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All Chronic Rhinosinusitis Endotype Clusters Demonstrate Improvement in Patient Reported and Clinical Outcome Measures after Endoscopic Sinus Surgery

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All Chronic Rhinosinusitis Endotype Clusters Demonstrate Improvement in Patient Reported and Clinical Outcome Measures after Endoscopic Sinus Surgery

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Abbreviated Title: All CRS Endotype Clusters Exhibit Improvement in Patient Reported and Objective Measures after ESS

Keywords: chronic rhinosinusitis; sinus surgery; outcome assessment (healthcare); endotype; cytokine; biomarker

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Abstract :

Background: It is unclear if chronic rhinosinusitis (CRS) endotypes show differential response to endoscopic sinus surgery (ESS). We explored mucus inflammatory cytokine expression in a cohort with CRS and associations with both patient-reported and clinically measured postoperative outcome measures.

Methods: Patients with CRS were prospectively recruited between 2016-2021 into a multi-center observational study. Mucus was collected from the olfactory cleft preoperatively and evaluated for 26

biomarkers using cluster analysis. Patient reported outcome measures included the Sino-Nasal Outcome Test (SNOT-22) and Questionnaire of Olfactory Dysfunction (QOD). Additional clinical measures of disease severity included Threshold, Discrimination, and Identification (TDI) scores using Sniffin' Stick testing and Lund-Kennedy endoscopic scores (LKES).

Results: A total of 115 patients were clustered into type 2 inflammatory, non-type 2 inflammatory, non-inflammatory, and 2 indeterminate clusters based upon individual protein levels. Overall, the type 2 inflammatory cluster was found to report the highest mean improvement in both SNOT-22 (-28.3 [SD±16.2]) and TDI (6.5 [SD±7.9]) scores 6 months after ESS. However, all endotype clusters demonstrated improvement in all outcome measures after ESS on average, without statistically significant between-group differences in SNOT-22 (p=0.738), QOD (p=0.306), TDI (p=0.358), or LKES (p=0.514) measures.

Conclusions: All CRS endotype clusters respond favorably to surgery and show improvement in patient reported and objective outcome measures. Thus, ESS should be considered a more generalized CRS therapy, and benefits appear to not be limited to specific endotypes.

Introduction:

Chronic rhinosinusitis (CRS) is a sinonasal inflammatory disease impacting up to 12% of the United States population.[1] CRS patients have been traditionally classified according to phenotypic presentation, most commonly CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Recent studies have shown that categorization of CRS is more complex than previously thought, with patients belonging to one of several inflammatory endotypes that characterize their underlying disease process.[2-7] Research in recent years has increasingly focused on mucus cytokine profiles and cluster analysis to better categorize CRS subtypes. The potential to better characterize individual disease course and inform ideal treatment selection has broad implications for patient quality of life outcomes and reduction of overall cost of care.[8,9]

As we enter the era of personalized medicine for CRS, biologics and other targeted therapies show substantial promise, however, comparative efficacy among ideal target populations is currently unclear. [6,8,10-12] The effectiveness of biologics is also highly variable and currently limited to patients with CRSwNP.[10,12] There is ongoing discussion on the role of endotyping and how it can be used to guide clinical care given available outcomes data for medical and surgical treatment options. [10] Existing treatment guidelines and consensus statements support endoscopic sinus surgery (ESS) as a mainstay of treatment for CRS refractory to medical management.[13-15] It is currently unclear if CRS endotypes show differential response to endoscopic sinus surgery (ESS). The purpose of this exploratory study is to evaluate whether inflammatory endotypes showed differential outcomes for both preoperative and postoperative clinically measured and patient reported outcome measures (PROMs).

By analyzing these outcome measures in relation to the inflammatory endotypes, we aimed to determine if specific endotypes exhibit differential responses to ESS. Understanding the impact of endotypes on surgical outcomes can help guide treatment decisions and optimize patient care. Additionally, it may contribute to the ongoing debate regarding the role of endotyping in CRS management.

