Rom J Morphol Embryol 2025, 66(4):693–701 ISSN (print) 1220–0522, ISSN (online) 2066–8279 doi: 10.47162/RJME.66.4.07

ORIGINAL PAPER

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Clinical, laboratory, and histopathological factors associated with revision surgery in chronic rhinosinusitis with nasal polyps

ALEX IULIAN MILEA[1,2], IONUŢ TĂNASE[2,3], ANDREEA ELENA MILEA[1,3], CONSTANTIN IOAN BUSUIOC[4], CARMEN AURELIA MOGOANTĂ[5], CAIUS CODRUŢ SARAFOLEANU[2,3]

[1] *Doctoral School, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[2] *Department of Otorhinolaryngology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[3] *Department of Otorhinolaryngology and Head and Neck Surgery, Sf. Maria Hospital, Bucharest, Romania*

[4] *Department of Pathology, Sf. Maria Hospital, Bucharest, Romania*

[5] *Department of Otorhinolaryngology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

The aim of this study was, firstly, to classify patients with chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) into inflammatory endotypes and, secondly, to investigate the relationships between blood and tissue eosinophilia and clinical outcomes in CRSwNP, including disease severity, and recurrence. This cross-sectional, observational, nonrandomized study has been realized between January 2023–December 2024 enrolling a sample of 469 consecutive patients with chronic rhinosinusitis, of which 239 patients with CRSwNP and 230 patients with CRSsNP. The classification of CRSwNP and CRSsNP into inflammatory endotypes was performed by analyzing the levels of blood and tissue eosinophilia. The prevalence of asthma and allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) in the two groups was also analyzed. In the group of patients with CRSwNP, the severity of the disease and the level of quality of life impairment were evaluated, depending on the degree of tissue eosinophilia. The importance of the association between blood *vs.* tissue eosinophilia and the relapse of CRSwNP was also assessed. The proportion of patients with elevated blood eosinophil levels was higher in CRSwNP than CRSsNP (17.4% *vs.* 4.35%). Tissue eosinophilia was identified in 163 of 235 (69.4%) patients with CRSwNP compared with 29 of 230 (12.6%) patients with CRSsNP. From an inflammatory perspective, revision surgery was strongly associated with tissue eosinophilia. In contrast, elevated blood eosinophil levels were only moderately associated with revision surgery.

Keywords: chronic rhinosinusitis, eosinophils, revision surgery.

Introduction

Chronic rhinosinusitis (CRS) is a condition characterized by sustained symptomatic, nasal and paranasal inflammation. CRSwNP is present in almost 4% of patients and it is correlated with a remarkable impaired overall well-being related to health status [1–3]. Typical manifestations of CRS are rhinorrhea (anterior or posterior nasal drip), nasal obstruction, facial pain/pressure, decreased/loss of sense of smell [4, 5].

Current *European Position Paper on Rhinosinusitis and Nasal Polyps 2020* (EPOS2020) differentiate CRS in two phenotypes based on nasal endoscopic findings in chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) [4]. Endotypically, CRSwNP is more often associated with type 2 eosinophilic inflammation, while CRSsNP is considered as type 1 and type 3 inflammation with neutrophils and increased levels of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-8, IL-6, IL-17 [2, 6, 7]. Type 2 inflammation is defined by immunoglobulin E (IgE), eosinophilic inflammation and the cytokines (IL-4, IL-5, IL-13) [8, 9]. It is known that type 2 inflammation is associated with CRSwNP and asthma. It is important to highlight that patients with mixed T1, T2 endotype inflammation exhibited the highest rate of asthma comorbid in patients with CRSwNP, whereas this association was not observed in patients with CRSsNP [10, 11].

Early studies reported that nasal polyps are characterized by high levels of IL-5, in particular in allergic and eosinophilic CRSwNP, pointed out IL-5 as an important survival factor for eosinophils in nasal polyp tissue [2, 12, 13]. Subsequent investigations across different population confirmed the widespread correlation between eosinophilic inflammation and IL-5 in CRSwNP, reinforcing its main role in type 2 inflammation [6, 14–18]. Clinical trials which used anti-IL-5 monoclonal antibodies therapy with Reslizumab and Mepolizumab showed significant reduction of nasal polyp size in 50–60% of cases with IL-5 levels from nasal secretion as a potential biomarker of treatment response [19–23]. The mechanism of action of Reslizumab and Mepolizumab involves binding to IL-5, which suppresses IL-5 activity by preventing the interaction with the IL-5 receptor [21]. Reslizumab, which specifically binds to IL-5 limit eosinophil differentiation, activation, chemotaxis and survival resulting in

decreased eosinophilic inflammation [24, 25]. Mepolizumab is a monoclonal antibody targeting IL-5, preventing its interaction with IL-5 receptors on eosinophils, mast cells (MCs) and other target cells, which results in selective suppression of eosinophilic inflammation [26, 27].

In CRSwNP, inflammation differs depending on the regional characteristics and race. There are studies which reported that in Western countries were eosinophils in nasal polyps in 70–90% of CRSwNP [2, 17, 28–30]. In Korea and Japan, it has been reported that less than 50% of patients with CRSwNP had eosinophilic inflammation in nasal polyps [31–34]. In China, nasal polyps are positive for IL-5 in 32.47% of patients with CRSwNP [35].

Several pathways are involved in the local recruitment, retention, survival, and activation of eosinophils. Their selective recruitment contains cell surface adhesion molecules such as β_1 integrins, β_2 integrins and P-selectin, which bind to their ligands [P selectin glycoprotein ligand-1 (PSGL-1) or cluster of differentiation (CD)162, intercellular adhesion molecule-1 (ICAM-1) or CD54, vascular cell adhesion molecule-1 (VCAM-1) or CD106] expressed on the inflamed sinus mucosal endothelium [36–39].

The histological features of nasal polyps contain infiltration of eosinophils in eosinophilic nasal polyps and the basement membrane (BM) is thick, while non-eosinophilic nasal polyps consist of infiltration of inflammatory cells, which mostly are lymphocytes and plasma cells and the BM is thinner [32].

Some studies have investigated the regional variation of eosinophilia in sinonasal cavity and even fewer have assessed its association with both longitudinal and cross-sectional clinical outcomes in CRS [40, 41]. Eosinophilic cationic protein (ECP) is a granule protein that exhibits important correlation with cytokines such as IL-13, IL-5, chemokines such as eotaxin-3 [CC motif chemokine ligand 26 (CCL)26] and eotaxin-2 (CCL24)], peripheral blood and tissue eosinophil levels. It has been reported that ECP level in uncinate tissue was lower than in nasal polyps. ECP levels from uncinate tissue were associated with type 2 mediators (eotaxins, IL-13) and radiographic severity [40–42].

Coexistence of eosinophilia and nasal polyps during sinus surgery has been associated with increased postoperative medication requirements, more frequent recurrences and subsequent revision procedures [43–47]. Appropriately, accurately spotting high-risk patients for relapse is crucial for an individualized management approach. With the enlargement of therapeutic perspective of biological agents, which are targeting key pathways if eosinophilic inflammation, to recognize those patients which are more susceptible to pathogenic eosinophilic processes is now regarded as a key consideration in clinical practice [48–50].

Aim

The aim of this study was, first, to classify patients with CRSwNP and CRSsNP into inflammatory endotypes based on blood and tissue eosinophil levels and, second, to investigate the relationships between blood and tissue eosinophilia and clinical outcomes in CRSwNP, including disease severity, and recurrence.

