A Structured Histopathology-Based Analysis of Surgical Outcomes in Chronic Rhinosinusitis With and Without Nasal Polyps

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Objectives: Structured histopathology reporting has been recently described for detailing immunopathological characteristics of chronic rhinosinusitis (CRS), and can be utilized for subtyping CRS and personalizing management. This study scrutinized elements of structured histopathology to identify characteristics that prognosticate outcomes following endoscopic sinus surgery (ESS) for CRS patients with nasal polyps (CRSsNP) and without nasal polyps (CRSwNP).

Methods: Outcomes following ESS were measured using the patient-reported 22-item sinonasal outcome test (SNOT-22). Changes in total SNOT-22 scores at 6 and 12 months postoperatively were analyzed. Thirteen parameters reported in structured histopathology of sinus surgical tissue were studied for association with outcomes post-surgery. The overall cohort of all CRS patients was studied, along with subgroup analyses of CRSsNP and CRSwNP patients.

Results: In the entire CRS cohort (n = 171), eosinophil count >10 per high power field (HPF) was associated with greater improvement in SNOT-22 scores at 6 months post-ESS (P = .039). At 12 months follow-up, no histopathological characteristic was associated with change in total SNOT-22 score. In the CRSwNP (n = 66) subgroup, the presence of fibrosis (P = .006) and eosinophil count ≤10 per HPF (P = .025) were associated with less favorable changes in SNOT-22 scores at 12 months follow-up. Fibrosis remained statistically significant in multivariable analysis (P = .007).

Conclusions: At 6 months post-ESS, tissue eosinophilia is associated with significantly higher improvement in SNOT-22 scores, but this difference is diluted by 12 months. Fibrosis was associated with less favorable outcomes in SNOT-22 scores for CRSwNP patients at 12 months and may be a prognosticator for poorer long-term outcomes.

Key Words: Chronic rhinosinusitis, nasal polyps, outcomes, histopathology, endoscopic sinus surgery.

Level of Evidence: 4

INTRODUCTION

Chronic rhinosinusitis (CRS) is an inflammatory disease that affects the lining of the paranasal sinuses and the nasal passages.1 CRS has substantial impact on quality of life, and this has been well demonstrated.2,3 Treatment modalities for CRS include medical therapy, as well as endoscopic sinus surgery (ESS).4,5 Treatment has been shown to improve cardinal symptoms and outcomes of patients,6 yet for some poorly controlled disease and symptoms continue despite standard of care.7 The heterogeneity of pathophysiological mechanisms that result in inflammation of the sinonasal mucosa may be a critical factor that determines success or failure from standard of care. Therefore, there has been increased interest to identify underlying pathophysiological mechanisms on a personalized level to target optimal medical and surgical treatment.

Structured histopathology of sinonasal tissue is a tool that can potentially be utilized by all clinicians in understanding pathophysiological features specific to the patient.8 While clinically CRS is classified into phenotypes with nasal polyps (CRSsNP) or without nasal polyps (CRSwNP), diverse inflammatory mechanisms may drive each subtype.9 Tissue eosinophilia, which has classically been described as a hallmark of patients with CRSsNP in the United States, may also be present in patients without nasal polyps. A recent study demonstrated that as many as 30% of CRSsNP patients had tissue eosinophilia.10 Histopathologic features have also been used to differentiate CRS subtypes, and may aid the clinician in treatment plan and prognosis.8,11–15 Classifying CRS according to inflammatory profiles rather than exclusively by phenotype, based on the presence or absence of nasal polyps, may be useful for guiding management and personalizing treatment to individual patients. Structured histopathology of routine surgical specimens can be performed at most centers by pathologists.8

Associations of patient reported outcomes according to histologic features have not been fully investigated.22-item sinonasal outcome test (SNOT-22) offers a validated inventory for measuring quality life impact of CRS and improvement following medical therapy and surgery.16 In a recent study, Lal and Hopkins noted that CRSsNP patients with more severe symptoms were characterized by tissue eosinophilia and had more significant improvement in the SNOT 22 scores.10 Understanding the effect of histologic features on changes in SNOT-22 score following ESS may be useful in identifying patients at risk for poorer outcomes. Treatment plans might also be modified according to histopathologic features in specific patients. This study applied...
a structured histopathologic analysis to examine surgical outcomes in a large group of CRS patients following ESS. Postoperative change in SNOT-22 score at 6 and 12 months follow-up was used at the primary endpoint in measuring surgical outcomes. Subgroup analysis was also performed among patients with CRSwNP and CRSsNP.

