

Symptom-Based Clustering in Chronic Rhinosinusitis Relates to History of Aspirin Sensitivity and Postsurgical Outcomes

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What is already known about this topic? Patients with chronic rhinosinusitis (CRS) with aspirin sensitivity have a higher disease burden and poorer postsurgical outcomes. Without a clear history of aspirin reaction, there are no good clinical tools to predict a history of aspirin sensitivity.

What does this article add to our knowledge? Patients with CRS exhibit a heterogeneous symptom burden with varying emphasis on individual 22-item SinoNasal Outcome Test symptoms. This heterogeneity was associated with history of aspirin sensitivity and was related to treatment outcomes.

How does this study impact current management guidelines? The study result facilitates the recognition of symptom heterogeneity in CRS, which should aid in the workup of CRS and in the prediction of aspirin sensitivity and which relates to response to treatment such as surgery.

BACKGROUND: Symptoms burden in chronic rhinosinusitis (CRS) may be assessed by interviews or by means of validated tools such as the 22-item SinoNasal Outcome Test (SNOT-22). However, when only the total SNOT-22 scores are used, the pattern of symptom distribution and heterogeneity in patient symptoms is lost.

OBJECTIVES: To use a standardized symptom assessment tool (SNOT-22) on preoperative symptoms to understand symptom heterogeneity in CRS and to aid in characterization of distinguishing clinical features between subgroups.

METHODS: This was a retrospective review of 97 surgical patients with CRS. Symptom-based clusters were derived on the basis of presurgical SNOT-22 scores using unsupervised analysis and network graphs. Comparison between clusters was performed for clinical and demographic parameters, postsurgical symptom scores, and presence or absence of a history of aspirin sensitivity.

RESULTS: Unsupervised analysis reveals coclustering of specific symptoms in the SNOT-22 tool. Using symptom-based clustering, patients with CRS were stratified into severe overall (mean total score, 90.8), severe sinonasal (score, 62), moderate sinonasal (score, 40), moderate nonsinonasal (score, 37) and mild sinonasal (score, 16) clusters. The last 2 clusters were associated with lack of history of aspirin sensitivity. The first cluster had a rapid relapse in symptoms postoperatively, and the last cluster demonstrated minimal symptomatic improvement after surgery.

CONCLUSION: Symptom-based clusters in CRS reveal a distinct grouping of symptom burden that may relate to aspirin sensitivity and treatment outcomes. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:934-40)

Key words: Chronic rhinosinusitis; Aspirin sensitivity; CRS symptoms; SNOT-22; Aspirin exacerbated respiratory disease

Chronic rhinosinusitis (CRS) is defined as 12 weeks or longer of 2 or more symptoms of mucopurulent drainage, nasal obstruction, facial congestion or pressure, or decreased sense of smell and objective documentation of inflammation by mucopurulent drainage, presence of polyps in nasal cavity, and/or radiographic imaging showing inflammation of paranasal sinuses.¹ Because the criteria for defining CRS emphasizes

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Abbreviations used

AT- aspirin tolerant
CRS- chronic rhinosinusitis
CT- Computerized tomography
H-AS- history of aspirin sensitivity
IQR- interquartile range
LM- Lund-Mackay
SNOT-22- 22-item SinoNasal Outcome Test

symptoms, measuring and comparing individual or groups of symptoms in CRS is important in assessing disease severity and treatment outcomes. Addition of 2 questions, impairment of taste/smell and blockage or congestion of the nose, to the well-validated CRS 20-item SinoNasal Outcome Test questionnaire² has provided an additional measure of sinonasal disease burden and has also been validated (22-item SinoNasal Outcome Test [SNOT-22]).³ Previous studies have used overall SNOT-22 scores,^{4,5} individual scores,⁶ or *predefined* combinations of symptoms^{7,8} and have documented differences in *a priori*-defined CRS subtypes (including aspirin sensitivity) in regard to symptom burden.³ Cluster analysis of symptoms to define such subgroups has recently been attempted,^{9,10} but pretherapy and posttherapy differences using unsupervised methods have not been extensively studied. In this article, we obtained preoperative SNOT-22 scores of patients who underwent endoscopic sinus surgery for CRS, used *unsupervised learning* to model symptom-based patient clusters, and studied differences between these clusters for select clinical parameters, including history of aspirin intolerance and surgical outcomes.

METHODS

Study design

This was a retrospective study of adults with physician-confirmed CRS seen in the Department of Otorhinolaryngology and the Division of Allergic Diseases at Mayo Clinic, Rochester, Minnesota, from 2012 to 2014. The study was approved by the institutional review board, and clinical data from patients' medical record were used in the study.