Patients, Materials and Methods

This cross-sectional, observational, nonrandomized study has been realized between January 2023–December 2024 enrolling a sample of 469 consecutive patients with CRS, of which 239 patients with CRSwNP (group A) and 230 patients with CRSsNP (group B), treated with functional endoscopic sinus surgery (FESS). Four patients initially classified as having CRSwNP were excluded after histopathological (HP) examination identified other pathologies, leaving a total of 465 patients included in the study. Patients were identified in the Easy Medical computer system. This sample is representative of patients with CRSwNP and CRSsNP diagnosed and treated at the Department of Otorhinolaryngology and Head and Neck Surgery, Sf. Maria Hospital, Bucharest, Romania. All patients satisfied criteria defined by EPOS2020 for CRSwNP and CRSsNP. Prior to hospital admission, all patients underwent cranial computed tomography (CT) scanning; upon admission, each patient had a nasal endoscopic examination, nasal exudate sampling under endoscopic guidance, and blood sample collection. Asthma was diagnosed by a pulmonologist based on peak expiratory flow measurements, and nonsteroidal anti-inflammatory drug (NSAID) intolerance was determined using serum-specific IgE testing and/or skin prick testing. Patients with blood eosinophil value higher than $0.6\times10^3/\mu L$ were considered to have eosinophilia.

Disease severity was evaluated using endoscopic assessment of nasal polyp size using the Meltzer grading system and by radiological assessment using the Lund–Mackay scoring system. Assessment of quality of life (QoL) impairment was performed using the Sinonasal Outcome Test-22 (SNOT-22) questionnaire.

Biopsy samples were collected from sinonasal mucosa and nasal polyps during surgical procedures and the research assessed the presence and density of eosinophils within the biopsy sample. Sinonasal mucosal specimens were consistently collected during FESS from the ethmoid sinuses, specifically from the area lateral to the middle turbinate at the level of the ethmoid bulla or the suprabullar recess. After collection, tissues were fixed in formalin and embedded in paraffin, sectioned at 4 μm and stained with Hematoxylin–Eosin (HE) for HP evaluation and eosinophil quantification. An experienced hospital pathologist performed the HP evaluation and eosinophil quantification of tissue. Eosinophils were quantified on HE-stained sections by evaluating the whole field of the specimen at 200× magnification. Based on eosinophil count, tissue eosinophilia was categorized as absent, rare, or frequent. Blinding to clinical information was not performed, as tissue specimens were processed in accordance with standard pathology practice.

Statistical analysis was carried out using GraphPad Prism 9.3.0. Proportions are presented with 95% confidence intervals (CIs) calculated using the exact binomial (Clopper–Pearson) method. Categorical data are shown as frequencies and percentages, while continuous data are reported as mean ± standard deviation (SD). Associations between tissue eosinophil grade (absent/rare/frequent) and disease severity measures (Meltzer endoscopic grade and Lund–Mackay score) and QoL (SNOT-22) were evaluated using Spearman's rank correlation and the Kruskal–Wallis test. Group comparisons of SNOT-22 by comorbidity status (asthma, NSAID-exacerbated disease) were performed using the Mann–Whitney *U*-test. Associations with revision surgery

status were analyzed using Fisher's exact test, and odds ratios (ORs) were reported. A p-value <0.05 was considered statistically significant.

Results

Demographic data and comorbidities

A total of 465 patients meet inclusion criteria for this study. CRSwNP was present in 235 patients (group A) and CRSsNP in 230 patients (group B). In this study, 52% were men (245 patients) and 48% were women (223 patients). CRSwNP was more frequent in men (62%, n=146 patients) than women (38%, n=89 patients). While among patients with CRSsNP, women (57%, n=132 patients) were more often than men (43%, n=98 patients). Average age was almost the same, such as in group A it was 48 years and in group B it was 47 years.

Asthma was reported in 30% of patients with CRSwNP and in 3% of patients with CRSsNP. Allergy to NSAIDs had 19% of patients from group A. Among patients with CRSsNP (group B) the allergy to NSAIDs was absent. Previous sinus surgery was performed in 40% of the patients with CRS and nasal polyps and only in 5% of those with CRSsNP (Table 1).

Laboratory outcomes

The proportion of patients with elevated blood eosinophil levels was higher in CRSwNP than CRSsNP (17.4% *vs.* 4.35%), and this difference was statistically significant (Fisher's exact test, p<0.0001).

Staphylococcus aureus was isolated from nasal swabs in 20 of 235 patients with CRSwNP [8.5%, 95% CI: 5.2–12.9%] and in 10 of 230 patients with CRSsNP (4.3%, 95% CI: 2.1–7.8%). Although *S. aureus* colonization was more frequent in CRSwNP, the difference did not reach statistical significance (χ^2=2.68, p=0.0598; OR 2.140).

Table 1 – ***Patient demographics and associated comorbidities***

Characteristics	CRSwNP (n=235); n (%)	CRSsNP (n=230); n (%)
Age, mean ± SD [years]	51.46±14.04	47.29±15.18
Male	146 (62%)	98 (43%)
Female	89 (38%)	132 (57%)
Asthma	70 (30%)	6 (3%)
NSAIDs	45 (19%)	0
Previous sinus surgery	95 (40%)	12 (5%)

CRSsNP: Chronic rhinosinusitis without nasal polyps; CRSwNP: Chronic rhinosinusitis with nasal polyps; n: No. of cases; NSAIDs: Non-steroidal anti-inflammatory drugs; SD: Standard deviation.

Histopathological findings

Tissue eosinophilia was identified in 163 of 235 patients with CRSwNP (69.4%; 95% CI: 63.5–75.3%), compared with 29 of 230 patients with CRSsNP (12.6%; 95% CI: 8.3–16.9%). This difference was highly statistically significant (χ^2=152.1, p<0.0001), with an OR of 15.69, indicating a markedly higher likelihood of tissue eosinophilia in CRSwNP.

Among CRSwNP patients, eosinophils were absent in 30.6%, rare in 10.6%, and frequent in 58.7% of cases (Figure 1, A–C).

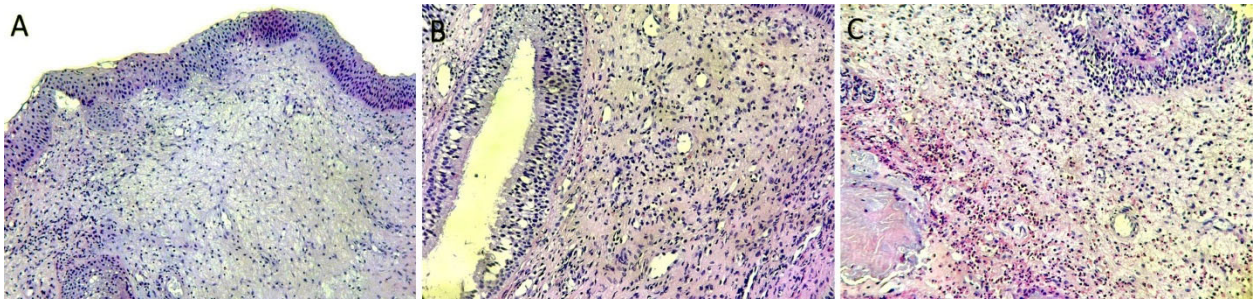

Figure 1 – ***Presence of eosinophils in nasal polyps: (A) Absent eosinophils; (B) Rare eosinophils; (C) Frequent eosinophils. Hematoxylin–Eosin (HE) staining: (A–C) ×200.***

Endoscopic, imaging, and quality of life results in CRSwNP group

The mean polyposis grade in the 235 patients analyzed using the Meltzer grading system was 2.72±0.85.