Methods:

2.1 - Recruitment and Study Population

Patients with a diagnosis of chronic rhinosinusitis (CRS) were prospectively recruited between 2016-2021 from rhinology clinics at the Medical University of South Carolina (MUSC, Charleston, SC), Oregon Health and Science University (OHSU, Portland, OR), the University of Utah (Salt Lake City, UT), the University of Colorado (Aurora, CO), and the University of Virginia (Charlottesville, VA). A total of 115 study participants that underwent ESS were included in this study. All patients met diagnostic criteria for CRS according to the American Academy of Otolaryngology – Head and Neck Surgery. [15] Exclusion criteria included patients with a diagnosis of cystic fibrosis, primary ciliary dyskinesia, systemic inflammatory disease (granulomatosis with polyangiitis, sarcoidosis, eosinophilic granulomatosis with polyangiitis), and those who had taken systemic corticosteroids within 1 month prior to enrollment. The local Institutional Review Board at each institution provided ethical oversight and subjects provided written informed consent prior to study participation.

2.2 – Demographics, Comorbidities, and Disease Severity

Patients underwent preoperative sinonasal computed tomography (CT) scanning as part of the standard of care for CRS. CT scans were graded using the standard Lund-Mackay scoring method, with reviewers blinded to olfaction data.[16] Patients also underwent bilateral sinonasal endoscopy and were scored using the Lund-Kennedy endoscopy score (LKES) system.[17] The olfactory cleft (OC) was also specifically assessed during sinonasal endoscopy to generate Olfactory Cleft Endoscopy Scale (OCES) scores for patients. Physicians quantified the severity of discharge, edema, polyps, crusting and scarring of the OC using a Likert score from 0–2 for each attribute. Results for each side were recorded separately and combined for a final OCES score that ranged from 0–20, with higher scores representing increased disease severity.[18] CT and endoscopy scores were graded by the enrolling surgeon at the time of baseline enrollment and/or follow-up.

All patient outcome measures were collected 6 months after ESS. Both the 22-item Sinonasal Outcome Test (SNOT-22; ©2006, Washington University, St. Louis) and Sinus Control Test (SCT) measure sinus-specific quality of life.[19,20] The SNOT-22 is a 22-item questionnaire where each question is rated on a scale of 0 to 5. The total score ranges from 0 to 110 with higher scores signifying worse quality of life. [19] Individual domain scores of the SNOT-22 were operationalized following guidelines that have been previously described into five distinct domains including. [21,22] For the purpose of this study, we specifically focused on the rhinologic symptom sub-domain. The SCT is a 4-item questionnaire with questions graded on a scale of 0 to 4. Overall scores range from 0 to 16 with higher scores indicating worse control of CRS. [20]

Health state utility values were assessed using the SF-6D survey instrument, a classification derived from the Medical Outcomes Study SF-12 Health Survey.[23,24] Standardized health utility values ranging from 0.0 = "death" to 1.0 = "perfect health" were calculated using survey responses provided by each subject before and after ESS. Patients additionally completed the Patient Health Questionnaire 9 (PHQ-9), a validated clinical screening tool to screen for depression. [25]

2.3 – Olfactory Specific Assessments

Subjects underwent psychophysical olfactory testing using "Sniffin' Sticks" (Burghart Messtechnik, Wedel, Germany). [26] This test evaluates three separate domain items of olfactory function including: odorant threshold (T, score range: 1–16), odorant discrimination (D, score range: 0–16), and odorant identification (I, score range: 0–16). Responses are summarized into a composite total TDI score (score range: 1–48) with higher scores representing better olfaction.

Participants were also asked to complete 17 negatively termed questions of the Questionnaire of Olfactory Dysfunction (QOD-NS).[27,28] The QOD-NS is a validated, olfactory-specific survey with Likert scale responses from 0 ("Disagree") to 3 ("Agree"). Higher composite scores (score range: 0–51) signify higher global impacts of olfactory impairment.