Study population and data collection

This was a retrospective review of patients who met criteria for CRS based on symptoms and objective findings for more than 12 weeks.¹ All patients underwent endoscopic sinus surgery in the Department of Otorhinolaryngology. Ninety-seven consecutive patients who had consented previously to participation in research at the Mayo Clinic were included. Exclusion criteria included the presence of secondary causes of recurrent or chronic sinusitis including cystic fibrosis, primary ciliary dyskinesia, or primary immune deficiency. The study was approved by the institutional review board. The median interval for presurgical score was 26 days (interquartile range [IQR], 7-41).

Follow-up SNOT-22 scores were obtained at an initial postoperative period (median day 21 IQR, 14-36) and at a subsequent second visit (median day 97 IQR, 58-198) after surgery. Additional clinical data were gathered (listed in Table I). Upon further review, 14 of 22 patients who reported a history of aspirin sensitivity underwent a challenge/desensitization postsurgery in the Division of Allergic Diseases.

Clinical and laboratory testing

Vitamin D₃ and serum IgE assessment was done at Mayo Medical Laboratory. Eosinophil count before surgery and the highest eosinophil count in the medical record were recorded. The allergy status of the participants was determined using a standard panel by skin prick testing congruent with their geographic location.

Network graphs and clustering

SNOT-22 scores for each question item were converted into a format suitable for use with Gephi 0.8.2 (www.Gephi.org), an open-source, interactive visualization and exploration tool.¹¹ Weighted degree centrality, which is the cumulative measure of quantity and weight of connections made with a node, was calculated and represented by a node size set between 12 and 60. Force-directed algorithm (such as Force-Atlas),¹² was applied to the resultant network to reveal patterns of association. Hierarchical agglomerative clustering was applied to standardized data to reveal cluster membership and boundaries.

Statistical analysis

The χ^2 test was used to assess for significance in categorical data. Means and ANOVA were used for assessing significance in continuous data, with significant difference between all pairs calculated using the Tukey HSD test or the Wilcoxon rank sum test. A *P* value of less than .05 was considered statistically significant. Analysis was performed using JMP software (v10, SAS institute Inc, Cary, NC) and Microsoft Office (2010 Microsoft corporation, Redmond, Wash).

RESULTS

Characteristics of the subjects in the study

Table I presents basic characteristics of subjects included in the study. Thirty-three percent of the subjects were women (*n* = 32 of 97), and the mean age of the subjects was 51 years. Among the subjects, approximately 23% (*n* = 22) reported an "allergic reaction" with aspirin and approximately 61% (*n* = 59 of 97) carried a diagnosis of physician-diagnosed asthma. For the purpose of the study, the patients who had a history of reactions to aspirin were designated as "history of aspirin sensitivity" (H-AS) whereas those who did not were designated as "aspirin tolerant" (AT). Among those with H-AS, 45% were women, whereas among those who did not endorse such history, 29% were women (*P* = .19). The mean age of patients in the 2 groups was different, with those with H-AS being younger (mean, 45.7 years) than those in the AT group (mean, 52.5 years; *P* = .04).

Select laboratory parameters and clinical variables between these 2 groups of patients (Table I) are also shown as part of baseline comparison. Presurgical peripheral eosinophil count was similar between the H-AS group (mean, 463 cells/mm³) and the AT group (437 cells/mm³; *P* = .74). The highest recorded eosinophil count was greater in the H-AS group (mean, 916 cells/mm³) compared with the AT group (mean, 574 cells/mm³; *P* = .002). The mean level of vitamin D in patients with H-AS was 25.7 ng/mL compared with 33.9 ng/mL in the AT group (*P* = .11). There were no significant differences between total serum IgE levels or atopic status between the 2 groups. All patients in the H-AS group had nasal polyps (100%; *n* = 22) compared with 80% in the AT group (*P* = .01). The mean Lund-Mackay (LM) computerized tomography (CT) score for sinus disease was 15.7 ± 0.9 in the H-AS group compared with 13.7 ± 0.5 in

TABLE I. Demographic characteristics of patients in the study and comparison of clinical parameters in patients with CRS with and without H-AS (AT)

Characteristic	No.	%	
Sex: female	32/97	33	
Age (y), mean $\pm$ SEM	51 $\pm$ 1.4		
History of aspirin sensitivity	22/97	23	
Physician-diagnosed asthma	59/97	61	
Characteristic/clinical parameter	No H-AS (AT)	H-AS	P value
Sex: female, n (%)	22 of 75 (29)	10 of 22 (45)	.19
Age (y), mean $\pm$ SE	52.5 $\pm$ 2	45.7 $\pm$ 3	.04
Peripheral eosinophil count (cells/mm ³), mean $\pm$ SD			
Presurgical	437 $\pm$ 38	463 $\pm$ 69	.74
Highest	574 $\pm$ 52	916 $\pm$ 94	.002
Serum vitamin D lowest (ng/mL), mean $\pm$ SD	33.9 $\pm$ 2	25.7 $\pm$ 5	.11
Serum IgE (IU/L), mean $\pm$ SD	361 $\pm$ 87	371 $\pm$ 143	.95
Allergen sensitivity by skin test (any), n (%)	35 (58)	13 (70)	.41
Asthma, n (%)	38 (50%)	21 (95)	<.001
Nasal polyps, n (%)	60 (80)	22 (100)	.01
LM CT sinus score (total), presurgical, mean $\pm$ SD	13.7 $\pm$ 0.5	15.7 $\pm$ 1	.06
Total SNOT-22 score presurgery, mean $\pm$ SD	39.6 $\pm$ 2	57.8 $\pm$ 4	<.001