The radiological evaluation based on the Lund–Mackay scale showed a mean score of 15.8±5.43.

Assessment of QoL using the SNOT-22 questionnaire demonstrated a mean score of 36±18.4; 28.1% of patients had scores ≥50 (Table 2).

Table 2 – ***Distribution of endoscopic, radiological and quality of life outcomes***

Characteristics	Value (n=235); n (%)
Nasal polyposis grade, mean ± SD	2.72±0.85
Lund–Mackay scale, mean ± SD	15.8±5.43
SNOT-22 score, mean ± SD	36±18.4
SNOT-22 scores ≥50 [%]	28.1

n: No. of cases; SD: Standard deviation; SNOT-22: Sinonasal Outcome Test-22.

Distribution of variables based on CRSwNP severity (endoscopic, imaging, and QoL results)

When stratified by tissue eosinophil grade, significant differences were observed.

Endoscopic disease severity increased significantly with higher tissue eosinophil levels. The mean Meltzer grade rose from 1.99±0.62 in patients without eosinophils to 2.36±0.64 in those with rare eosinophils and 3.16±0.68 in those with frequent eosinophils (Kruskal–Wallis H=98.86, p<0.0001) (Figure 2).

Radiological severity showed a similar pattern. The mean Lund–Mackay score increased from 11.22±3.60 (absent) to 13.36±4.16 (rare) and 18.59±4.53 (frequent) (H=92.68, p<0.0001) (Figure 3).

QoL impairment also increased with tissue eosinophil burden. Mean SNOT-22 scores were 20.49±9.02 in the absent group, 27.80±11.97 in the rare group, and 45.44±16.69 in the frequent group (H=96.38, p<0.0001) (Figure 4).

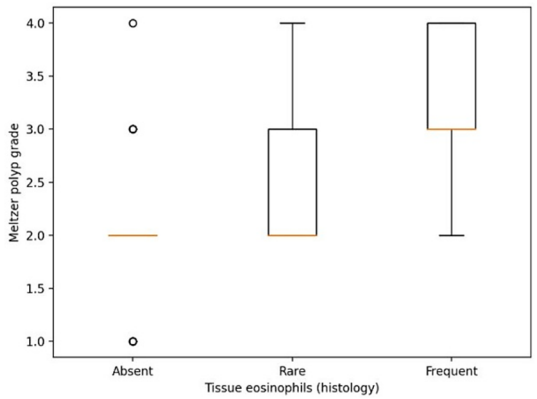

Figure 2 – ***Distribution of Meltzer polyp grades according to tissue eosinophilia status.***

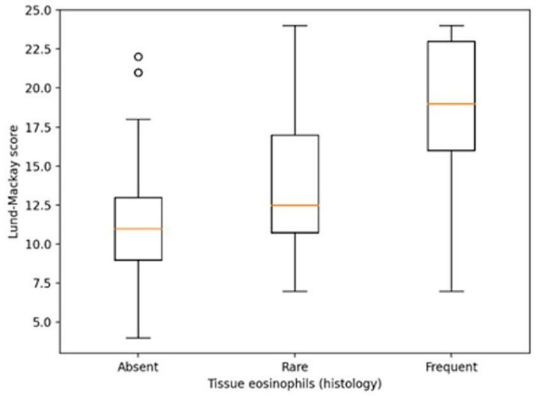

Figure 3 – ***Lund–Mackay radiological scores according to tissue eosinophilia status.***

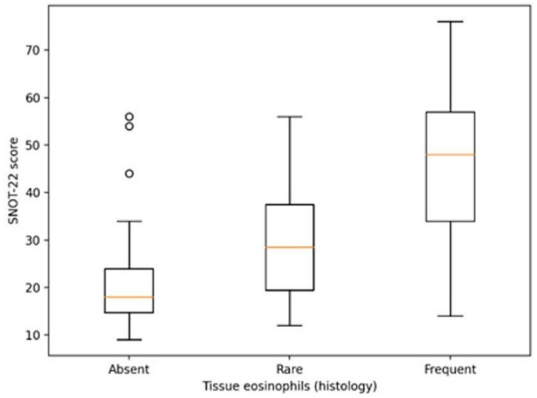

Figure 4 – ***Quality of life impairment (SNOT-22 score) according to tissue eosinophilia status. SNOT-22: Sinonasal Outcome Test-22.***

Asthma was present in 30% of patients and NSAID allergy in 19%.

Patients with asthma had significantly worse QoL than those without asthma (SNOT-22: 55.29±12.26 *vs.* 27.62±13.67, $p<0.0001$) (Figure 5).

Similarly, patients with NSAID allergy had higher SNOT-22 scores (58.64±11.18 *vs.* 30.66±15.44, $p<0.0001$) (Figure 6).

Comparison between primary and revision surgery in CRSwNP

Patients undergoing revision surgery differed significantly from those undergoing primary surgery across several clinical, endoscopic, radiological, and inflammatory parameters.

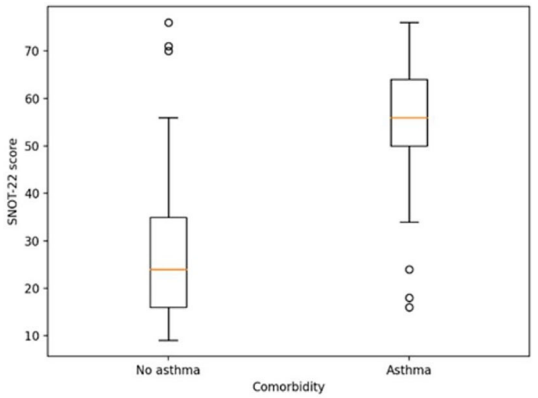

Figure 5 – ***SNOT-22 score distribution by asthma status in chronic rhinosinusitis with nasal polyps. SNOT-22: Sinonasal Outcome Test-22.***

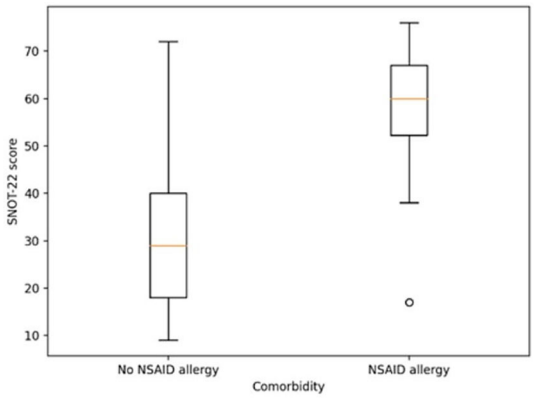

Figure 6 – ***Quality of life assessed by SNOT-22 in relation to NSAID intolerance in chronic rhinosinusitis with nasal polyps. NSAIDs: Non-steroidal anti-inflammatory drug; SNOT-22: Sinonasal Outcome Test-22.***

Asthma was more frequent among patients requiring revision surgery (45.3%) compared with those undergoing primary surgery (19.3%), and this difference was statistically significant (OR 3.716, $p<0.0001$). Similarly, NSAID allergy was more prevalent in the revision group (34.7% *vs.* 8.6%, OR 7.292, $p<0.0001$).