2.4 – Mucus Biomarkers

Immediately prior to the initiation of ESS, subjects had mucus collected from the OC. Utilizing rigid nasal endoscopy, a Leukosorb filter paper (Pall Scientific, Port Washington, NY) strip was placed directly into the OC of each side by the treating rhinologist and allowed to dwell for 3 minutes, as

described and validated previously.[29-31] This process generates average mucus yields of 150-160µl. used for directed cytokine analysis. Sinonasal mucus samples were transferred to properly equipped lab facilities and cold centrifuged at 4°C, 10,000 rpm for 10 minutes to extract the entire sample from the filter paper. Samples were transferred by pipette to cryovials, flash-frozen in liquid nitrogen, labeled and stored in a -80°C environment until time of batched transfer to the Medical University of South Carolina for processing and assay.

An array of 26 OC biomarkers was assessed in the laboratory to capture the heterogeneity of CRS, including cytokines, chemokines, and growth factors within the detection threshold. These biomarkers were chosen for analysis based on previous evidence suggesting a role in CRS endotypes, olfactory dysfunction, or inflammation/remodeling. All proteins, except those noted below, were quantified by LegendPlex Mix & Match Cytometric Bead Array (BioLegend, San Diego, CA) following the manufacturer's recommended protocol and read on a Guava easy Cyte 8HT flow cytometer (EMD Millipore, Burlington, MA). Data analysis was performed with LegendPlex software provided by the manufacturer. Total IgE was quantified via ELISA following the kit instructions (GenWay Biotech. Inc, San Diego, CA).

2.5 – Surgical Intervention

Surgical approach was directed by the intraoperative judgement of the treating rhinologist at each location. Study participants electing ESS were not randomized or assigned surgical intervention. Study participants were either primary or revision ESS cases while surgical procedures consisted of unilateral or bilateral maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, and/or frontal sinusotomy (Draf I, IIa/b, or III) conducted under general anesthesia. Inferior turbinate

reduction and/or septoplasty procedures were also completed, as needed for optimal ventilation. Postoperative medical therapy consisted of nasal saline irrigation accompanied by topical corticosteroid sprays/rinses in all patients with addition of adjunctive therapy as prescribed by the treating physician. None of the patients were being treated with monoclonal antibodies for their CRS during the follow up period.

2.6 - Statistical Analysis

Data were analyzed using the IBM SPSS 25.0 software package (SPSS Inc., Armonk, NY). Using a stepwise procedure, 10 of the cytokines were retained as useful for predicting cluster membership. These clusters were previously described and validated in our previous publications (Table 2). Analysis and cluster membership comparisons were performed as previously published and previously described by our group. [5,29] Based on hierarchical clustering strategy and optimizing power, individual endotype clusters were merged into larger and potentially clinically relevant groups. Clusters 2 and 10 were combined into a type 2 high inflammatory group, clusters 6, 7, and 9 were combined into a non-type 2 inflammatory group, and clusters 3, 4, and 5 were combined into a non-inflammatory group. Clusters 1 and 8 were kept as separate clusters. This clustering scheme allowed for adequate study power and created clinically relevant clusters for statistical comparison. For continuous variables, results are expressed as means and standard deviations and modified heat maps. One-way analyses of variance (ANOVAs) or Kruskal-Wallis rank testing were used for between group comparisons; when heterogeneous within-group variances were indicated, Games-Howell and Welch tests were conducted to assess the sensitivity of the ANOVA-based conclusions to this violation. For categorical variables, likelihood ratio chi-square tests were used to assess differences across groups. Statistical significance was defined as $p \leq 0.050$

Results:

A total of 115 patients with CRS were enrolled in this multi-institutional study. The mean age was 48.7 years, and majority of the participants (53.9%) were female. Within the cohort 56.5% of patients had nasal polyps, 45.2% had history of asthma, and 15.7% had history of AERD / ASA sensitivity. Demographics and baseline characteristics of the overall cohort are found in Table 1.

The change in disease severity outcomes following ESS was initially compared across individual clusters (Table 2). There were no significant differences across clusters when considering change in OCES, LKES, SCT, SF-6D, PHQ-9, and SNOT-22. Individual endotype clusters were subsequently merged into larger groups based on inflammatory profile. Clusters #2 and #10 were combined into a type 2 inflammatory group, clusters #6, #7, and #9 were combined into a non-type 2 inflammatory group, and clusters #3, #4, and #5 were combined into a non-inflammatory group. Clusters #1 and #8 were kept as separate clusters. Analysis of combined groups showed similar results with improvement across most outcome metrics (Table 3). There were no statistically significant differences in the change of OCES, LKES, SCT, SF-6D, PHQ-9, and SNOT-22 scores across these combined groups.