Missing values: number of patients whose values were unavailable/missing. LM score (3), eosinophil count (10), vitamin D (44), IgE (30), allergen testing (20).

the AT group ($P = .06$). Finally, there was a significant difference in total presurgical SNOT-22 scores between the 2 groups, with patients with H-AS having a mean total SNOT-22 score of 57.8 compared with 39.6 for the AT group ($P < .001$).

Because subjects with H-AS had quantitative differences in the total SNOT-22 score compared with subjects with AT, we performed univariate analyses of all individual elements in the SNOT-22 tool to assess which of the elements in the history were significantly different between the 2 groups (Table II). In subjects with H-AS, scores for need to blow nose (Q1), sneezing (Q2), runny nose (Q3), postnasal discharge (Q5), thick nasal discharge (Q6), ear fullness (Q7), ear pain/pressure (Q9), waking up tired (Q13), lack of good night's sleep (Q14), sad (Q19), embarrassed (Q20), (lack of) sense of taste/smell (Q21), and blockage/congestion of nose (Q22) were higher compared with subjects with AT ($P < .05$). Using adjusted significance values (Bonferroni) for multiple variable comparisons and significance of .05, scores for only need to blow nose (Q1, $P < .002$), runny nose (Q3, $P < .006$), thick nasal discharge (Q6, $P = .01$), ear pain/pressure (Q9, $P = .05$), and (lack of) sense of taste/smell (Q21, $P < .002$) were higher between subjects with H-AS and subjects with AT.

Next, we wished to study whether CRS symptoms in the entire cohort demonstrated inherent patterns of association of individual symptom elements without stratification using presupposed criteria. To this end, we performed an *unsupervised* pairwise correlation analysis to investigate the co-occurrence of CRS symptoms without a presupposition bias (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Sinonasal symptoms (questions 1-6 and 21-22) clustered together. Another group of symptoms related to the ear (questions 7-10), emotion (questions 19 and 20), and sleep and function (questions 11-18) clustered as well. This indicated that inherent to the patient symptom responses, there are patterns and that an *unsupervised* symptom-based clustering of patients would be feasible.

CRS symptoms stratify patients on the basis of magnitude and differential expression and relate to history of aspirin sensitivity

Because univariate analysis of H-AS and AT showed differences in select items, we wished to determine whether symptom analysis could differentiate subjects. To this end, we used the *unsupervised* method of bipartite network graphs and cluster analysis. Select steps in the generation of the bipartite graph are shown in Figure E2 in this article's Online Repository at www.jaci-inpractice.org. A connected bipartite network graph depicts the connection between all patients with CRS and all their individual SNOT item responses as nodes. Random spatial allocation of each type of node is generated (in Figure E2, A, see patients as gray nodes outside and symptoms as white nodes inside). After application of force-directed algorithm, Force-Atlas,¹² and weighted degree centrality,¹³ the resultant network revealed a distinct structure (Figure E2, B). The larger symptom nodes thus represent higher cumulative frequencies of those symptoms, whereas the larger patient nodes represent patients with higher disease burdens.

The resultant graph is a mathematical model depicting associations (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org) and reveals the heterogeneous expression of symptoms in patients and differential affinities of the patient clusters to the symptom clusters. Boundaries of node clusters were identified using *hierarchical agglomerative analysis*, and break points were set on the basis of pattern of symptom expression (dendrogram, Figure E3 inset) and revealed 5 clusters (named A-E). Because the network itself is ignorant of the aspirin sensitivity status and is a mathematical model of the outcome of SNOT-22 itemized scores alone, we overlaid the "condition" of history of aspirin sensitivity (H-AS and AT) onto the network. Only 1 of 23 (4.3%) patients in cluster E and none of 10 (0%) patients in cluster D had H-AS. This suggests that groups of symptoms may be able to help in determining the likelihood of

TABLE II. Comparison of individual SNOT-22 item scores between patients with CRS with and without H-AS (AT)