**PATIENTS AND METHODS**

Patients undergoing ESS for the treatment of CRSwNP and CRSsNP with available structured histopathology reports in the senior author’s (DL) practice between July 1, 2011 and December 31, 2016 were considered for study inclusion. Diagnosis of CRS was made in accordance with the American Academy of Otolaryngology contemporary clinical practice guideline on adult sinusitis, and all patients had a sinus computed tomography scan prior to surgery. Patients were routinely treated with appropriate medical therapy, including oral steroids and antibiotics, prior to decision for surgery, but were not routinely prescribed systemic medications in the period before surgery. Exclusion criteria were incomplete structured histopathology reports, incomplete SNOT-22 questionnaires at both 6 and 12 months follow-up, and age less than 18 years.

Structured histopathology reports included 13 parameters (Table I), and were completed by the reviewing pathologist from sinonasal contents collected during surgery. Tissue was collected at the time of surgery from the paranasal sinus mucosa and was sent as a single specimen fixed in formalin. While harvested tissue was not from a specific sinus, other nasal tissue was not included in the analyzed specimen. Histopathological analysis of hematoxylin and eosin stained slides was performed and recorded as described by Snidvongs et al. Eosinophil counts were reported per high power field (HPF), and dichotomized to ≤10 versus >10 eosinophils per HPF. Inflammatory predominance reported as “neutrophilic,” “lymphohistiocytic,” and “other” was combined into a single category of “other” due to the low number reported for each of these categories. Snidvongs et al described reporting for neutrophilic infiltrate as “absent,” “focal,” and “diffuse”; however, this was dichotomized to “absent” and “present” for the purposes of this study. Reporting of fibrosis as absent, partial, and extensive was similarly dichotomized.

SNOT-22 questionnaires were completed by patients preoperatively, and at 6 and 12 month follow-up visits. SNOT-22 questionnaires and pathology reports were retrospectively collected from the medical record for the purposes of this study. The mean change in SNOT-22 scores at both 6 and 12 months follow-up was compared for each parameter of the structured histopathology report. An overall analysis was performed including all patients, as well as subgroup analysis among the CRSwNP and CRSsNP cohorts. Two-sample independent t tests were used to compare two groups, while one-way analysis of variance (ANOVA) was used to compare three or more groups. Post hoc testing was performed for significant ANOVA comparisons using Tukey’s honestly significant difference (HSD). Multivariable analysis of significant factors was also performed using generalized regression models. Statistical analysis was performed using JMP Pro, version 14.1.0 (SAS Institute, Inc, Cary, NC), and P values <.05 were considered significant. The study was approved by the institutional review board of the Mayo Clinic, Phoenix, AZ.

**RESULTS**

A total of 199 patients met inclusion and exclusion criteria, with 89 in the CRSwNP group and 110 in the CRSsNP group. Among all patients, 171 had completed SNOT-22 questionnaires at 6 months follow-up and 127 had completed the 12-month questionnaire. In the CRSwNP group, 76 patients had follow-up at 6 months, with 66 completing follow-up at the 12-month visit. In the CRSsNP cohort, 95 patients completed SNOT-22 questionnaires at 6 months, while 61 were complete at 12 months. When comparing patients who completed 12 month follow-up versus incomplete structured histopathology reports, incomplete SNOT-22 questionnaires at both 6 and 12 months follow-up was compared for each parameter of the structured histopathology report. An overall analysis was performed including all patients, as well as subgroup analysis among the CRSwNP and CRSsNP cohorts.