The change in TDI and QOD-NS scores between individual clusters was also not statistically significant. TDI generally improved across clusters with a few exceptions (clusters #3, #7, and #9). Cluster 3 also did not have demonstrate improvement in SCT and cluster 7 did not demonstrate improvement in QOD-NS, PHQ-9, and SCT.. The difference in change in TDI and QOD-NS across combined groups was not statistically significant.

Discussion:

We now know that mucus biomarkers, including those collected from the olfactory cleft and middle meatus, can be used to identify clinically-relevant endotypes and correlate with psychophysical testing in CRS patients.[5,12,32,33] Mucus sampling has the advantage that it can readily be performed in clinic without the need for an invasive biopsy[33]. The patient's endotype may then factor into clinical decision-making, such as adjusting medical therapy, or proceeding with surgery or biologic therapy. This exploratory study aimed to investigate the relationship between inflammatory endotypes and postoperative improvement in patient-reported outcome measures (PROMs) and clinically measured outcome measures after ESS. Our findings demonstrate that all CRS endotype clusters, including type 2 inflammatory, non-type 2 inflammatory, non-inflammatory, and 2 indeterminate clusters, respond favorably to surgery and show improvement in PROMs and objective outcome measures at 6-month follow-up. While there was some variability among the individual endotypes, no statistically significant differences were observed between endotype clusters in our outcome measures.

Interestingly, the "high inflammation" clusters (Type 2 inflammatory and non-Type 2 inflammatory groups) showed the highest mean improvement in total and rhinologic specific SNOT-22 scores post-ESS. For example, these patients showed the greatest mean postoperative improvement in SNOT-22 scores (reduction of 28.3 and 23.9, respectively). Cluster #1 is also characterized by Type 2 mediators as well as broad elevations in other pro-inflammatory cytokines, including those typical of Type 1 and Th-17 inflammation. [5] Cluster #1 showed the greatest improvement in total SNOT-22 score, rhinologic specific sub-domain of SNOT-22, as well as QOD-NS. The high inflammatory clusters also showed an improvement in olfactory outcomes as measured by the TDI and QOD-NS outcome measures (Table 3). Despite lack of statistically significant differences compared to the low

inflammatory endotypes, this indicates that high inflammatory endotypes respond well to surgery, which may act overall to reduce inflammation in conjunction with postoperative topical medication. This is consistent with several prior studies showing a general reduction in Type 2 inflammatory mediators postoperatively, particularly in Th2 CRSwNP patients. [34,35]

Nonetheless, the "low inflammatory" and non-inflammatory clusters (Clusters #3, #4, #5) also showed notable improvement in PROMs and objective measures. In this cluster, there was SNOT-22 reduction of -21.4 (-10.1 for rhinologic sub-domain) and QOD-NS total score of -5.6. Overall, all endotype groups demonstrated improvement of all outcome measures after ESS on average, with not statistically significant between-group differences in SNOT-22 (p=0.738), QOD (p=0.306), as well as TDI (p=0.358). This was also true for clinically measured outcome measures: OCES (p=0.917) and LKES (p=0.514) measures (Table 3).

Endoscopic sinus surgery relieves sinus outflow obstruction, debrides inflamed tissue, and provides improved access for topical agents.[36] It is thought to decrease Th1 and Th3 inflammation by reducing mucous stasis and microbial overgrowth and Th2 inflammation by decreasing polypoid burden, edema and improving access to topical steroids. [10,37] Our results align with previous studies that have reported generalized improvement in patient-reported outcomes following ESS regardless of phenotypes. For instance, a recent study demonstrated clinically meaningful improvement in postoperative SNOT-22 scores across different CRS subtypes, including CRSsNP, CRSwNP, aspirin-exacerbated respiratory disease (AERD), allergic fungal rhinosinusitis (AFRS), granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. [38] Our findings suggest that ESS is a generalized multi-modal therapy that leads to the overall improvement likely regardless of the specific