Endoscopic severity was higher in the revision group, with a mean Meltzer grade of 3.18±0.71 compared with 2.41±0.79 in the primary surgery group ($p<0.0001$). Radiological severity followed the same pattern, with higher Lund–Mackay scores in revision cases (18.75±4.64 *vs.* 13.79±5.01, $p<0.0001$).

QoL was significantly worse in patients undergoing revision surgery, with higher SNOT-22 scores compared to primary surgery patients (46.35±16.91 *vs.* 29.01±16.00, $p<0.0001$).

From an inflammatory perspective, revision surgery was strongly associated with tissue eosinophilia. Frequent tissue eosinophilia was markedly more prevalent among patients undergoing revision surgery compared with those undergoing primary surgery (90.5% *vs.* 37.1%, $p<0.0001$).

In contrast, elevated blood eosinophil levels were only moderately associated with revision surgery, being more common in revision cases than in primary surgery cases (34.7% *vs.* 12.1%, OR 3.85, $p<0.0001$).

Discussions

CRS is a common, persistent inflammatory disease of the upper airways, with an estimated prevalence of about 10% worldwide, while the prevalence of CRSwNP is approximately 4% worldwide [51].

Despite not being life-threatening, the high global prevalence of CRS results in marked QoL impairment and a considerable socioeconomic burden [52, 53].

CRSwNP is predominantly characterized by a type 2 inflammatory response [10] largely driven by IL-4, IL-5, and IL-13. Markers signaling type 2 inflammation include periostin, IgE, thymus and activation-regulated chemokine, eotaxin-3, and ECP. The nasal mucosa in CRSwNP is enriched with eosinophils, MCs, T helper 2 (Th2) lymphocytes, type 2 innate lymphoid cells (ILC2s), and hyperplastic goblet cells, among other inflammatory and structural cells [54, 55].

Disease severity has been shown to correlate with eosinophil- and IL-5-enriched nasal polyps and is associated with an increased risk of repeated surgical interventions over a patient's lifetime [2, 54].

Eosinophilic inflammation is well-established as a distinctive characteristic of CRSwNP; however, considerable heterogeneity exists among CRS phenotypes, and a subset of patients with CRSwNP exhibit non-eosinophilic inflammatory patterns. Recent studies estimate that approximately 15% of CRSwNP cases in Western populations are non-eosinophilic [10, 56, 57].

Although the presence of nasal polyps is generally associated with increased tissue eosinophilia, eosinophilic inflammation is not exclusive to CRSwNP and can also be observed in CRSsNP. The extent to which peripheral blood eosinophil counts reflect eosinophilic inflammation within the sinonasal mucosa remains controversial, and direct assessment of tissue eosinophilia continues to be considered an important unmet need in routine HP reporting [58, 59].

Recent years have seen major progress in understanding of the complex immunological and inflammatory patterns underlying the clinically heterogeneous forms of CRS [60]. Although medical and surgical management of CRS has improved, recurrence remains a significant obstacle, indicating the importance of identifying factors that determine relapse [5, 61].

In this cross-sectional study, we assessed peripheral blood and tissue eosinophilia, as well as the prevalence of asthma and NSAID intolerance, in patients with CRSwNP in comparison with patients with CRSsNP undergoing sinonasal surgery in our hospital in Romania over a two-year period. We further examined the associations between blood and tissue eosinophilia and disease severity, assessed by endoscopic polyp grade and the radiological Lund–Mackay score, QoL impairment, the presence of asthma and NSAID intolerance, and disease recurrence, defined as the need for revision sinonasal surgery, in patients with CRSwNP.

In this heterogeneous cohort of patients with CRS from across Romania, CRSwNP was predominantly associated with type 2 inflammation, whereas CRSsNP was more commonly linked to non-type 2 inflammatory patterns.

According to the EPOS2020 guideline, classifying a CRS patient as having type 2 inflammation is based on evidence of type 2 immune activation using clinical and inflammatory biomarkers. A patient with CRS is considered to have evidence of type 2 inflammation if one or more of the following are present: the presence of tissue eosinophilia, increased levels of blood eosinophilia and high levels of total IgE [62].

In our cohort, patients with CRSwNP revealed an obviously different inflammatory and clinical profile compared with those without nasal polyps. Blood eosinophilia was more frequently observed in patients with CRSwNP than in those with CRSsNP, and this difference was even more noticeable at the tissue level, where eosinophilic inflammation was identified in nearly two thirds of patients undergoing surgery for CRSwNP, compared with only a small group of patients with CRSsNP. These findings further support the concept that CRSwNP is predominantly associated with a type 2 inflammatory endotype, whereas CRSsNP more commonly reflects non-type 2 inflammatory pathway.

Consistent with this inflammatory profile, type 2-associated comorbidities were substantially more prevalent in the CRSwNP group. Asthma and NSAID intolerance were frequently observed among patients with CRSwNP but were rare or absent in patients with CRSsNP, reinforcing the close relationship between nasal polyposis, systemic type 2 inflammation, and respiratory comorbidities.

With regard to microbiological findings, *S. aureus* was isolated more often in patients with CRSwNP than in those with CRSsNP; however, this difference did not reach statistical significance. These results should be interpreted with caution, as culture-based techniques may underestimate or incompletely characterize the sinonasal microbiota. Indeed, culture methods are limited in their ability to detect non-cultivable organisms and to reflect the true microbial diversity of the sinonasal environment. Recent studies employing deoxyribonucleic acid (DNA)-based bacterial profiling have demonstrated a far more complex microbiome in CRSwNP, identifying hundreds of bacterial genera within sinonasal samples. In such analyses, *Staphylococcus* frequently emerges as a dominant genus, particularly in patients with recurrent disease, alongside other genera such as *Corynebacterium* and *Sphingomonas*. These observations suggest that while *S. aureus* may play a role in the inflammatory milieu of CRSwNP, especially in recurrent disease, conventional culture techniques likely provide an incomplete representation of microbial involvement [63].

The statistically significant differences in the prevalence of blood and tissue eosinophilia, as well as type 2-associated comorbidities such as asthma and NSAID intolerance, between patients with CRSwNP and those without nasal polyps support the predominance of type 2 inflammation in CRSwNP and non-type 2 inflammation in CRSsNP in this cohort of 465 patients treated in our hospital in Romania.

In this cohort of patients with CRSwNP, disease severity was substantial, as reflected by high endoscopic and radiological scores and a marked impairment in QoL. A considerable proportion of patients required revision surgery, underscoring the recurrent nature of CRSwNP in a significant subset of cases.

Asthma and NSAID intolerance were frequent comorbidities and were consistently associated with worse patient-reported outcomes and a higher likelihood of revision surgery. Patients with these comorbidities experienced significantly greater QoL impairment and were overrepresented among revision cases, supporting the concept that CRSwNP associated with systemic type 2 comorbidities represents a more severe and treatment-resistant disease phenotype.

A key finding of this study is the strong association between tissue eosinophilia and disease severity, QoL impairment, and recurrence. Increasing tissue eosinophil burden was associated with progressively higher endoscopic and radiological disease scores and markedly worse SNOT-22 results. Moreover, frequent tissue eosinophilia was highly prevalent in patients requiring revision surgery and showed a very strong association with recurrence. In contrast, despite the fact that elevated blood eosinophil levels were more common in revision cases, their association with recurrence was significantly weaker than that observed for tissue eosinophilia.