**TABLE I.**

| Variable                     | Reported Categories |
|------------------------------|---------------------|
| Degree of inflammation       | Mild, moderate, severe |
| Eosinophil count             | ≤10 per HPF, >10 per HPF |
| Neutrophil infiltrate        | Absent, present     |
| Inflammatory predominance    | Lymphocytic, lymphoplasmacytic, eosinophilic, other |
| Basement membrane thickening | <7.5 microns, 7.5–15 microns, >15 microns |
| Subepithelial edema          | Absent/mild, moderate, severe |
| Hyperplastic/papillary change| Absent, present     |
| Mucosal ulceration           | Absent, present     |
| Squamous metaplasia          | Absent, present     |
| Fibrosis                     | Absent, present     |
| Fungal elements              | Absent, present     |
| Charcot-Leyden crystals      | Absent, present     |
| Eosinophil aggregates        | Absent, present     |

HPF = high power field.

**TABLE II.**

| Characteristic               | All Patients (n = 199)* | CRSwNP (n = 89)* | CRSsNP (n = 110)* |
|------------------------------|-------------------------|------------------|-------------------|
| Age (yr)                     | 53.9 (51.8, 56.0)       | 53.6 (50.3, 57.0) | 54.1 (51.3, 56.8) |
| Male                         | 99 (45.2%)              | 45 (50.1%)       | 45 (40.9%)        |
| Female                       | 109 (54.8%)             | 44 (49.4%)       | 65 (59.1%)        |
| Preoperative                 | 43.6 (40.7, 46.6)       | 44.0 (39.8, 48.2) | 43.4 (39.2, 47.5) |
| SNOT-22 Preoperative LMS     | 11.3 (10.5, 12.1)       | 14.1 (13.0, 15.3)| 9.3 (8.3, 10.2)   |
| Revision surgery             | 76 (38.2%)              | 41 (46.1%)       | 35 (31.8%)        |
| Maxillary antrostomy         | 184 (92.4%)             | 84 (94.4%)       | 100 (90.9%)       |
| Ethmoidectomy                | 184 (92.4%)             | 88 (98.9%)       | 96 (87.3%)        |
| Sphenoidotomy                | 161 (80.9%)             | 84 (94.4%)       | 77 (70.0%)        |
| Frontal sinusotomy           | 155 (77.9%)             | 83 (93.3%)       | 72 (65.5%)        |

*Values are count with percentage, or mean with 95% confidence interval.
CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyps; LMS = Lund-Mackay score; SNOT-22 = 22-item sinonasal outcome test.
of the patients that were lost to follow-up, there were no statistical differences between the two groups for any of the considered histopathological features. The patient demographics and clinical characteristics are shown in Table II. Mean change in SNOT-22 score between primary surgery (20.9, 95% confidence interval [CI] [16.5, 25.4]) and revision surgery