endotype cluster. It is important to note that patients undergoing ESS are usually treated with ongoing postoperative medical treatment, which usually includes nasal irrigations, intranasal steroids and sometimes oral antibiotics and corticosteroids. Corticosteroids have potent anti-inflammatory properties and suppress predominantly Type 2, but also Type 1 and Type 3. [39,40] Hence, the generalized improvement of PROMs and objective clinical measures post-ESS across all endotypes can be attributed to surgery as well as multimodal postoperative medical care.

The concept of "endotype switching" may also be present, where patients may transition from one endotype to another over time or following intervention. This phenomenon has been previously observed in up to half of surgical patients and may have implications for postoperative outcomes. [34] Switching from a high inflammatory endotype to a low inflammatory profile could contribute to the overall favorable response to surgery observed across all endotype clusters, although we did not specifically evaluate for this in this study. Future studies investigating the longitudinal changes in endotype status and their impact on outcomes following ESS may provide valuable insights.

This was a generalized exploratory analysis of all clusters among several PROMs and clinically measured outcome measures, and we do not suggest that endotype status is not an important predictor of postoperative outcomes. There have been several previous studies that have reported prognostic value for individual inflammatory biomarkers and specific endotypes. [41,42] These findings are somewhat reassuring, because we currently offer ESS to patients based on their phenotypic status and failure of appropriate medical therapy, and not endotype status. These results contribute to the ongoing debate on the role of endotyping and how it can be used to guide clinical care. While our results indicate that all endotypes respond favorably to ESS, it is reasonable to believe that ongoing

medical treatment may be able to be targeted to the specific endotype in the future. Understanding individual patient's endotype may also inform and the post-operative management, including drive the need to incorporate postoperative targeted biologic therapy.[6,43]

While our study contributes to the understanding of the relationship between inflammatory endotypes and surgical response in CRS, there are several limitations to consider. First, the classification of endotype status is somewhat variable and influenced by study populations analytical approaches towards clustering analysis. [6,34] Also, since the CT and endoscopy scores were graded by the enrolling surgeon at the time of baseline enrollment and/or follow-up, small inter-observer variability could affect the results of the study Additionally, our study was not powered to detect smaller differences between individual endotypes. Outcome measures were assessed at 6 months post-ESS. While longer term follow-up would be ideal for a chronic condition like CRS, our previous work demonstrated that at the cohort level, improvements in QOL after ESS do not appear to significantly change between 6 and 20 months. [44,45] Further research is needed to explore and characterize potential associations between specific inflammatory biomarkers, patient endotypes, and discernible postoperative outcomes.

In conclusion, our study suggests that surgical response in patients with CRS is not limited to specific endotypes clusters and that ESS remains an effective treatment across endotypes of CRS.

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Potential Conflict of Interest Disclosures:

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Table 1: Preoperative descriptive measures of final study cohort (n=115)

Characteristics:	N (%)	Mean [±SD]	Range
Age (years)	----	48.7 [±15.9]	20.0 – 77.0
Males	53 (46.1%)	----	----
Females	62 (53.9%)	----	----
White / Caucasian	101 (87.8%)	----	----
African American	12 (10.4%)	----	----
Asian	1 (0.9%)	----	----
Hispanic / Latino	7 (6.1%)	----	----
Nasal polyposis	65 (56.5%)	----	----
Asthma	52 (45.2%)	----	----
AERD / ASA sensitivity	18 (15.7%)	----	----
Revision ESS	59 (51.3%)	----	----
Allergic rhinitis	59 (51.3%)	----	----
Diabetes mellitus (type I/II)	12 (10.4%)	----	----
Depression*	36 (31.3%)	----	----
Anxiety*	30 (26.1%)	----	----
Obstructive sleep apnea	23 (20.0%)	----	----
Current smoking/tobacco use	5 (4.3%)	----	----
Current alcohol use	57 (49.6%)	----	----
GERD	33 (28.7%)	----	----
Autoimmune disorder, NOS	11 (9.6%)	----	----
Lund-Mackay CT score	----	13.6 [±5.7]	2.0 – 24.0
Lund-Kennedy endoscopy score	----	7.2 [±3.5]	0.0 – 18.0

