Article

Comparison of Clinical Presentation and Surgical Outcomes Between Recurrent Acute Rhinosinusitis and Chronic Rhinosinusitis

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Abstract

Introduction: The authors assessed clinical presentations and anatomic variants among patients with recurrent acute rhinosinusitis (RARS), chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP), and CRS with nasal polyps (CRSwNP). Additionally, differences in the postoperative improvement of each category were evaluated.

Methods: The authors performed an analysis of 304 patients who underwent endoscopic sinus surgery. They were divided into groups with RARS, CRSsNP, and CRSwNP. Patients had to complete the Sino-Nasal Outcome Test (SNOT-20) on surgery 1 day before and 6 months after surgery. Patient demographics and comorbidities were reviewed. We reviewed all patients' computed tomographic findings to analyze anatomic variants.

Results: No significant differences were found among the average preoperative SNOT-20 scores of the 3 groups. Patients with RARS were significantly more likely to show agger nasi cells, Haller cells, and septal deviation on computed tomography. Those with CRSwNP had significantly smaller mean infundibular widths. All groups showed significantly improved SNOT-20 scores postoperatively.

Conclusion: The different anatomic variants found among patients with RARS, CRSsNP, and CRSwNP can facilitate surgical prognostic evaluation.

Keywords

sinusitis, nasal polyps, tomography

Introduction

Recurrent acute rhinosinusitis (RARS) is defined by a threshold of 4 episodes of acute bacterial rhinosinusitis per year.[1-3] Chronic rhinosinusitis (CRS) is a common condition characterized by mucosal inflammation in the nose and sinuses that lasts more than 3 months. CRS can be clinically classified as with or without polyps.[4] Unlike patients with CRS, those with RARS experience the resolution of sinus-specific symptoms between episodes of acute bacterial rhinosinusitis. Despite symptom relief between disease exacerbations, it is now recognized that patients with RARS report the diminishment of quality of life (QOL) to levels that often parallel those of their counterparts with CRS.[2] Clinicians usually choose surgical intervention for patients with RARS or CRS when the patients wish to become candidates for endoscopic sinus surgery (ESS) or when they are refractory to medical management, such as in CRS.[5]

Patients with RARS and those with CRS show chronicity and share a variety of symptoms, but few studies have compared their characteristics. Additionally, few studies have reported on RARS, and the characteristics of the disease remain unclear. Some studies have reported that ESS can improve productivity in patients with RARS.[5,6] The overall disease burden of RARS has been measured primarily using Sino-Nasal Outcome Test (SNOT-20) scores, and patients with CRS have been assessed using the same

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method.[5,6] Therefore, the aim of this study was to compare the underlying disease, symptoms, and anatomic variants of the paranasal sinuses of patients with RARS, CRS without nasal polyps (CRSsNP), and CRS with nasal polyps (CRSwNP).

After analysis, the values for patients with RARS were matched with those of patients with CRSsNP and those with CRSwNP to determine the modifiable factors correlated with disease. Such results can be used to not only design new treatment strategies but also help clinicians understand the anatomic variants of each disease group and provide a prognosis for the productivity of ESS. We hypothesized that similar to patients with CRS, those with RARS who chose ESS would report significant improvement in daily productivity measures.

Methods

Patient Population

Institutional review board approval (2017-022) was obtained before participant enrollment. We examined 304 adults aged 18 years and older who were hospitalized for ESS at our hospital between January 2014 and June 2016. To diagnose RARS and CRS, we predominantly used patient medical records, endoscopic findings, and computed tomography. RARS was defined as a patient history of 4 or more distinct episodes of acute rhinosinusitis within a 12-month period, with each episode lasting less than 4 weeks and with complete clinical resolution of symptoms and sinonasal inflammatory findings between episodes.[2,3] The diagnosis is difficult because of the lack of clinical and radiologic findings between acute episodes. Therefore, we tried to perform rigorous histories and endoscopic examinations, as proper diagnosis of RARS requires that each episode meet the criteria for acute bacterial rhinosinusitis. At least 1 of the acute bacterial rhinosinusitis episodes was diagnosed by 1 rhinologist (N.-K.Y.) on the basis of the patient's history, office-based otolaryngologic examination, and diagnostic nasal endoscopy demonstrating sinonasal inflammatory changes, including mucosal edema, mucopurulence, and/or erythema.[2] The clinical history provided by the patient was used to determine the frequency and overall duration of the RARS pattern. Patients with a clinical evaluation suggestive of CRS, including persistent sinonasal symptoms, and/or inflammatory examination findings for more than 12 weeks and demonstrable pathology on both radiologic and clinical examination were diagnosed with CRSsNP or CRSwNP according to the presence of nasal polyposis.