Item	Description	H-AS, mean $\pm$ SEM	AT, mean $\pm$ SEM	P value	Corrected
1	Need to blow nose	3.7 $\pm$ 0.3	2.3 $\pm$ 0.2	<.001	<.001
2	Sneezing	2.2 $\pm$ 0.3	1.5 $\pm$ 0.2	.03	.66
3	Runny nose	3.6 $\pm$ 0.3	2.1 $\pm$ 0.2	<.001	<.006
4	Cough	2.0 $\pm$ 0.3	1.7 $\pm$ 0.2	.34	
5	Postnasal discharge	3.2 $\pm$ 0.3	2.4 $\pm$ 0.2	.03	.66
6	Thick nasal discharge	3.6 $\pm$ 0.4	2.2 $\pm$ 0.2	<.001	.01
7	Ear fullness	2.6 $\pm$ 0.4	1.5 $\pm$ 0.2	.008	.17
8	Dizziness	1.4 $\pm$ 0.3	0.9 $\pm$ 0.2	.13	
9	Ear pain/pressure	1.4 $\pm$ 0.2	0.5 $\pm$ 0.1	.002	.05
10	Facial pain/pressure	2.2 $\pm$ 0.3	1.8 $\pm$ 0.2	.33	
11	Difficulty falling asleep	2.0 $\pm$ 0.3	1.4 $\pm$ 0.2	.13	
12	Waking up at night	2.5 $\pm$ 0.3	2.0 $\pm$ 0.2	.13	
13	Waking up tired	2.8 $\pm$ 0.3	1.8 $\pm$ 0.2	.01	.22
14	Lack of good night's sleep	3.0 $\pm$ 0.3	2.2 $\pm$ 0.2	.03	.66
15	Fatigue during the day	2.7 $\pm$ 0.4	2.1 $\pm$ 0.2	.10	
16	Reduced productivity	2.3 $\pm$ 0.3	1.7 $\pm$ 0.2	.14	
17	Reduced concentration	2.3 $\pm$ 0.4	1.8 $\pm$ 0.2	.21	
18	Frustrated/restless/irritable	2.3 $\pm$ 0.3	1.6 $\pm$ 0.2	.08	
19	Sad	1.1 $\pm$ 0.2	0.5 $\pm$ 0.1	.01	.22
20	Embarrassed	1.3 $\pm$ 0.3	0.5 $\pm$ 0.1	.004	.08
21	Sense of taste/smell	4.6 $\pm$ 0.4	2.9 $\pm$ 0.2	<.001	<.002
22	Blockage/congestion of nose	4.0 $\pm$ 0.3	3.0 $\pm$ 0.2	.008	.17

Individual symptoms that are still significant after correction for multiple comparisons are shown in bold. Bonferroni correction was applied to adjust for *P* value. *P* values less than .05 considered significant after correction.

aspirin sensitivity. Furthermore, aspirin sensitivity was confirmed in 11 of 14 patients with H-AS in clusters A, B, and C who underwent aspirin challenges (Table III).

Cluster A had high affinity to both sinonasal and nonsinonasal symptoms ($P = 1$) and formed the dense core of the network (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Clusters B and C were significantly closer to sinonasal symptoms ($P < .001$) but differed in the proximity to the nonsinonasal symptom cluster. Clusters D and E comprised mostly patients in the periphery of the network, with cluster D significantly closer to nonsinonasal symptoms ($P < .001$) and cluster E associated with sinonasal symptoms ($P < .001$). Thus, *unsupervised learning* reveals the heterogeneity in presurgical CRS symptoms and shows that symptoms co-occur in specific patterns, forming the basis of categorization of patients. This symptom heterogeneity was related to history of aspirin sensitivity.

Comparison of select clinical parameters among symptom-based clusters

We then wished to analyze other clinical parameters including asthma or atopy among these symptom-based clusters. There were no significant differences across clusters for presence of atopy or history of asthma, vitamin D levels, and blood eosinophil counts (Table III). The clusters themselves were fairly matched in age and sex composition. Cluster A patients had the highest total SNOT-22 scores (90.8 ± 3), whereas cluster E had the lowest total SNOT-22 scores (16.4 ± 2), and the total SNOT-22 differences were significant ($P < .001$) between the groups except for between cluster C and cluster D. The LM CT sinus score was highest in cluster C (mean, 15.8) and lowest in cluster A (mean, 11.6; overall $P = .02$). As to the medication usage history, overall corticosteroid