Olfactory cleft endoscopy score	----	4.7 [±4.0]	0.0 – 14.0
SNOT-22 total score	----	52.0 [±21.7]	1.0 – 101.0
Rhinologic symptom domain	----	16.9 [±7.1]	0.0 – 30.0
Sinus Control Test score	----	9.2 [±3.5]	0.0 – 16.0
SF-6D health utility score	----	0.72 [±0.14]	0.34 – 1.00
PHQ-9 total score	----	7.5 [±5.7]	0.0 – 26.0
Sniffin' Sticks total score	----	21.6 [±9.5]	6.5 – 39.5
Threshold (T) score	----	3.6 [±3.0]	1.0 – 11.5
Discrimination (D) score	----	9.0 [±3.6]	1.0 – 16.0
Identification (I) score	----	8.9 [±4.3]	1.0 – 16.0
QOD-NS total score	----	13.3 [±11.2]	0.0 – 40.0

Legend: SD, standard deviation; AERD, aspirin exacerbated respiratory disease; ASA, acetylsalicyclic acid; ESS, endoscopic sinus surgery; * self-reported during interview; GERD, gastroesophageal reflux disease; NOS, not otherwise specified; CT, computed tomography; SNOT-22, 22-item SinoNasal Outcome Test survey; SF-6D, short form 6-dimensional; PHQ-9, 9-item Patient Health Questionnaire depression screening tool; QOD-NS, Questionnaire for Olfactory Dysfunction-Negative Statements survey.

Table 2: Changes in patient-reported and clinically measured outcome measures 6 months following ESS across individual endotypes.

CLUSTER MEMBERSHIP:	Δ SNOT-22 total score	Δ SNOT-22 rhinologic	Δ QOD-NS total score	Δ SF-6D HUV	Δ PHQ-9	Δ SCT total score	Δ TDI total score	Δ LKES	Δ OCES
	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]
1	-30.7 [±20.8]	-10.4 [±6.4]	-9.0 [±6.9]	0.07 [±0.08]	-2.1 [±1.2]	-3.9 [±3.3]	4.9 [±10.6]	-3.8 [±2.3]	-2.0 [±1.6]
2	-25.9 [±19.5]	-7.1 [±6.1]	-4.5 [±7.9]	0.02 [±0.09]	-2.9 [±5.5]	-4.8 [±3.2]	6.7 [±10.2]	-2.0 [±4.1]	-1.7 [±3.2]

3	-7.9 [±28.9]	-2.2 [±7.0]	-1.8 [±5.2]	0.08 [±0.16]	-1.9 [±6.0]	0.3 [±6.2]	-3.9 [±7.6]	-2.1 [±5.6]	-1.1 [±4.1]
4	-60.0 [±17.0]	-14.5 [±4.9]	-17.5 [±21.9]	0.25 [±0.12]	-8.5 [±0.7]	-4.5 [±9.2]	11.3 [±6.0]	-0.5 [±0.7]	----
5	-28.4 [±15.8]	-7.8 [±6.1]	-10.5 [±10.1]	0.11 [±0.19]	-3.0 [±4.8]	-5.8 [±3.8]	1.9 [±6.2]	-1.8 [±4.0]	-0.4 [±3.9]
6	-26.7 [±24.2]	-9.1 [±7.2]	-4.0 [±6.0]	0.09 [±0.15]	-3.4 [±5.8]	-5.2 [±4.8]	4.3 [±7.0]	-4.3 [±3.5]	-2.4 [±3.1]
7	-15.8 [±7.5]	-6.4 [±6.7]	1.0 [±6.7]	0.01 [±0.08]	0.5 [±1.7]	0.0 [±2.9]	-0.4 [±8.3]	-2.8 [±3.9]	-3.5 [±3.5]
8	-23.3 [±19.8]	-5.8 [±10.4]	-3.6 [±7.5]	0.02 [±0.14]	-1.7 [±3.6]	-5.4 [±6.3]	0.7 [±3.0]	-4.0 [±2.8]	-2.6 [±4.7]
9	-15.0 [±2.8]	-4.5 [±2.1]	-5.0 [±7.1]	0.04 [±0.13]	-2.5 [±3.5]	-4.0 [±4.2]	0.0 [± ---]	-2.6 [±6.2]	----
10	-29.8 [±14.4]	-12.6 [±7.1]	-6.2 [±5.3]	0.01 [±0.08]	-4.0 [±4.5]	-5.2 [±4.0]	6.3 [±7.1]	-3.0 [±4.3]	-2.0 [±6.0]
Test statistic	**13.60**	**16.39**	**13.66**	**8.66**	**11.41**	**13.28**	**11.98**	**4.99**	**2.63**
DF	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**
p-value	**0.137**	**0.059**	**0.135**	**0.469**	**0.248**	**0.150**	**0.214**	**0.758**	**0.917**
Total N	**88**	**97**	**87**	**90**	**90**	**90**	**66**	**74**	**49**