All patients with RARS chose adjunctive ESS as subsequent treatment for symptom alleviation after the failure of previous medical management, including at least 2 weeks of broad-spectrum or culture-directed antibiotic therapy. Patients with CRS whose symptoms were resistant to medicine for more than 12 weeks and who continuously reported sinonasal symptoms were listed for surgery. Of these subjects, those with histories of previous nasal procedures and facial trauma were excluded. Patients with fungal or allergic fungal sinusitis, retention cysts, mucoceles, and benign or malignant tumor lesions were also excluded.

ESS

All ESS procedures were performed by 1 ear, nose, and throat doctor specializing in rhinology (N.-K.Y.). The surgical extent was determined at her discretion and reflected the progression of sinus disease in the individual patient according to the computed tomographic and endoscopic findings. The ESS consisted of either unilateral or bilateral maxillary antrostomy, partial or total ethmoidectomy, sphenoidotomy, frontal sinusotomy (Draf I, IIa, IIb, or III), or partial or complete middle turbinate resection. In patients with CRS, we sought on ESS to remove polyps if present, open obstructed ostia, clear inspissated secretions, and reduce the overall burden of inflammatory disease. On the other hands, in patients with RARS, the aim of ESS was to enlarge the middle meatus by removing deviated septum, Haller cells, and concha bullosa, because patients with RARS did not have actual mucosal lesions if they were not in episode.

All surgical cases were followed with postoperative therapeutic regimens, including daily nasal saline rinses. Subsequent medical therapy with antibiotics and analgesics was continued up to 2 weeks postoperatively. In patients with CRSwNP, use of topical steroids was also recommended up to 4 weeks postoperatively.

Study Design

The medical records of the study cohort were retrospectively reviewed for the following patient demographics: age, gender, pertinent comorbidities (allergic rhinitis, asthma, immune deficiency, and aspirin sensitivity), and smoking history. The severity of RARS was determined by the frequency of sinusitis episodes per year and the number of years with a RARS pattern. Both were determined by patient-reported history.

The patients were assessed using the SNOT-20 1 day preoperatively and 6 months postoperatively. Patients with RARS were requested to report their symptoms during episodes. The SNOT-20 is a validated survey developed to evaluate disease-specific QOL in sinonasal diseases.[7] Individual item scores are determined by patient-selected responses on a Likert-type scale, with higher scores indicating worse symptom severity, as follows: 0 = no problem, 1 = very mild problem, 2 = mild or slight problem, 3 = moderate problem, 4 = severe problem, and 5 = problem as bad as it can be. Twenty items address rhinologic symptoms

Table 1. Characteristics and Comorbidities of Patients With RARS, CRSsNP, and CRSwNP (n = 203).[a]

Characteristic	RARS (n = 43)	CRSsNP (n = 41)	CRSwNP (n = 119)	*P*
Age, y	30.39 ± 13.624	45.46 ± 15.761	44.50 ± 17.901	<.001
Gender				
Male	31 (72.1)	23 (56.1)	79 (66.4)	.278
Female	12 (27.9)	18 (43.9)	40 (33.6)	
Smoking	5 (11.6)	6 (14.6)	29 (24.4)	.124
Allergy	25 (58.1)	27 (65.9)	64 (53.8)	.390
Asthma	0 (0)	0 (0)	14 (11.8)	.030

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps, CRSwNP, chronic rhinosinusitis with nasal polyps; RARS, recurrent acute rhinosinusitis.
[a]Data are expressed as mean ± SD or number (percentage).

(score range, 0-30), ear and/or facial symptoms (score range, 0-20), psychological dysfunction (score range, 0-25), and sleep dysfunction (score range, 0-25). Higher subdomain and total SNOT-20 scores (score range, 0-100) represent worse QOL and symptom severity.