usage was found to be different across groups ($P = .02$). Three of 10 (30%) patients in group D had received systemic corticosteroids before SNOT-22 assessment (day 48, 51, and 14). Two of 6 (33%) patients in group A received prednisone on day 9 and on day of assessment of SNOT-22. For those in cluster D who received systemic corticosteroids, the total SNOT-22 score was 33.3 ± 6 compared with 39.5 ± 4 ($P = .19$) for those who did not. Sixty-seven percent (4 of 6) of the subjects in cluster A had nasal polyps compared with 100% nasal polyposis in cluster D (10 of 10; overall $P = .06$). The mean total SNOT-22 score at first follow-up was 44 ± 7 (cluster A, $n = 4$), 21.3 ± 3 (cluster B, $n = 16$), 24 ± 3 (cluster C, $n = 16$), 16.8 ± 5 (cluster D, $n = 8$), and 12.9 ± 4 (cluster E, $n = 10$), respectively ($P = .006$). First SNOT-22 assessment postsurgery showed a significant improvement in all clusters ($P < .001$) except E ($P = .50$) compared with presurgical scores. The mean SNOT-22 score at second follow-up was 55.6 ± 9 (cluster A, $n = 3$), 20.6 ± 4 (cluster B, $n = 20$); 27 ± 4 (cluster C, $n = 18$), 9.5 ± 6 (cluster D, $n = 7$), and 13.6 ± 4 (cluster E, $n = 15$), respectively (overall $P < .001$). Clusters B, C, and D continued to maintain symptom resolution at second visit postsurgical intervention (median, 97 days), whereas cluster A had an increase in SNOT-22 scores between the first and second postoperative visits. This difference was, however, not significant ($P = .52$).

DISCUSSION

CRS has a profound impact on quality of life in patients. There have been several well-validated tools that attempt to enumerate the symptom burden using standardized questionnaires.¹⁴ Clinical evaluations of CRS often rely on total symptom score or select symptoms. Moreover, comparison of symptoms

TABLE III. Intercluster comparison between clinical variables

Variable	Cluster A (n = 6)	Cluster B (n = 28)	Cluster C (n = 30)	Cluster D (n = 10)	Cluster E (n = 23)	P value
Age (y), mean $\pm$ SEM	47 $\pm$ 6	48.5 $\pm$ 3	52.7 $\pm$ 3	47.2 $\pm$ 4	54.6 $\pm$ 3	.40
Sex: female, n (%)	4 (67)	11 (39)	8 (27)	3 (30)	6 (26)	.32
Vitamin D ₃ (ng/mL), mean $\pm$ SD	23.4 $\pm$ 7	30.7 $\pm$ 4	35.8 $\pm$ 4	27 $\pm$ 6	38.3 $\pm$ 5	.33
Eosinophil cells/mm ³ , mean $\pm$ SD	472 $\pm$ 195	835 $\pm$ 87	601 $\pm$ 81	507 $\pm$ 145	607 $\pm$ 100	.15
LM CT total score, presurgical, mean $\pm$ SEM	11.6 $\pm$ 2	14.5 $\pm$ 1	15.8 $\pm$ 1	12.4 $\pm$ 1	12.8 $\pm$ 1	.02
Total presurgical SNOT-22 score, mean $\pm$ SD	90.8 $\pm$ 3	62 $\pm$ 1	40.3 $\pm$ 1	37.7 $\pm$ 2	16.4 $\pm$ 2	<.001
Symptom cluster affinity	Both	Sinonasal	Sinonasal	Nonsinonasal	Sinonasal	
H-AS, n (%)	3 (50)	11 (39)	7 (23)	0 (0)	1 (4)	.006
Proportion of patients with H-AS who were challenged and were positive	1 of 1 (100%)	6 of 8 (75%)	4 of 5 (80%)	—	0	
Nasal polyposis, n (%)	4 (67)	27 (96)	24 (80)	10 (100)	17 (74)	.06
Asthma, n (%)	3 (50)	21 (75)	16 (53)	6 (60)	13 (56)	.47
Atopy, n (%) [*]	2 (50)	12 (54)	14 (56)	8 (100)	11 (61)	.20
Any systemic corticosteroid use, n (%) [†]	2 (33)	1 (4)	1 (3)	3 (30)	2 (8)	.02
Postsurgical follow-up, mean $\pm$ SD						
Total postsurgical SNOT-22 score (visit 1)	44 $\pm$ 7	21.3 $\pm$ 3	24 $\pm$ 3	16.8 $\pm$ 5	12.9 $\pm$ 4	.006
Total postsurgical SNOT-22 score (visit 2)	55.6 $\pm$ 9	20.6 $\pm$ 4	27 $\pm$ 4	9.5 $\pm$ 6	13.6 $\pm$ 4	<.001

Overall significance between groups depicted, with $P < .05$ considered significant.

^{*}Total N for which skin testing was available for cluster A = 4, B = 22, C = 25, D = 8, and E = 18.

[†]Injection triamcinolone within 2 mo or oral prednisone within 1 mo of assessment.

one at a time between preassigned groups does not offer the complete picture of symptom burden and the interrelationship of symptoms in CRS. As such, we conducted an unsupervised analysis using network graphs to reveal the patterns of symptoms in patients with CRS.