| Histopathology Parameter | SNOT-22 Change (All Patients) P Value | SNOT-22 Change (CRSwNP) P Value | SNOT-22 Change (CRSsNP) P Value |
|--------------------------|---------------------------------------|----------------------------------|---------------------------------|
| Degree of inflammation   | .575                                  | .722                             | .722                            |
| Mild                     | 24.1 (27.3, 25.3)                     | 29.7 (21.5, 37.9)                | 21.9 (16.4, 27.4)               |
| Moderate                 | 27.3 (23.1, 31.6)                     | 29.5 (23.7, 35.2)                | 25.2 (19.1, 21.4)               |
| Severe                   | 25.3 (18.1, 32.5)                     | 25.6 (17.2, 34.1)                | 24.4 (9.9, 39.0)                |
| Eosinophil count         | .039*                                 | .115                             | .408                            |
| ≤10 per HPF              | 22.5 (18.4, 26.7)                     | 23.5 (16.7, 30.4)                | 22.3 (17.2, 27.3)               |
| >10 per HPF              | 28.5 (24.6, 32.3)                     | 30.1 (25.2, 35.0)                | 25.6 (19.2, 32.1)               |
| Neutrophil infiltrate    | .314                                  | .553                             | .128                            |
| Absent                   | 26.7 (23.2, 30.1)                     | 28.4 (23.6, 33.2)                | 25.3 (20.3, 30.3)               |
| Present                  | 23.6 (18.5, 28.7)                     | 29.0 (20.7, 37.4)                | 19.2 (13.0, 25.5)               |
| Inflammatory predominance| .049*                                 | .073                             | .439                            |
| Lymphocytic              | 27.3 (21.6, 33.0)                     | 37.4 (25.1, 49.6)                | 24.9 (18.2, 31.5)               |
| Lymphoplasmacytic        | 23.2 (19.0, 27.4)                     | 25.2 (18.5, 31.8)                | 22.1 (16.7, 27.6)               |
| Eosinophilic             | 25.1 (19.6, 30.7)                     | 26.7 (20.7, 32.6)                | 19.3 (6.6, 32.1)                |
| Other                    | 39.6 (28.6, 50.6)                     | 41.3 (28.2, 54.4)                | 36.8 (17.6, 55.9)               |
| Basement membrane thickening | .140                                | .684                             | .082                            |
| <7.5 microns             | 20.9 (19.4, 27.6)                     | 26.5 (16.5, 36.4)                | 18.4 (11.4, 25.4)               |
| 7.5–15 microns           | 28.24 (23.1, 33.4)                    | 26.6 (18.6, 34.6)                | 29.3 (22.6, 36.0)               |
| >15 microns              | 26.7 (22.6, 30.9)                     | 30.2 (24.7, 35.7)                | 22.5 (16.1, 28.8)               |
| Subepithelial edema      | .217                                  | .036*                            | .707                            |
| Absent/mild              | 23.5 (19.4, 27.6)                     | 23.9 (17.4, 30.4)                | 23.3 (18.4, 28.2)               |
| Moderate                 | 29.0 (23.8, 34.3)                     | 35.4 (28.9, 41.9)                | 22.4 (15.1, 29.8)               |
| Severe                   | 26.6 (21.3, 31.8)                     | 25.7 (18.0, 33.4)                | 29.7 (14.0, 45.4)               |
| Hyperplastic/papillary change | .210                              | .283                             | .408                            |
| Absent                   | 26.5 (23.5, 29.5)                     | 29.8 (25.6, 34.0)                | 24.0 (19.8, 28.2)               |
| Present                  | 20.7 (12.0, 29.5)                     | 22.3 (8.5, 36.2)                 | 18.8 (6.0, 31.6)                |
| Mucosal ulceration       | .091                                  | .498                             | .280                            |
| Absent                   | 24.8 (21.9, 27.7)                     | 28.0 (23.4, 32.6)                | 22.5 (18.7, 26.3)               |
| Present                  | 33.9 (23.5, 44.4)                     | 31.5 (21.6, 41.5)                | 40.2 (1.0, 79.4)                |
| Squamous metaplasia      | .798                                  | .857                             | .782                            |
| Absent                   | 25.9 (22.9, 29.0)                     | 28.9 (24.3, 33.3)                | 23.7 (19.6, 27.8)               |
| Present                  | 24.8 (16.7, 33.0)                     | 27.8 (16.8, 38.7)                | 21.9 (8.3, 35.4)                |
| Fibrosis                 | .687                                  | .298                             | .705                            |
| Absent                   | 26.6 (21.4, 31.9)                     | 32.2 (23.4, 41.0)                | 22.4 (15.9, 28.9)               |
| Present                  | 25.4 (22.0, 28.8)                     | 27.1 (22.5, 31.8)                | 23.9 (18.9, 28.9)               |
| Fungal elements          | .406                                  | .258                             | .797                            |
| Absent                   | 26.0 (23.0, 29.1)                     | 29.1 (24.7, 33.5)                | 23.6 (19.4, 27.8)               |
| Present                  | 22.8 (15.4, 30.22)                    | 23.9 (14.6, 33.1)                | 22.0 (9.0, 35.0)                |
| Charcot-Leyden crystals  | .124                                  | .116                             | .224                            |
| Absent                   | 24.6 (21.4, 27.7)                     | 25.9 (21.1, 30.6)                | 23.9 (19.8, 28.0)               |
| Present                  | 30.3 (23.5, 37.2)                     | 32.8 (25.4, 40.2)                | 15.6 (0.0, 31.2)                |
| Eosinophil aggregates    | .212                                  | .365                             | .858                            |
| Absent                   | 24.5 (21.3, 27.8)                     | 26.7 (21.7, 31.7)                | 23.6 (19.4, 27.8)               |
| Present                  | 28.7 (23.0, 34.4)                     | 30.4 (23.9, 37.0)                | 22.5 (9.6, 35.3)                |
(24.5, 95% CI [20.9, 28.1]) was not statistically significant through 12 months follow-up ($P = .217$). The presence of fibrosis was also not different between primary and revision surgery ($P = .118$), including CRSsNP ($P = .080$) and CRSwNP ($P = .979$) subgroups. Patients having revision surgery were more likely to have frontal sinusotomy ($P < .001$), and Draf 3 procedure was restricted to two patients having revision surgery.