Computed tomographic scans of the paranasal sinuses were obtained when ESS was considered or planned for a patient. Most patients with RARS underwent computed tomography while they were not having episodes of acute rhinosinusitis. Two doctors (I.S.R. and Y.J.S.) who were blinded to patients' symptoms evaluated the anatomic variations using preoperative computed tomography. Images were also staged by 2 doctors in accordance with the Lund-Mackay (LM) scoring system (score range, 0-24), which quantifies the severity of image opacification in the maxillary, ethmoidal, sphenoidal, ostiomeatal complex, and frontal sinus regions. Computed tomography was used to evaluate preoperative anatomic variants, such as agger nasi cells, Haller cells, nasal septal deviation, and concha bullosa, in both the sagittal and coronal planes. The images were also used to measure the infundibulum width. The minimum widths of each infundibulum (left and right) were recorded using the measuring function; a line perpendicular to the infundibulum was drawn from the soft tissue borders, and the resulting distance was recorded.[8]

We compared patient characteristics, sinonasal symptoms, LM scores, and anatomic variants of the paranasal sinuses in the RARS, CRSsNP, and CRSwNP groups. We also analyzed the differences in postoperative improvement among the 3 groups.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 for Windows (SPSS). Paired analysis of variance and the Mantel-Haenszel χ^2 test were used to analyze the patients' comorbidities and anatomic variants and to compare the SNOT-20 scores of each disease group. The Wilcoxon signed rank test was used to evaluate matched pairings over time. Statistical significance was set at $P < .05$.

Results

Patient Characteristics and Comorbidities

Of the 304 patients screened, 203 completed 6-month postoperative follow-up to evaluate their sinonasal symptoms. There were 130 male and 73 female patients; they had a mean age of 41.65 years (range, 12-82 years). The RARS group had a significantly younger mean age (30.39 ± 13.624 years) than the CRSsNP (45.46 ± 15.761 years) and CRSwNP (44.50 ± 17.901 years) groups ($P < .001$). These data indicated that although there were no differences in gender, there were differences in age among the 3 groups. Regarding smoking history, there were no significant differences among the 3 groups ($P = .124$). No significant differences were found regarding allergy history ($P = .390$). However, a history of asthma was only found among patients with CRSwNP (RARS 0% vs CRSsNP 0% vs CRSwNP 11.8%, $P = .03$) (Table 1).

Computed Tomographic Findings

The preoperative LM computed tomographic scores for each group were significantly different ($P < .001$). The mean LM score for RARS was 1.6 (range, 0-6), which was the lowest score among the 3 groups. The mean LM score for CRSsNP was 7.75 (range, 5-18), and CRSwNP showed the highest mean LM score, at 12.88 (range, 6-22).

The computed tomographic findings for each disease group were analyzed to compare the anatomic variants among the groups. Patients with RARS were significantly more likely to have agger nasi cells ($P = .007$). Haller cells were more strongly associated with patients with RARS than with patients in the other groups ($P = .025$), and the same results were found for septal deviation ($P < .001$).

Table 2. Computed Tomographic Findings of Patients With RARS, CRSsNP, and CRSwNP (n = 203).[a]

Finding	RARS (n = 43)	CRSsNP (n = 41)	CRSwNP (n = 119)	*P*
Agger nasi cells				
Right	43 (100)	38 (92.7)	101 (84.9)	.007
Left	43 (100)	38 (92.7)	101 (84.9)	.007
Haller cells				
Right	26 (60.5)	17 (41.5)	29 (24.4)	<.001
Left	23 (53.5)	16 (39.0)	36 (30.3)	.025
Septal deviation	37 (86.5)	17 (41.5)	67(56.3)	<.001
Concha bullosa				
Right	13 (30.2)	13 (31.7)	22 (18.5)	.115
Left	13 (30.2)	10 (24.4)	26 (21.8)	.541
Infundibulum width, mm				
Right	1.787 ± 0.420	1.841 ± 0.313	1.638 ± 0.322	.002
Left	1.890 ± 0.429	1.794 ± 0.266	1.606 ± 0.370	.001

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps, CRSwNP, chronic rhinosinusitis with nasal polyps; RARS, recurrent acute rhinosinusitis.
[a]Data are expressed as number (percentage) or mean ± SD.