In this study, we identify 5 clusters of patients with CRS using a standardized presurgical questionnaire (SNOT-22). These clusters, derived from unsupervised analysis of symptom scores, differ in symptom severity and expression and relate to clinical features. We chose SNOT-22 as an instrument because it is validated and has shown reliability, responsiveness, and ease of use.^{3,15} Baseline descriptive statistical analysis of our patients was performed comparing the H-AS and AT groups. Peripheral eosinophilia has been variably reported in patients with CRS to be significantly different in patients with aspirin sensitivity versus those without.^{16,17} We report similar findings; however, note that presurgical eosinophil counts did not differ between patients with CRS with or without H-AS (AT), but there was significant serum eosinophilia in subjects with H-AS when the highest recorded eosinophil count was compared between the 2 groups. We speculate that optimization of medical intervention before surgical intervention may have accounted for the lack of difference between presurgical eosinophil numbers. Serum IgE or atopy did not correlate with history of aspirin sensitivity, which confirms previous findings.¹⁷ In regard to symptoms, univariate analysis revealed that 5 elements of the SNOT-22 questionnaire were significantly different between the H-AS group and the AT group, with need to blow nose, runny nose, thick nasal discharge, ear pain/pressure, and (lack) of sense of taste/smell being symptomatically worse in the H-AS group.

The presence of a history of aspirin sensitivity is a useful clinical guide for planning medical management postsurgery, but there is often underreporting of this history¹⁸ or a definitive history is not available in some cases (up to 50% in one report).¹⁹ Thus, there is a need for the identification of clinical features,

either singly or in a group, that can aid in predicting the presence or absence of aspirin sensitivity, especially in those undergoing surgery. Recent studies do hint toward urinary leukotriene E₄ excretion as a marker of aspirin sensitivity,²⁰ but at present a validated clinical biomarker is lacking.²¹ Thus, identifying patterns in patient symptoms that may be able to suggest aspirin sensitivity would be valuable.

Conventional analyses conducted on *a priori* classified groups such as aspirin-sensitive or aspirin-tolerant have been performed and have demonstrated that aspirin sensitivity is related to a higher burden of disease, more inflammation, and repeated surgical interventions.²² Such comparisons between *pre-determined* groups (typically 2 or 3) are extremely useful but are at risk for missing all patterns; hence, identification of patterns in data analyzed without presupposition is an important and novel contribution of unsupervised analyses that complements conventional analyses. We found that symptom-based clustering was able to distinguish subgroups with and without history of aspirin sensitivity. Our data reassuringly affirm the broad overview of patterns of symptoms in patients with CRS seen with conventional analyses but also reveals subtle heterogeneities in CRS subpopulations that would otherwise not be apparent. Our study also corroborates the finding that LM CT scores do not strongly correspond to the total SNOT-22 score,²³ but using the symptom-based clustering we found differences in the LM CT scan scores. How these clusters relate to the recently described volumetric CT staging system²⁴ remains to be seen.

Previous studies have shown mixed influences of aspirin sensitivity on surgical outcomes.^{6,25} Symptom-based clustering revealed differences in postsurgical response among the groups. Patients with lowest burden of disease and sinonasal predominant symptoms preoperatively (cluster E) did not improve significantly postprocedure compared with clusters A to D, which had great improvement in the total SNOT-22 score postsurgery. Thus, these patients represent a group whose clinical

symptoms apparently respond to medical therapy before surgery and continue to do so postoperatively.

We confirmed the well-known relationship between a history of aspirin sensitivity and a history of asthma in our cohort. The highest proportion of subjects with asthma (75%) was seen in cluster B, which also demonstrated aspirin sensitivity, sinonasal symptom affinity, relative eosinophilia, and nasal polyposis, although differences in the proportion of subjects with asthma across all the clusters were not significant. There are a few possible reasons that could explain this finding. The diagnosis of asthma was historical or physician-diagnosed and not clinically verified by bronchoprovocation or pulmonary function testing. As such, there may have been overreporting of asthma status in the cohort. Second, the SNOT-22 by itself does not have any respiratory elements (beside cough) and is not designed to identify asthma per se. Thus, the basis of the clustering is symptoms that may be not as directly related to asthma status, precluding a direct association. Third, the SNOT-22 score used for network analysis was specifically a presurgical symptom score with the expectation that the patients were optimized for surgery and presumably not at their worst. Thus, although the magnitude or quality of the symptom burden correlated well with the history of aspirin sensitivity, asthma status did not in our study. Finally, the study may not be powered to show differences in subjects with and without asthma using the SNOT-22 tool.