### TABLE IV.
**12-Month SNOT-22 Change According to Structured Histopathology.**

| Histopathology Parameter                           | SNOT-22 Change (All Patients)† | $P$ Value | SNOT-22 Change (CRS w/ NP)† | $P$ Value | SNOT-22 Change (CRS w/o NP)† | $P$ Value |
|----------------------------------------------------|---------------------------------|-----------|-----------------------------|-----------|-----------------------------|-----------|
| Degree of inflammation                              |                                 |           |                             |           |                             |           |
| Mild                                               | 22.8 (17.2, 28.3)               | .792      | 31.3 (22.7, 39.9)           | .130      | 17.9 (10.4, 25.3)           | .685      |
| Moderate                                           | 21.9 (16.6, 27.2)               |           | 21.5 (14.8, 28.2)           |           | 22.4 (13.8, 30.9)           |           |
| Severe                                             | 19.0 (9.9, 28.2)                |           | 19.8 (10.4, 29.1)           |           | 15.3 (−9.3, 40.0)           |           |
| Eosinophil count                                    |                                 |           |                             |           |                             |           |
| ≤ 10 per HPF                                       | 18.7 (13.3, 24.2)               | .139      | 15.6 (7.8, 23.4)            | .025*     | 20.0 (27.1)                 | .851      |
| > 10 per HPF                                       | 24.1 (19.4, 28.8)               |           | 26.3 (20.8, 31.9)           |           | 18.9 (27.7)                 |           |
| Neutrophil infiltrate                               |                                 |           |                             |           |                             |           |
| Absent                                             | 22.0 (17.8, 26.3)               | .839      | 23.3 (17.7, 28.9)           | .687      | 20.7 (14.1, 27.4)           | .470      |
| Present                                            | 21.3 (14.6, 27.9)               |           | 25.4 (16.0, 34.9)           |           | 16.6 (6.8, 26.3)           |           |
| Inflammatory predominance                           |                                 |           |                             |           |                             |           |
| Lymphocytic                                        | 23.8 (17.1, 30.4)               | .089      | 26.0 (18.1, 31.5)           | .016*     | 22.8 (14.0, 31.5)           | .780      |
| Lymphoplasmacytic                                   | 17.0 (11.5, 22.5)               |           | 17.1 (15.2, 36.8)           |           | 16.9 (8.9, 24.8)           |           |
| Eosinophilic                                       | 24.5 (17.7, 31.3)               |           | 24.8 (9.4, 24.7)            |           | 22.3 (8.8, 43.7)           |           |
| Other                                              | 33.3 (19.4, 47.1)               |           | 49.0 (31.1, 67.0)           |           | 17.5 (−4.0, 39.0)           |           |
| Basement membrane thickening                       |                                 | .066      | .473                        | <.001*     |                             |           |
| < 7.5 microns                                      | 14.3 (6.9, 21.7)                |           | 27.4 (15.8, 38.9)           |           | 5.9 (−3.3, 15.1)           |           |
| 7.5–15 microns                                     | 22.9 (17.9, 28.0)               |           | 19.7 (11.1, 28.2)           |           | 31.7 (23.0, 40.4)           |           |
| > 15 microns                                       | 25.5 (19.2, 31.8)               |           | 25.2 (18.8, 31.7)           |           | 19.7 (12.1, 27.3)           |           |
| Subepithelial edema                                 |                                 | .607      | .307                        | .890       |                             |           |
| Absent/mild                                        | 20.1 (15.1, 25.1)               |           | 20.2 (12.3, 28.1)           |           | 20.1 (13.4, 26.7)           |           |
| Moderate                                           | 24.1 (17.8, 30.3)               |           | 28.5 (20.8, 36.3)           |           | 17.8 (7.4, 28.2)           |           |
| Severe                                             | 22.6 (14.1, 31.1)               |           | 22.5 (13.8, 31.2)           |           | 23.3 (−1.4, 48.1)           |           |
| Hyperplastic/papillary change                       |                                 | .906      | .682                        | .925       |                             |           |
| Absent                                             | 21.9 (18.1, 25.8)               |           | 24.4 (19.3, 29.6)           |           | 19.5 (13.7, 26.7)           |           |
| Present                                            | 21.3 (11.7, 31.0)               |           | 21.8 (9.2, 34.4)            |           | 20.3 (−0.4, 41.0)           |           |
| Mucoosal ulceration                                 |                                 | .227      | .170                        | .804       |                             |           |
| Absent                                             | 22.5 (18.9, 26.2)               |           | 25.4 (20.5, 30.3)           |           | 19.8 (14.2, 25.3)           |           |
| Present                                            | 14.3 (10.1, 28.8)               |           | 14.2 (−2.3, 30.8)           |           | 14.5 (−195.2, 224.2)        |           |
| Squamous metaplasia                                 |                                 | .558      | .224                        | .888       |                             |           |
| Absent                                             | 22.4 (18.5, 26.2)               |           | 25.3 (19.9, 30.7)           |           | 19.4 (13.8, 24.9)           |           |
| Present                                            | 19.4 (10.1, 28.8)               |           | 18.6 (8.4, 28.7)            |           | 20.8 (0.8, 42.4)           |           |
| Fibrosis                                           |                                 | .302      | .006*                       | .293       |                             |           |
| Absent                                             | 24.9 (17.4, 32.4)               |           | 34.4 (25.4, 43.3)           |           | 14.9 (3.8, 26.1)           |           |
| Present                                            | 20.5 (16.6, 24.5)               |           | 19.7 (14.5, 24.9)           |           | 21.5 (15.2, 27.8)           |           |
| Fungal elements                                     |                                 | .956      | .832                        | .807       |                             |           |
| Absent                                             | 21.8 (18.1, 25.5)               |           | 24.1 (19.1, 29.0)           |           | 19.3 (13.7, 24.9)           |           |
| Present                                            | 22.2 (7.9, 36.5)                |           | 22.2 (1.1, 43.2)            |           | 22.2 (−5.8, 50.1)           |           |
| Charcot-Leyden crystals                             |                                 | .162      | .105                        | .775       |                             |           |
| Absent                                             | 20.2 (16.5, 23.9)               |           | 20.5 (15.7, 25.4)           |           | 19.9 (14.4, 25.4)           |           |
| Present                                            | 26.9 (18.0, 35.0)               |           | 29.1 (19.7, 38.5)           |           | 15.8 (−21.0, 52.6)          |           |
| Eosinophil aggregates                               |                                 | .180      | .141                        | .795       |                             |           |
| Absent                                             | 20.1 (16.1, 24.1)               |           | 20.4 (15.0, 25.9)           |           | 19.9 (14.2, 25.6)           |           |
| Present                                            | 25.6 (18.5, 32.7)               |           | 27.4 (19.6, 35.1)           |           | 17.3 (−5.1, 39.7)           |           |