However, concha bullosa did not show a significant difference among the 3 groups ($P = .541$). The maxillary sinus infundibulum widths were smallest in the CRSwNP group compared with the other groups ($P = .001$), and significant differences were demonstrated using 1-way analysis of variance (Table 2).

Extent of Surgery

The types of surgery performed and frequency of each procedure are shown in Table 3. Similar proportions of each group underwent maxillary antrostomy ($P = .575$). Patients with RARS were more likely to undergo septoplasty and inferior turbinate reduction ($P < .001$ and $P = .019$), whereas patients with CRS were more likely to undergo ethmoidectomy, sphenoidotomy, or frontal surgery ($P < .001$ for all). In particular, patients with CRSwNP underwent ethmoidectomy, sphenoidotomy, or frontal surgery the most. No other differences in middle turbinate reduction were found among the 3 groups ($P = .115$).

QOL Outcome Measures

Differences in preoperative mean SNOT-20 scores were compared among the RARS, CRSsNP, and CRSwNP groups. The means total SNOT-20 score was 33.28 for the RARS group, 37.44 for the CRSsNP group, and 32.9 for the CRSwNP group. No significant differences were reported among the participants with RARS, CRSsNP, and CRSwNP in the preoperative QOL outcome measure ($P = .239$) (Table 4). The postoperative mean SNOT-20 scores were compared among the subjects with RARS, CRSsNP, and CRSwNP (Table 4). No differences were found among the 3 groups (23.67 vs 19.85 vs 20.51, $P = .242$).

Participants with RARS showed significant improvements across all mean QOL measures, including postoperative SNOT-20 score. Similarly, patients with CRSsNP and CRSwNP showed significant improvements in the mean QOL measures after ESS (Table 5). Patients with RARS showed significantly less improvement in average SNOT-20 score than did patients with CRS (Δ9.6047 vs Δ17.5854 vs Δ12.4286, $P = .020$).

Discussion

Our study is the first report to simultaneously compare the clinical presentations, anatomic characteristics, and outcomes of ESS in patients with RARS, CRSsNP, and CRSwNP. In this study, we found that the patients with RARS were younger than those with CRS and that patients with CRSwNP were more likely to have comorbid asthma than those with RARS and CRSsNP. Additionally, we demonstrated that the patients with RARS were more likely to have agger nasi cells, Haller cells, and nasal septal deviation than those with CRSsNP and CRSwNP. All groups showed significant symptomatic improvement after ESS.

Similar gender distributions, smoking histories, and allergy ratios were found among the patients with RARS, CRSsNP, and CRSwNP. A history of asthma was significantly more common among the CRSwNP patients. Poetker et al[2] showed that patients with CRSsNP had a higher prevalence of asthma than those with RARS. In contrast, Steele et al[9] reported that patients with RARS did not differ from those with CRSsNP in terms of social and medical history

Table 3. Other Combined Operative Procedures During Endoscopic Sinus Surgery in the RARS, CRSsNP, and CRSwNP Groups (n = 203).[a]

Procedure	RARS (n = 43)	CRSsNP (n = 41)	CRSwNP (n = 119)	*P*
Maxillary antrostomy				
Right	42 (97.7)	38 (92.7)	112 (94.1)	.575
Left	43 (100)	32 (78.0)	118 (99.2)	<.001
Ethmoidectomy				
Right	14 (32.6)	31 (75.6)	110 (92.4)	<.001
Left	15 (34.9)	25 (61.0)	117 (98.3)	<.001
Frontal sinusotomy				
Right	2 (4.7)	8 (19.5)	71 (59.7)	<.001
Left	3 (7.0)	9 (22.0)	81 (68.1)	<.001
Sphenoidotomy				
Right	0 (0.0)	3 (7.3)	33 (27.7)	<.001
Left	1 (2.3)	1 (2.4)	36 (30.3)	<.001
Middle turbinate reduction				
Right	13 (30.2)	13 (31.7)	22 (18.5)	.115
Left	13 (30.2)	10 (24.4)	26 (21.8)	.541
Inferior turbinate reduction	41 (95.3)	31 (75.6)	95 (79.8)	.019
Septoplasty	37 (86.0)	17 (41.5)	67 (56.3)	<.001

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps, CRSwNP, chronic rhinosinusitis with nasal polyps; RARS, recurrent acute rhinosinusitis.
[a]Data are expressed as number (percentage).