In combination, these findings suggest that local eosinophilic inflammation plays a central pathogenic role in driving disease severity and recurrence in CRSwNP. Tissue eosinophilia appears to be a more reliable marker of aggressive disease behavior than systemic eosinophilia. This highlights the importance of HP analysis of eosinophilic inflammation in routine practice and supports the role of tissue-based biomarkers in identifying patients at high risk of recurrence who may benefit from targeted anti-type 2 therapeutic strategies.

Patients undergoing revision surgery exhibited significantly greater endoscopic and radiological disease severity, as reflected by higher Meltzer grades and Lund–Mackay scores, and also markedly worse QoL impairment.

Study limitations

Limitations of this study include its retrospective design and the lack of evaluation of additional inflammatory markers, such as total IgE and cytokines, which may further influence disease progression. In addition, assessment of the sinonasal microbiota was based on conventional bacterial culture rather than DNA-based sequencing techniques. As culture methods may underestimate microbial diversity and fail to detect non-cultivable organisms, this approach may have limited the accurate characterization of the sinonasal microbiome and its potential role in disease severity and recurrence.

Conclusions

In our cohort, CRSwNP was characterized by a type 2 inflammatory profile, while CRSsNP polyps was associated with non-type 2 inflammation. Tissue eosinophilia showed a stronger association with disease severity, control, and recurrence in patients with CRSwNP than peripheral blood eosinophilia. In our cohort, blood eosinophil levels were unreliable markers of disease recurrence, whereas tissue eosinophil burden emerged as a key indicator of disease severity and recurrent CRSwNP. Revision surgery in CRSwNP is associated with a more severe clinical phenotype characterized by higher disease burden, worse QoL, and a higher prevalence of asthma and NSAID allergy.

Conflict of interests

The authors declare that they have no conflict of interests. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement

Written consent was obtained from the patients participating in this study.

References

[1] Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: a prospective questionnaire and clinical cross-sectional study. Clin Otolaryngol, 2013, 38(6): 474–480. https://doi.org/10.1111/coa.12189 PMID: 24131818

[2] Orlandi RR, Kingdom TT, Smith TL, Bleier B, DeConde A, Luong AU, Poetker DM, Soler Z, Welch KC, Wise SK, Adappa N, Alt JA, Anselmo-Lima WT, Bachert C, Baroody FM, Batra PS, Bernal-Sprekelsen M, Beswick D, Bhattacharyya N, Chandra RK, Chang EH, Chiu A, Chowdhury N, Citardi MJ, Cohen NA, Conley DB, DelGaudio J, Desrosiers M, Douglas R, Eloy JA, Fokkens WJ, Gray ST, Gudis DA, Hamilos DL, Han JK, Harvey R, Hellings P, Holbrook EH, Hopkins C, Hwang P, Javer AR, Jiang RS, Kennedy D, Kern R, Laidlaw T, Lal D, Lane A, Lee HM, Lee JT, Levy JM, Lin SY, Lund V, McMains KC, Metson R, Mullol J, Naclerio R, Oakley G, Otori N, Palmer JN, Parikh SR, Passali D, Patel Z, Peters A, Philpott C, Psaltis AJ, Ramakrishnan VR, Ramanathan M Jr, Roh HJ, Rudmik L, Sacks R, Schlosser RJ, Sedaghat AR, Senior BA, Sindwani R, Smith K, Snidvongs K, Stewart M, Suh JD, Tan BK, Turner JH, van Drunen CM, Voegels R, Wang Y, Woodworth BA, Wormald PJ, Wright ED, Yan C, Zhang L, Zhou B. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021. Int Forum Allergy Rhinol, 2021, 11(3):213–739. https://doi.org/10.1002/alr.22741. Erratum in: Int Forum Allergy Rhinol, 2022, 12(7):974. https://doi.org/10.1002/alr.22987 PMID: 33236525

[3] Lam K, Schleimer R, Kern RC. The etiology and pathogenesis of chronic rhinosinusitis: a review of current hypotheses. Curr Allergy Asthma Rep, 2015, 15(7):41. https://doi.org/10.1007/s11882-015-0540-2 PMID: 26143392 PMCID: PMC4874491

[4] Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, Toppila-Salmi S, Bernal-Sprekelsen M, Mullol J, Alobid I, Terezinha Anselmo-Lima W, Bachert C, Baroody F, von Buchwald C, Cervin A, Cohen N, Constantinidis J, De Gabory L, Desrosiers M, Diamant Z, Douglas RG, Gevaert PH, Hafner A, Harvey RJ, Joos GF, Kalogjera L, Knill A, Kocks JH, Landis BN, Limpens J, Lebeer S, Lourenco O, Meco C, Matricardi PM, O'Mahony L, Philpott CM, Ryan D, Schlosser R, Senior B, Smith TL, Teeling T, Tomazic PV, Wang DY, Wang D, Zhang L, Agius AM, Ahlstrom-Emanuelsson C, Alabri R, Albu S, Alhabash S, Aleksic A, Aloulah M, Al-Qudah M, Alsaleh S, Baban MA, Baudoin T, Balvers T, Battaglia P, Bedoya JD, Beule A, Bofares KM, Braverman I, Brozek-Madry E, Richard B, Callejas C, Carrie S, Caulley L, Chussi D, de Corso E, Coste A, El Hadi U, Elfarouk A, Eloy PH, Farrokhi S, Felisati G, Ferrari MD, Fishchuk R, Grayson W, Goncalves PM, Grdinic B, Grgic V, Hamizan AW, Heinichen JV, Husain S, Ping TI, Ivaska J, Jakimovska F, Jovancevic L, Kakande E, Kamel R, Karpischenko S, Kariyawasam HH, Kawauchi H, Kjeldsen A, Klimek L, Krzeski A, Kopacheva Barsova G, Kim SW, Lal D, Letort JJ, Lopatin A, Mahdjoubi A, Mesbahi A, Netkovski J, Nyenbue Tshipukane D, Obando-Valverde A, Okano M, Onerci M, Ong YK, Orlandi R, Otori N, Ouennoughy K, Ozkan M, Peric A, Plzak J, Prokopakis E, Prepageran N, Psaltis A, Pugin B, Raftopulos M, Rombaux P, Riechelmann H, Sahtout S, Sarafoleanu CC, Searyoh K, Rhee CS, Shi J, Shkoukani M, Shukuryan AK, Sicak M, Smyth D, Sindvongs K, Soklic Kosak T, Stjarne P, Sutikno B, Steinsvag S, Tantilipikorn P, Thanaviratananich S, Tran T, Urbancic J, Valiulius A, Vasquez de Aparicio C, Vicheva D,

Virkkula PM, Vicente G, Voegels R, Wagenmann MM, Wardani RS, Welge-Lussen A, Witterick I, Wright E, Zabolotniy D, Zsolt B, Zwetsloot CP. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology, 2020, 58(Suppl S29):1–464. https://doi.org/10.4193/Rhin20.600 PMID: 32077450

[5] Radabaugh JP, Han JK, Moebus RG, Somers E, Lam K. Analysis of histopathological endotyping for chronic rhinosinusitis phenotypes based on comorbid asthma and allergic rhinitis. Am J Rhinol Allergy, 2019, 33(5):507–512. https://doi.org/10.1177/1945892419846263 PMID: 31046407