*P value significant.
†Mean value with 95% confidence interval.
CRSsNP = chronic rhinosinusitis without nasal polyposis; CRSwNP = chronic rhinosinusitis with nasal polyps; HPF = high power field; SNOT-22 = 22-item sinonasal outcome test.
SNOT-22 score change at 6 months follow-up for all patients, as well as CRSwNP and CRSSS subgroup, is demonstrated in Table III. When all patients were considered, eosinophil counts ≤10 per HPF were associated with less change in SNOT-22 scores \((P = .039)\). Preoperative SNOT-22 scores were higher in the group of patients with eosinophil counts >10 per HPF \((P = .002)\). Inflammatory predominance reported as “other” was associated with a greater change in SNOT-22 scores \((P = .049)\), although a limited number of patients were in this category \((n = 11)\) and Tukey’s HSD did not reveal statistical difference between the other categories. By multivariable generalized regression, eosinophil count ≤10 per HPF remained statistically significant for decreased SNOT-22 score change \((P = .016)\). In the CRSwNP subgroup, moderate subepithelial edema was associated with greater SNOT-22 score change \((P = .036)\). Only mild and moderate subepithelial edema were statistically different by Tukey’s HSD \((P = .040)\). None of the variables reported in the structured histopathology reports were associated with statistically significant differences in SNOT-22 score change in the CRSSS subgroup at 6 months follow-up.