Table 4. Preoperative and Postoperative Sino-Nasal Outcome Test Scores of Patients With RARS, CRSsNP, and CRSwNP (n = 203).[a]

SNOT-20	RARS (n = 43)	CRSsNP (n = 41)	CRSwNP (n = 119)	*P*
Preoperative				
Total score	33.28 (29.14-37.42)	37.44 (32.56-42.32)	32.94 (30.18-35.70)	.705
Rhinologic symptoms	13.19 (11.80-14.58)	13.71 (12.02-15.40)	13.07 (12.04-14.10)	.088
Ear or facial symptoms	4.70 (3.71-5.69)	5.78 (4.53-7.03)	4.71 (4.02-5.39)	.426
Sleep dysfunction	6.81 (5.63-7.99)	7.51 (6.05-8.98)	6.61 (5.77-7.44)	.761
Physiologic dysfunction	8.58 (7.04-10.12)	10.44 (8.38-12.50)	8.56 (7.65-9.48)	.076
Postoperative				
Total score	23.67 (19.88-27.47)	19.85 (16.23-23.48)	20.51 (18.43-22.60)	.999
Rhinologic symptoms	9.84 (8.69-10.99)	6.61 (5.40-7.82)	7.76 (7.00-8.53)	.325
Ear or facial symptoms	4.07 (3.22-4.91)	3.66 (2.82-4.49)	3.5 (3.06-4.02)	.926
Sleep dysfunction	4.35 (3.15-5.55)	3.39 (2.40-4.38)	3.92 (3.34-4.51)	.577
Physiologic dysfunction	5.49 (4.12-6.85)	6.24 (4.68-7.81)	5.31 (4.59-6.04)	.446

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps, CRSwNP, chronic rhinosinusitis with nasal polyps; RARS, recurrent acute rhinosinusitis.
[a]Data are expressed as mean (95% confidence interval).

cofactors, including age, gender, race, nasal polyposis, depression, allergy, aspirin sensitivity, current tobacco and alcohol use, ciliary dyskinesia, corticosteroid dependency, immunodeficiency, autoimmunity, diabetes mellitus, and asthma. Previous large epidemiologic studies of CRS performed at the population level have reported an association between asthma and allergic rhinitis.[4,10,11] A recent cohort study analysis reported that CRSwNP and CRSsNP were associated with asthma in fully adjusted models.[12] Another recent study revealed significantly higher asthma prevalence among patients with CRSwNP than those with CRSsNP.[13] Steinke and Borish[14] suggested that eosinophilic

Table 5. Improvement After Endoscopic Sinus Surgery in Patients With RARS, CRSsNP, and CRSwNP (n = 203).[a]

	SNOT-20 Score			
	Preoperative	Postoperative	Change	*P*
RARS (n = 43)	33.28 (29.14-37.42)	23.67 (19.88-27.47)	9.604 (5.135-14.075)	<.001
CRSsNP (n = 41)	37.44 (32.56-42.32)	19.85 (16.23-23.48)	17.564 (13.498-21.673)	<.001
CRSwNP (n = 119)	32.94 (30.18-35.70)	20.51 (18.43-22.60)	12.427 (10.105-14.753)	<.001

Abbreviations: CRSsNP, chronic rhinosinusitis without nasal polyps, CRSwNP, chronic rhinosinusitis with nasal polyps; RARS, recurrent acute rhinosinusitis; SNOT-20, Sino-Nasal Outcome Test.
[a]Data are expressed as mean (95% confidence interval).

CRS shares many histologic and immunologic features with asthma regardless of the presence of nasal polyposis and that nasal polyposis may only poorly predict the presence of an underlying eosinophilic process. One limitation of our study is that there was no histopathologic evaluation of eosinophilic inflammation, because of the absence of a mucosal biopsy.