[6] Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, Bachert C. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy, 2006, 61(11):1280–1289. https://doi.org/10.1111/j.1398-9995.2006.01225.x PMID: 17002703

[7] Turner JH, Chandra RK, Li P, Bonnet K, Schlundt DG. Identification of clinically relevant chronic rhinosinusitis endotypes using cluster analysis of mucus cytokines. J Allergy Clin Immunol, 2018, 141(5):1895–1897.e7. https://doi.org/10.1016/j.jaci.2018.02.002 PMID: 29452200 PMCID: PMC5938108

[8] Tomassen P, Vandeplas G, Van Zele T, Cardell LO, Arebro J, Olze H, Förster-Ruhrmann U, Kowalski ML, Olszewska-Ziąber A, Holtappels G, De Ruyck N, Wang X, Van Drunen C, Mullol J, Hellings P, Hox V, Toskala E, Scadding G, Lund V, Zhang L, Fokkens W, Bachert C. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol, 2016, 137(5):1449–1456.e4. https://doi.org/10.1016/j.jaci.2015.12.1324 PMID: 26949058

[9] Kato A. Immunopathology of chronic rhinosinusitis. Allergol Int, 2015, 64(2):121–130. https://doi.org/10.1016/j.alit.2014.12.006 PMID: 25838086 PMCID: PMC4675657

[10] Stevens WW, Peters AT, Tan BK, Klingler AI, Poposki JA, Hulse KE, Grammer LC, Welch KC, Smith SS, Conley DB, Kern RC, Schleimer RP, Kato A. Associations between inflammatory endotypes and clinical presentations in chronic rhinosinusitis. J Allergy Clin Immunol Pract, 2019, 7(8):2812–2820.e3. https://doi.org/10.1016/j.jaip.2019.05.009 PMID: 31128376 PMCID: PMC6842686

[11] De Boeck I, Wittouck S, Martens K, Claes J, Jorissen M, Steelant B, van den Broek MFL, Seys SF, Hellings PW, Vanderveken OM, Lebeer S. Anterior nares diversity and pathobionts represent sinus microbiome in chronic rhinosinusitis. mSphere, 2019, 4(6):e00532-19. https://doi.org/10.1128/mSphere.00532-19 PMID: 31776238 PMCID: PMC6881717

[12] Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. J Immunol, 1997, 158(8):3902–3908. https://doi.org/10.4049/jimmunol.158.8.3902 PMID: 9103460

[13] Hamilos DL, Leung DYM, Wood R, Cunningham L, Bean DK, Yasruel Z, Schotman E, Hamid Q. Evidence for distinct cytokine expression in allergic *versus* nonallergic chronic sinusitis. J Allergy Clin Immunol, 1995, 96(4):537–544. https://doi.org/10.1016/s0091-6749(95)70298-9 PMID: 7560666

[14] Polzehl D, Moeller P, Riechelmann H, Perner S. Distinct features of chronic rhinosinusitis with and without nasal polyps. Allergy, 2006, 61(11):1275–1279. https://doi.org/10.1111/j.1398-9995.2006.01132.x PMID: 17002702

[15] Jankowski R, Bouchoua F, Coffinet L, Vignaud JM. Clinical factors influencing the eosinophil infiltration of nasal polyps. Rhinology, 2002, 40(4):173–178. https://doi.org/10.4193/Rhin PMID: 12526243

[16] Park SJ, Kim TH, Jun YJ, Lee SH, Ryu HY, Jung KJ, Jung JY, Hwang GH, Lee SH. Chronic rhinosinusitis with polyps and without polyps is associated with increased expression of suppressors of cytokine signaling 1 and 3. J Allergy Clin Immunol, 2013, 131(3):772–780. https://doi.org/10.1016/j.jaci.2012.12.671 PMID: 23375208

[17] Zhang N, Van Zele T, Perez-Novo C, Van Bruaene N, Holtappels G, DeRuyck N, Van Cauwenberge P, Bachert C. Different types of T-effector cells orchestrate mucosal inflammation in chronic sinus disease. J Allergy Clin Immunol, 2008, 122(5):961–968. https://doi.org/10.1016/j.jaci.2008.07.008 PMID: 18804271

[18] Van Bruaene N, Pérez-Novo CA, Basinski TM, Van Zele T, Holtappels G, De Ruyck N, Schmidt-Weber C, Akdis C, Van Cauwenberge P, Bachert C, Gevaert P. T-cell regulation in chronic paranasal sinus disease. J Allergy Clin Immunol, 2008, 121(6):1435–1441, 1441.e1–3. https://doi.org/10.1016/j.jaci.2008.02.018 PMID: 18423831

[19] Gevaert P, Van Bruaene N, Cattaert T, Van Steen K, Van Zele T, Acke F, De Ruyck N, Blomme K, Sousa AR, Marshall RP, Bachert C. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol, 2011, 128(5):989–995.e1–8. https://doi.org/10.1016/j.jaci.2011.07.056 PMID: 21958585

[20] Gevaert P, Lang-Loidolt D, Lackner A, Stammberger H, Staudinger H, Van Zele T, Holtappels G, Tavernier J, van Cauwenberge P, Bachert C. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. J Allergy Clin Immunol, 2006, 118(5):1133–1141. https://doi.org/10.1016/j.jaci.2006.05.031 PMID: 17088140

[21] Maza-Solano J, Calvo-Henríquez C, Alobid I, Álvarez-Cendrero M, Palomares Ó, Moreno-Luna R, Santos-Perez J, González-García J, Sánchez-Gómez S. Nasal symptoms in asthmatic patients under treatment with anti-IL-5 monoclonal antibodies. A real-life cohort study. J Clin Med, 2022, 11(23):7056. https://doi.org/10.3390/jcm11237056 PMID: 36498632 PMCID: PMC9740481

[22] Kartush AG, Schumacher JK, Shah R, Patadia MO. Biologic agents for the treatment of chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy, 2019, 33(2):203–211. https://doi.org/10.1177/1945892418814768 PMID: 30587005

[23] Weinstein SF, Katial RK, Bardin P, Korn S, McDonald M, Garin M, Bateman ED, Hoyte FCL, Germinaro M. Effects of Reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract, 2019, 7(2):589–596.e3. https://doi.org/10.1016/j.jaip.2018.08.021 PMID: 30193936

[24] Boiko N, Stagnieva I, Lodochkina O. Chronic rhinosinusitis with polyps and comorbid asthma: results of Reslizumab treatment. SEE J Immunol, 2023, 6(1):39–44. https://doi.org/10.3889/seejim.2023.6039

[25] Koennecke M, Klimek L, Mullol J, Gevaert P, Wollenberg B. Subtyping of polyposis nasi: phenotypes, endotypes and comorbidities. Allergo J Int, 2018, 27(2):56–65. https://doi.org/10.1007/s40629-017-0048-5 PMID: 29564208 PMCID: PMC5842507

[26] Emma R, Morjaria JB, Fuochi V, Polosa R, Caruso M. Mepolizumab in the management of severe eosinophilic asthma in adults: current evidence and practical experience. Ther Adv Respir Dis, 2018, 12:1753466618808490. https://doi.org/10.1177/1753466618808490 PMID: 30354852 PMCID: PMC6204623