12-month follow up SNOT-22 score change for all groups is shown in Table IV. When all patients were considered, there were no statistical differences in SNOT-22 score change for any of the parameters captured in the structured histopathology reports. In the CRSSS subgroup, basement membrane thickening of 7.5–15 microns was associated with greater SNOT-22 score change \((P < .001)\). Tukey’s HSD was only significant when 7.5–15 microns of basement membrane thickening was compared to < 7.5 microns \((P < .001)\). Among patients with CRSwNP, fibrosis \((P = .006)\) and eosinophil counts ≤10 per HPF \((P = .025)\) were associated with decreased change in SNOT-22 scores. Preoperative SNOT-22 scores were higher in the patients with eosinophil counts >10 per HPF \((P = .010)\), although these were not statistically different according to presence or absence of fibrosis \((P = .105)\). Inflammatory predominance of “other” was associated with increased changes in SNOT-22 scores \((P = .016)\); however, a small number of patients were in this category \((n = 4)\) and the other categories were not statistically different by Tukey’s HSD. Using multivariable generalized regression, the presence of fibrosis remained statistically significant for decreased SNOT-22 score change \((P = .007)\).

**DISCUSSION**

Routine use of structured histopathology reporting in CRS has been suggested as a means for diagnosing CRS subtypes and recognizing potential prognostic implications of these subtypes. Histopathologic differences in CRS have since been identified according to nasal polyp status, radiation history, gender, immunosuppressive therapy, and odontogenic infection. Moreover, sinus cultures have been associated with histopathologic changes among CRS patients. The relationship of patient-reported outcomes with structured histopathology parameters has not been completely defined following ESS. Ideally, identifying histologic features associated with better or worse patient outcomes might help direct treatment following ESS by aligning management strategies with pathologic mechanisms in specific patients.

CRS endotypes have been described in several studies through cluster analysis of inflammatory markers. The heterogeneity of inflammatory mechanisms in CRS generally, and even among CRS phenotypes, is apparent using endotypes. The techniques used to identify inflammatory markers, some of which are commercially available, have not been routinely applied to clinical practice. On the other hand, structured histopathology can be routinely performed on surgical specimens, and has been previously proposed as a strategy for understanding pathologic mechanisms in CRS. Furthermore, these synoptic pathology reports have been successfully implemented in our practice for all patients having ESS for CRS.

When considering all patients with CRS collectively, no single histopathologic feature was associated with a significantly different change in SNOT-22 scores through 12 months follow-up. In part, this is consistent with difficulty in correlating subjective symptoms with objective markers of disease. This also likely reflects the previously mentioned heterogeneity of CRS pathophysiology in combination with the general effectiveness of ESS and currently available postoperative medical therapies. While patients in this study did have treatment directed by histopathology reporting, the potential effect of targeted therapies according to these reports cannot be assessed in this retrospective study. Nevertheless, our group published a recent study utilizing endotype directed therapy with structured histopathology as one of the markers for directing management. The operators noted that the rates of revision surgery were lower using this subtype directed approach.

