger, multicenter cohorts is warranted to validate and expand upon these findings.

Ethics Committee Approval	Ethics committee approval was received for this study from the ethics committee of Ankara Bilkent City Hospital (Date:19.10.2022, No: E1-22-2964,).
Informed Consent	Written informed consent was obtained from all participants who participated in this study.
Author Contributions	Conception/Design of Study- E.E.T., M.C., A.A., Z.B.P.; Data Acquisition- E.E.T., M.C., A.A., Z.B.P.; Data Analysis/Interpretation- E.E.T., M.C., A.A., Z.B.P.; Drafting Manuscript- E.E.T., M.C., A.A., Z.B.P.; Critical Revision of Manuscript- E.E.T., M.C.; Final Approval and Accountability- E.E.T., M.C., Z.B.P.
Conflict of Interest	The authors have no conflict of interest to declare.
Financial Disclosure	The authors declared that this study has received no financial support.

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