[27] Plaza V, Alobid I, Alvarez C, Blanco M, Ferreira J, García G, Gómez-Outes A, Gómez F, Hidalgo A, Korta J, Molina J, Pellegrini FJ, Pérez M, Plaza J, Praena M, Quirce S, Sanz J. Spanish Asthma Management Guidelines (GEMA) VERSION 5.1. Highlights and controversies. Arch Bronconeumol, 2022, 58(2):150–158. https://doi.org/10.1016/j.arbres.2021.05.010 PMID: 34167859

[28] Payne SC, Borish L, Steinke JW. Genetics and phenotyping in chronic sinusitis. J Allergy Clin Immunol, 2011, 128(4):710–720; quiz 721–722. https://doi.org/10.1016/j.jaci.2011.05.022 PMID: 21704364

[29] Bochner BS, Stevens WW. Biology and function of eosinophils in chronic rhinosinusitis with or without nasal polyps. Allergy Asthma Immunol Res, 2021, 13(1):8–22. https://doi.org/10.4168/aair.2021.13.1.8 PMID: 33191674 PMCID: PMC7680832

[30] Bachert C, Brusselle G, Castillo Vizuete JA, Dávila I, Laudien M, Seccia V, Schmid-Grendelmeier P, Vultaggio A, Kallinikou K, Walrave L, Klimek L. Consensus from European experts on severe eosinophilic asthma and chronic rhinosinusitis with nasal polyps: results from the OverSEA Delphi study. J Allergy Clin Immunol Glob, 2025, 4(4):100529. https://doi.org/10.1016/j.jacig.2025.100529 PMID: 40832363 PMCID: PMC12359228

[31] Yoshimura K, Kawata R, Haruna S, Moriyama H, Hirakawa K, Fujieda S, Masuyama K, Takenaka H. Clinical epidemiological study of 553 patients with chronic rhinosinusitis in Japan. Allergol Int, 2011, 60(4):491–496. https://doi.org/10.2332/allergolint.10-OA-0234 PMID: 21778815

[32] Kim JW, Hong SL, Kim YK, Lee CH, Min YG, Rhee CS. Histological and immunological features of non-eosinophilic

nasal polyps. Otolaryngol Head Neck Surg, 2007, 137(6): 925–930. https://doi.org/10.1016/j.otohns.2007.07.036 PMID: 18036422

[33] Ikeda K, Shiozawa A, Ono N, Kusunoki T, Hirotsu M, Homma H, Saitoh T, Murata J. Subclassification of chronic rhinosinusitis with nasal polyp based on eosinophil and neutrophil. Laryngoscope, 2013, 123(11):E1–E9. https://doi.org/10.1002/lary.24154 PMID: 23670893

[34] Ioannidis DG, Lachanas VA, Florou Z, Bizakis JG, Petinaki E, Skoulakis CE. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*: a comparative study in patients with nasal polyposis and healthy controls. J Laryngol Otol, 2015, 129(9): 865–869. https://doi.org/10.1017/s0022215115001590 PMID: 26223662

[35] Gan W, Xiang Y, Wei B, Liu S, Liu F. The inflammatory microenvironment of nasal polyps in patients with chronic rhinosinusitis and the relationship of this microenvironment with the nasal microbiome. Asian J Surg, 2024, 47(1):124–133. https://doi.org/10.1016/j.asjsur.2023.08.096 PMID: 37659949

[36] Shin HW, Kim DK, Park MH, Eun KM, Lee M, So D, Kong IG, Mo JH, Yang MS, Jin HR, Park JW, Kim DW. IL-25 as a novel therapeutic target in nasal polyps of patients with chronic rhinosinusitis. J Allergy Clin Immunol, 2015, 135(6):1476–1485.e7. https://doi.org/10.1016/j.jaci.2015.01.003 PMID: 25725991

[37] Beck LA, Stellate C, Beall LD, Schall TJ, Leopold D, Bickel CA, Baroody F, Bochner BS, Schleimer RP. Detection of the chemokine RANTES and endothelial adhesion molecules in nasal polyps. J Allergy Clin Immunol, 1996, 98(4):766–780. https://doi.org/10.1016/s0091-6749(96)70126-4 PMID: 8876553

[38] Jahnsen FL, Haraldsen G, Aanesen JP, Haye R, Brandtzaeg P. Eosinophil infiltration is related to increased expression of vascular cell adhesion molecule-1 in nasal polyps. Am J Respir Cell Mol Biol, 1995, 12(6):624–32. https://doi.org/10.1165/ajrcmb.12.6.7539273 PMID: 7539273

[39] Symon FA, Walsh GM, Watson SR, Wardlaw AJ. Eosinophil adhesion to nasal polyp endothelium is P-selectin-dependent. J Exp Med, 1994, 180(1):371–376. https://doi.org/10.1084/jem.180.1.371 PMID: 7516413 PMCID: PMC2191567

[40] Min JY, Ocampo CJ, Stevens WW, Price CPE, Thompson CF, Homma T, Huang JH, Norton JE, Suh LA, Pothoven KL, Conley DB, Welch KC, Shintani-Smith S, Peters AT, Grammer LC 3rd, Harris KE, Hulse KE, Kato A, Modyanov NN, Kern RC, Schleimer RP, Tan BK. Proton pump inhibitors decrease eotaxin-3/CCL26 expression in patients with chronic rhinosinusitis with nasal polyps: possible role of the nongastric H,K-ATPase. J Allergy Clin Immunol, 2017, 139(1):130–141.e11. https://doi.org/10.1016/j.jaci.2016.07.020 PMID: 27717558 PMCID: PMC5222859

[41] Ochkur SI, Kim JD, Protheroe CA, Colbert D, Condjella RM, Bersoux S, Helmers RA, Moqbel R, Lacy P, Kelly EA, Jarjour NN, Kern R, Peters A, Schleimer RP, Furuta GT, Nair P, Lee JJ, Lee NA. A sensitive high throughput ELISA for human eosinophil peroxidase: a specific assay to quantify eosinophil degranulation from patient-derived sources. J Immunol Methods, 2012, 384(1–2):10–20. https://doi.org/10.1016/j.jim.2012.06.011 PMID: 22750539 PMCID: PMC3432656

[42] Weibman AR, Huang JH, Stevens WW, Suh LA, Price CPE, Lidder AK, Conley DB, Welch KC, Shintani-Smith S, Peters AT, Grammer LC, Kato A, Kern RC, Schleimer RP, Tan BK. A prospective analysis evaluating tissue biopsy location and its clinical relevance in chronic rhinosinusitis with nasal polyps. Int Forum Allergy Rhinol, 2017, 7(11):1058–1064. https://doi.org/10.1002/alr.22005 PMID: 28863237 PMCID: PMC5966315

[43] Van Zele T, Holtappels G, Gevaert P, Bachert C. Differences in initial immunoprofiles between recurrent and nonrecurrent chronic rhinosinusitis with nasal polyps. Am J Rhinol Allergy, 2014, 28(3):192–198. https://doi.org/10.2500/ajra.2014.28.4033 PMID: 24980230

[44] Tosun F, Arslan HH, Karslioglu Y, Deveci MS, Durmaz A. Relationship between postoperative recurrence rate and eosinophil density of nasal polyps. Ann Otol Rhinol Laryngol, 2010, 119(7):455–459. https://doi.org/10.1177/000348941011900705 PMID: 20734966