This study's results raise additional interesting questions. Clusters B and C have a similar clinical type (age, CT scan score, sinonasal symptom predominance, aspirin sensitivity, nasal polyposis, and atopy), yet disease perception as measured by the total SNOT-22 score was more in one group (B) than in the other. Whether this is related to other factors (such as comorbidities) influencing symptom perception is intriguing. Wasan et al²⁶ have reported an association between psychiatric comorbidities and increased symptoms in CRS. The additional burden of non-sinus-related symptoms is exemplified by cluster A, which has high scores to begin with, both sinonasal and non-sinonasal symptom dominance, and demonstrates worsening symptoms by the second visit after endoscopic sinus surgery. Remarkably, clusters D and E have similar LM CT scan scores but very different symptom perceptions (systemic, ie, non-sinonasal, versus local, ie, sinonasal). Whether this could relate to systemic effects of local inflammation²⁷ in one group or the effect of other factors is a question for future study.

There are a few limitations to the study. First, this was a group of patients referred to a tertiary care facility and the study population does not reflect trends in the general population. Second, this was a retrospective chart review of patients and as such deficiencies in the data (there was some attrition of the data seen with follow-up in the first and second follow-up visits but we were able to maintain the temporal relationship of change in symptoms) or variances in the timing of testing could not be controlled for. To be specific in the timing of collection of SNOT-22 symptoms, the score most immediate before surgery and 2 responses after surgery was used for the analysis. Third, aspirin sensitivity was assessed by patient-provided history and we do not routinely perform aspirin challenge on all patients without a history of reaction to aspirin or nonsteroidal anti-inflammatory drugs. Fourth, lack of rigorous histopathological analyses or comprehensive immunological hallmarks is a limitation.

However, this study has several unique strengths. To date, this is the first unsupervised network analysis of standardized

presurgical symptoms in patients with CRS. Unsupervised cluster analysis of SNOT-22 questionnaire has been recently used to derive reduced meaningful "factors" as they relate to clinical characteristics.^{9,10} In their study, Sedaghat et al¹⁰ have used principal-component analysis of SNOT-22 to describe 4 components in patient history (symptoms related to sleep, nasal, otologic, and emotion) as they relate to clinical characteristics, whereas in the study by Soler et al⁹ SNOT-22 was part of a group of variables (including depression and 12-item short-form health survey questionnaires). Network graphs are unique because they allow spatial visualization of differences and similarities in data (as represented by mathematical relationships) to inform of associations that can rapidly be used to discover patterns.²⁸ In comparison with other published studies that used hierarchical methods,⁹ k-means,²⁹ or component analysis,¹⁰ bipartite graphs allow for comprehension of data structure by simultaneous visualization of both subjects (their clusters) and variables (and their clusters) [hence *bipartite*] and the relationships between them. Bipartite network graphs are being increasingly used to newer fields of application to acquire a high-level view of data, for example, biomarkers, human disease, drug discovery, systems biology, or microbiome research.^{27,30-34} In a previous study, using this approach we were able to discern subpopulations of patients presenting with "sinus headaches" but no CRS that differ in clinical characteristics.³⁵ The results of the present study suggest that building symptom-based models in CRS could still play an important role in patient classification and phenotyping. Our results highlight the heterogeneity of symptom expression in patients with CRS and indicate that proper recognition of these differences may assist a clinician to institute individualized treatment regimens specifically tailored to subgroups.

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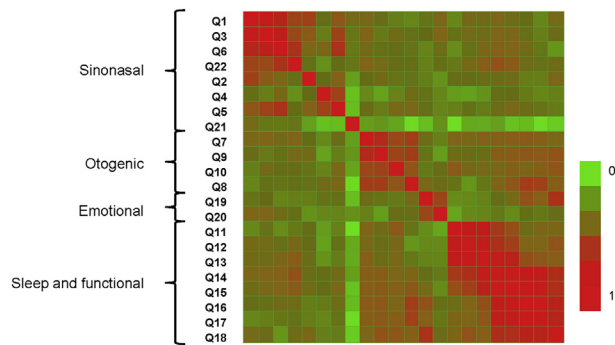


FIGURE E1. Heat map depicting clustering of individual items in SNOT-22 questionnaire in patients with CRS. Pairwise correlation matrix with clustering was used to place increasingly associated symptoms together. Color represents degree of similarity, with highly similar cells in red.