Legend: *p-value range 0.010-0.050; **p-value range 0.001-0.009; ***p-value <0.001; R, Δ represents within-group differences from pre-postop in cohort electing ESS. Kruskall-Wallis test = nonparametric global ANOVA to detect differences between any two clusters.

Table 3: Changes in patient-reported and clinically measured outcome measures 6 months following ESS across clinically relevant endotype clusters.

CLUSTER MEMBERSHIP:	Δ SNOT-22 total score	Δ SNOT-22 rhinologic subdomain	Δ QOD-NS total score	Δ SF-6D HUV	Δ PHQ-9	Δ SCT total score	Δ TDI total score	Δ LKES	Δ OCES
	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]	Mean [±SD]
Cluster 1	-30.7 [±20.8]	-10.4 [±6.4]	-9.0 [±6.9]	0.07 [±0.08]	-2.1 [±1.2]	-3.9 [±3.3]	4.9 [±10.6]	-3.8 [±2.3]	-2.0 [±1.6]
Clusters 3,4,5 Non-inflammatory	-21.4 [±26.8]	-5.7 [±7.3]	-7.2 [±10.3]	0.10 [±0.17]	-2.9 [±5.4]	-3.0 [±5.9]	0.6 [±7.8]	-1.8 [±4.5]	-0.8 [±3.9]
Clusters 2,10 Type-2 inflammatory	-28.3 [±16.2]	-10.1 [±7.1]	-5.6 [±6.3]	0.02 [±0.09]	-3.6 [±4.8]	-5.0 [±3.6]	6.5 [±7.9]	-2.4 [±5.5]	-1.9 [±5.2]
Clusters 6,7,9 Non-Type-2 inflammatory	-23.9 [±21.5]	-8.2 [±6.9]	-3.3 [±6.2]	0.07 [±0.14]	-2.7 [±5.3]	-4.2 [±4.8]	3.0 [±7.2]	-4.0 [±3.6]	-2.6 [±3.0]
Cluster 8	-23.3 [±19.8]	-5.8 [±10.4]	-3.6 [±7.5]	0.02 [±0.14]	-1.7 [±3.6]	-5.4 [±6.3]	0.7 [±3.0]	-4.0 [±2.8]	-2.6 [±4.7]
Test statistic	**KW=1.99**	**KW=5.32**	**KW=4.82**	**KW=4.78**	**KW=2.49**	**KW=1.68**	**KW=4.37**	**KW=3.27**	**KW=2.31**
DF	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
p-value	**0.738**	**0.256**	**0.306**	**0.311**	**0.647**	**0.794**	**0.358**	**0.514**	**0.680**
Total N	**88**	**97**	**87**	**90**	**90**	**90**	**66**	**74**	**49**

Legend: *p-value range 0.010-0.050; **p-value range 0.001-0.009; ***p-value <0.001; R, two-sided Spearman's correlation coefficient for non-parametric associations; Δ represents within-group differences from pre-postop in cohort electing ESS

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