[45] Grgić MV, Ćupić H, Kalogjera L, Baudoin T. Surgical treatment for nasal polyposis: predictors of outcome. Eur Arch Otorhinolaryngol, 2015, 272(12):3735–3743. https://doi.org/10.1007/s00405-015-3519-7 PMID: 25634061

[46] Vlaminck S, Vauterin T, Hellings PW, Jorissen M, Acke F, Van Cauwenberge P, Bachert C, Gevaert P. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. Am J Rhinol Allergy, 2014, 28(3):260–264. https://doi.org/10.2500/ajra.2014.28.4024 PMID: 24980239

[47] Nakayama T, Yoshikawa M, Asaka D, Okushi T, Matsuwaki Y, Otori N, Hama T, Moriyama H. Mucosal eosinophilia and recurrence of nasal polyps – new classification of chronic rhinosinusitis. Rhinology, 2011, 49(4):392–396. https://doi.org/10.4193/Rhino10.261 PMID: 21991563

[48] Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. J Allergy Clin Immunol, 2015, 136(6):1431–1440. https://doi.org/10.1016/j.jaci.2015.10.010 PMID: 26654192

[49] Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland ER. Effect of subcutaneous Dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA, 2016, 315(5):469–479. https://doi.org/10.1001/jama.2015.19330 PMID: 26836729

[50] Yang SK, Cho SH, Kim DW. Interpretation of clinical efficacy of biologics in chronic rhinosinusitis with nasal polyps *via* understanding the local and systemic pathomechanisms. Allergy Asthma Immunol Res, 2022, 14(5):465–478. https://doi.org/10.4168/AAIR.2022.14.5.465 PMID: 36174990 PMCID: PMC9523422

[51] Xie X, Xuan L, Zhao Y, Wang X, Zhang L. Diverse endotypes of chronic rhinosinusitis and clinical implications. Clin Rev Allergy Immunol, 2023, 65(3):420–432. https://doi.org/10.1007/s12016-023-08976-y PMID: 38175322

[52] Anand VK. Epidemiology and economic impact of rhinosinusitis. Ann Otol Rhinol Laryngol Suppl, 2004, 193:3–5. https://doi.org/10.1177/00034894041130s502 PMID: 15174752

[53] Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, Mullol J, Gevaert P, Klimek L, Prokopakis E, Knill A, Cavaliere C, Hopkins C, Hellings P. EUFOREA Expert Board Meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: definitions and management. J Allergy Clin Immunol, 2021, 147(1):29–36. https://doi.org/10.1016/j.jaci.2020.11.013 PMID: 33227318

[54] Iordache A, Balica NC, Horhat ID, Morar R, Tischer AA, Milcu AI, Salavat MC, Borugă VM, Niculescu B, Iovănescu G, Popa ZL. Allergic rhinitis associated with nasal polyps and rhinosinusitis – histopathological and immunohistochemical study. Rom J Morphol Embryol, 2022, 63(2):413–419. https://doi.org/10.47162/RJME.63.2.12 PMID: 36374146 PMCID: PMC9801672

[55] Bachert C, Laidlaw TM, Cho SH, Mullol J, Swanson BN, Naimi S, Classe M, Harel S, Jagerschmidt A, Laws E, Ruddy M, Praestgaard A, Amin N, Mannent LP. Effect of Dupilumab on type 2 biomarkers in chronic rhinosinusitis with nasal polyps: SINUS-52 study results. Ann Otol Rhinol Laryngol, 2023, 132(12):1649–1661. https://doi.org/10.1177/00034894231176334 PMID: 37322842 PMCID: PMC10571440

[56] Marino MJ, Garcia JO, Zarka MA, Lal D. Inflammatory cell predominance and patterns in chronic rhinosinusitis with and without nasal polyposis patients. Laryngoscope Investig Otolaryngol, 2019, 4(6):573–577. https://doi.org/10.1002/lio2.328 PMID: 31890873 PMCID: PMC6929577

[57] Sánchez-Collado I, Mora T, Muñoz-Cano R, Ribó P, Mullol J, Valero A. Prevalence of chronic rhinosinusitis with nasal polyps in Catalonia (Spain): a retrospective, large-scale population-based study. Rhinology, 2022, 60(5):384–396. https://doi.org/10.4193/Rhin21.364 PMID: 36150155

[58] Snidvongs K, Lam M, Sacks R, Earls P, Kalish L, Phillips PS, Pratt E, Harvey RJ. Structured histopathology profiling of chronic rhinosinusitis in routine practice. Int Forum Allergy Rhinol, 2012, 2(5):376–385. https://doi.org/10.1002/alr.21032 PMID: 22419386

[59] Delemarre T, Bochner BS, Simon HU, Bachert C. Rethinking neutrophils and eosinophils in chronic rhinosinusitis. J Allergy

Clin Immunol, 2021, 148(2):327–335. https://doi.org/10.1016/j.jaci.2021.03.024 PMID: 33895002 PMCID: PMC8355033
[60] Hoorn EJ, Zietse R. Disorders of calcium and magnesium balance: a physiology-based approach. Pediatr Nephrol, 2013, 28(8):1195–1206. https://doi.org/10.1007/s00467-012-2350-2 PMID: 23142866
[61] Alobid I, Colás C, Castillo JA, Arismendi E, Del Cuvillo A, Gómez-Outes A, Sastre J, Mullol J; POLINA Group. Spanish Consensus on the Management of Chronic Rhinosinusitis with Nasal Polyps (POLIposis NAsal/POLINA 2.0). J Investig Allergol Clin Immunol, 2023, 33(5):317–331. https://doi.org/10.18176/jiaci.0910 PMID: 37070949
[62] van der Lans R, Otten JJ, Adriaensen GFJPM, Benoist LBL, Cornet ME, Hoven DR, Rinia AB, Fokkens WJ, Reitsma S. Eosinophils are the dominant type2 marker for the current indication of biological treatment in severe uncontrolled chronic rhinosinusitis with nasal polyps. Rhinology, 2024, 62(3):383–384. https://doi.org/10.4193/Rhin23.081 PMID: 38478151
[63] Uzunoğlu E, Kalkancı A, Kılıç E, Kızıl Y, Aydil U, Diker KS, Uslu SS. Bacterial and fungal communities in chronic rhinosinusitis with nasal polyps. PLoS One, 2024, 19(5):e0304634. https://doi.org/10.1371/journal.pone.0304634 PMID: 38820284 PMCID: PMC11142431

Corresponding authors

Caius Codruţ Sarafoleanu, Professor, MD, PhD, Department of Otorhinolaryngology, Carol Davila University of Medicine and Pharmacy, Bucharest; Department of Otorhinolaryngology and Head and Neck Surgery, Sf. Maria Hospital, 37–39 Ion Mihalache Avenue, Sector 1, 011172 Bucharest, Romania; Phone +40766–531 775, e-mail: csarafoleanu@gmail.com

Ionuţ Tănase, Lecturer, MD, PhD, Department of Otorhinolaryngology, Carol Davila University of Medicine and Pharmacy, Bucharest; Department of Otorhinolaryngology and Head and Neck Surgery, Sf. Maria Hospital, 37–39 Ion Mihalache Avenue, Sector 1, 011172 Bucharest, Romania; Phone +40766–531 775, e-mail: ionut_tanase1987@yahoo.com

Received: January 20, 2026

Accepted: March 1, 2026