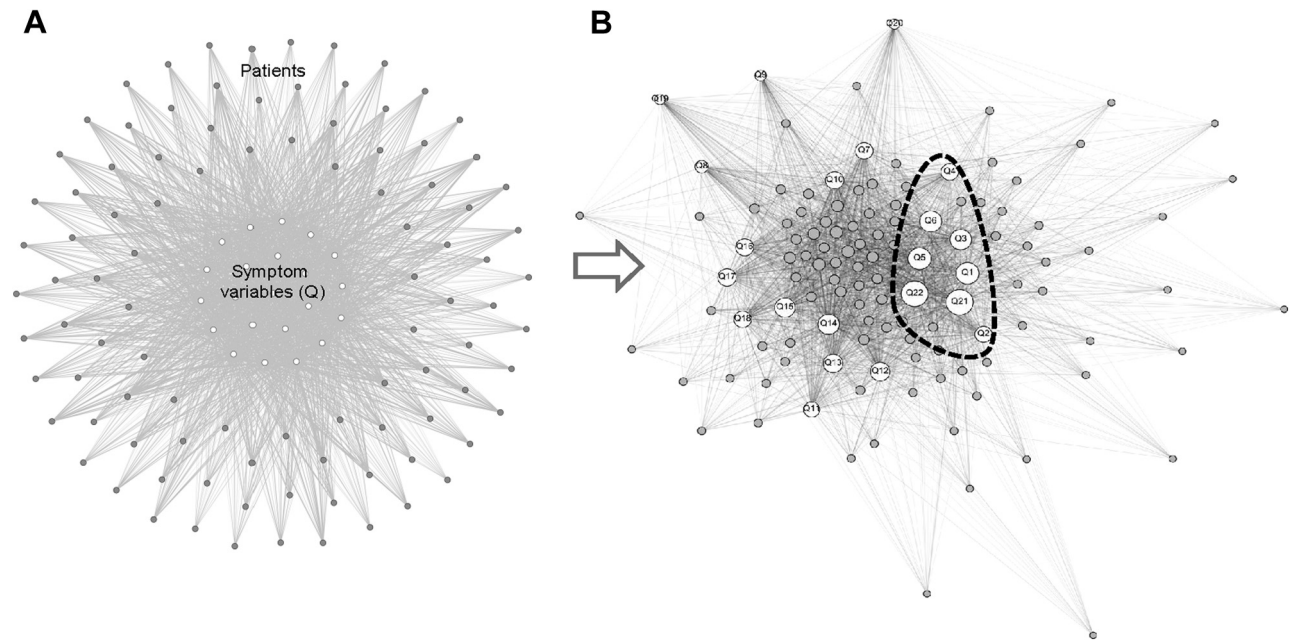


FIGURE E2. **A**, Organized but random layout of patients (gray nodes) and symptoms (white nodes, center). **B**, Network depicting a layout after the application of force-directed and weighted degree centrality algorithms revealing structure to the symptom patterns. Size of variable nodes (white, symptoms) corresponds to degree centrality.

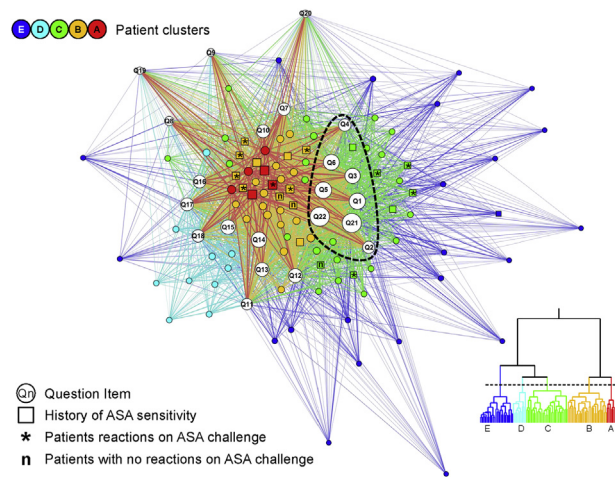


FIGURE E3. Final network reveals symptom heterogeneity. Node size corresponds to weighted degree centrality. The clusters are red (**A**), orange (**B**), green (**C**), cyan (**D**), and blue (**E**) color. Dendrogram clustering is shown (inset). Black dashed line represents sinonasal symptom cluster. Patients with H-AS, square nodes ($\square$); patients without H-AS (AT), circular nodes ($\circ$). Asterisk represents ASA-challenged patients confirmed ASA sensitivity. ASA, Aspirin.

TABLE E1. Network analysis involving distance metric

Cluster	(Distance) ⁻¹ Mean ± SD (AU)		<i>P</i>	Affinity to cluster
	(Mean distance) ⁻¹ to sinonasal symptom cluster (dotted line)	(Mean distance) ⁻¹ to nonsinonasal symptoms		
A (6)	4.14 ± 1.3	4.14 ± 1.3	1	Both
B (28)	3.35 ± 1.3	2.7 ± 1.5	.0001	Sinonasal
C (30)	2.87 ± 1.4	1.51 ± 1.4	.0001	Sinonasal
D (10)	1.3 ± 1.5	2.06 ± 1.6	.0006	Nonsinonasal
E (23)	1.37 ± 1.3	0.62 ± 1	.0001	Sinonasal

Proximity of each cluster to predominant symptom clusters was calculated using mean weights. Edge weight (computed from the patient response to individual SNOT item) is inversely proportional to distance between nodes; thus, higher edge weights represent shorter internode distance and therefore closely associating nodes.

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