In the subgroup of patients with nasal polyps, there was a decreased change in SNOT-22 scores at 12 months follow-up when fibrosis and eosinophil counts ≤10 per HPF were present. These findings may seem to contradict a previous report of increased tissue eosinophil counts as a factor for refractory CRSwNP. Recently, a study by Brescia et al described decreased tissue eosinophil counts in first revision surgery among CRSwNP patients compared to the initial procedure. There was a further decrease in eosinophil counts at a second revision surgery, although small sample size limited statistical analysis. The study by Bassiouni et al, while identifying higher tissue eosinophil counts as a risk factor for refractory disease, also found a relative decrease in tissue eosinophilia at the revision surgery. Increased basement membrane thickening was also seen in revision surgery in the Brescia et al’s study. The current association of decreased eosinophil counts and fibrosis with lower SNOT-22 score change postoperatively may reflect a group of CRSwNP patients refractory to traditional medical therapies. This may support the hypothesis suggested by Brescia et al of dynamic tissue remodeling in response to medical and surgical therapy for CRSwNP. Eosinophil counts ≤10 per HPF were also significant for decreased SNOT-22 score change at 6 months follow-up for all patients with CRS (Table III). This appears to be driven by the CRSwNP patients, although statistically significance was not achieved in polyg subgroup at 6 months follow-up. Furthermore, patients with eosinophil counts ≤10 per HPF had lower preoperative SNOT-22 scores, and may have decreased ability for improvement as measured by SNOT-22 scores. Preoperative SNOT-22 scores have been recognized as an important factor influencing symptom score.
change following ESS. The presence of fibrosis, however, remained statistically significant in multivariable analysis, and preoperative SNOT-22 scores were not different. Fibrosis may be particularly associated with poorer long-term outcomes following ESS for CRSwNP patients.

Interestingly, presence of fibrosis was not significantly different between primary and revision surgery, including CRSwNP patients. To this extent, fibrosis does not appear to represent tissue remodeling as a result of ESS. Tissue remodeling due to the duration of local inflammation and medication use resulting in fibrosis, however, cannot be fully captured in this study. These factors have also been described to result in tissue changes in CRS patients, including collagen deposition. Investigating time to surgery as a factor for the presence of fibrosis on histology might clarify if fibrosis is a result of tissue remodeling in CRS, and whether this contributes to postsurgical outcomes.

Several other factors achieved statistical significance, although the clinical value of these is difficult to interpret. Inflammatory predominance of “other” was associated with increased change in SNOT-22 scores at 6 months follow-up for all CRS patients, and at 12 months follow-up for CRSwNP patients. A small number of patients were classified as “other” for both of these results, and post hoc testing did not reveal statistical significance between the remaining categories. Subepithelial edema classified as moderate was associated with increased SNOT-22 score change in CRSwNP patients at 6 months of follow-up. This did not remain significant at 12 months of follow-up. Among CRSwNP patients, basement membrane thickening between 7.5 and 15 microns was associated with greater change in SNOT-22 score at 12 months follow-up. The statistical significance for subepithelial edema and basement membrane thickening was not linear in both instances, making clinical interpretation difficult. Additional sampling might resolve this apparent nonlinearity because post hoc testing was only significant for a single comparison within each ANOVA analysis.

The present study has several limitations. Postoperative treatment was not recorded in a standard fashion and therefore could not be assessed. Targeted treatment, particularly in accordance with CRS subtypes identified by structured histopathology, might better optimize patient outcomes. Furthermore, given the retrospective nature of this study, postoperative treatment was not uniformly standardized. This certainly may impact patient reported outcomes and associations or lack thereof with histopathologic parameters. Nevertheless, patients were treated postoperatively with conventional medical therapies, and to this extent the reported outcomes represent a real world experience through 12 months following ESS. Similarly, preoperative medical treatment was not uniformly standardized, and this could conceivably impact histopathology.

CONCLUSION

In patients with CRSwNP, eosinophil counts ≤10 per HPF and presence of fibrosis were associated with decreased change in SNOT-22 score at 12 months follow-up. Fibrosis remained statistically significant in multivariable analysis, and may represent a particular group of patients with nasal polyps at risk for poorer outcomes following ESS. At 6 months post-ESS, presence of tissue eosinophilia was associated with significantly higher improvement in SNOT-22 scores, but this difference is diluted by 12 months. No particular characteristic of the study parameters considered in structured histopathology reporting was predictive of significantly different SNOT-22 score 12 months following ESS when all patients with CRS were considered collectively. Multivariable studies that include all features of histopathology in combination with clinical and serial loss features may offer guidance on a precision treatment approach to CRS.

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