Although the RARS, CRSsNP, and CRSwNP groups had some common disease characteristics, we found a significantly greater prevalence of anatomic variants, such as agger nasi cells, Haller cells, and nasal septal deviation, on computed tomographic findings in the RARS group. We also observed the smallest maxillary sinus infundibulum sizes in the CRSwNP group. Although there was no comparison between case controls and disease groups in our study, Alkire and Bhattacharyya[8] found that only the presence of Haller cells was significantly greater in patients with RARS than in controls, while concha bullosa and meatal impinging septal deviation were not. Patients with CRS demonstrated significantly smaller maxillary infundibular widths, implicating the infundibulum in the occurrence of RARS. The detection of a single anatomic variant itself does not establish the disease; before a causal relationship between an anatomic variant and sinusopathy is suggested, these conditions should be considered in conjunction with the clinical picture. Therefore, we performed ESS in patient with CRS to remove polyps if present, open obstructed ostia, clear inspissated secretions, and reduce the overall burden of inflammatory disease. On the other hand, we performed ESS in patients with RARS to enlarge the middle meatus by removing deviated septum, Haller cells, and concha bullosa, even though RARS patients did not have actual mucosal lesions if they were not in episode. As a result, patients with RARS had underwent more septoplasties and inferior turbinate reduction in this study.

In our study, patients with RARS were found to have similar baseline and postoperative SNOT-20 scores compared with those with CRSsNP and CRSwNP, indicating that no greater level of QOL differences was observed in the disease process. Our study supports the findings of previous studies regarding the postoperative QOL outcomes in patients with RARS. ESS may help improve the QOL of patients with RARS and CRS, as several studies have reported significant improvements following surgical intervention.[15,16] Given the chronicity of CRS compared with the intermittent nature of RARS, we suspected that the average reported QOL would be worse in the CRS cohorts. Both the baseline and postoperative QOL measures were similar for these groups, suggesting that the RARS disease process has a greater daily impact than initially thought.

Using the SNOT-20 survey instrument, we found significant improvement in the QOL of patients with RARS following ESS. These data both support and augment the literature regarding postoperative QOL outcomes in patients with RARS. Poetker et al[2] evaluated the postoperative QOL using the Rhinosinusitis Disability Index in 14 patients with RARS and found significant postoperative improvement in total Rhinosinusitis Disability Index scores and within the physical and functional subdomains with an average of 8 months of follow-up. Bhattacharyya[17] noted significant improvement in the inventory of rhinosinusitis symptoms with a minimum of 12 months of follow-up data. Steele et al[9] also found improvement in all disease-specific QOL measures following ESS and in several medication measures. An interesting finding of our study is that the degree of improvement was lowest in patients with RARS. Previous studies compared the degree of QOL improvement among patients with CRS and confirmed that the improvement in QOL after surgery was more pronounced in patients with nasal polyps than in patients with CRS without polyps.[18,19] However, our study showed the most improvement in patients with CRSsNP, followed by those with CRSwNP and RARS. Although the primary outcome of ESS is QOL improvement, some patients with CRSwNP experience recurrent mucosal swelling as a result of intrinsic mucosal inflammation[20] and thus experience less improvement than patients with CRSsNP. Patients with RARS experience frequent sinus inflammation, but these sinus changes completely resolve after such events.[21]

Our study has several limitations. First, we had no control group of patients who did not undergo an operation. Therefore, we cannot directly determine whether surgery is more effective than conservative treatment. Because most patients who are conservatively treated do not require a

computed tomographic scan or sinus disease–specific QOL survey, we could not analyze that group in our studies. Second, a 6-month follow-up period may be somewhat short. However, patients with RARS do not necessarily require tertiary rhinologic care or strict long-term follow-up visits. Despite these factors, this study is strengthened by being the first attempt to analyze the characteristics of RARS, CRSsNP, and CRSwNP in parallel. Additionally, compared with previous studies, substantial data from Korean patients with RARS were gathered and reviewed. Several factors may be responsible for the differences found among the disease groups.

The presence of agger nasi cells, Haller cells, and nasal septal deviation was associated much more strongly with RARS than with CRSsNP and CRSwNP. Infundibular widths were smallest in the CRSwNP group. Patients with RARS also reported significant symptomatic improvement following ESS such as CRSsNP and CRSwNP. These results can be used to design new treatment strategies and to help clinicians understand the anatomic variants of each disease group, which can facilitate the prognostic evaluation for ESS.

Declaration of Conflicting Interests

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